NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ravulizumab for treating paroxysmal nocturnal haemoglobinuria [ID1457]

Document B

Company evidence submission

September 2020

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Contents

Tables and Figures

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

B.1.1. Decision problem

The submission covers ravulizumab'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	Adults with paroxysmal nocturnal haemoglobinuria: • who have haemolysis with clinical symptom(s) indicative of high disease activity or • whose disease is clinically stable after having eculizumab for at least 6 months	Adults with paroxysmal nocturnal haemoglobinuria: • who have haemolysis with clinical symptom(s) indicative of high disease activity or • whose disease is clinically stable after having been treated with eculizumab for at least 6 months	Not applicable
Intervention	Ravulizumab	Ravulizumab	Not applicable
Comparator(s)	Eculizumab	Eculizumab	Not applicable
Outcomes	The outcome measures to be considered include: • overall survival • haemolysis (measured by lactate • dehydrogenase [LDH] level) • breakthrough haemolysis • transfusion avoidance • stabilized haemoglobin • thrombotic events • adverse effects of treatment • health-related quality of life (for patients and carers)	The outcome measures to be considered include: • overall survival • haemolysis (measured by lactate • dehydrogenase [LDH] level) • breakthrough haemolysis • transfusion avoidance • stabilized haemoglobin • thrombotic events • adverse effects of treatment • health-related quality of life (for patients and carers)	Overall survival was not a pre-specified endpoint in the ravulizumab trial programme, although deaths were captured as a safety outcome. Eculizumab has aligned the life expectancy of paroxysmal nocturnal haemoglobinuria patients to the general population (see Section B.1.3.2) such that the economic model uses standard mortality estimates. Health-related quality of life data collection was limited to patients in the ravulizumab trial programme. Thus, health-related quality of life for carers is only considered in a qualitative sense and not captured in the economic model (see Section B.2.12).

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 in the terminal complement pathway. As a terminal complement inhibitor, ravulizumab prevents the uncontrolled complement activation responsible for triggering chronic haemolysis in paroxysmal nocturnal haemoglobinuria (PNH), while preserving earlier components of complement activation essential to the immune system.

Ravulizumab was designed by re-engineering eculizumab, the current standard of care in PNH, 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.

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 Figure 2.

Table 2 summarizes ravulizumab for the PNH indication 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

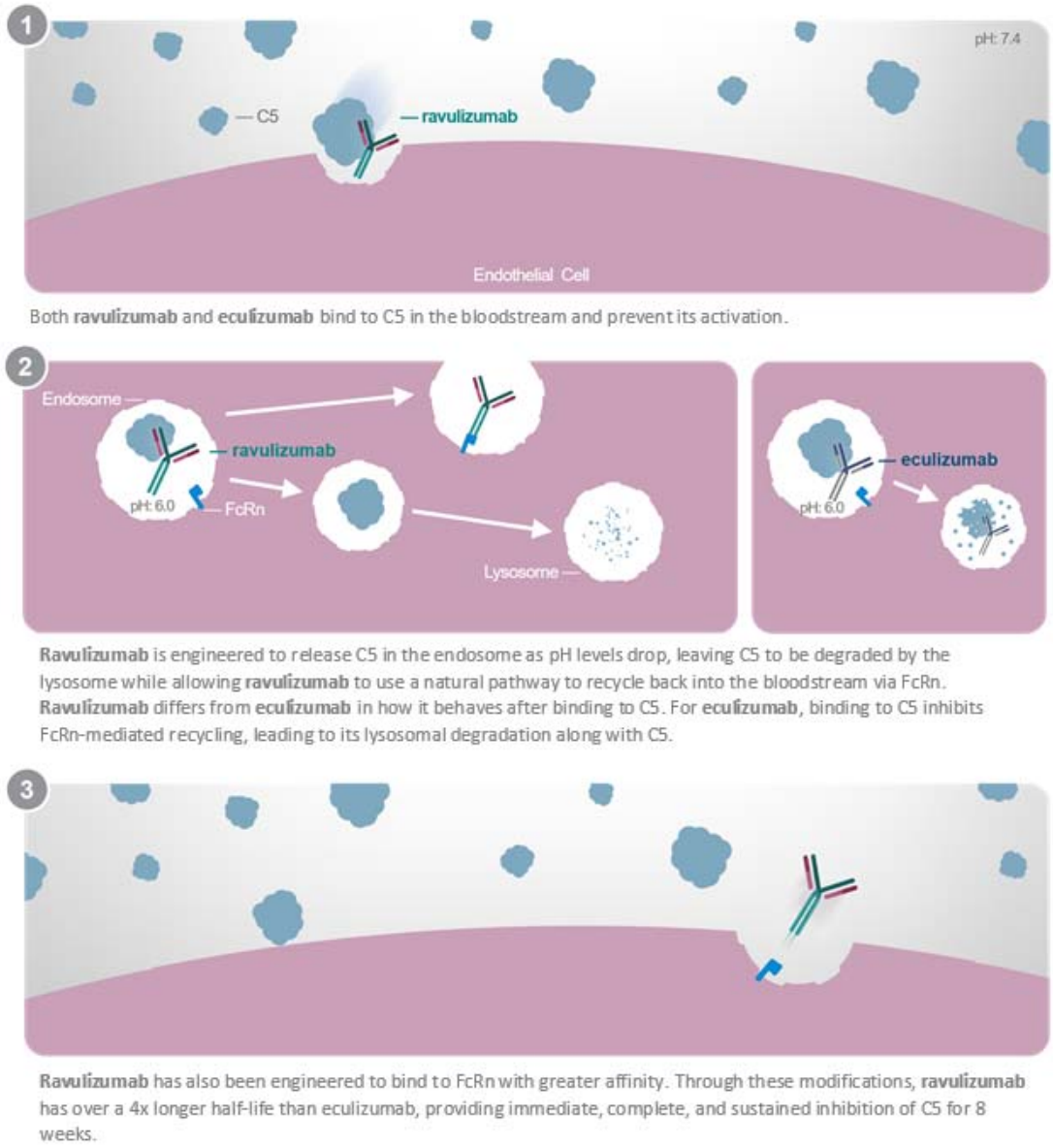


Table 2: Ravulizumab in PNH product characteristics

UK approved name Brand name	Ravulizumab Ultomiris®
Mechanism of action	Ravulizumab is a humanized 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.
Marketing authorization status	Positive CHMP opinion was attained on 26 April 2019 with European Commission marketing authorization granted on 2 July 2019.

<table>
<tr><td>Indications and any restriction(s) as described in the Summary of product characteristics</td><td>‘Ultomiris is indicated in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH):
• in patients with haemolysis with clinical symptom(s) indicative of high disease activity
• in patients who are clinically stable after having been treated with eculizumab for at least the past 6 months’</td></tr>
<tr><td>Method of administration and dosage</td><td>Ravulizumab is administered by intravenous infusion.
Dosage is determined by weight as detailed in the table below.
Dosing schedule consists of an initial loading dose, followed by maintenance dosing, starting 2 weeks after the loading dose.

<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>
Treatment is recommended to continue for the patient’s lifetime, unless discontinuation is clinically indicated, for example, in the rare circumstance of spontaneous remission or recovery due to bone marrow transplant for underlying bone marrow failure.</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 marketing authorization expected to extend to these vial sizes by [redacted]
• [redacted] for 3 mL vial (100 mg/mL)
• [redacted] for 11 mL vial (100 mg/mL)
• Cost per mg: [redacted] (for all vial sizes)
Average cost of treatment per month: £27,217</td></tr>
<tr><td>Patient access scheme</td><td>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] (for all vial sizes)
Average cost of treatment per month: [redacted]</td></tr>
<tr><td colspan="2">Key: CHMP, Committee for Medicinal Products for Human Use; PAS, patient access scheme.
Source: Ultomiris summary of product characteristics.[1]</td></tr>
</table>

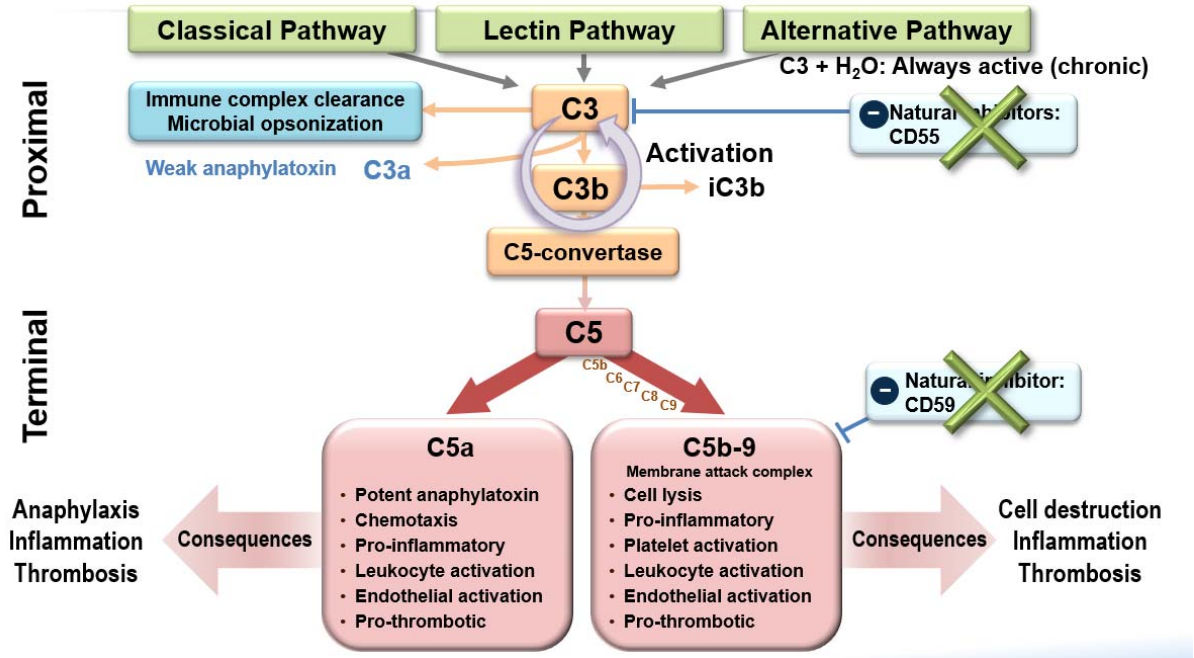
B.1.3. Health condition and position of the technology in the treatment pathway

B.1.3.1. Disease overview

PNH is caused by a somatic (acquired) mutation in the *PIG-A* gene in haematopoietic stem cells[2, 3] that leads to either a partial or absolute deficiency in proteins linked to the cell membrane by a glycosylphosphatidylinositol (GPI) anchor. It is an extremely rare condition, with an estimated 725 people in the UK diagnosed with PNH at the end of 2018.[4]

PNH is a progressive, life-threatening haematological disorder characterized by uncontrolled activation of the terminal complement pathway that can lead to intravascular haemolysis (red cell destruction), anaphylaxis, inflammation and thrombosis, as depicted in Figure 2.

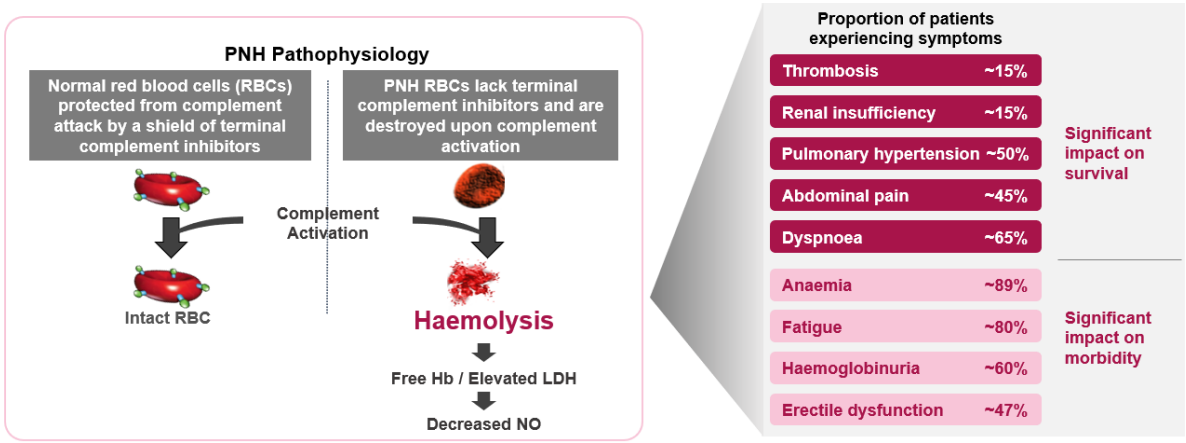
Figure 2: Complement pathway and consequences of uncontrolled activation



Source: Adapted from Figueroa and Denson 1991[5]; Loirat et al. 2008[6]; Noris et al. 2012[7]; Rother et al. 2007[8]; Walport 2001[9]; Zipfel et al. 2008.[10]

Chronic haemolysis is the underlying cause of progressive morbidity and premature mortality in PNH and can result in multiple symptoms of varying severity, including anaemia, fatigue, dyspnoea (breathlessness), haemoglobinuria (haemoglobin in the urine), pulmonary hypertension, thrombosis and others, as summarized in Figure 3. Such debilitating symptoms markedly reduce patient quality of life and negatively impact activities of daily living. In a multi-national survey of disease burden associated with PNH (n = 29), 76% of patients were forced to modify their daily activities to manage their PNH, and 17% of patients were unable to work because of their disease.[11]

Figure 3: Impact of chronic haemolysis



Key: Hb, haemoglobin; LDH, lactate dehydrogenase; NO, nitric oxide; PNH, paroxysmal nocturnal haemoglobinuria; RBC, red blood cell.
Source: Adapted from Brodsky et al. 2005[12]; Hill et al. 2007.[13]; Hill et al. 2010[14]; Hillmen et al. 2010[15]; Jang et al. 2016[16]; Lee et al. 2010[17]; Meyers et al. 2007[11]; Rother et al. 2005[18]; Schrezenmeier et al. 2014.[19]

The clinical course of PNH is highly variable .and unpredictable: some patients have sudden symptom onset and rapid progression to death, while others experience chronic illness with limited life-threatening complications.[20] Without complement-inhibitor treatment, the majority of patients (up to 75%) die within 20 years of diagnosis, and median survival is estimated at approximately 10 years (from diagnosis).[21] With a median age at disease onset of approximately 40 years[21], PNH is therefore a severely life-limiting condition.

B.1.3.2. Clinical pathway of care

The clinical pathway of care for patients with PNH in NHS England is managed through a PNH National Service that was initiated in April 2009.[4] The PNH National Service has two main centres: one at St James' University Hospital in Leeds, and the second at King's College Hospital in London; and a further eight outreach clinics around the UK (Birmingham, Bristol, Lanarkshire, Liverpool, Manchester, Oxford, Peterborough and Southampton). Referrals to the service are received from around the UK on suspicion of PNH (normally from local haematologists), and on confirmed diagnosis of PNH, patients are managed on a shared care basis between the PNH National Service and referring haematologists.

Adult patients with PNH and haemolysis with clinical symptom(s) indicative of high disease activity in the UK are currently treated with eculizumab.[22] Like ravulizumab, eculizumab is a complement inhibitor that binds to the complement protein C5 in the terminal complement pathway; indeed, eculizumab provided the backbone of ravulizumab. The exact criteria used by the PNH National Service to determine treatment eligibility are:

- Thrombosis related to PNH
- Complications associated with haemolysis:
  - Renal failure
  - Pulmonary hypertension
- Pregnancy (and for at least 3 months post-partum)
- Haemolytic (lactate dehydrogenase [LDH] levels > 1.5 times the upper limit of normal [ULN]) PNH with either of the following:
  - With anaemia (Hb < 9 g/L) or
  - With agreement with Joint Service colleagues at multidisciplinary team (MDT)
- Exceptional cases (not fulfilling the above criteria) with approval across PNH National Service centres and the National Commissioners

In the treatment initiation phase, patients receive eculizumab 600 mg via 25–45 minute intravenous infusion every week for the first 4 weeks.[23] In the treatment maintenance phase, patients receive eculizumab 900 mg via 25–45 minute intravenous infusion every 14 ± 2 days. For patients in England, up to the first five

eculizumab doses (often only the first dose) are administered at one of the PNH National Service centres, after which most patients choose to have treatment administered at their home through a homecare service.[24, 25] This homecare service, including the delivery of the drug to the patient's home and the nurse 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).

Eculizumab has transformed the prognosis of patients with haemolytic PNH, significantly reducing progressive morbidity and aligning the life expectancy of patients to that of the general population.[16, 20, 23, 26-32]

B.1.3.3. Remaining unmet need

Despite the revolutionary nature of eculizumab in terms of patient prognosis, there are some remaining areas of unmet need in the PNH setting.

Approximately 20% of patients with PNH reportedly experience breakthrough haemolysis while receiving label dose of eculizumab (900 mg) treatment (reported range: 5–29%).[26, 33-35] Breakthrough haemolysis can occur when the blood concentration of complement inhibitor is insufficient to provide complete C5 inhibition, or as a result of a concomitant complement-amplifying condition (CAC) such as pregnancy or infection.[34, 36] Patients experiencing breakthrough haemolysis have an increased risk of potentially fatal thromboembolic events and other debilitating PNH-related symptoms (Figure 3).

Although complement-inhibitor treatment cannot prevent breakthrough haemolysis due to a CAC, it should prevent breakthrough haemolysis due to incomplete C5 inhibition. However, due to the flat dosing nature of eculizumab treatment, this is not always the case when patients are treated at the standard recommended dose (label dose of 900 mg bi-weekly). In confirmed cases of incomplete terminal complement inhibition, the PNH National Service recommend permanent 'up-dosing' of eculizumab to 1,200 mg and potentially higher if initial 'up-dosing' is insufficient.[37] According to UK data from the International PNH Registry (2 October 2018; data on file) and PNH National Service data (March 2019[38]), approximately [redacted]% of patients treated in current practice are receiving a higher dose of eculizumab than the label dose. A recent cost analysis of breakthrough haemolysis in patients with PNH in the

US estimated that the total cost of BTH management was $9,379 for eculizumab-treated patients with the majority of costs resulting from this higher dosing need.[39]

Eculizumab is also associated with a high administration burden due to its relatively short half-life, with patients requiring bi-weekly infusions to maintain C5 inhibition. Patients with PNH have expressed that such a high frequency of regular infusions remains a treatment burden related to their disease.[40] An ethnographic study of 10 PNH patients described the need for patients to coordinate logistics for the infusion day and various responsibilities in anticipation of their absence from work, school or other activities.[41] In addition, carers may accompany patients, which also results in carers coordinating logistics for their absence from work, school or other activities.[41] In a later series of concept elicitation interviews (conducted to inform the development of a patient preference questionnaire), the impact of frequent treatment on patients ability to take vacations or plan activities was a particularly salient burden among PNH patients.[42]

In a series of interviews with patients and carers in England, participants noted the negative effect of bi-weekly infusions on their quality of life.[43] This ranged from anxiety on the day of their infusion, loss of their independence and disruption to their professional and personal lives. Table 3 presents some of the statements made during these interviews.

Table 3: Interviews with patients and carers – snapshot of statements

Statements on eculizumab administration burden
Anxiety on the day of infusion • 'I do get a bit stressed because they sometimes have difficulty getting the cannula in… I worry about it a bit, put it that way' – Patient • 'Occasionally we have problems in that it's very stressful for him. I think we have had, recently, a nurse rung, supposed to come at 8 in the morning and she rung and said she was waiting for delivery of someone else's drugs that hasn't turned up. So, she won't be there, and she doesn't know when and I think he finds that very stressful. And I can understand because that makes me stressed as well' – Carer
Impact on travel and independence • 'It would be nice to have longer so I could go away' – Patient • 'Our visits abroad tend to be much more limited and we tend to holiday and do various things in the UK rather than abroad' – Carer
Disruption to work • 'There was a bit of friction. The boss is a bit awkward about it' – Patient

• ‘I will delay going to work until it’s happened. It makes me late for work’ – Carer
Source: Interviews to Elicit the Burden of Paroxysmal Nocturnal Haemoglobinuria and Treatment with Eculizumab in Patients and Caregivers.[43]

B.1.3.4. Proposed position of ravulizumab

The proposed position of ravulizumab is as an alternative to eculizumab to address the remaining areas of unmet need in the PNH setting. The evidence to support this proposed position is presented throughout Section B.2.

Ravulizumab is intended to be used to treat adult patients with PNH and haemolysis with clinical symptom(s) indicative of high disease activity, according to the same criteria used to determine eligibility for eculizumab treatment in current practice. However, it should be noted that ravulizumab has not been assessed in pregnant women. Ravulizumab is also intended to treat adult patients with PNH who are clinically stable after having been treated with eculizumab for at least the past 6 months.

Treatment decisions will continue to be made by the PNH National Service, with ravulizumab provided through the PNH National Service centres and outreach clinics and subsequently the Alexion-funded homecare service, which would extend to ravulizumab.

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 adult patients with PNH: ALXN1210-PNH-301 and ALXN1210-PNH-302, as summarized in Table 4. Both are randomized controlled trials (RCTs) providing direct evidence of the comparative benefits of ravulizumab compared with eculizumab; both report outcomes of relevance to the decision problem and are used to populate the subsequent economic modelling.

Table 4: Clinical effectiveness evidence

	ALXN1210-PNH-301 NCT02946463					**ALXN1210-PNH-302 NCT03056040**				
Study design	Phase III Open-label; parallel assignment Non-inferiority					Phase III Open-label; parallel assignment Non-inferiority				
Population	Adult patients with PNH who are complement-inhibitor naïve					Adult patients with PNH who are clinically stable following ≥ 6 months treatment with eculizumab				
Intervention(s)	Ravulizumab					Ravulizumab				
Comparator(s)	Eculizumab					Eculizumab				
Trial supports application for marketing authorization	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 PNH and haemolysis with clinical symptom(s) indicative of high disease activity.					Pivotal evidence of the clinical benefits of ravulizumab in adult patients with PNH who are clinically stable after having been treated with eculizumab for at least the past 6 months.				

	ALXN1210-PNH-301 **NCT02946463**	**ALXN1210-PNH-302** **NCT03056040**
Reported outcomes specified in the decision problem	• Haemolysis (measured by LDH levels) • **Breakthrough haemolysis** • Transfusion avoidance • Stabilized haemoglobin • Thrombotic events • **Adverse effects of treatment** • **HRQL (for patients)**	• Haemolysis (measured by LDH levels) • **Breakthrough haemolysis** • Transfusion avoidance • Stabilized haemoglobin • Thrombotic events • **Adverse effects of treatment** • **HRQL (for patients)**
All other reported outcomes	• **Transfusion units** • PK and PD endpoints	• **Transfusion units** • PK and PD endpoints
Complete published reports	Lee et al. 2019[44] Brodsky et al. 2020[45]	Kulasekararaj et al. 2019[46] Brodsky et al. 2020[45]
Conference proceedings	ASH: Brodsky et al. 2018[34] ASH: de Latour et al. 2018[47] ASH: Hill et al. 2019[48] ASH: Weitz et al. 2018[49] BSH: Brodsky et al. 2019[50] BSH: de Latour et al. 2019[51] DGHO: Schrezenmeier et al. 2018[52] DGHO: Roth et al. 2019[53] ECTH: Roth et al. 2019[54] EHA: Lee et al. 2018[55] EHA: Schrezenmeier et al. 2019[56] EHA: Kulasekararaj et al. 2020[57] JSH: Lee et al. 2018[58] SIE: Risitano et al. 2019[59] THS: Lee et al. 2018[60]	ASH: Brodsky et al. 2018[34] ASH: de Latour et al. 2018[47] ASH: Hill et al. 2019[48] ASH: Kulasekararaj et al. 2018[61] ASH: Kulasekararaj et al. 2019[62] BSH: Brodsky et al. 2019[50] BSH: de Latour et al. 2019[51] DGHO: Risitano et al. 2019[63] ECTH: Risitano et al. 2019[64] SIE: Risitano et al. 2019[59]
Regulatory materials	European Public Assessment Report[65] Summary of Product Characteristics[1]	European Public Assessment Report[65] Summary of Product Characteristics[1]
Clinical study reports	Clinical study report[66] 52-week data addendum[67]	Clinical study report[68] 52-week data addendum[69]

Key: ASH, American Society of Hematology; BSH, British Society for Haematology; DGHO, German Society for Hematology and Medical Oncology; ECTH, European Congress on Thrombosis and Haemostasis; EHA, European Hematology Association; HRQL, health-related quality of life; JSH, Japanese Society of Hematology; LDH, lactate dehydrogenase; PD, pharmacodynamic; PK, pharmacokinetic; PNH, paroxysmal nocturnal haemoglobinuria; SIE, Italian Society of Hematology; THS, Turkish Society of Hematology.
Notes: Outcomes in bold are those directly used in the economic modelling.

Two earlier phase ravulizumab trials provide additional safety data on patients with PNH treated with ravulizumab, which are detailed in Appendix F.

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

The methodologies adopted in studies ALXN1210-PNH-301 and ALXN1210-PNH-302 are summarized below, with additional details provided in Table 5.

B.2.3.1. Summary of methodology

ALXN1210-PNH-301

ALXN1210-PNH-301 is a Phase III RCT, designed to assess the non-inferiority of ravulizumab compared with eculizumab in adult patients with PNH who are complement-inhibitor naïve. Patients with symptomatic PNH who had no current or previous treatment with a complement inhibitor were enrolled and randomized (1:1) to receive ravulizumab or eculizumab, according to dosing schedules detailed in Table 5.

The study consisted of a 4-week Screening Period and a 26-week Randomized Period that made up the Primary Evaluation Period. At the end of the Primary Evaluation Period, all patients were invited to enter an Extension Period where they would either continue to receive ravulizumab or switch from eculizumab to ravulizumab (dependent on their randomized treatment group).

Co-primary efficacy endpoints were:

- transfusion avoidance, defined as the proportion of patients who remained transfusion-free and did not require a transfusion per protocol-specified guidelines and
- haemolysis, as measured by lactate dehydrogenase-normalization (LDH-N), defined as LDH levels ≤ 1 x upper limit of normal (ULN).

Primary efficacy analyses were conducted at Week 26, representing the end of the Randomized Period; an Extension Period of up to 2 years is currently ongoing. Data are currently available for up to 52 weeks of ravulizumab treatment.

ALXN1210-PNH-302

ALXN1210-PNH-302 is a Phase III RCT, designed 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. Patients with documented PNH who had been treated with eculizumab according to the labelled dosing recommendation for PNH for at least 6 months were enrolled and randomized to receive ravulizumab or continue on eculizumab, according to dosing schedules detailed in Table 5.

The study consisted of a 4-week Screening Period and a 26-week Randomized Period that made up the Primary Evaluation Period. At the end of the Primary Evaluation Period, all patients were invited to enter an Extension Period where they would either continue to receive ravulizumab or switch to ravulizumab (dependent on their randomized treatment group).

The primary efficacy endpoint was haemolysis, as measured by percentage change in LDH. Primary efficacy analyses were conducted at Week 26, representing the end of the Randomized Period; an Extension Period of up to 2 years is currently ongoing. Data are currently available for up to 52 weeks of ravulizumab treatment.

Table 5: Methodology of ALXN1210-PNH-301 and ALXN1210-PNH-302

	ALXN1210-PNH-301 **NCT02946463**	**ALXN1210-PNH-302** **NCT03056040**
Trial design	Phase III, open-label, randomized, active-controlled, multicentre study. 123 sites across 25 countries including the UK ([redacted] patients treated in England). Randomization was stratified into six groups based on patient's transfusion history (0, 1 to 14, or > 14 units of pRBCs in the 1 year prior to first dose of study drug) and screening LDH levels (1.5 to < 3 or ≥ 3 x ULN). Patients were randomly assigned in a 1:1 ratio. Treatment group assignment was determined by a computer-generated random sequence using an IVRS or WRS.	Phase III, open-label, randomized, active-controlled, multicentre study. 52 sites across 12 countries including the UK ([redacted] patients treated in England; [redacted] patients treated in Scotland). Randomization was stratified into two groups based on patient's transfusion history (received a transfusion of pRBCs in the 1 year prior to first dose of study drug, yes or no). Patients were randomly assigned in a 1:1 ratio. Treatment group assignment was determined by a computer-generated random sequence using an IVRS or WRS.
Trial periods	Screening Period: 4 weeks Randomized Period: 26 weeks Extension Period: up to 2 years The Primary Evaluation Period includes the Screening Period and the Randomized Period. In the Extension Period, all patients were treated with ravulizumab.	Screening Period: 4 weeks Randomized Period: 26 weeks Extension Period: up to 2 years The Primary Evaluation Period includes the Screening Period and the Randomized Period. In the Extension Period, all patients were treated with ravulizumab.
Inclusion criteria	1. Male or female, 18 years of age or older 2. Documented diagnosis of PNH, confirmed by high sensitivity flow cytometry evaluation or RBCs and WBCs with granulocyte or monocyte clone size of ≥ 5% 3. Presence of one or more of the following PNH-related signs or symptoms within 3 months of screening: • Fatigue • Haemoglobinuria	1. Male or female, 18 years of age or older 2. Treated with eculizumab according to the labelled dosing recommendation for PNH for at least 6 months prior to Day 1 3. LDH ≤ 1.5 x ULN at screening 4. Documented diagnosis of PNH, confirmed by high sensitivity flow cytometry evaluation or RBCs and WBCs with granulocyte or monocyte clone size of ≥ 5%

	ALXN1210-PNH-301 NCT02946463	ALXN1210-PNH-302 NCT03056040
	• Abdominal pain • Shortness of breath (dyspnoea) • Anaemia (haemoglobin < 10 g/dL) • History of major adverse vascular event, including thrombosis • Dysphagia • Erectile dysfunction • History of pRBC transfusion due to PNH 4. LDH ≥ 1.5 x ULN at screening 5. Vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating study drug. Patients who initiated study drug treatment less than 2 weeks after receiving a meningococcal vaccine were required to have received treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination 6. Female patients of childbearing potential and male patients with female partners of childbearing potential must have followed protocol-specified guidance for avoiding pregnancy while on treatment 7. Patients must have been willing and able to give written informed consent and to comply with all study visits and procedures	5. Vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating study drug. Patients who initiated study drug treatment less than 2 weeks after receiving a meningococcal vaccine were required to have received treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination 6. Female patients of childbearing potential and male patients with female partners of childbearing potential must have followed protocol-specified guidance for avoiding pregnancy while on treatment 7. Patients must have been willing and able to give written informed consent and to comply with all study visits and procedures
Exclusion criteria	1. Current or previous treatment with a complement inhibitor 2. Platelet count < 30,000/mm^3 at screening 3. Absolute neutrophil count < 500/µl at screening 4. History of bone marrow transplantation 5. Body weight < 40 kg at screening	1. LDH value > 2 x ULN in the 6 months prior to Day 1 2. Major adverse vascular event in the 6 months prior to Day 1 3. Platelet count < 30,000/mm^3 at screening 4. Absolute neutrophil count < 500/µl at screening 5. History of bone marrow transplantation

	ALXN1210-PNH-301 **NCT02946463**	**ALXN1210-PNH-302** **NCT03056040**
	6. History of *N. meningitidis* infection 7. History of unexplained, recurrent infection 8. Active systemic bacterial, viral or fungal infection within 14 days prior to study drug administration on Day 1 9. Presence of fever ≥ 38°C within 7 days prior to study drug administration 10. HIV infection 11. Immunized with a live-attenuated vaccine within 1 month prior to study drug administration 12. History of malignancy within 5 years of screening with the exception of nonmelanoma skin cancer or carcinoma in situ of the cervix that had been treated with no evidence of recurrence 13. History of or ongoing major cardiac, pulmonary, renal, endocrine or hepatic disease that, in the opinion of the Investigator or Alexion, precluded the patient's participation in an investigational clinical trial 14. Unstable medical conditions that would have made the patient unlikely to tolerate the requirements of the protocol 15. Concomitant use of anticoagulants was prohibited if the patient was not on a stable regimen for at least 2 weeks prior to Day 1 16. History of hypersensitivity to any ingredient contained in the study drug, including hypersensitivity to murine proteins 17. Female patients who planned to become pregnant or were currently pregnant or breastfeeding	6. Body weight < 40 kg at screening 7. History of *N. meningitidis* infection 8. History of unexplained, recurrent infection 9. Active systemic bacterial, viral or fungal infection within 14 days prior to study drug administration on Day 1 10. Presence of fever ≥ 38°C within 7 days prior to study drug administration 11. HIV infection 12. Immunized with a live-attenuated vaccine within 1 month prior to study drug administration 13. History of malignancy within 5 years of screening with the exception of nonmelanoma skin cancer or carcinoma in situ of the cervix that had been treated with no evidence of recurrence 14. History of or ongoing major cardiac, pulmonary, renal, endocrine or hepatic disease that, in the opinion of the Investigator or Alexion, precluded the patient's participation in an investigational clinical trial 15. Unstable medical conditions that would have made the patient unlikely to tolerate the requirements of the protocol 16. Concomitant use of anticoagulants was prohibited if the patient was not on a stable regimen for at least 2 weeks prior to Day 1 17. History of hypersensitivity to any ingredient contained in the study drug, including hypersensitivity to murine proteins 18. Female patients who planned to become pregnant or were currently pregnant or breastfeeding

<table>
<tr><th></th><th>ALXN1210-PNH-301
NCT02946463</th><th>ALXN1210-PNH-302
NCT03056040</th></tr>
<tr><td></td><td>18. Female patients who had a positive pregnancy test at screening or on Day 1
19. 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
20. Known or suspected history of drug or alcohol abuse or dependence within 1 year prior to the start of screening
21. Known medical or psychological condition or risk factor that might have interfered with the patient's full participation in the study, post any additional risk for the patient, or confound the assessment of the patient or outcome of the study</td><td>19. Female patients who had a positive pregnancy test at screening or on Day 1
20. 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
21. Known or suspected history of drug or alcohol abuse or dependence within 1 year prior to the start of screening
22. Known medical or psychological condition or risk factor that might have interfered with the patient's full participation in the study, post any additional risk for the patient, or confound the assessment of the patient or outcome of the study</td></tr>
<tr><td>Trial drugs</td><td>Ravulizumab (n = 125): Loading dose was given on Day 1 with maintenance doses on Days 15, 71 and 127 by IV infusion. Dosages were based on the patient's body weight as shown below:
<table>
<tr><th>Body weight</th><th>Loading dose (Day 1)</th><th>Maintenance dose (Day 15, 71, 127)</th></tr>
<tr><td>≥ 40 to < 60 kg</td><td>2400 mg</td><td>3000 mg</td></tr>
<tr><td>≥ 60 to < 100 kg</td><td>2700 mg</td><td>3300 mg</td></tr>
<tr><td>≥ 100 kg</td><td>3000 mg</td><td>3600 mg</td></tr>
</table>
Eculizumab (n = 121): 600 mg induction doses on Days 1, 8, 15 and 22 followed by 900 mg maintenance doses</td><td>Ravulizumab (n = 97): Loading dose was given on Day 1 with maintenance doses on Days 15, 71 and 127 by IV infusion. Dosages were based on the patient's body weight as shown below:
<table>
<tr><th>Body weight</th><th>Loading dose (Day 1)</th><th>Maintenance dose (Day 15, 71, 127)</th></tr>
<tr><td>≥ 40 to < 60 kg</td><td>2400 mg</td><td>3000 mg</td></tr>
<tr><td>≥ 60 to < 100 kg</td><td>2700 mg</td><td>3300 mg</td></tr>
<tr><td>≥ 100 kg</td><td>3000 mg</td><td>3600 mg</td></tr>
</table>
Eculizumab (n = 98): 900 mg on Days 1, 15, 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, and 169 by IV infusion.</td></tr>
</table>

	ALXN1210-PNH-301 **NCT02946463**	**ALXN1210-PNH-302** **NCT03056040**
	on Days 29, 43, 57, 71, 85, 99, 113, 127, 141, 155 and 169 by IV infusion.	
Permitted and disallowed concomitant medications	Any concomitant medication deemed necessary for the patient's standard of care, or for the treatment of any AE, was given at the discretion of the investigator but fully recorded. Concomitant use of anticoagulants was prohibited if the patient was not on a stable dose regimen for ≥ 2 weeks prior to Day 1. Use of complement inhibitors other than the patient's assigned study treatment was prohibited.	Any concomitant medication deemed necessary for the patient's standard of care, or for the treatment of any AE, was given at the discretion of the investigator but fully recorded. Concomitant use of anticoagulants was prohibited if the patient was not on a stable dose regimen for ≥ 2 weeks prior to Day 1. Use of complement inhibitors other than the patient's assigned study treatment was prohibited.
Primary outcome(s)	Co-primary efficacy endpoints: • Transfusion avoidance, defined as the proportion of patients who remained transfusion-free and did not require a transfusion per protocol-specified guidelines through Day 183 (Week 26) • Haemolysis as measured by LDH-N, defined as LDH levels ≤ 1 x ULN, from Day 29 through Day 183 (Week 26)	Primary efficacy endpoint: • Percent change in LDH, assessed as the difference between treatment groups in percent change in LDH from baseline to Day 183 (Week 26)
Key secondary outcomes	Key secondary efficacy endpoints tested in a hierarchical manner: • Percentage change in LDH from baseline to Day 183 (Week 26) • Change in QoL assessed via the FACTIT-Fatigue Scale from baseline to Day 183 (Week 26) • Proportion of patients with BTH, defined as at least one new or worsening symptom or sign of intravascular haemolysis (including fatigue, haemoglobinuria, abdominal pain, shortness of breath, anaemia	Key secondary efficacy endpoints tested in a hierarchical manner: • Proportion of patients with BTH, defined as at least one new or worsening symptom or sign of intravascular haemolysis (including fatigue, haemoglobinuria, abdominal pain, shortness of breath, anaemia [Hb < 10 g/dL], major adverse vascular events, dysphagia or erectile dysfunction) in the presence of elevated LDH (defined as ≥ twice the ULN)

	ALXN1210-PNH-301 NCT02946463	ALXN1210-PNH-302 NCT03056040
	[Hb < 10 g/dL], major adverse vascular events, dysphagia or erectile dysfunction) in the presence of elevated LDH (defined as ≥ twice the ULN) • Proportion of patients with stabilized Hb, defined as avoidance of a ≥ 2 g/dL decrease in haemoglobin level from baseline in the absence of transfusion through Day 183 (Week 26)	• Change in QoL assessed via the FACIT-Fatigue Scale from baseline to Day 183 (Week 26) • Transfusion avoidance, defined as the proportion of patients who remained transfusion-free and did not require a transfusion as per protocol-specified guidelines from baseline through Day 183 (Week 26) • Proportion of patients with stabilized Hb, defined as avoidance of a ≥ 2 g/dL decrease in haemoglobin level from baseline in the absence of transfusion through Day 183 (Week 26)
Other outcomes	Other secondary efficacy endpoints included: • Change in EORTC QLQ-C30 from baseline to Day 183 (Week 26) • Time to first occurrence of LDH-N (defined as LDH levels ≤ 1 x ULN) • Total number of units of pRBCs transfused through Day 183 (Week 26) • Change in clinical manifestations of PNH (fatigue, haemoglobinuria, abdominal pain, shortness of breath, chest pain, dysphagia and erectile dysfunction) from baseline to Day 183 (Week 26) • Proportion of patients experiencing MAVEs from baseline to Day 183 (Week 26) PK and PD endpoints: • Change in serum concentration of ravulizumab and of eculizumab over time • Change in cRBC haemolytic activity over time (exploratory)	Other secondary efficacy endpoints included: • Change in EORTC QLQ-C30 from baseline to Day 183 (Week 26) • Haemolysis as measured by LDH-N, defined as LDH levels ≤ 1 x ULN, from Day 29 through Day 183 (Week 26) • Total number of units of pRBCs transfused through Day 183 (Week 26) • Change in clinical manifestations of PNH (fatigue, haemoglobinuria, abdominal pain, shortness of breath, chest pain, dysphagia and erectile dysfunction) from baseline to Day 183 (Week 26) • Proportion of patients experiencing MAVEs from baseline to Day 183 (Week 26) PK and PD endpoints: • Change in serum concentration of ravulizumab and of eculizumab over time • Change in cRBC haemolytic activity over time (exploratory)

	ALXN1210-PNH-301 NCT02946463	ALXN1210-PNH-302 NCT03056040
	• Change in free complement C5 concentration over time Safety endpoints: The safety and tolerability of ravulizumab compared with eculizumab up to Week 26 were evaluated by: • Physical examinations • Vital signs • Electrocardiograms • Laboratory assessments • Incidence of AEs • Incidence of SAEs • Proportion of patients who developed ADAs	• Change in free complement C5 concentration over time Safety endpoints: The safety and tolerability of ravulizumab compared with eculizumab up to Week 26 were evaluated by: • Physical examinations • Vital signs • Electrocardiograms • Laboratory assessments • Incidence of AEs • Incidence of SAEs • Proportion of patients who developed ADAs

Key: ADAs, antidrug antibodies; AEs, adverse events; BTH, breakthrough haemolysis; cRBC, chicken red blood cell; CV, cardiovascular; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FACIT, Functional Assessment of Chronic Illness Therapy; Hb, haemoglobin; HIV, human immunodeficiency virus; IV, intravenous; IVRS, interactive voice response system; LDH, lactate dehydrogenase; LDH-N, normalization of lactate dehydrogenase levels; MAVE, major adverse vascular event; PD, pharmacodynamics; PK, pharmacokinetics; PNH, paroxysmal nocturnal haemoglobinuria; PP, per protocol; pRBC, packed red blood cells; q8w, every 8 weeks; QoL, quality of life; RBC, red blood cell; SAEs, serious adverse events; SD, standard deviation; ULN, upper limit of normal; WBC, white blood cell; WRS, web response system.
Sources: ALXN1210-PNH-301 CSR[66]; ALXN1210-PNH-302 CSR.[68]

B.2.3.2. Baseline characteristics

Table 6 summarizes demographic and clinical characteristics of patients enrolled to ALXN1210-PNH-301 and ALXN1210-PNH-302.

Baseline characteristics were generally well balanced across treatment groups in individual trials. Key differences in baseline characteristics across trials included:

- A higher proportion of Asian patients in ALXN1210-PNH-301
- A lower mean weight and proportion of patients >60 kg in ALXN1210-PNH-301
- A higher mean LDH in ALXN1210-PNH-301
- A higher proportion of patients with 1-14 units of pRBC transfusion in ALXN1210-PNH-301
- A lower proportion of patients with a history of a major adverse vascular event (MAVE) in ALXN1210-PNH-301

With the exception of the higher proportion of Asian patients and associated weight impact, these differences were expected a priori and are related to differences in the study design and objectives (that is, the enrolment of patients with newly diagnosed disease in ALXN1210-PNH-301 versus stable disease in ALXN1210-PNH-302).

Generalizability of these baseline characteristics to the UK patient population is discussed in Section B.2.13.

Table 6: Baseline characteristics of patients in the relevant clinical effectiveness evidence

	ALXN1210-PNH-301		**ALXN1210-PNH-302**	
	Ravulizumab (n=125)	Eculizumab (n=121)	Ravulizumab (n=97)	Eculizumab (n=98)
Male, n (%)	65 (52.0)	69 (57.0)	50 (51.5)	48 (49.0)
Race, n (%)				
Asian	72 (57.6)	57 (47.1)	23 (23.7)	19 (19.4)
White/Caucasian	43 (34.4)	51 (42.1)	50 (51.5)	61 (62.2)
Black/African	2 (1.6)	4 (3.3)	5 (5.2)	3 (3.1)
American Indian/Alaska	1 (0.8)	1 (0.8)	–	–
Other/Unknown	7 (5.6)	8 (6.6)	19 (19.6)	15 (15.3)
Age at diagnosis	n=123	n=118		
Mean years (SD)	37.9 (14.9)	39.6 (16.7)	34.1 (14.4)	36.8 (14.1)

	ALXN1210-PNH-301		ALXN1210-PNH-302	
	Ravulizumab (n=125)	Eculizumab (n=121)	Ravulizumab (n=97)	Eculizumab (n=98)
Age at first infusion Mean years (SD)	44.8 (15.2)	46.2 (16.2)	46.6 (14.4)	48.8 (14.0)
Years on eculizumab before study infusion, mean (SD)	NA	NA	6.0 (3.5)	5.6 (3.5)
Weight, mean kg (SD)	68.2 (15.6)	69.2 (14.9)	72.4 (16.8)	73.4 (14.6)
Weight at first infusion, % < 40 kg 40 to < 60 kg 60 to < 100 kg ≥ 100 kg Unknown	[redacted]	[redacted]	[redacted]	[redacted]
LDH, mean U/L (SD)[a]	1633.5 (778.8)	1578.3 (727.1)	228.0 (48.7)	235.2 (49.7)
LDH ratio, n (%) 1.5 to < 3 x ULN[a] ≥ 3 ULN	 18 (14.4) 107 (85.6)	 16 (13.2) 105 (86.6)	NA[b]	NA[b]
pRBC units received within 1 year prior to first dose, n (%)[c] 0 1-14 units >14 units	 23 (18.4) 102 (81.6) 23 (18.4)	 21 (17.4) 100 (82.6) 22 (18.2)	 84 (86.6) 13 (13.4) –	 86 (87.8) 12 (12.2) –
PNH clone size, mean % (SD) Type II RBCs[d] Type III RBCs[d] Total RBCs Granulocytes Monocytes	 12.4 (20.5) 26.3 (17.2) 38.4 (23.7) 84.2 (21.0) 86.9 (18.1)	 13.7 (17.7) 25.2 (16.9) 38.7 (23.2) 85.3 (19.0) 89.2 (15.2)	 14.9 (19.6) 44.6 (30.5) 60.6 (32.5) 82.6 (23.6) 85.6 (20.5)	 16.3 (23.6) 43.5 (29.7) 59.5 (31.4) 84.0 (21.4) 86.1 (19.7)
Haemoglobin, mean g/L (SD)[e]	[redacted]	[redacted]	110.8 (18.4)	109.1 (18.4)
Haptoglobin, g/L (SD)[f]	[redacted]	[redacted]	0.283 (0.235)	0.255 (0.174)
History of MAVE, n (%)	17 (13.6)	25 (20.7)	28 (28.9)	22 (22.4)
History of aplastic anaemia, n (%)	[redacted]	[redacted]	34 (35.1)	39 (39.8)

Key: NA, not applicable; GPI, glycophosphatidylinositol; MAVE, major adverse vascular event; PNH, paroxysmal nocturnal haemoglobinuria; SD, standard deviation.
Notes: [a], Normal range defined as 120–246 U/L, ULN defined as 246 U/L; [b], patients enrolled to Study 302 had stable disease and thus LDH within normal range; [c], randomization strata; [d], n = 124 for ravulizumab arm and n = 120 for eculizumab arm of Study 301; [e], normal range defined as 11.5–16.0 g/dL for women and 13.0–17.5 g/dL for men; [f], normal range defined as 0.4–2.4 g/dL.
Sources: ALXN1210-PNH-301 CSR[66]; ALXN1210-PNH-302 CSR[68]; Kulasekararaj et al. 2019[46]; Lee et al. 2019.[44]

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 study groups in ALXN1210-PNH-301 and ALXN1210-PNH-302.

The hypothesis tested in both trials was the non-inferiority of ravulizumab compared with eculizumab, with non-inferiority margins informed by the best available data for each patient group (complement-inhibitor naïve and eculizumab-exposed).

The primary population for efficacy analyses in both trials was the full analysis set (FAS), defined as patients who received at least one dose of treatment and had at least one efficacy assessment. Sensitivity analyses were conducted using the per protocol (PP) analysis set.

Table 7: Statistical analysis in ALXN1210-PNH-301 and ALXN1210-PNH-302

	ALXN1210-PNH-301	**ALXN1210-PNH-302**
Primary objective	To assess the non-inferiority of ravulizumab compared with eculizumab in adult patients with PNH who are complement-inhibitor naïve.	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.
Statistical testing	Non-inferiority was tested for co-primary efficacy endpoints, with a 2-sided 95% CI calculated. Ravulizumab was concluded to be non-inferior to eculizumab if (i) the lower bound of the 95% CI for the difference in transfusion avoidance rate (ravulizumab–eculizumab) was greater than the NIM of -20% and (ii) the lower bound of the 95% CI for the odds ratio for LDN-N (ravulizumab vs eculizumab) was greater than 0.39. If non-inferiority was met for both co-primary endpoints, key secondary endpoints were tested using a closed-testing procedure with the order as per presentation of key secondary endpoints above and 2-sided 95% CI calculated. Point	Non-inferiority was tested for the primary efficacy endpoint, with a 2-sided 95% CI calculated. Ravulizumab was concluded to be non-inferior to eculizumab if the lower bound of the 95% CI for the difference (ravulizumab–eculizumab) was greater than the NIM of -15%. If non-inferiority was met for the primary endpoint, key secondary endpoints were tested using a closed-testing procedure with the order as per presentation of key secondary endpoints above and 2-sided 95% CI calculated. Point estimates and CIs were computed for all key secondary efficacy endpoints regardless of the hierarchical testing procedure.

	ALXN1210-PNH-301	ALXN1210-PNH-302
	estimates and CIs were computed for all key secondary efficacy endpoints regardless of the hierarchical testing procedure. If non-inferiority was achieved for all key secondary endpoints, testing for superiority was also to be performed with the following order, using a 2-sided 0.05 test for each parameter: • Proportion of patients with BTH through Day 183 (Week 26) • Percentage change in LDH from baseline to Day 183 (Week 26) • LDH-N from Day 29 through Day 183 (Week 26) • Change from baseline in FACIT-Fatigue to Day 183 (Week 26) • Proportion of patients with Hb stabilization through Day 183 (Week 26) • Transfusion avoidance All analyses and calculations were performed by Alexion or its designee, using SAS® release Version 9.4.	If non-inferiority was achieved for all key secondary endpoints and a larger effect for ravulizumab was observed, testing for superiority was also to be performed with the following order, using a 2-sided 0.05 test for each parameter: • Percentage change in LDH from baseline to Day 183 (Week 26) • Change from baseline in FACIT-Fatigue to Day 183 (Week 26) • Proportion of patients with BTH through Day 183 (Week 26) • Proportion of patients with Hb stabilization through Day 183 (Week 26) • Transfusion avoidance All analyses and calculations were performed by Alexion or its designee, using SAS® release Version 9.4.
Power calculation	Approximately 214 patients were planned to be randomly assigned to ensure at least 193 evaluable patients (assumes ≤10% dropout). Using a NIM of 0.39 for the co-primary endpoint of LDH-N and a Type I error of 1-sided 2.5%, a minimum of 142 patients would be expected to provide 80% power to demonstrate non-inferiority of ravulizumab to eculizumab. Using a NIM of 20% for the co-primary endpoint of transfusion avoidance, a minimum of 193 patients would be expected to provide 80% power to demonstrate non-inferiority of ravulizumab to eculizumab. The NIMs were based on the TRIUMPH study: a randomized, placebo-controlled trial of eculizumab in patients with PNH.[70]	Approximately 192 patients were planned to be randomly assigned to ensure at least 172 evaluable patients (assumes ≤10% dropout). Using a NIM of 15% for the primary endpoint, a Type I error of 1-sided 2.5% and SD of 30%, a minimum of 172 patients would be expected to provide 90% power to demonstrate non-inferiority of ravulizumab to eculizumab. The NIM was based on data from Alexion's PNH registry.
Analysis sets	**FAS:** primary population for all efficacy analyses – included all patients who received at least one	**FAS:** primary population for all efficacy analyses - included all patients who received at least one

	ALXN1210-PNH-301	ALXN1210-PNH-302
	dose of randomized treatment and had at least one efficacy assessment. **PP:** sensitivity population for co-primary and key secondary efficacy endpoints – included patients in the FAS who: • Missed no doses of ravulizumab or no more than one dose of eculizumab in the 26-week Randomized Period • Met inclusion criteria #2, 3 and 4 • Did not meet exclusion criteria #1, 2, 3 or 4 • Never received the wrong randomized treatment • Followed the protocol-specified transfusion guidelines. **Safety:** population for all safety analyses – included all patients who received at least one dose of randomized treatment. **PK:** population for all PK analyses – included all patients who received at least one dose of treatment and who had evaluable PK data.	dose of randomized treatment and had at least one efficacy assessment. **PP:** sensitivity population for primary and key secondary efficacy endpoints – included patients in the FAS who: • Missed no doses of ravulizumab or no more than one dose of eculizumab in the 26-week Randomized Period • Met inclusion criteria #2, 3 and 4 • Did not meet exclusion criteria #1, 2, 3 or 4 • Never received the wrong randomized treatment • Followed the protocol-specified transfusion guidelines. **Safety:** population for all safety analyses – included all patients who received at least one dose of randomized treatment. **PK:** population for all PK analyses – included all patients who received at least one dose of treatment and who had evaluable PK data.
Missing data	Missing data were not imputed for the co-primary endpoint of LDH-N. For the co-primary endpoint of transfusion avoidance, patients who withdrew from the study due to lack of efficacy were considered non-responders and counted as requiring transfusion; data for patients who withdrew for other reasons were used up to the time of their withdrawal.	Missing data were not imputed for the primary endpoint of percent change in LDH.

Key: BTH, breakthrough haemolysis; CI, confidence interval; FACIT, Functional Assessment of Chronic Illness Therapy; FAS, full analysis set; Hb, haemoglobin; LDH-N, normalization of lactate dehydrogenase levels; NIM, non-inferiority margin; PK, pharmacokinetic; PNH, paroxysmal nocturnal haemoglobinuria; PP, per protocol.
Sources: ALXN1210-PNH-301 CSR[66]; ALXN1210-PNH-302 CSR.[68]

B.2.4.2. Patient disposition data

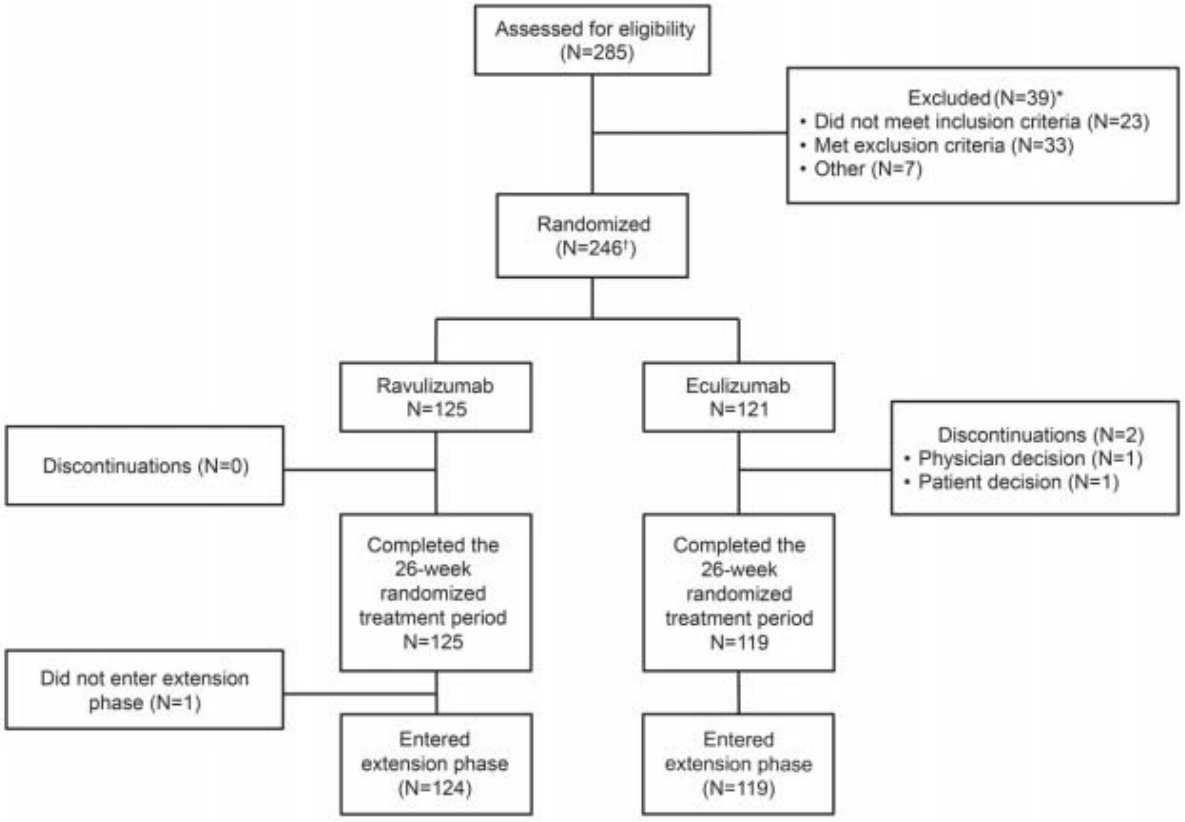
ALXN1210-PNH-301

Figure 4 summarizes patient disposition data to Extension Period entry.

Of the 246 patients randomized, one from each arm were excluded from the PP analysis set as they had not received transfusion as per the protocol-specific guidelines at any point during the Primary Evaluation Period.[66]

A total of 243 patients entered the Extension Period of the study and were treated with ravulizumab. Of the 124 patients who continued on ravulizumab (the ravulizumab–ravulizumab arm), 121 completed the Extension Period up to 52 weeks: discontinuations were due to patient withdrawal, pregnancy and C5-polymorphism.[56] Of the 119 patients who switched to ravulizumab (the eculizumab–ravulizumab arm), 114 completed the Extension Period up to 52 weeks: discontinuations were due to an adverse event (AE) in two cases, physician decision in two cases, and death in one case.

Figure 4: Participant flow in ALXN1210-PNH-301



Notes: *patients can be counted in more than one category; †from countries across the Asia-Pacific region (n = 124), Europe (n = 91), North America (n = 9), and South America (n = 22).
Source: Lee et al. 2019.[44]

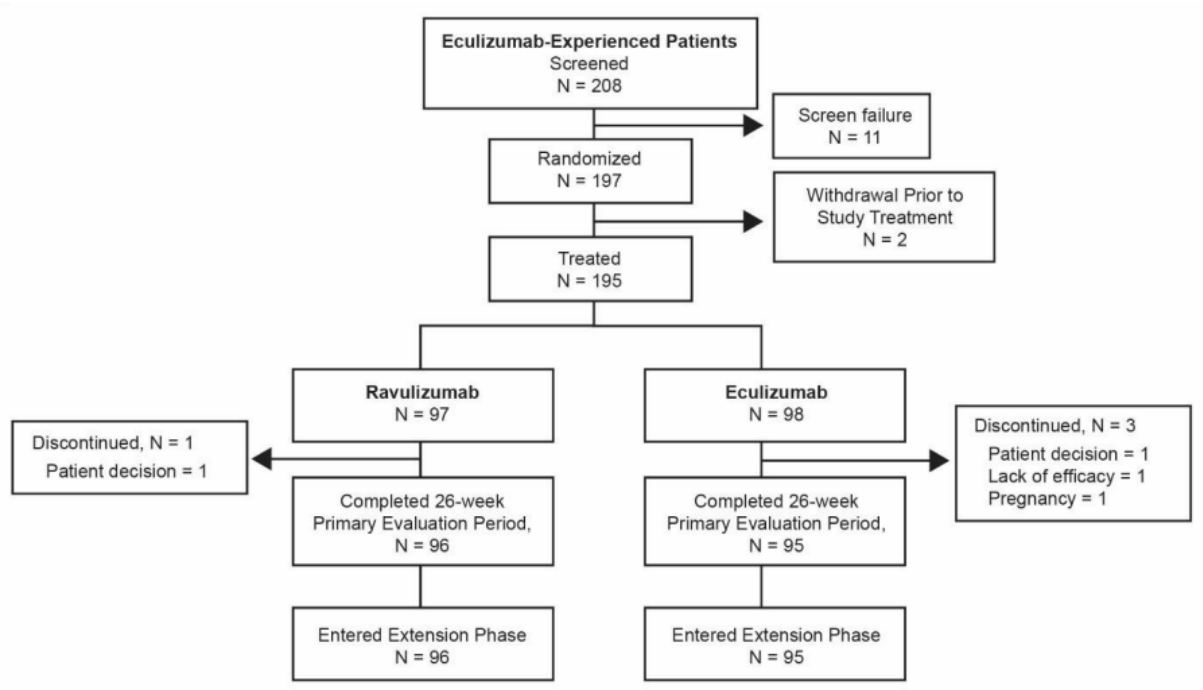
ALXN1210-PNH-302

Patient disposition data are summarized up to Extension Period entry in Figure 5.

Of the 197 patients randomized, four from the ravulizumab arm and five from the eculizumab arm were excluded from the PP analysis set as they had not received transfusion as per the protocol-specified guidelines at any point during the Primary Evaluation Period (n=5); were determined not to have received eculizumab as per labelled dosing recommendation for at least 6 months prior to Day 1 (n=2); or were determined to have an LDH value > 2 x ULN in the 6 months prior to Day 1 (n=2).[68]

A total of 191 patients entered the Extension Period of the study and were treated with ravulizumab. Of the 96 patients who continued on ravulizumab (the ravulizumab–ravulizumab arm), 95 completed the Extension Period up to 52 weeks: the one discontinuation was due to patient withdrawal.[62] Of the 95 patients who switched to ravulizumab (the eculizumab–ravulizumab arm), 94 completed the Extension Period up to 52 weeks: the one discontinuation was due to physician decision.

Figure 5: Participant flow in ALXN1210-PNH-302



Source: Kulasekararaj et al. 2019.[46]

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

The complete quality assessment for ALXN1210-PNH-301 and ALXN1210-PNH-302 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, the primary endpoints of both trials were 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 had at least one efficacy assessment and is considered a more appropriate approach for the non-inferiority trial designs.

The ALXN1210-PNH-301 and ALXN1210-PNH-302 trials also directly reflect the decision problem of interest with respect to population, intervention, comparator and outcomes: providing head-to-head data versus eculizumab (the only treatment ravulizumab would displace if recommended) in both complement-inhibitor naïve and eculizumab-exposed patients. While the eligibility criteria of the trials were not explicitly matched to the PNH National Service treatment eligibility criteria (see Section B.1.3.2), they closely align and the patients enrolled show similar clinical characteristics to patients treated in clinical practice (see Section B.2.3.2).

B.2.6. Clinical effectiveness results of the relevant trials

B.2.6.1. Randomized Period

Table 8 provides an overview of efficacy results for the Randomized Period of ALXN1210-PNH-301 and ALXN1210-PNH-302 for the FAS population. Primary, key secondary and other outcomes of interest are summarized in turn below.

PP population analyses are provided in Appendix L.

Table 8: Summary of efficacy results from ALXN1210-PNH-301 and ALXN1210-PNH-302: Randomized Period (FAS)

	ALXN1210-PNH-301			ALXN1210-PNH-302		
	Ravulizumab (n=125)	Eculizumab (n=121)	Treatment effect[a] (95% CI)	Ravulizumab (n=97)	Eculizumab (n=98)	Treatment effect[a] (95% CI)
Transfusion avoidance rate, % (95% CI)	73.6 (65.87, 81.33)	66.1 (57.68, 74.55)	6.8 (-4.66, 18.14)	87.6 (81.1, 94.2)	82.7 (75.2, 90.2)	5.5 (-4.3, 15.7)
LDH-normalization rate, % (95% CI)	53.6 (45.9, 61.2)	49.4 (41.7, 57.0)	1.19 (0.80, 1.77)	66.0[b]	59.2[b]	–
Percent change in LDH, LSM (95% CI)	-76.84 (-79.96, -73.73)	-76.02 (-79.20, -72.83)	0.83 (-3.56, 5.21)	-0.82 (-7.8, 6.1)	8.4 (1.5, 15.3)	9.21 (-0.42, 18.8)
Change in FACIT-Fatigue score, LSM (95% CI)	7.07 (5.55, 8.60)	6.40 (4.85, 7.96)	0.67 (-1.21, 2.55)	2.0 (0.6, 3.4)	0.54 (-0.8, 1.9)	1.5 (-0.2, 3.2)
≥ 3-point improvement in FACIT-Fatigue score, n (%)	77 (61.6)	71 (58.7)	2.2 (-9.9, 14.3)	36 (37.1)	33 (33.7)	–
Breakthrough haemolysis rate, % (95% CI)	4.0 (0.56, 7.44)	10.7 (5.23, 16.26)	6.7 (-0.18, 14.21)	0 (0, 3.7)	5.1 (1.7, 11.5)	5.1 (-8.9, 19.0)
Haemoglobin stabilization rate, % (95% CI)	68.0 (59.82, 76.18)	64.5 (55.93, 72.99)	2.9 (-8.80, 14.64)	76.3 (67.8, 84.8)	75.5 (67.0, 84.0)	1.4 (-10.4, 13.3)
EORTC QLQ-C30 GHS/QOL Absolute change, mean (SD) ≥ 10-point improvement, n (%)	13.2 (21.4) n = 124 64 (51.2)	12.9 (21.8) n = 118 55 (45.5)	4.8 (-7.7, 17.1)	1.15 (16.51) 18 (18.6)	-1.93 (15.34) 14 (14.3)	4.2 (-6.6, 15.0)
EORTC QLQ-C30 PF Absolute change, mean (SD) ≥ 10-point improvement, n (%)	13.2 (15.7) 60 (48.0)	11.5 (17.6) n=119 53 (43.8)	3.7 (-8.7, 16.0)	3.26 (8.71) 21 (21.6)	1.20 (8.89) 12 (12.2)	9.1 (-1.9, 19.7)

	ALXN1210-PNH-301					ALXN1210-PNH-302				
	Ravulizumab (n=125)		Eculizumab (n=121)		Treatment effect[a] (95% CI)	Ravulizumab (n=97)		Eculizumab (n=98)		Treatment effect[a] (95% CI)
EORTC QLQ-C30 Fatigue Absolute change, mean (SD) ≥ 10-point improvement, n (%)	-20.2 (24.5) 92 (73.6)		-18.6 (24.5) n=119 77 (63.6)		9.1 (-2.5, 20.5)	-4.97 (17.26) 41 (42.3)		-0.71 (15.27) 31 (31.6)		9.6 (-4.1, 22.9)
Number (%) of patients who received any pRBC transfusions	32 (25.6)		40 (33.1)		–	10 (10.3)		14 (14.3)		–
Number of transfusions per patient, mean (SD)	3.3 (4.2)		3.6 (3.1)		–	2.7 (2.8)		2.0 (1.3)		–
Total number of pRBC units transfused per transfusion, mean (SD)	4.8 (5.1)		5.6 (5.9)		–	4.3 (4.8)		3.4 (3.0)		–
Patients with MAVE, n (%)	2 (1.6)		1 (0.8)		–	0		0		–
Clinical manifestations of PNH, %	BL	D183	BL n = 119	D183 n = 119		BL n = 96	D183 n = 96	BL n = 95	D183 n = 95	
Fatigue	64.0	28.8	63.9	30.3	–	30.2	43.8	40.0	37.9	–
Abdominal pain	13.6	4.8	12.6	5.0		5.2	5.2	6.3	12.6	
Dyspnoea	33.6	14.4	31.9	14.3		6.3	6.3	10.5	17.9	
Dysphagia	10.4	2.4	13.4	0.8		2.1	5.2	2.1	5.2	
Chest pain	4.0	2.4	14.3	5.9		0	2.1	1.1	5.2	
Haemoglobinuria	56.8	10.4	47.5	9.3		4.2	8.3	7.4	9.5	
Erectile dysfunction[c]	12.8	8.0	17.6	4.2		10.0	12.0	14.6	12.5	

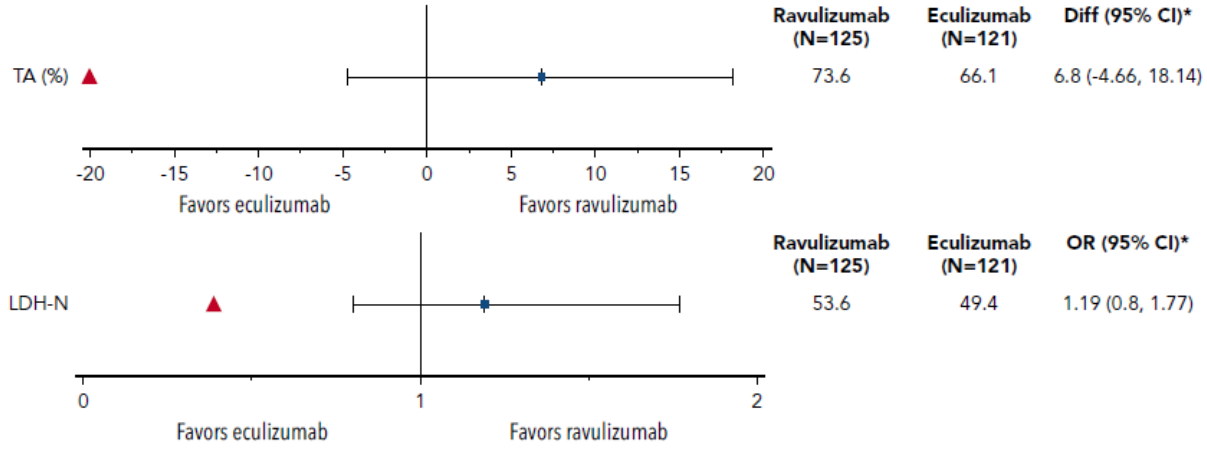
	ALXN1210-PNH-301			ALXN1210-PNH-302		
	Ravulizumab (n=125)	Eculizumab (n=121)	Treatment effect[a] (95% CI)	Ravulizumab (n=97)	Eculizumab (n=98)	Treatment effect[a] (95% CI)

Key: BL, baseline; CI, confidence interval; D183, Day 183; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FACIT, Functional Assessment of Chronic Illness Therapy; FAS, full analysis set; GHS, global health score; LDH, lactate dehydrogenase; LSM, least squares mean; MAVE, major adverse vascular event; PF, physical function; PNH, paroxysmal nocturnal haemoglobinuria; pRBC, packed red blood cells; SD, standard deviation; QOL, quality of life.
Notes: Grey shaded cells denote primary endpoints of trial; [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 and for LDH normalization that is estimated as odds ratio: ravulizumab versus eculizumab; [b], , 95% CI not calculated as LDH normalization was not a primary or key secondary outcome in the ALXN1210-PNH-302 trial; [c], proportion calculated based on male population.
Sources: Kulasekararaj et al. 2019[46]; Lee et al. 2019.[44]

ALXN1210-PNH-301

Co-primary endpoints: ravulizumab met the objective of non-inferiority compared with eculizumab on both co-primary endpoints, with point estimates favouring ravulizumab as depicted in Figure 6.

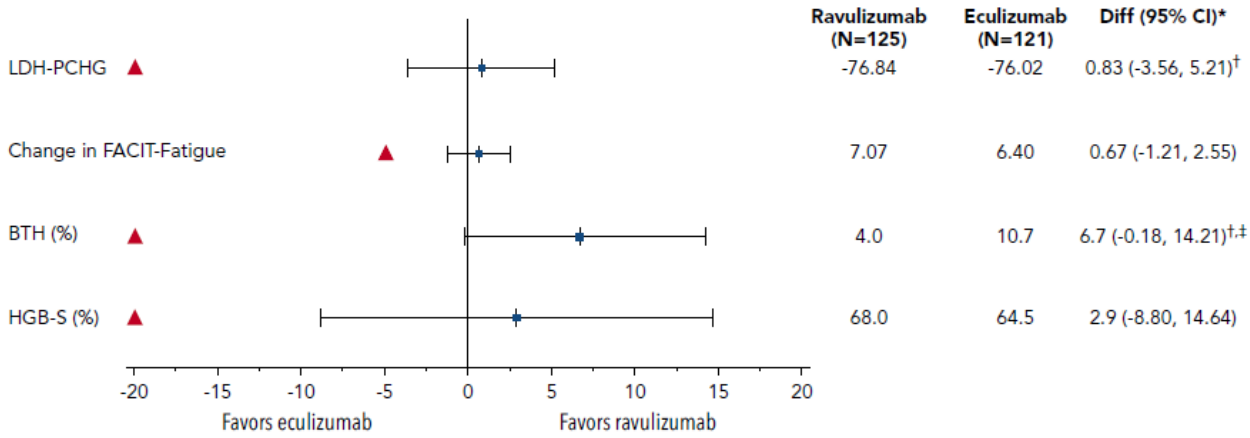
Figure 6: Forest plot of treatment effect for co-primary endpoints in ALXN1210-PNH-301



Key: CI, confidence interval; Diff, treatment difference (ravulizumab–eculizumab); LDH-N, lactate dehydrogenase-normalization; OR, odds ratio; TA, transfusion avoidance.
Notes: *, Red triangle indicates the non-inferiority margin.
Source: Lee et al. 2019.[44]

Key secondary endpoints: ravulizumab was non-inferior to eculizumab on all key secondary endpoints, with point estimates again favouring ravulizumab as depicted in Figure 7.

Figure 7: Forest plot of treatment effect for key secondary endpoints in ALXN1210-PNH-301



Key: BTH, breakthrough haemolysis; CI, confidence interval; Diff, treatment difference; FACIT, Functional Assessment of Chronic Illness Therapy; HGB-S, haemoglobin stabilization; LDH-PCHG, lactate dehydrogenase-percent change.
Notes: *, Red triangle indicates the non-inferiority margin; †, treatment difference is estimated for ravulizumab–eculizumab except for LDH-PCHG and BTH, where treatment difference is based on eculizumab–ravulizumab; ‡$p < 0.06$ for the lower bound of the 95% CI.
Source: Lee et al. 2019.[44]

Because non-inferiority was achieved for all key secondary endpoints, hierarchal superiority testing was performed for breakthrough haemolysis. While 6.7% fewer patients experienced breakthrough haemolysis in the ravulizumab arm than the eculizumab arm, the difference was not statistically significant ($p < 0.6$).[44] As such, no further hierarchical testing was performed.

Of the breakthrough haemolysis events that did occur, none in the ravulizumab arm (0/5) were associated with elevated free C5 levels, compared with 47% of events (7/15) in the eculizumab arm.[45]

Other secondary efficacy endpoints:

Baseline European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) scores reflected a patient population with symptomatic disease.[44] Improvements in EORTC QLQ-C30 global health status/quality of life and physical functioning assessment scores were similar in both

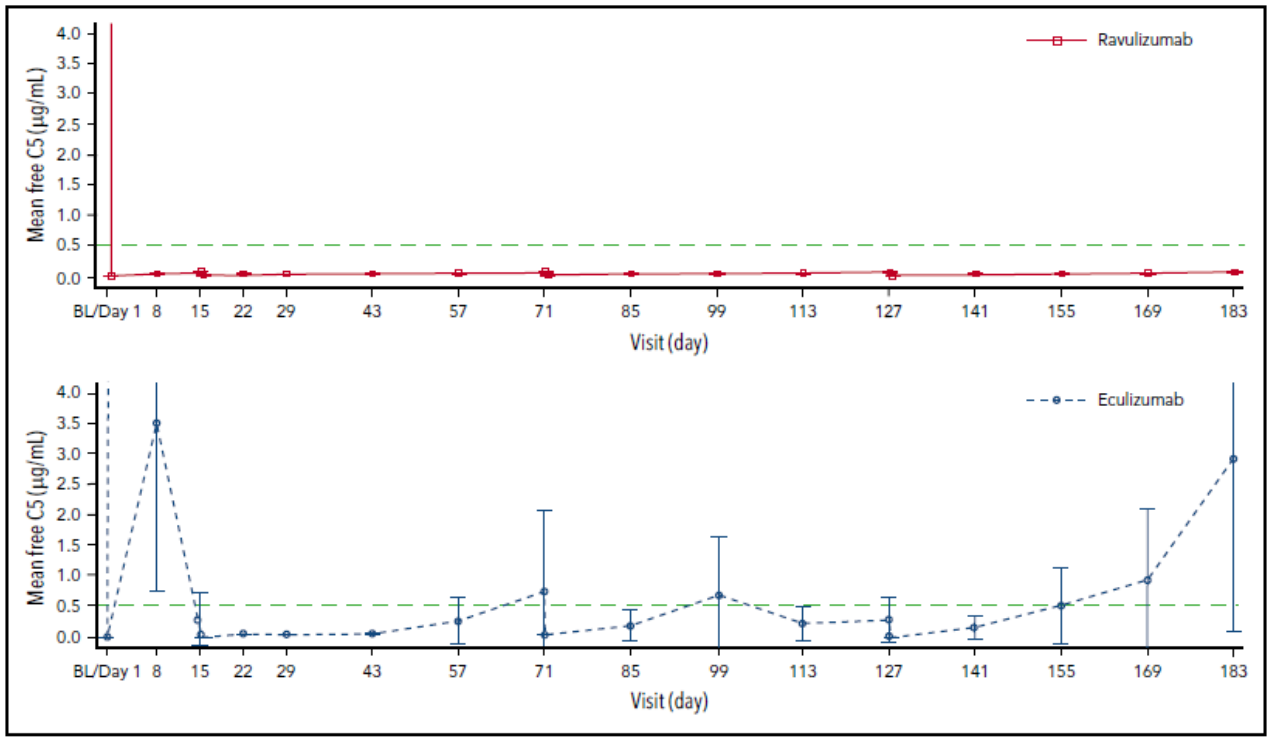
groups; improvements in fatigue (EORTC QLQ-C30 Fatigue and FACIT-Fatigue assessment scores) were slightly more prominent in the ravulizumab group (Table 8).

Median time to first occurrence of LDH-N was 5 days shorter in the ravulizumab group; in addition, the total and mean number of units transfused was lower in ravulizumab treated patients. Patients in both groups reported improvements from baseline in clinical manifestations of PNH (Table 8).

Three patients experienced MAVEs: one patient in the ravulizumab group who was taking concomitant oral contraceptive medication experienced an event of lower leg deep vein thrombosis; another patient in the ravulizumab group had a history of lower leg pain and oedema and was taking an oral anticoagulant, which was discontinued after initiation of study drug; one patient in the eculizumab group with a history of aplastic anaemia experienced an event of mesenteric venous thrombosis with concurrent neutropenic colitis.[44]

PK/PD endpoints: Ravulizumab achieved complete 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 183-day treatment period in all patients. This threshold was not consistently met in patients receiving eculizumab, as depicted in Figure 8.

Figure 8: Mean (95% CI) free C5 concentration over time (BL–D183) in ALXN1210-PNH-301

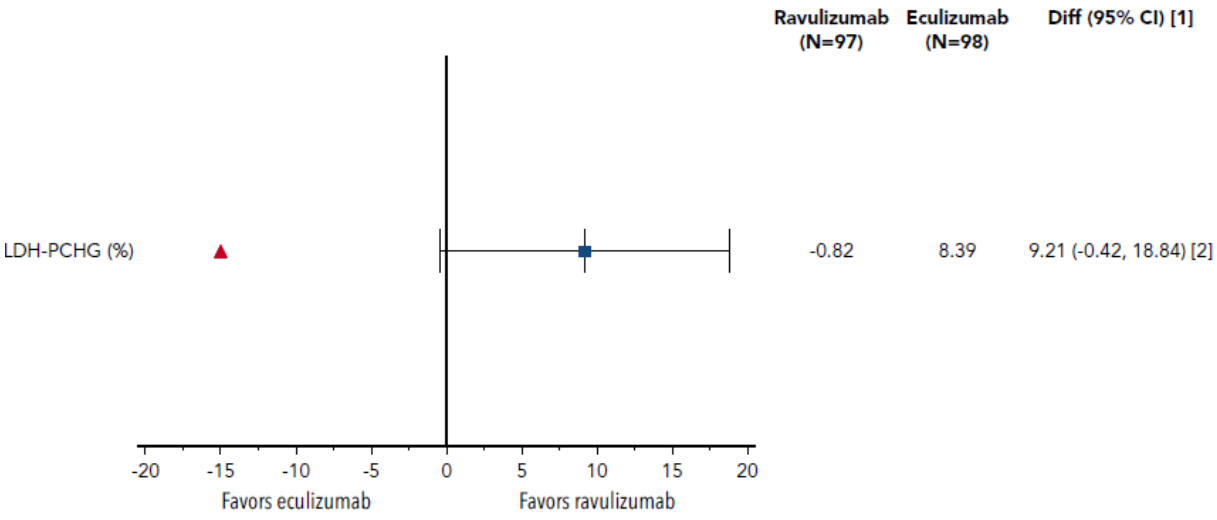


Key: BL, baseline; CI, confidence interval; D183, Day 183.
Source: Lee et al., 2019.[44]

ALXN1210-PNH-302

Primary endpoint: ravulizumab met the objective of non-inferiority compared with eculizumab for the primary endpoint of percentage change in LDH, with point estimates favouring ravulizumab as depicted in Figure 9.

Figure 9: Forest plot of treatment effect for primary endpoint in ALXN1210-PNH-302



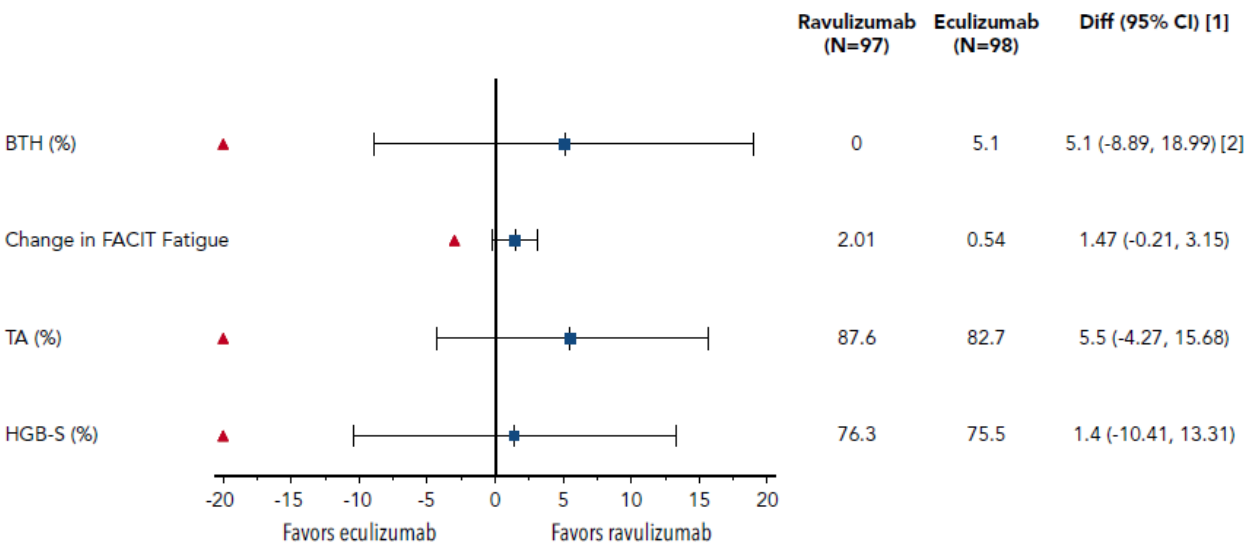
Key: CI, confidence interval; Diff, treatment difference; LDH-PCHG, lactate dehydrogenase-percent change.
Notes: Red triangle indicates the non-inferiority margin; [1], treatment difference is based on estimated difference in percentage with 95% CI for eculizumab–ravulizumab.
Source: Kulasekararaj et al., 2019.[46]

Key secondary endpoints: ravulizumab was non-inferior to eculizumab on all key secondary endpoints, with point estimates again favouring ravulizumab as depicted in Figure 10.

Because non-inferiority was achieved for all key secondary endpoints, hierarchical superiority testing was performed for percentage change in LDH. While the average percentage change was 9.2% greater in the ravulizumab arm than the eculizumab arm, the difference was not statistically significant (p = 0.058).[46] As such, no further hierarchical testing was performed.

No breakthrough haemolysis events occurred in the ravulizumab arm. Of events that occurred in the eculizumab arm, 57% (4/7) were associated with elevated free C5 levels.[45]

Figure 10: Forest plot of treatment effect for key secondary endpoints in ALXN1210-PNH-302



Key: BTH, breakthrough haemolysis; CI, confidence interval; Diff, treatment difference; FACIT, Functional Assessment of Chronic Illness Therapy; HGB-S, haemoglobin stabilization; TA, transfusion avoidance.
Notes: Red triangle indicates the non-inferiority margin; [1], treatment difference is based on estimated difference in percentage with 95% CI except for FACIT-Fatigue, which is based on estimated difference in change from baseline with 95% CI; [2], treatment difference is estimated for ravulizumab–eculizumab except for BTH, where treatment difference is estimated for eculizumab–ravulizumab.
Source: Kulasekararaj et al. 2019.[46]

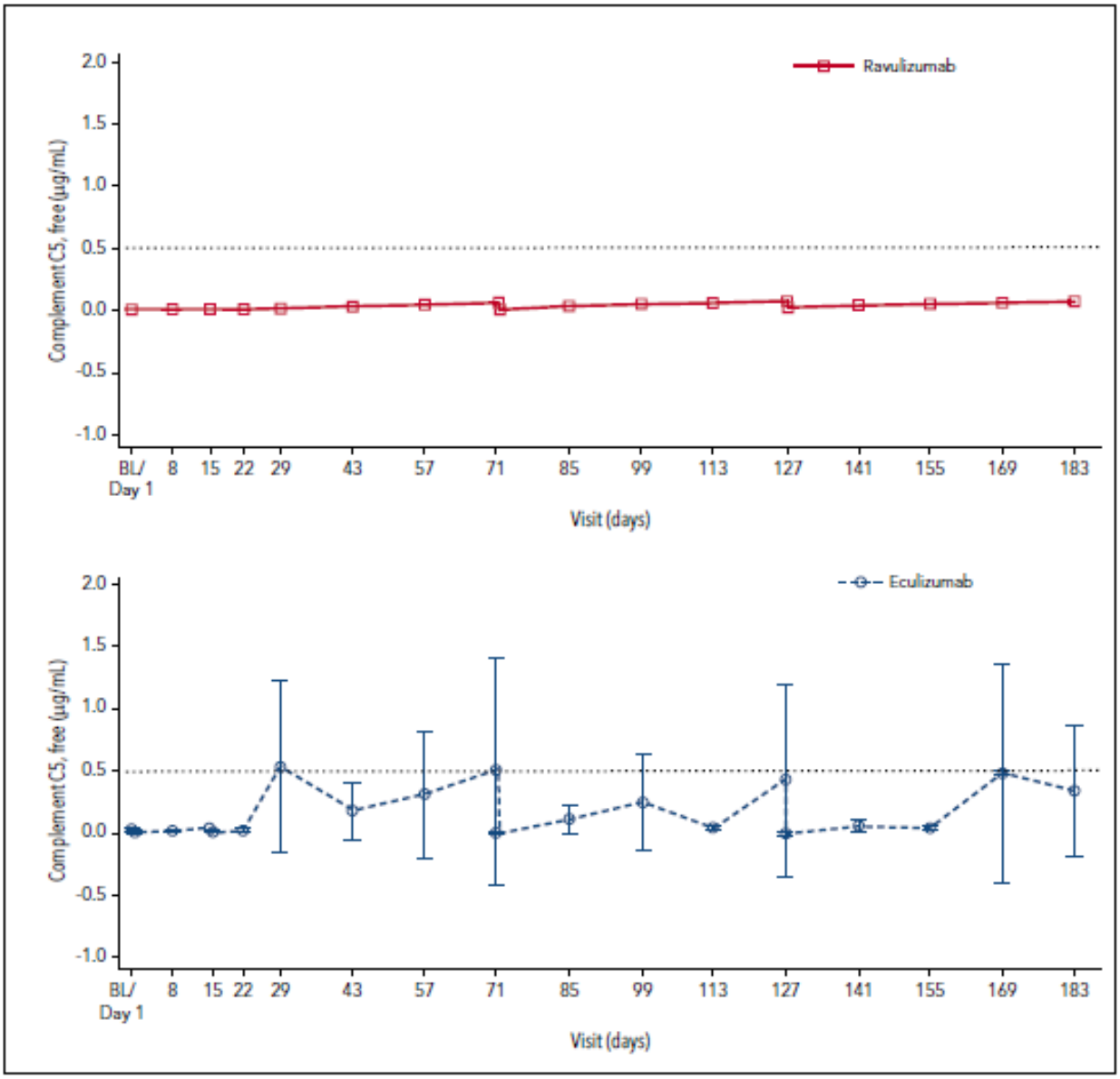
Other secondary efficacy endpoints:

Baseline EORTC QLQ-C30 scores reflected a patient population with stable disease.[46] Improvements in EORTC QLQ-C30 global health status/quality of life assessment scores were similar in both groups; improvements in physical functioning and fatigue (EORTC QLQ-C30 Fatigue and FACIT-Fatigue assessment scores) were slightly more prominent in the ravulizumab group (Table 8).

As expected in a patient population that was clinically stable on eculizumab therapy, the proportion of patients who achieved LDH-N was relatively stable over time.[46] The proportion of patients who received any pRBC transfusions was, however, lower in the ravulizumab group; no patients experienced a MAVE and shifts in clinical manifestations of PNH were infrequent in both groups (Table 8).

PK/PD endpoints: ravulizumab achieved complete 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 183-day treatment period in all patients. This threshold was not consistently met in patients receiving eculizumab, as depicted in Figure 11.

Figure 11: Mean (95% CI) free C5 concentration over time (BL–D183) in ALXN1210-PNH-302



Key: BL, baseline; CI, confidence interval; D183, Day 183.
Source: Kulasekararaj et al. 2019.[46]

B.2.6.2. Extension Period

ALXN1210-PNH-301

Table 9 provides an overview of efficacy results for the Extension Period of ALXN1210-PNH-301, up to 52 weeks, and key outcomes are summarized below.

Table 9: Summary table of efficacy results from ALXN1210-PNH-301: Extension Period up to 52 weeks

	ALXN1210-PNH-301			
	Ravulizumab to ravulizumab (n=124)		Eculizumab to ravulizumab (n=119)	
	0–26 weeks	27–52 weeks	0–26 weeks	27–52 weeks
Transfusion avoidance, n (%)	92 (73.6)	95 (76.6)	79 (66.4)	80 (67.2)
LDH-normalization, n (%)	60 (48.4)	54 (43.6)	50 (42.1)	48 (40.4)
Percent change in LDH, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change in FACIT-Fatigue score, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Breakthrough haemolysis, n (%)	5 (4.0)	4 (3.2)	13 (10.7)	2 (1.7)
Haemoglobin stabilization, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Key: FACIT, Functional Assessment of Chronic Illness Therapy; LDH, lactate dehydrogenase.
Sources: ALXN1210-PNH-301 52-Week data addendum[67]; Schrezenmeier et al. 2019.[56]

Similar proportions of patients avoided transfusion, achieved LDH normalization, achieved haemoglobin stabilization and experienced improved HRQL in both study periods (0–26 weeks and 27–52 weeks) across both treatment arms (Table 9).

Over 90% of patients who had avoided transfusion in the Randomized Period (0–26 weeks) and continued on ravulizumab (n = 83) maintained this avoidance through Week 52; of patients who had avoided transfusion in the Randomized Period with eculizumab and switched to ravulizumab (n = 69), 87% maintained this avoidance through Week 52.[56]

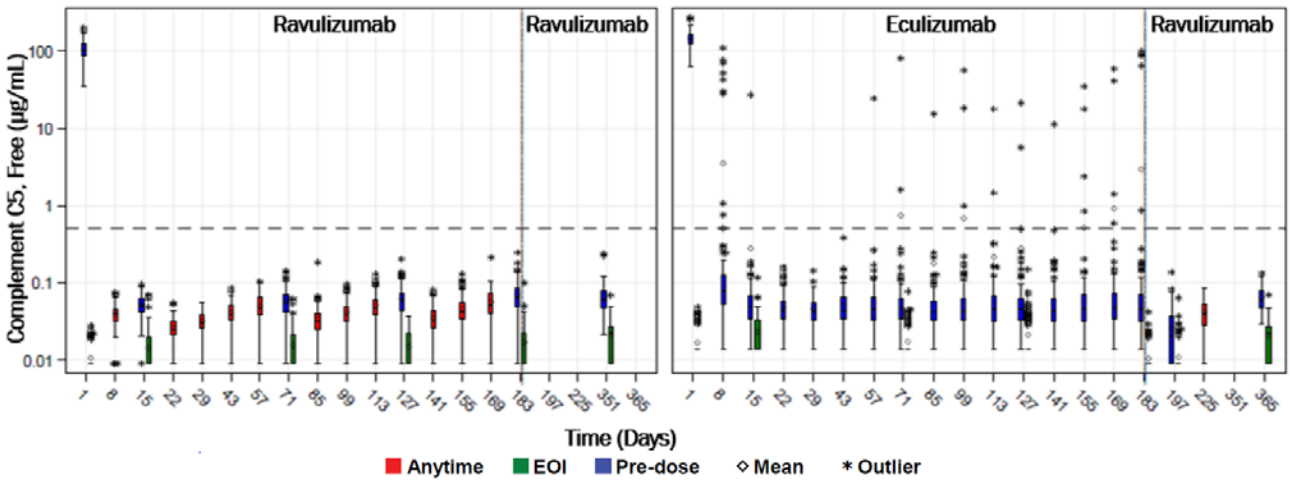
The absolute change in FACIT-Fatigue score was higher in the ravulizumab arm (Table 9) and a higher proportion of patients in the ravulizumab to ravulizumab arm had a clinically meaningful improvement in fatigue (≥ 3-point improvement in FACIT-

Fatigue score) at 52 weeks, compared with patients in the eculizumab to ravulizumab arm ([redacted]% vs [redacted]%).[67]

Four patients in the ravulizumab to ravulizumab arm had breakthrough haemolysis in the Extension Period (27–52 weeks) (Table 9). As was the case with events occurring in the ravulizumab arm of the Randomized Period, none of these events were associated with elevated free C5 levels.[56] Breakthrough haemolysis rates reduced with a switch to ravulizumab with only two patients in the eculizumab to ravulizumab arm experiencing breakthrough haemolysis in the Extension Period (Table 9); neither of these events were associated with elevated free C5 levels.

Such improved free C5 control following a switch to ravulizumab is depicted in Figure 12. All patients initially randomized to ravulizumab continued to show complete terminal complement inhibition (defined as serum free C5 < 0.5 ug/mL) throughout the 52-week treatment period. Patients initially randomized to eculizumab achieved complete terminal complement inhibition by the end of the first infusion of ravulizumab and this was sustained through Week 52.

Figure 12: Free C5 concentration over time (BL–D365) in ALXN1210-PNH-301



Key: BL, baseline; D365, Day 365; EOI, end of infusion.
Notes: The median is indicated by a horizontal line in the middle of each box. The mean is indicated by a diamond. The 75th and 25th percentiles (interquartile range) are indicated by the top and the bottom borders of the box, respectively. The whiskers represent the 1.5 interquartile range of the lower and upper quartiles, respectively. Outliers are represented by asterisks beyond the whiskers.
Source: Schrezenmeier et al. 2019.[56]

ALXN1210-PNH-302

Table 10 provides an overview of efficacy results for the Extension Period of ALXN1210-PNH-302, up to 52 weeks, and key outcomes are summarized below.

Table 10: Summary table of efficacy results from ALXN1210-PNH-302: Extension Period up to 52 weeks

	ALXN1210-PNH-302			
	Ravulizumab to ravulizumab		Eculizumab to ravulizumab	
	0–26 weeks (n=97)	27–52 weeks (n=96)	0–26 weeks (n=98)	27–52 weeks (n=95)
Transfusion avoidance, n (%)	85 (87.6)	83 (86.5)	81 (82.7)	79 (83.2)
LDH-normalization, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Percent change in LDH, Mean (SD)	2.9 (26)	8.8 (29)	6.5 (31)	5.8 (27)
Change in FACIT-Fatigue score, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Breakthrough haemolysis, n (%)	0	3 (3.1)	5 (5.1)	1 (1.1)
Haemoglobin stabilization, n (%)	74 (76.3)	78 (81.2)	74 (75.5)	77 (81.1)

Key: FACIT, Functional Assessment of Chronic Illness Therapy; LDH, lactate dehydrogenase.
Source: ALXN1210-PNH-302 CSR[68]; ALXN1210-PNH-302 52-Week data addendum[69]; Kulasekararaj et al. 2019.[62]

Similar proportions of patients avoided transfusion, achieved LDH normalization, achieved haemoglobin stabilization and maintained HRQL in both study periods (0–26 Weeks and 27–52 Weeks) across both treatment arms (Table 10).

Mean percent change in LDH was slightly higher in the ravulizumab to ravulizumab arm during the Extension Period (27–52 weeks) compared with the Randomized Period (0–26 weeks), but comparable across study periods for the eculizumab to ravulizumab arm (Table 10). While random variations in percentage change values were observed, mean LDH levels in both arms were generally maintained at approximately 1.0 x ULN (< 246 U/L) during the Extension Period.[62]

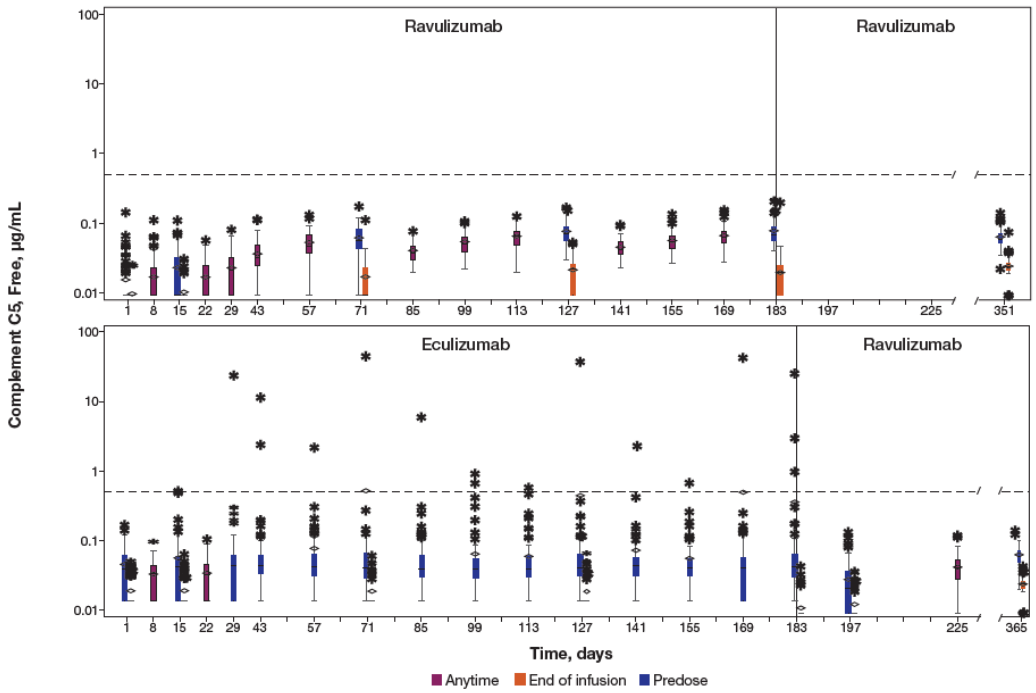
The absolute change in FACIT-Fatigue score was similar across treatment arms (Table 10), as was the proportion of patients who had a clinically meaningful improvement in fatigue (≥ 3-point improvement in FACIT-Fatigue score) at 52 weeks

([redacted]% vs [redacted]% in the ravulizumab to ravulizumab arm and eculizumab to ravulizumab arm, respectively).[69]

Three patients in the ravulizumab to ravulizumab arm had breakthrough haemolysis in the Extension Period (27–52 weeks); none of these events were associated with elevated free C5 levels.[62] Breakthrough haemolysis rates reduced with a switch to ravulizumab with only one patient in the eculizumab to ravulizumab arm experiencing breakthrough haemolysis in the Extension Period; this event was not associated with elevated free C5 levels.

Such improved free C5 control following a switch to ravulizumab is depicted in Figure 13. All patients initially randomized to ravulizumab continued to show complete terminal complement inhibition (defined as serum free C5 < 0.5 ug/mL) throughout the 52-week treatment period. Patients initially randomized to eculizumab achieved complete terminal complement inhibition by the end of the first infusion of ravulizumab and this was sustained through Week 52.

Figure 13: Free C5 concentration over time (BL–D365) in ALXN1210-PNH-302



Key: BL, baseline; D365, Day 365.
Notes: The median is indicated by a horizontal line in the middle of each box. The mean is indicated by a diamond. The 75th and 25th percentiles (interquartile range) are indicated by the top and the bottom borders of the box, respectively. The whiskers represent the 1.5 interquartile range of the lower and upper quartiles, respectively. Outliers are represented by asterisks beyond the whiskers.
Source: Kulasekararaj et al. 2019.[62]

B.2.7. Subgroup analysis

In both trials, subgroup analysis was conducted for the subgroups of the randomization stratification variables (transfusion history and screening LDH levels in ALXN1210-PNH-301 and transfusion history in ALXN1210-PNH-302) and subgroups based on sex, race, region and age at first study drug infusion.

No evidence of sensitive subgroups was observed with findings confirming the non-inferiority conclusion of the primary analyses, irrespective of baseline demographics or key clinical characteristics.

Forest plots of subgroup analysis are provided in Appendix E.

B.2.8. Meta-analysis

Meta-analysis was not appropriate because the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials provide data for distinct populations: complement-inhibitor naïve and eculizumab exposed patients, respectively.

B.2.9. Indirect and mixed treatment comparisons

Indirect treatment comparison was not required as the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials provide head-to-head data for ravulizumab versus eculizumab, which is the only treatment ravulizumab would displace if recommended.

B.2.10. Adverse reactions

Safety data from the pivotal ALXN1210-PNH-301 and ALXN1210-PNH-302 are provided in this section. Additional safety data from pooled analyses of these pivotal trials and from two earlier phase trials are provided in Appendix F.

B.2.10.1. Randomized Period

Table 11 provides treatment exposure data for the Randomized Period of ALXN1210-PNH-301 and ALXN1210-PNH-302.

In both arms of both studies infusion interruption needs (that is, the need to stop infusing treatment once started for any reason, including patient wellbeing) were low, but were slightly higher in complement-inhibitor naïve patients as expected (Table

11). Only one patient randomized to switch to ravulizumab from eculizumab in ALXN1210-PNH-302 required an infusion interruption; this was not due to AE. All infusion interruptions were temporary and all infusions were ultimately completed.[65]

Drug compliance was > 99% in both trials, but the number of infusions were substantially higher in the eculizumab arms, due to the differences in dosing regimens. The median number of ravulizumab infusions was 4.0 compared with a median number of eculizumab infusions of 15.0 in complement-inhibitor naïve patients and 13.0 in complement-inhibitor stable patients (Table 11).

Table 11: Treatment exposure within ALXN1210-PNH-301 and ALXN1210-PNH-302 (Day 1–183)

	ALXN1210-PNH-301		ALXN1210-PNH-302	
	Ravulizumab (n=125)	Eculizumab (n=121)	Ravulizumab (n=97)	Eculizumab (n=98)
Treatment duration Mean days (SD) Median days (range)	 181.9 (1.83) 182 (175–191)	 179.6 (18.63) 182 (10–186)	 180.3 (18.32) 182.0 (2–187)	 178.8 (19.72) 182.0 (9–185)
Total patient years of exposure	62.3	59.5	47.9	48.0
Treatment duration < 13 weeks, n (%) 13 to < 26 weeks, n (%) ≥ 26 weeks, n (%)	 0 33 (26.4) 92 (73.6)	 2 (1.7) 31 (25.6) 88 (72.7)	 1 (1.0) 15 (15.5) 81 (83.5)	 1 (1.0) 23 (23.5) 74 (75.5)
Number of infusions Mean (SD) Median (range)	 4.0 (0.0) 4.0 (4–4)	 14.8 (1.38) 15.0 (2–15)	 4.0 (0.30) 4.0 (1–4)	 12.8 (1.37) 13.0 (1–14)
Infusion interruption, n (%)	10 (8.0)	12 (9.9)	1 (1.0)	5 (5.1)
Number of infusions interrupted Total Mean (SD) Median (range)	 12 1.2 (0.63) 1.0 (1–3)	 14 1.2 (0.39) 1.0 (1–2)	 1 (NA) 1.0 (1–1)	 7 1.4 (0.89) 1.0 (1–3)
Number of infusions interrupted due to AEs Total Mean (SD) Median (range)	 4 2.0 (1.41) 2.0 (1–3)	 1 (NA) 1.0 (1–1)	 0	 4 (1.41) 2.0 (1–3)

	ALXN1210-PNH-301		ALXN1210-PNH-302	
	Ravulizumab (n=125)	Eculizumab (n=121)	Ravulizumab (n=97)	Eculizumab (n=98)
Drug compliance, n (%) 100% ≥ 80 to < 100%	 125 (100) 0	 120 (99.2) 1 (0.8)	 97 (100) 0	 98 (100) 0
Key: AE, adverse event; NA, not applicable; SD, standard deviation. **Source:** Ultomiris EPAR.[65]				

Table 12 provides an overview of safety results for the Randomized Period of ALXN1210-PNH-301 and ALXN1210-PNH-302. Key safety outcomes for these pivotal trials are summarized below.

Table 12: Summary of safety results from ALXN1210-PNH-301 and ALXN1210-PNH-302: Randomized Period (safety set)

	ALXN1210-PNH-301		ALXN1210-PNH-302	
	Ravulizumab (n=125)	Eculizumab (n=121)	Ravulizumab (n=97)	Eculizumab (n=98)
Patients with any AE, n (%)	110 (88.0)	105 (86.8)	85 (87.6)	86 (87.8)
Common adverse events[a], n (%)				
Headache	45 (36.0)	40 (33.1)	26 (26.8)	17 (17.3)
Nasopharyngitis	11 (8.8)	18 (14.9)	21 (21.6)	20 (20.4)
Nausea	11 (8.8)	10 (8.3)	8 (8.2)	9 (9.2)
Upper respiratory tract infection	13 (10.4)	7 (5.8)	18 (18.6)	10 (10.2)
Pyrexia (fever)	6 (4.8)	13 (10.7)	9 (9.3)	5 (5.1)
Viral upper respiratory tract infection	9 (7.2)	10 (8.3)	–	–
Arthralgia (pain in joint)	8 (6.4)	8 (6.6)	–	–
Dizziness	9 (7.2)	7 (5.8)	3 (3.1)	7 (7.1)
Pain in extremity	9 (7.2)	7 (5.8)	5 (5.2)	4 (4.1)
Diarrhoea	10 (8.0)	5 (4.1)	9 (9.3)	7 (7.1)
Myalgia (pain in muscle)	7 (5.6)	9 (7.4)	–	–
Abdominal pain	7 (5.6)	7 (5.8)	6 (6.2)	9 (9.2)
Oropharyngeal pain	8 (6.4)	6 (5.0)	4 (4.1)	9 (9.2)
Back pain	7 (5.6)	6 (5.0)	–	–
Cough	4 (3.2)	8 (6.6)	5 (5.2)	10 (10.2)
Hypokalaemia	6 (4.8)	6 (5.0)	–	–
Dyspepsia (indigestion)	4 (3.2)	6 (5.0)	–	–
Insomnia	2 (1.6)	6 (5.0)	–	–
Constipation	–	–	7 (7.2)	5 (5.1)
Influenza-like illness	–	–	7 (7.2)	8 (8.2)
Anaemia	–	–	6 (6.2)	3 (3.1)
Fatigue	–	–	6 (6.2)	6 (6.1)

	ALXN1210-PNH-301		ALXN1210-PNH-302	
	Ravulizumab (n=125)	Eculizumab (n=121)	Ravulizumab (n=97)	Eculizumab (n=98)
Vomiting	–	–	6 (6.2)	4 (4.1)
Rhinitis	–	–	5 (5.2)	4 (4.1)
Chest pain	–	–	3 (3.1)	9 (9.2)
Musculoskeletal pain	–	–	2 (2.1)	5 (5.1)
Dyspnoea (shortness of breath)		–	0	6 (6.1)
Patients with any SAE, n (%)	11 (8.8)	9 (7.4)	4 (4.1)	8 (8.2)
Serious adverse events, n (%)				
Pyrexia	1 (0.8)	2 (1.7)	0	3 (3.1)
Anaemia	1 (0.8)	0	0	0
Aplastic anaemia	1 (0.8)	0	0	0
Neutropenia	1 (0.8)	0	0	0
Thrombocytopenia	1 (0.8)	0	0	0
Left ventricular failure	1 (0.8)	0	0	0
Myocardial ischemia	1 (0.8)	0	0	0
Leptospirosis	1 (0.8)	0	0	0
Systemic infection	1 (0.8)	0	0	0
Laceration	1 (0.8)	0	0	0
Uterine leiomyoma	1 (0.8)	0	0	0
Renal colic	1 (0.8)	0	0	0
Deep vein thrombosis	1 (0.8)	0	0	0
Ileus	0	1 (0.8)	0	0
Neutropenic colitis	0	1 (0.8)	0	0
Limb abscess	0	1 (0.8)	0	0
Cellulitis	0	1 (0.8)	0	0
Infection	0	1 (0.8)	0	0

	ALXN1210-PNH-301		ALXN1210-PNH-302	
	Ravulizumab (n=125)	Eculizumab (n=121)	Ravulizumab (n=97)	Eculizumab (n=98)
Pneumonia	0	1 (0.8)	0	0
Viral upper respiratory tract infection	0	1 (0.8)	0	0
Adenocarcinoma of colon	0	1 (0.8)	0	0
Lung adenocarcinoma	0	1 (0.8)	0	0
PNH	0	1 (0.8)	0	0
Haemolysis	0	0	0	2 (2.0)
Palpitations	0	0	0	1 (1.0)
Colitis	0	0	1 (1.0)	0
Hyperthermia	0	0	1 (1.0)	0
Cholelithiasis	0	0	0	1 (1.0)
Influenza	0	0	1 (1.0)	0
Lower respiratory tract infection	0	0	1 (1.0)	0
Pyelonephritis acute	0	0	0	1 (1.0)
Epilepsy	0	0	1 (1.0)	0
Respiratory failure	0	0	1 (1.0)	0
Meningococcal infections, n (%)	0	0	0	0
Other serious infections, n (%)	2 (1.6)	4 (3.3)	2 (2.1)	1 (1.0)
Discontinuation due to AE, n (%)	0	1 (0.8)[b]	0	0
Death, n (%)	0	1 (0.8)[b]	0	0

Key: AE, adverse event; SAE, serious adverse event.
Notes: [a], Defined as ≥ 5% of patients in either treatment group – dashes represent events not meeting these criteria in individual trials; [b], one patient in the eculizumab arm died of lung adenocarcinoma (unrelated to treatment) during the Extension Period of the study but symptoms started in the Randomized Period. For safety outcomes, this discontinuation was assigned to the Randomized Period; for patient disposition outcomes, this discontinuation was assigned to the Extension Period.
Sources: Ultomiris EPAR[65]; Kulasekararaj et al. 2019[46]; Lee et al. 2019.[44]

ALXN1210-PNH-301

Ravulizumab and eculizumab were both generally well tolerated in complement-inhibitor naïve patients. Although most patients in both arms experienced an AE, only 8% of patients (20/246) experienced a serious adverse event (SAE) (Table 12).

The most common AE in both treatment arms was headache, reported by approximately 35% of patients; the only other AEs experienced by more than 10% of patients in either treatment arm were upper respiratory tract infection (URTI) and pyrexia (Table 12). Pyrexia was also the only SAE to occur in more than one patient. With the exception of one case of deep vein thrombosis in the ravulizumab group and one case of lung adenocarcinoma in the eculizumab group, all SAEs were resolved.[65] This case of lung adenocarcinoma (in the eculizumab group) resulted in discontinuation and death (unrelated to treatment) during the Extension Period of the study. No clear differences were observed in the safety profiles of ravulizumab versus eculizumab, but AEs with a ≥ 5% difference between treatment arms included nasopharyngitis and pyrexia, both of which were more common in the eculizumab group (Table 12).

No cases of meningococcal infections, aspergillus infections, or sepsis were reported in either treatment arm.[44] Six patients experienced other serious infections: two patients in the ravulizumab arm (leptospirosis and systemic infection) and four patients in the eculizumab arm (limb abscess, cellulitis, infection, pneumonia and viral upper respiratory tract infection). The causative agent was not identified for any serious infection and all were resolved without sequelae.

Immunogenicity of complement-inhibitor treatment (ravulizumab or eculizumab) was low with only one treatment-emergent antidrug antibody-positive sample in each group.[44] Antibody titres were low (≤ 1) and not neutralizing, with no apparent effects on pharmacokinetics/pharmacodynamics or safety.

ALXN1210-PNH-302

Ravulizumab and eculizumab were similarly well tolerated in complement-inhibitor stable patients. Although most patients in both arms experienced an AE, only 6% of patients (12/195) experienced an SAE (Table 12).

The most common AE in both treatment arms was headache, reported by 17% of patients in the eculizumab arm and 27% of patients in the ravulizumab arm (Table 12). The only other AEs experienced by more than 10% of patients in either treatment arm were nasopharyngitis, URTI and cough (Table 12). Along with headache, AEs with a ≥ 5% difference between treatment arms included URTI (more common in the ravulizumab group), cough, chest pain and dyspnoea (more common in the eculizumab group) (Table 12). Pyrexia and haemolysis were the only SAEs to occur in more than one patient (three and two patients, respectively, in the eculizumab group) (Table 12); all SAEs were resolved.[65]

No cases of meningococcal infections, aspergillus infections or sepsis were reported in either treatment arm.[46] Three patients experienced other serious infections: two patients in the ravulizumab arm (influenza and lower respiratory tract infection [without positive culture]) and one patient in the eculizumab arm (acute pyelonephritis [causative agent not identified]). All serious infections were resolved without sequelae.

No immunogenicity of ravulizumab was observed with no treatment-emergent anti-drug antibodies detected in the ravulizumab group.[46]

B.2.10.2. Extension Period

ALXN1210-PNH-301

Table 13 provides an overview of safety results for the Extension Period of ALXN1210-PNH-301, up to 52 weeks. Key safety outcomes are summarized below.

Table 13: Summary table of safety results from ALXN1210-PNH-301: Extension Period up to 52 weeks

	ALXN1210-PNH-301			
	Ravulizumab to ravulizumab		Eculizumab to ravulizumab	
	0–26 weeks (n=125)	27–52 weeks (n=124)	0–26 weeks (n=121)	27–52 weeks (n=119)
Patients with any AE, n (%)	110 (88.0)	79 (63.7)	105 (86.8)	89 (74.8)
Most common AEs[a], n (%)				
Headache	45 (36.0)	6 (4.8)	40 (33.1)	10 (8.4)
URTI	13 (10.4)	10 (8.1)	7 (5.8)	5 (4.2)
Pyrexia (fever)	6 (4.8)	7 (5.6)	13 (10.7)	0
Nasopharyngitis	11 (8.8)	8 (6.5)	19 (15.7)	15 (12.6)
Patients with any SAE, n (%)	11 (8.8)	9 (7.3)	9 (7.4)	7 (5.9)
DC due to AE, n (%)	0	0	1 (0.8)[b]	1 (0.8)
Death, n (%)	0	0	1 (0.8)[b]	0

Key: AE, adverse event; DC, discontinuation; SAE, serious adverse event; URTI, upper respiratory tract infection.
Notes: [a], Defined as > 5% of patients in either treatment group in the Extension Period; [b], one patient in the eculizumab arm died of lung adenocarcinoma (unrelated to treatment) during the Extension Period of the study but symptoms started in the Randomized Period. For safety outcomes, this discontinuation was assigned to the Randomized Period; for patient disposition outcomes, this discontinuation was assigned to the Extension Period.
Source: Schrezenmeier et al. 2019.[56]

Ravulizumab was generally well tolerated in complement-inhibitor naïve patients through 52 weeks, and rates of events decreased in frequency at 27–52 weeks (Table 13).

The most common AE in the Extension Period was nasopharyngitis, which was experienced by slightly more patients switching from eculizumab at Week 26 compared with those patients who continued to receive ravulizumab; the only other AEs experienced by more than 10% of patients in either treatment arm were headache and urinary tract infection (Table 13).

There was one further discontinuation due to AE in the Extension Period due to [redacted] not considered to be related to treatment[67], but no new AEs resulting in death (please note earlier reference to the case of lung adenocarcinoma

[in the eculizumab group] that resulted in discontinuation and death [unrelated to treatment]) occurred during the Extension Period of the study).

ALXN1210-PNH-302

Table 14 provides an overview of safety results for the Extension Period of ALXN1210-PNH-302, up to 52 weeks. Key safety outcomes are summarized below.

Table 14: Summary table of safety results from ALXN1210-PNH-302: Extension Period up to 52 weeks

	ALXN1210-PNH-302			
	Ravulizumab to ravulizumab		Eculizumab to ravulizumab	
	0–26 weeks (n=97)	27–52 weeks (n=96)	0–26 weeks (n=98)	27–52 weeks (n=95)
Patients with any AE, n (%)	89 (91.8)	76 (79.2)	86 (87.8)	71 (74.7)
Most common AEs[a], n (%)				
Headache	27 (27.8)	6 (6.3)	19 (19.4)	10 (10.5)
URTI	18 (18.6)	9 (9.4)	11 (11.2)	8 (8.4)
Pyrexia (fever)	9 (9.3)	6 (6.3)	5 (5.1)	6 (6.3)
Nasopharyngitis	21 (21.6)	6 (6.3)	20 (20.4)	7 (7.4)
Fatigue	7 (7.2)	13 (13.5)	7 (7.1)	13 (13.7)
Diarrhoea	9 (9.3)	6 (6.3)	7 (7.1)	5 (5.3)
Pain in extremity	5 (5.2)	4 (4.2)	3 (3.1)	5 (5.3)
Dizziness	3 (3.1)	2 (2.1)	7 (7.1)	6 (6.3)
Anaemia	6 (6.2)	1 (1.0)	3 (3.1)	5 (5.3)
Back pain	4 (4.1)	1 (1.0)	4 (4.1)	6 (6.3)
Patients with any SAE, n (%)	4 (4.1)	8 (8.3)	8 (8.2)	5 (5.3)
DC due to AE, n (%)	0	0	0	0
Death, n (%)	0	0	0	0

Key: AE, adverse event; DC, discontinuation; SAE, serious adverse event; URTI, upper respiratory tract infection.
Notes: [a], Defined as > 5% of patients in either treatment group in the Extension Period.
Source: Kulasekararaj et al. 2019.[62]

Ravulizumab was generally well tolerated in complement-inhibitor stable patients through 52 weeks, and rates of events decreased in frequency at 27–52 weeks (Table 14).

The most common AE in the Extension Period was fatigue, which was experienced by 13 patients in each arm; the only other AE experienced by more than 10% of patients in either treatment arm was headache (Table 14).

There were no meningococcal infections, deaths or discontinuations due to AEs through Week 52, and no new treatment-emergent anti-drug antibodies were reported during Weeks 27–52.[62]

B.2.10.3. Safety overview

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. These were pre-defined AEs of special interest in the Phase III trial programme, but few events of this nature occurred.

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 and receive additional prophylactic antibiotics if ravulizumab is initiated less than 2 weeks from vaccination.[1] Although no cases of meningococcal infection have been observed in the Phase III clinical trial programme to date, three cases were reported in earlier clinical trials (see Appendix F). All three cases were completely resolved without ravulizumab treatment interruption.[1]

Overall, the conclusion of the EMA on the clinical safety of ravulizumab, was that its safety profile appears similar to that of eculizumab in patients with PNH, both in complement-inhibitor naïve patients and in patients clinically stable on eculizumab treatment.[65] They did recognize the need for longer-term safety data to the Randomized Period and requested submission of Extension Period data on availability (52 week data since supplied and included in the EPAR[65]).

B.2.11. Ongoing studies

Extension periods of both trials (ALXN1210-PNH-301 and ALXN1210-PNH-302) are ongoing. Further data reporting up to 104 weeks are expected [redacted].

Regulatory review of two new vial sizes (3 mL and 11 mL) containing 100 mg/mL of ravulizumab is also ongoing, with marketing authorization expected to extend to these vial sizes by [redacted]. 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. With the new vial sizes, the minimum infusion time ranges from 25–45 minutes for the loading dose and 30–55 minutes for maintenance doses, bringing infusion times for ravulizumab generally in line with those of eculizumab.[71] As the new vial sizes should be authorized before ravulizumab market launch in the UK, 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 and the technologies share over 99% homology, the small difference between their design is substantial with regard to its 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: alleviating the risk of breakthrough haemolysis due to incomplete C5 inhibition observed with eculizumab, and reducing the frequency of regular infusions to 6–7 per year in the treatment maintenance phase, compared with the 26 needed for effective eculizumab treatment.

Due to the difficulty in quantifying the full impact of breakthrough haemolysis and treatment burden (particularly on carers), health-related benefits of ravulizumab treatment are likely to exist outside the formal quality-adjusted life year (QALY) calculations. For example, although the immediate impact of breakthrough haemolysis on patient quality of life is considered in the economic modelling, there could be longer-term morbidity and mortality consequences that would impact both quality of life and survival that are not formally considered (see Section B.3.4).

In addition, although the impact of reduced frequency of regular infusions on patients is considered in the model, this is based on a discrete choice experiment (DCE) where the general public were asked about their willingness to trade various treatment attributes.[72] This was necessary as patients attended the same schedule of study visits and assessments in the clinical trial programme, irrespective of randomized treatment, and therefore health-related quality of life (HRQL) data collected in the Randomized Period of the clinical trial programme could not capture the impact of differences in infusion schedules on patient quality of life. However, DCE participants may underestimate the true impact of a lifelong 2-week dosing schedule. Furthermore, the resulting disutility applied considers the impact of receiving an infusion every 2 weeks that takes 1 hour, compared with receiving an infusion every 8 weeks that takes 3 hours; with the new ravulizumab vial sizes, the appropriate comparison is an infusion every 8 weeks that takes 1 hour (see Section B.2.13).

A patient preference study enrolling 95 patients who switched from eculizumab to ravulizumab in the ALXN1210-PNH-302 trial and interview series provide further support of the potential positive impact ravulizumab could have on patients' lives. In the patient preference study, 93% of patients reported a preference for ravulizumab (compared with eculizumab): the factors for which the greatest proportions of patients preferred ravulizumab were 'frequency of infusions' (98%), 'being able to plan activities' (98%), and 'overall quality of life' (88%).[73] As with the DCE, this study is likely to underestimate the impact of ravulizumab on patient quality of life due to treatment burden when considering the new vial sizes. In the series of interviews with patients and carers in England, several potential benefits resulting from a reduced frequency of infusions were conferred, as summarized in Table 15. Similarly, in patients who had received eculizumab prior to receiving ravulizumab and were included in the patient preference questionnaire series of concept elicitation interviews, the positive impact of ravulizumab dosing on their lives were enthusiastically described with ravulizumab allowing them to feel independent, plan future activities and travel.[42]

Table 15: Interview series with patients and carers – statements snapshot

Statements on the potential benefits of a treatment with reduced frequency of infusions
Anxiety associated with infusion-related adverse events • 'If you get something once every 8 weeks or once every 2 weeks it's a huge change in your life. I know the benefits to your veins if the drug can be developed for longer periods' – Patient
Impact on travel and independence • 'I think he would like that, not having to have the limitation on when he can travel' – Carer
Disruption to work • 'I know it's a long infusion, but I work full-time, so if I could get an infusion once every two months instead of every two weeks it would just make my life so much easier' – Patient
General benefits • '[A longer dosing interval] would be very beneficial, give you a little bit more flexibility. There would be less intrusion. As it's every fortnight, it is always on your mind in a way' – Patient • 'It just frees up so much time. It would just fit into my lifestyle so much better' – Patient • 'I think he's willing to trade-off a much longer infusion for a lower frequency. I think if it takes longer, I think he would still feel that is a good trade-off' – Carer • 'A one-off treatment every now and again rather than every two weeks, that would be the Rolls Royce' – Carer
Source: Interviews to Elicit the Burden of Paroxysmal Nocturnal Haemoglobinuria and Treatment with Eculizumab in Patients and Caregivers.[43]

Although carers were interviewed alongside patients, the potential benefits they reported were mainly focused on patients' lives. In practice, the benefits they report would also improve their own lives, but such benefits could not be quantified for formal inclusion in the economic analysis. Perceived benefits resulting from reduced cannulation were also not captured in the economic analysis. However, the prospect of unsuccessful cannulation, which can cause pain and infusion delays, led to anxiety on infusion days for several patients and carers interviewed, as did the potential of long-term damage to veins through repeat cannulation. Ravulizumab could reduce such anxiety.

Wider societal benefits could also result from increased productivity, as well as the 'freeing-up' of healthcare professional time that could be used to provide care elsewhere. Increased productivity would also benefit the patients themselves. Assuming a loss of earnings of £15/hour (based on full-time employee weekly

earning reported for the UK[74]), eculizumab home infusions cost each patient approximately £728 per year on average, while equivalent lost earnings for ravulizumab home infusions are approximately £375 per year on average. This represents a potential gain of £353 per patient per year. For carers that attend home infusions, similar loss of earnings would apply.

B.2.13. Interpretation of clinical effectiveness and safety evidence

B.2.13.1. Principal findings from the clinical evidence

Ravulizumab was found to be statistically non-inferior to eculizumab for all primary and key secondary endpoints across the pivotal ALXN1210-PNH-301 and ALXN1210-PNH-302 trials, with point estimates favouring ravulizumab. Ravulizumab thus demonstrated the same efficacy that has transformed the prognosis of patients with haemolytic PNH. This efficacy was shown to be consistent and durable over 52 weeks of treatment in adult PNH patients who are complement-inhibitor naïve and have high disease activity, and in eculizumab-exposed patients with stable disease. Ravulizumab was also found to offer comparable tolerability to eculizumab that similarly showed consistency over 52 weeks of treatment.

Ravulizumab offers an optimized weight-based dosing approach and extended half-life compared with eculizumab that results in immediate, complete and sustained terminal complement inhibition throughout an 8-week dosing period. All patients treated with ravulizumab achieved complete terminal complement inhibition (defined as serum free C5 < 0.5 ug/mL) by the end of the first infusion and this was sustained over 52 weeks of treatment with dosing every 8 weeks. This threshold was not consistently met in patients receiving eculizumab with several episodes of serum free C5 exceeding 0.5 ug/mL. As a result, there were 11 breakthrough haemolysis events in eculizumab treated patients due to incomplete C5 inhibition across the pivotal clinical trial programme (compared with no such events in ravulizumab treated patients). Although the impact of the reduced frequency of infusions on patient quality of life could not be fully captured in the pivotal trial programme, supportive data from a DCE, patient preference study and interview series with patients and carers clearly show the wide breadth of positive impacts this would provide.

The impact of complete and sustained terminal complement inhibition on the cost of treatment is fully explored in the cost effectiveness analysis presented and shows that ravulizumab offers cost savings to NHS England. This conclusion is supported in the recent cost analysis of breakthrough haemolysis in patients with PNH in the US that estimated that the total cost of BTH management was $407 for ravulizumab-treated patients compared to the $9,379 BTH management cost for eculizumab-treated patients ($386 vs $3,472 when pregnant women were not included).[39]

B.2.13.2. Strengths and limitations of the evidence base

Applicability of the evidence base to the decision problem

The pivotal clinical trial programme supporting the use of ravulizumab consists of the two largest RCTs conducted in the PNH patient population to date and provides data of direct relevance to the decision problem of interest.

The outcomes assessed in ALXN1210-PNH-301 and ALXN1210-PNH-302 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 haemolysis), to clinical outcomes (transfusions, haemoglobin stabilization, PNH symptoms) and safety outcomes. Furthermore, this clinical trial programme has established breakthrough haemolysis as a clinically relevant endpoint to objectively assess the return of haemolysis in PNH, as measured by elevated LDH in conjunction with at least one associated sign or symptom.

HRQL outcomes were also assessed in ALXN1210-PNH-301 and ALXN1210-PNH-302 and show the positive impact of ravulizumab treatment on disease-related quality of life. However, the impact of the reduced frequency of infusions with ravulizumab compared with eculizumab could not be captured in the Randomized Period of the clinical trial programme, due to protocol-denoted assessment needs.

Generalizability of trial populations to patients in clinical practice

Patients enrolled to ALXN1210-PNH-301 and ALXN1210-PNH-302 are considered to generally reflect those patients considered eligible for treatment according to PNH

National Service criteria. Clinical characteristics of patients enrolled are generally comparable with those of UK patients 'ever treated' according to International PNH Registry data, as summarized in Table 16.

Table 16: Characteristics of patients enrolled in ravulizumab trials versus UK patients 'ever treated' in the International PNH Registry (up to 8 July 2019)

	ALXN1210-PNH-301 (n=246)	**ALXN1210-PNH-302 (n=195)**	**UK patients ever treated (n[redacted])**
Male, n (%)	134 (54.4)	98 (50.3)	[redacted]
Race, n (%) Asian White/Caucasian Black/African American Indian/Alaska Other/Unknown	 129 (52.4) 94 (38.2) 6 (2.4) 2 (0.8) 15 (6.1)	 42 (21.5) 111 (56.9) 8 (4.1) – 34 (17.4)	[redacted]
Age at diagnosis Mean years (SD)	n=241 38.7 (15.8)	 35.5 (14.3)	[redacted]
Age at first infusion. Mean years (SD)	45.5 (15.7)	47.7 (14.2)	[redacted]
Weight, Mean kg (SD)	 68.7 (15.2)	 72.9 (15.7)	[redacted]
Weight at first infusion, % 40 to < 60 kg 60 to < 100 kg ≥ 100 kg	 [redacted]	 [redacted]	[redacted]
LDH Mean U/L (SD)[a]	 1606.4 (752.7)	 231.6 (49.2)	[redacted]
LDH ratio, n (%)[a] < 1.5 ≥ 1.5 x ULN	 0 246 (100)	NA[b]	[redacted]
pRBC units received within 1 year of study entry or RBC transfusions, n (%)[c] 0 ≥ 1	 44 (17.9) 202 (82.1)	 170 (87.2) 25 (12.8)	[redacted]
History of major adverse vascular event, n (%)	42 (17.1)	50 (25.6)	[redacted]

	ALXN1210-PNH-301 (n=246)	ALXN1210-PNH-302 (n=195)	UK patients ever treated (n[redacted])
History of aplastic anaemia (or hypoplastic anaemia in registry), n (%)	[redacted]	73 (37.4)	[redacted]

Key: GPI, glycophosphatidylinositol; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal haemoglobinuria; pRBC, packed red blood cell; RBC, red blood cell; SD, standard deviation.
Notes: [a], Normal range defined as 120–246 U/L, ULN defined as 246 U/L; [b], patients enrolled to Study 302 had stable disease and thus LDH within normal range; [c], randomization strata for Study 301 and Study 302 and RBC transfusions ever received for registry data.
Sources: ALXN1210-PNH-301 CSR[66]; Kulasekararaj et al. 2019[46]; Lee et al. 2019[44]; International PNH Registry data on file.

Although there are some differences in baseline LDH levels, transfusion history and a history of MAVE or aplastic anaemia (all generally higher in the UK population), these are likely due to differences in the management pathway at the time of study initiation/registry enrolment. There are no clear clinical indications that the clinical characteristics of patients enrolled in ALXN1210-PNH-301 and ALXN1210-PNH-302 are not generalizable to UK patients.

There are however clear demographic differences observed. A large proportion of patients in the ravulizumab clinical trial programme (particularly the ALXN1210-PNH-301 trial) were enrolled across Asian study sites, resulting in a higher proportion of Asian patients in the trials compared with the UK population. Although there is no known evidence that the treatment effects of either ravulizumab or eculizumab would be impacted by race/ethnicity, with subgroup analyses showing no significant difference (see Appendix E), associated difference in weight distributions could affect the pharmacokinetics and dosing needs of ravulizumab. However, clinical expert opinion is that weight is not predictive of the risk of breakthrough haemolysis resulting from incomplete C5 inhibition or other clinical outcomes.[36]

Of note, ravulizumab has not been assessed in pregnant women.

Eculizumab dosing in trials compared with clinical practice

An additional limitation in the UK context is that eculizumab dosing in ALXN1210-PNH-301 and ALXN1210-PNH-302 was set at the recommended posology: 600 mg for initial phase dosing and 900 mg for maintenance phase dosing.[23] This does not fully reflect clinical practice with the PNH National Service recommending permanent

escalation to at least 1,200 mg for eculizumab maintenance dosing in patients with repeated breakthrough haemolysis due to incomplete C5 inhibition (initially detected through haemoglobinuria or transfusion need).[37] There is therefore an evidence gap from the clinical trials conducted to date in terms of the efficacy and safety of switching patients currently receiving eculizumab ≥ 1,200 mg to ravulizumab. However, there is no clinical rationale as to why these patients would respond differently to the ALXN1210-PNH-302 trial who did not experience breakthrough haemolysis due to incomplete C5 inhibition after switching to ravulizumab in the study extension phase. Indeed, a recently published case study has confirmed that a patient on twice the standard eculizumab dose was switched to ravulizumab treatment with no loss of disease control.[75] Further, the patient experienced no breakthrough haemolysis events following switch to ravulizumab. To provide additional evidence, a Phase IV proof-of-concept study (ALXN1210-PNH-401) has been designed to formally investigate this in the UK with patients stable on high-dose eculizumab planned to switch to ravulizumab and observed for 52 weeks; the estimated study start and completion dates were January 2021 and February 2022, respectively, but this may be delayed due to a pause in recruitment relating to the COVID-19 pandemic.[76]

The lack of 'up-dosing' in the pivotal clinical trial programme compared with clinical practice may also result in slightly worse clinical outcomes for patients in the eculizumab arm of ALXN1210-PNH-301 and ALXN1210-PNH-302. In practice, patients who experience breakthrough haemolysis due to incomplete C5 inhibition are quickly given the opportunity to receive the higher dose of eculizumab to restore complete terminal complement inhibition. According to UK data from the International PNH Registry (2 October 2018; data on file) and PNH National Service data (March 2019[38]), approximately [redacted]% of patients treated in current practice are receiving a higher dose of eculizumab than the label dose.

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-PNH-301 and ALXN1210-PNH-302 were thus infused according to minimum infusion times recommended for this concentration of drug. The HRQL data from ALXN1210-PNH-

301 and ALXN1210-PNH-302, the patient preference study on a subset of patients who switched from eculizumab to ravulizumab in the ALXN1210-PNH-302 trial, and the DCE used to estimate the utility decrement associated with treatment burden all therefore compare patients receiving infusion every 2 weeks that takes 1 hour, compared with an infusion every 8 weeks that takes 3 hours.

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 containing 10 mg/mL ravulizumab. The new vial sizes offer reduced infusion times such that the appropriate comparison for treatment burden is patients receiving infusion every 2 weeks that takes 1 hour, compared with an infusion every 8 weeks that takes 1 hour. The quality of life data from the aforementioned studies are therefore likely to underestimate the real-world impact of ravulizumab on patient quality of life due to treatment burden.

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.

Longer-term effect of ravulizumab treatment

The relative immaturity of the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials could be seen as a limitation in that they currently provide up to 52 week data for a chronic condition requiring lifelong treatment (at this time; 104 week data are expected [redacted]). Nonetheless, given the similar safety and efficacy of ravulizumab compared with eculizumab, we would expect longer-term outcomes with ravulizumab to remain similar to eculizumab, which has aligned the life expectancy of PNH patients to that of the general population.[28]

B.2.13.3. Clinical effectiveness conclusion

Ravulizumab offers immediate, complete and sustained terminal complement inhibition, and benefits patients and carers by preventing breakthrough haemolysis associated with elevated C5 levels and reducing the treatment burden compared

with eculizumab, while maintaining clinical effectiveness. Ravulizumab thus addresses some remaining areas of unmet need in the PNH setting.

B.3. Cost effectiveness

B.3.1. Published cost-effectiveness studies

A systematic literature review (SLR) of existing economic evaluations in paroxysmal nocturnal haemoglobinuria (PNH) did not identify any previous cost-effectiveness studies for ravulizumab in PNH in the UK setting. The search strategy, originally run on 9 August 2018, was adapted and updated on 2 July 2020. Full details of these searches and the findings are reported in Appendix G. The search identified five studies reporting outcomes of cost effectiveness that met inclusion criteria relating to population, intervention/comparator and study design. Of these, two studies were identified that specifically assess the cost-effectiveness of ravulizumab compared with eculizumab for the treatment of PNH in non-UK settings.[77, 78] A further grey literature search of the Scottish Medicines Consortium (SMC) website identified a health technology assessment (HTA) submission assessing the cost effectiveness of eculizumab compared with current care.[79]

Consistent with our decision problem and final NICE scope (see Section B.1.1), which states that the intervention and comparator of interest in this analysis are ravulizumab and eculizumab, respectively, only the two studies that reflect this decision problem are summarized in Table 17. Details on the remaining four studies identified in the SLR search are provided in Appendix G.

The two economic evaluations that meet our decision problem are the two publications by O'Connell et al.; these report on the same model as per our submitted economic analysis, albeit for different country settings (US and Germany).[77, 78] In both studies, a cost-utility analysis was performed, showing ravulizumab to be dominant (higher QALYs, lower costs) compared to eculizumab. Although the same model was used for both the US and German analysis, different base case settings were used, hence the differences in the incremental QALYs reported. One of the key differences was the application of different utility values to adjust for the benefit of the reduced dose frequency for ravulizumab compared to eculizumab as the DCE had not reported at the time of the earlier O'Connell study. Further comparison of the studies is provided in Appendix G.

Given our submitted economic analysis utilizes the same model as that reported in the two studies by O'Connell et al., these publications provide useful references to validate our base case results. We discuss this further in Section B.3.9.

Table 17: Summary list 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)
O'Connell et al. (2020)[77]	2019	The structure of both models was informed by literature review, clinical expert input, and clinical trial data; in particular, ALXN1210-PNH-301 and ALXN1210-PNH-302 provided data on clinical outcomes between treatments. PNH-related outcomes were modelled over a lifetime, and included current, historical, or no breakthrough haemolysis; eculizumab dosage; remission; and avoidance of blood transfusion. A lifetime horizon was used. Note these publications refer to the model presented herein.	Adult patients with PNH. Clinical data derived from ALXN1210-PNH-301 and ALXN1210-PNH-302 trials. Three cohorts were modelled: • Cohort 1, patients naïve to eculizumab treatment (initiating labelled dosing at the start of the model) • Cohort 2, patients who are clinically stable on the approved maintenance dose of eculizumab (900 mg every 2 weeks) • Cohort 3, patients who are clinically stable on off-label use of a higher maintenance dose of eculizumab (92.5% on 1200 mg and 7.5% on 1500 mg, every 2 weeks, based on data on file).	Incremental QALYs (ravulizumab vs eculizumab): 1.67	Mean incremental costs: −$1,673,465	Dominant (i.e. higher QALYs, lower costs). Ravulizumab was dominant in 99.9% of Monte-Carlo simulations.
O'Connell et al. (2019)[78]	2019		Adult patients with PNH.	Incremental QALYs (ravulizumab vs eculizumab): 0.53	Mean incremental costs: −€1,906,440	Dominant (higher QALYs, lower costs), maintained in 91.7% of Monte-Carlo simulations.

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
			Clinical data derived from ALXN1210-PNH-301 and ALXN1210-PNH-302 trials. Three cohorts modelled: • Cohort 1 – adults who are naïve to eculizumab treatment (33% of patients) • Cohort 2 – adults who are clinically stable on eculizumab dosing based on the approved label (57% of patients) • Cohort 3 – adults who are clinically stable on a higher eculizumab dose than the approved label (10% of patients).			
Key: ICER, incremental cost-effectiveness ratio; paroxysmal nocturnal haemoglobinuria; QALYs, quality-adjusted life years.						

B.3.2. Economic analysis

As discussed above, none of the economic evaluations identified in the SLR were conducted from a UK perspective comparing ravulizumab with the current standard of care, eculizumab. Therefore, for the purposes of this submission, a de novo economic model was developed in Microsoft Excel®.

In line with NICE's request to consider this as an STA and not a fast track appraisal (FTA), a cost–utility analysis is presented. This allowed differential effectiveness to demonstrate the costs and outcomes from modelling the clinical trial data that compared the safety and efficacy of ravulizumab and eculizumab. The analysis modelled the observed clinical trial outcomes while also incorporating English clinical practice dosing; this assumed that after two incomplete C5 inhibition events, patients would be treated with eculizumab at a continuously higher dose than the licensed dose.

Health outcomes are expressed in terms of quality-adjusted life years (QALYs), and cost components included the costs associated with drug acquisition and administration costs, breakthrough haemolysis (BTH) event management and blood transfusions. This analysis demonstrated that ravulizumab is dominant (i.e. more effective [providing more QALYs] and cost saving) versus eculizumab.

A scenario analysis is also presented in which equal effectiveness was assumed. This analysis is consistent with the non-inferiority trial designs and provides a more conservative viewpoint, given that all endpoints in the trial were numerically in favour of ravulizumab. Similar to the main analysis, eculizumab dosing was modelled to be consistent with English clinical practice (i.e. a proportion of patients received a higher than licensed dose of eculizumab). This scenario analysis was conducted to evaluate the cost to NHS England of using ravulizumab for the treatment of patients with PNH who would otherwise be treated with eculizumab, and only considers costs directly relevant to NHS England, including drug acquisition and administration costs. This analysis demonstrates that ravulizumab is cost saving when compared with eculizumab in English clinical practice.

Both analyses used the same model structure, the difference being that some of the health states were effectively 'switched off' in the equal effectiveness scenario, given

the relative simplicity of this analysis. As the same structure and methodology were applied, both analyses are described together in the following sections and only the results are presented separately.

B.3.2.1. Model structure

In selecting the most appropriate model structure, the following factors were considered:

- The fact that ravulizumab has demonstrated non-inferiority to eculizumab in two clinical trials
- The status of PNH as an orphan disease and the consequent limitations in terms of data availability
- The primary treatment effect being a normalization of intravascular haemolysis and consequent management of BTH
- The evidence available from the trial data and the literature on the impact of PNH on health-related quality of life (HRQL) and resource use
- The need to assess different causes of breakthrough haemolysis and the subsequent impact on HRQL and resource use

The model was designed in such a way that effectiveness could easily be set to be equal and non-relevant health states turned off to provide an equal effectiveness scenario. A description of the model and key features of the analysis are presented in subsequent sections.

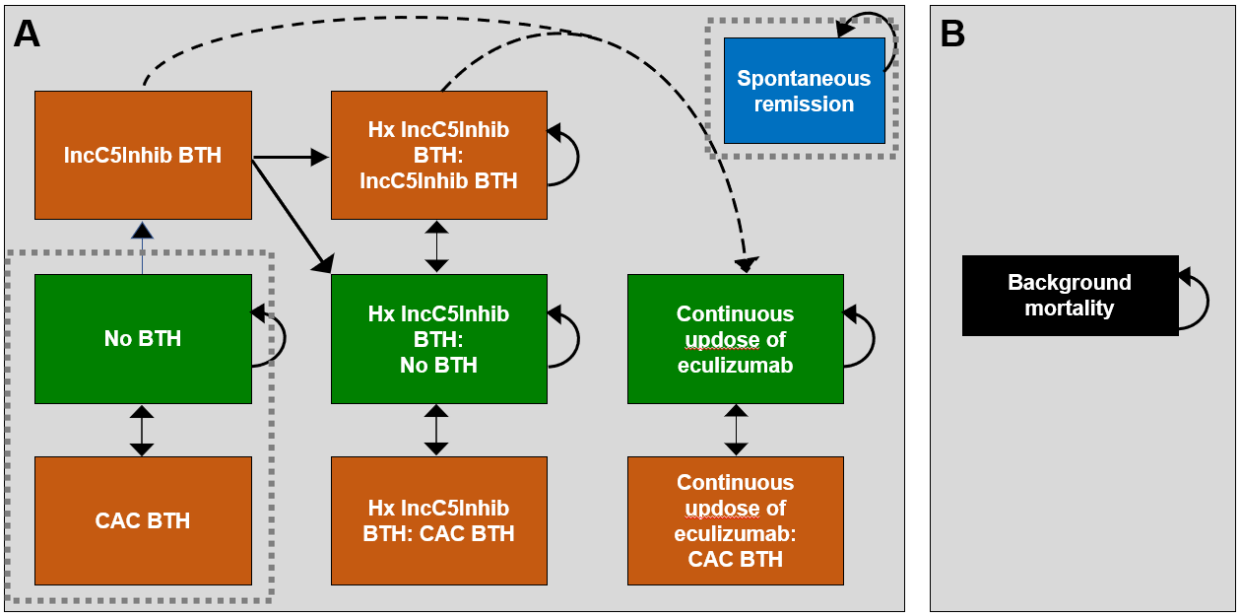
A state transition model was selected as the most appropriate based on consideration of the factors mentioned above. The chosen structure was additionally guided by health economics experts at a July 2018 Advisory Board meeting, where it was suggested that a cohort model may be the most appropriate for the cost-effectiveness analysis of ravulizumab versus eculizumab.[36] Attendees discussed the issue that data were not sufficiently suggestive of non-constant rates of transitions (other than for background mortality) to warrant the additional complexity of a discrete event simulation model.

The state transition model has 10 health states, as reflected in Figure 14. The health states included were based on clinically meaningful outcomes, as determined by the

clinical trials, published literature and expert clinical opinion. Specifically, there are eight BTH health states, one mortality-related health state, and a spontaneous-remission health state (included in scenario analysis only).

The equal effectiveness scenario considers a simplified number of health states, highlighted within the dashed boxes below (no BTH, CAC related BTH and spontaneous remission). The cost-utility analysis considers all health states.

Figure 14: Economic model diagram



Key: BTH, breakthrough haemolysis; CAC, complement-amplifying condition; Hx, history of; IncC5Inhib, incomplete C5 inhibitor.
Notes:
Panel A depicts haemolysis-related states; states without a breakthrough haemolysis (BTH) event are shaded green, and states with a BTH event are shaded orange.
Panel B depicts background mortality, a non-haemolysis-related state to which transitions from any living health state are possible.
Patients on eculizumab can receive a 'single' up-dose in response to an incomplete C5 inhibition-related or CAC-related BTH.
For patients on ravulizumab, a 'single' up-dose of eculizumab may be specified only in response to CAC-related BTH events (because no incomplete C5 inhibition-related events were observed for ravulizumab).
Continuous up-dosing to resolve an incomplete C5 inhibition-related event is only possible for eculizumab patients (depicted by the dashed line).

The health-state categories used are discussed in turn below.

B.3.2.2. Patient population

The cost–utility analysis and the equal effectiveness scenario consider adults with PNH who meet the criteria for complement-inhibitor treatment as outlined in the NHS

England Paroxysmal Nocturnal Haemoglobinuria Service (Adults and Adolescents) – Service Specification.[24] This is in accordance with the marketing authorization of ravulizumab and with the wording issued in the final NICE scope, as detailed in Section B.1.1.

As stated in Section B.2.13, while the eligibility criteria of the trial were not explicitly matched to the PNH service specification criteria for treatment initiation, they were designed to identify patients requiring active treatment to manage their disease versus those who do not. Patients in the trial were therefore considered representative of the population for whom ravulizumab is intended and for whom eculizumab is currently used.

No subgroup of interest was identified. Analysis of patients in the pivotal studies (ALXN1210-PNH-301 and ALXN1210-PNH-302) using primary and key secondary outcomes (see Section B.2.6) has not suggested that there is a group of patients for whom the treatment provides greater clinical benefits.

B.3.2.3. Patient cohorts included in the economic analysis

Patients who are eligible for ravulizumab (and eculizumab) can be considered to be either complement inhibitor naïve (treatment naïve, referred to as Cohort 1 in the model) or treatment experienced.

Patients who are deemed treatment experienced and clinically stable on eculizumab include patients on the licensed dose of eculizumab (900 mg – referred to as Cohort 2) or on a higher-than-labelled dose (1200 mg – referred to as Cohort 3).[25] In UK clinical practice, an increased dose of eculizumab is used to manage BTH. Based on data provided by the PNH National Service, this is necessary in [redacted] of the population, with the majority of patients remaining stable on the licensed eculizumab dose (900 mg).[38] This is consistent with data from Alexion's homecare service (data on file).

Approximately 20% of patients with PNH reportedly experience breakthrough haemolysis while receiving label dose of eculizumab (900 mg) treatment (reported range: 5–29%).[26, 33-35] Consequently, in the model, an additional cohort of patients

was used to reflect the proportion of patients who receive an eculizumab dose greater than 900 mg (higher-than-labelled dose), consistent with clinical practice.

Table 18 presents the proportion of patients modelled for each cohort in the base case analysis and equal effectiveness scenario.

B.3.2.4. Handling of eculizumab up-dosed patients

ALXN1210-PNH-301 and ALXN1210-PNH-302 did not allow for dosing changes for patients who experienced BTH events (incomplete C5 inhibition-related or complement-amplifying condition [CAC]-related) and thus do not fully reflect NHS England clinical practice in this respect. For this reason, in the equal effectiveness scenario analysis, Cohort 3 was included from the start of the model and consisted of patients with a history of two incomplete C5 inhibition BTH events who were treated with eculizumab at a continuously higher dose than the licensed dose.

For the base case analysis, Cohorts 1 and 2 reflected the profiles of patients in the clinical studies ALXN1210-PNH-301 and ALXN1210-PNH-302, respectively. For patients who experience a CAC-related BTH event or an incomplete C5 inhibition BTH, the model assumed that patients would receive one single up-dose of eculizumab to re-establish the blockade. Eculizumab patients with a history of one incomplete C5 BTH event, and who experienced a second incomplete C5 BTH event, moved to a continuously higher dose of eculizumab, aligning to UK clinical practice (this is detailed in Section B.3.3.1).

Although there are no clinical trial data available for switching eculizumab patients who have been treated with a higher-than-licensed dose currently, a Phase IV proof-of-concept study (ALXN1210-PNH-401) has been designed to formally investigate this in the UK with patients stable on high-dose eculizumab planned to switch to ravulizumab and observed for 52 weeks; the estimated study start and completion dates were January 2021 and February 2022, respectively, but this may be delayed due to a pause in recruitment relating to the COVID-19 pandemic.[76] Moreover, a recently published case study has confirmed that a patient on twice the standard eculizumab dose was switched to ravulizumab treatment with no loss of disease control.[75] The patient experienced no breakthrough haemolysis events following switch to ravulizumab, as observed in 52-week data from ALXN1210-PNH-301, in

which no patient switching to ravulizumab from eculizumab at 26 weeks experienced an incomplete C5 inhibition-related BTH event while on ravulizumab (including those who experienced an incomplete BTH event while on eculizumab). This provides evidence to support that patients who experience BTH on eculizumab due to incomplete C5 inhibition (i.e. those who require a higher dose of eculizumab) will not experience BTH due to incomplete C5 inhibition on ravulizumab. We have therefore assumed that when patients are treated with the labelled dose of ravulizumab, patients do not experience incomplete C5 inhibition-related BTH. We have also assumed that patients who receive a higher dose of eculizumab in clinical practice do not experience incomplete C5 inhibition-related BTH when on ravulizumab.

B.3.2.5. Numbers in each patient cohort

Eculizumab is being used to treat [redacted] patients in England, according to information provided by the Alexion Homecare service, as of May 2020 (data on file). Of these, [redacted] patients started treatment (i.e. were classed as treatment naïve) in 2019.

Based on data from the PNH National service, [redacted] of current English patients receive a higher than licensed dose of eculizumab as communicated by the PNH National Service.[38] This aligns to an alternate rate of [redacted]% derived from an analysis of the UK population in the PNH registry (data on file).

A further [redacted] patients in England are receiving ravulizumab through the ALXN1210-PNH-301 extension or ALXN1210-PNH-302 extension.[66, 68]

Base case analysis

For the base case analysis, a mixture of Cohorts 1 and 2 was modelled using a weighted average approach, based on the patient numbers from the Alexion Homecare service. For Cohort 1, this is based on the [redacted] treatment naïve patients who started treatment in 2019 (we are assuming that the proportion of patients starting treatment remains the same each year). For Cohort 2, there are [redacted] treatment experienced patients currently treated with eculizumab, including a further [redacted] patients on ravulizumab trials; this yields a total of [redacted] treatment experienced patients.

In line with the protocols of ALXN1210-PNH-301 and ALXN1210-PNH-302, patients cannot enter the model in Cohort 3 (higher than licensed dose of eculizumab).

Considering the patient numbers discussed above, on model entry, the proportions were:

- [redacted] in Cohort 1
- [redacted] in Cohort 2

Eculizumab-treated patients with a history of two incomplete C5 inhibition BTH events could transition into Cohort 3 throughout the model time horizon. Across the model time horizon of 20 years, patients spend 24.3% of their time in the up-dosed states which aligns to the [redacted] from the PNH National Service[38], the [redacted] from UK data from the International PNH Registry (data on file) and an average of 20% stated by UK clinicians at a PNH advisory board.[25]

A scenario was explored in which patients were allowed to start on a higher dose of eculizumab.

Equal effectiveness scenario

For the supporting equal effectiveness scenario, Cohorts 1, 2 and 3 were modelled using a weighted average approach, based on a combination of data from the Alexion Homecare Service and the PNH National service.

As per the base case analysis, [redacted] patients are treatment naïve and enter the model in Cohort 1. We have assumed that [redacted] of all eculizumab treatment experienced patients receive eculizumab at a higher than licensed dose; this is based on the PNH National Service data and is assumed to be generalizable to patients in NHS England.[38] An alternate rate of [redacted]% derived from an analysis of the UK population in the International PNH registry was tested in a scenario analysis (data on file).

In summary, on model entry, the proportions in each cohort were:

- [redacted]% in Cohort 1
- [redacted]% in Cohort 2
- [redacted]% in Cohort 3

In this analysis, we assumed that patients receiving their dose of eculizumab as per clinical practice would not be expected to experience incomplete C5 inhibition-related BTH. Therefore, clinical outcomes were assumed to be the same as for the ravulizumab treatment arm in Cohort 2.

Table 18: Patient groups included in the economic analysis

Population	Relevant trial	Formally modelled (from model start) Expected size in England clinical practice			
		Base case		Equal effectiveness scenario	
Cohort 1: Treatment-naïve	ALXN1210-PNH-301 (NCT02946463)	Yes	[redacted]	Yes	[redacted]
Cohort 2: Treatment-experienced, clinically stable at licensed eculizumab dose	ALXN1210-PNH-302 (NCT03056040)	Yes	[redacted]	Yes	[redacted]
Cohort 3: Treatment-experienced, higher than the licensed dose	Assumed the same as outcomes from ALXN1210-PNH-302 (NCT03056040)	No	[redacted]	Yes	[redacted]

B.3.2.6. Model health states

Breakthrough haemolysis events

BTH classification

BTH is defined as at least one new or worsening symptom or sign of intravascular haemolysis (fatigue, haemoglobinuria, abdominal pain, shortness of breath [dyspnoea], anaemia [haemoglobin <10 g/dL], major adverse vascular event [including thrombosis], dysphagia, or erectile dysfunction) in the presence of elevated lactate dehydrogenase (LDH) ≥2 × the upper limit of normal (ULN), after prior LDH reduction to <1.5 × ULN on therapy.[45] Clinical studies ALXN1210-PNH-301 and ALXN1210-PNH-302 reported three classifications of BTH events: incomplete C5 inhibitor-related, CAC-related and undetermined.[66, 68] In both clinical

studies, each BTH event was reviewed to evaluate the aetiological factors involved, including time-matched pharmacodynamic parameters (free and total serum C5 levels) and/or presence of a potential infection or other CAC (e.g. trauma, surgery or pregnancy).[66, 68]

An incomplete C5 inhibition-related BTH event was defined as a level of free C5 of greater than or equal to 0.5 µg/mL.[66, 68] Having free (or unbound) C5 in the serum suggests suboptimal C5 inhibition, as eculizumab and ravulizumab both work as C5 inhibitors by binding to the C5 protein. A direct comparison offers insight into the level of C5 inhibition achieved between ravulizumab and eculizumab.

A CAC-related BTH event was defined as any condition known to increase complement activity and result in a CAC-related increase in haemolysis. During the ALXN1210-PNH-301 and ALXN1210-PNH-302 studies, infection was the most common aetiology of CAC-related BTH events and resolved with treatment of the infection.[66, 68]

Undetermined BTH events represent the third classification reported in the ALXN1210-PNH-301 and ALXN1210-PNH-302 clinical studies. Undetermined cases were deemed to have neither incomplete C5 inhibition nor concomitant infection.[66, 68] These events lacked elevation in free C5 levels based on the data collected, but a CAC had not been reported. Therefore, the clinical experts were confident that these events were not incomplete C5 inhibition-related BTH events. However, it is possible that the aetiology was not adequately captured, so a CAC-related cause cannot be ruled out. Given this, BTH events of undetermined cause were treated in the model as CAC-related BTH events and thus having a CAC-related cause. This is further discussed in Section B.3.3.1.

BTH events

In the base case analysis, incomplete C5 inhibition-related and CAC-related BTH events were modelled. In the equal-effectiveness scenario, only CAC-related BTH events were modelled.

Data from clinical studies ALXN1210-PNH-301 and ALXN1210-PNH-302 were used to estimate the likelihood of transitioning from a non-BTH health state to one of the BTH health states specified in the model. The trial data allowed for the identification

of BTH events that had occurred since the last visit, as well as information on the type of event. In particular, events were 'adjudicated' to take one of five values:

- 'Free C5 ≥0.5 μg/mL'
- 'Free C5 ≥0.5 μg/mL and CAC'
- 'CAC'
- 'Undetermined'
- 'Missing value' (i.e. not 'adjudicated')

Internal medical staff from Alexion were consulted to confirm the meaning of 'adjudication values'. BTH events were classed as missing values when a patient experienced a BTH event in the previous visit, and the event had continued. In these instances, missing values were imputed to reflect the most recent adjudicated event.

Based on the above, BTH events were assigned to one of three health states:

- No BTH – no BTH event occurred
- Incomplete C5 inhibition-related BTH – a BTH event occurred and was associated with adjudication of one of:
  - 'Free C5 ≥0.5 μg /mL' or
  - 'Free C5 ≥0.5 μg /mL and CAC'
- CAC-related BTH – a BTH event occurred and was associated with adjudication of one of:
  - 'CAC' or
  - 'Undetermined'

As depicted in Figure 14, in the model, a patient's history of incomplete C5 inhibition-related BTH impacts the likelihood of experiencing a subsequent BTH event. Consequently, separate transition probabilities were estimated conditional on whether a patient had a history of incomplete C5 inhibition-related BTH events. This is described below.

History of incomplete C5 inhibition-related BTH

The persistence of incomplete C5 inhibition-related BTH events was defined as the probability of an incomplete C5 inhibition-related BTH event in the current cycle of

the model, conditional on having experienced an incomplete C5 inhibition-related BTH event in the previous cycle (i.e. whether there is a history of incomplete C5 inhibition-related BTH).

This was not relevant to the equal effectiveness scenario but was modelled in the base case analysis based on observed persistence of incomplete C5 inhibition-related BTH events in clinical studies ALXN1210-PNH-301 and ALXN1210-PNH-302.

Up-dosing due to BTH

CAC-related BTH event

To account for occurrences of CAC-related BTH events, the economic model (for both the base case analysis and equal effectiveness scenario) assumed one single up-dose was required in the eculizumab arm to re-establish the blockade.[36] Where a CAC-related BTH event occurred in the ravulizumab arm, an additional dose of eculizumab, as opposed to ravulizumab, was assumed. This is because no data are currently available on the effectiveness or safety of up-dosing ravulizumab, and thus there is no informed clinical rationale for doing this. Also, the additional eculizumab dose in ravulizumab patients experiencing a CAC-related BTH event was discussed and felt to be appropriate as a potential treatment strategy in the December 2018 Advisory Board meeting.[25]

Incomplete C5 inhibition-related BTH event

In the base case analysis, permanent (continuous) eculizumab up-dosing was included in line with the management algorithm that has been adopted in UK clinical practice for managing incomplete C5 inhibition-related BTH events.[25] Continuous up-dosing was modelled following the second incomplete C5 inhibition-related BTH event. For a patient's first incomplete C5 inhibition-related BTH event, a single up-dose is given, as per the approach used for treating CAC-related BTH events. When a patient experiences a second incomplete C5 inhibition-related BTH event, the patient is given another up-dose and thereafter continuously up-dosed for the model time horizon.

In the equal effectiveness scenario, a cohort of patients was assumed to be up-dosed from the start of the model, to reflect that all patients receive clinical practice dosing from the model start (Cohort 3, reflecting [redacted] of all patients, see Table 18).

Spontaneous remission

Spontaneous remission was first reported by Hillmen et al. (1995), who, remarking on a historical cohort, stated that: 'Of the 35 patients who survived 10 years or more, 12 had a spontaneous clinical recovery'.[21] It was concluded that in the long term, spontaneous remission can occur in PNH patients. Since the Hillmen et al. (1995) report, other accounts of remission have followed. Socie et al. (1996) reported on a sample of 220 patients, in which 5% experienced spontaneous remission.[80] Furthermore, Pulini et al. (2011) provided a case report of a man who achieved PNH remission and discontinued eculizumab.[81]

Due to uncertainty around the rate and causes of spontaneous remission, it was not considered in the base case of this analysis. However, it was modelled as a scenario, assuming that patients who achieve spontaneous remission will stop PNH-related treatment (including complement-inhibitor therapy). For this scenario, the same rate of spontaneous remission was assumed for both eculizumab- and ravulizumab-treated patients.

Background mortality

Background mortality has been included based on the mortality rate for the general population.[82] Given that PNH is an incomplete C5 inhibition-related disorder and the model uses a lifetime horizon, background mortality was included to reflect the age-adjusted mortality risk for all patients in the model.

The 52-week data from clinical studies ALXN1210-PNH-301 and ALXN1210-PNH-302 did not capture any mortality related to treatment in either the ravulizumab arm or in ravulizumab patients who switched from eculizumab.[67, 69] Therefore, evidence around excess mortality associated with PNH was retrieved from the published literature and clinical feedback.

Evidence suggests the clinical consequences of uncontrolled complement activity are diverse, but in severe instances include outcomes such as thrombotic events, endothelial damage, inflammation and ischaemia.[16] Persistent BTH events may lead to long-term uncontrolled haemolysis if they are left untreated; consequently, the model allows for some excess risk of mortality associated with BTH events.[34]

A scenario was therefore included to model an excess mortality risk associated with BTH events.

General model settings

The analysis perspective was that of the NHS and Personal Social Services in England for costs and direct health effects on individual patients for outcomes, in line with the NICE reference case.[83]

A 2-week cycle length was modelled. This aligned with the ALXN1210-PNH-301 and ALXN1210-PNH-302 clinical trials' data collection, which occurred every 2 weeks, and the treatment schedule for eculizumab. Given the short cycle length, a half-cycle correction was not applied to any cost or health outcomes.

A lifetime horizon (100 − mean age at baseline) was adopted to capture costs over a sufficient length of time and consistent with previous analyses in PNH.[79, 84, 85] Time horizons of 10 and 20 years were also tested in scenario analyses.

A discount rate of 3.5% per annum was applied to costs and QALYs, as also specified by the NICE reference case.[83]

Table 19 summarizes the features of the current economic appraisal.

Table 19: Features of the economic analysis

	Current appraisal	
Factor	**Chosen values**	**Justification**
Time horizon	Lifetime (Cohort 1: 55 years; Cohort 2/3: 52 years) Starting age • Cohort 1: 45 • Cohort 2/3: 48	Long enough to reflect all important differences in costs and outcomes between the technologies being compared, in line with the reference case.[83] This is also consistent with previous economic evaluations in PNH.[79, 84, 85]

	Current appraisal	
Factor	**Chosen values**	**Justification**
Treatment waning effect?	Not applied	Ravulizumab has demonstrated non-inferiority to eculizumab, with which it shares 99% homology, and which has been shown to provide a long-term treatment effect. The use of constant post-trial event rates was deemed appropriate at the December Advisory Board meeting.[25]
Source of utilities	EORTC QLQ-C30 data from the ALXN1210-PNH-301 and ALXN1210-PNH-302 studies mapped to EQ-5D-3L equivalent utility estimates, using the Longworth (2014) mapping algorithm.[86]	Mapping EQ-5D data reported directly from patients with utilities based on public preferences is NICE's preferred method.[83]
Source of costs	Standard UK sources including eMIT and MIMS for drug costs, and NHS reference costs.	UK sources considered most reflective of costs incurred by NHS England.
Key: eMIT, electronic market information tool; EORTC QLQ–C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D-3L, three-level EQ-5D; MIMS, Monthly Index of Medical Specialities; NHS, National Health Service; PNH, paroxysmal nocturnal haemoglobinuria.		

B.3.2.7. Intervention technology and comparators

Intervention

The intervention, ravulizumab, is implemented in the model as per the marketing authorization and is reflective of the decision problem described in Section B.1.1.

Ravulizumab is the first long-acting C5 inhibitor developed through targeted engineering to provide immediate, complete and sustained C5 inhibition with an 8-week dosing interval. Ravulizumab is administered intravenously, via a weight-based dosing regimen, with patients offered treatment at home via the existing Alexion home care service.

Comparator

As detailed in Section B.1.3.2, currently, adult patients with PNH and haemolysis with clinical symptom(s) indicative of high disease activity in NHS England are

treated with eculizumab. Eculizumab was approved by the National Commissioning Group, the National Specialised Commissioning Group, and Strategic Health Authorities in September 2008 for national commissioning in England. The current NHS England Service Specification 'Paroxysmal Nocturnal Haemoglobinuria service (Adults and Adolescents)' states how the PNH service has been set up to ensure the appropriate management of patients who require treatment with eculizumab.[24]

As discussed in Section B.1.3.2, since being approved for use in UK clinical practice, eculizumab has transformed the treatment landscape and natural history of PNH. However, despite its benefits (including improvements in survival, haemolysis events and transfusion dependency), an unmet need remains. Eculizumab patients may continue to experience BTH due to incomplete terminal complement inhibition, which increases the risk of progressive morbidity, impaired quality of life, and premature mortality, despite active treatment.[15, 87]

In UK clinical practice, an increased dose of eculizumab is used to manage BTH due to incomplete C5 inhibition. Data from the PNH national service indicate this is necessary for [redacted] of the population (see Section B.3.2.1), with the majority of patients remaining stable on the licensed eculizumab dose (900 mg). However, in the two pivotal Phase III trials, dose-escalation/up-dosing of eculizumab was not permitted.

In the base case analysis, all patients enter the model on the licensed 900 mg eculizumab dose, in line with the ALXN1210-PNH-301 and ALXN1210-PNH-302 clinical trials. Continuous up-dosing (1,200 and above) was modelled following two incomplete C5 inhibition-related BTH events. Note doses above 1200mg are funded by Alexion, therefore continuous-dosing to a cost of a 1200 mg was modelled. Conversely, in the equal effectiveness scenario, eculizumab dosing data from the PNH National service in was used to directly estimate the proportion of patients on the licensed 900 mg eculizumab dose and on a higher than licensed dose (1,200 mg and above).

The dosing of the comparator therapy, eculizumab, used in the model analyses is summarized in Table 20.

Table 20: Summary of comparator therapy included in the model

Eculizumab dose	Share of patients (from model start)	
	Base case	Equal effectiveness scenario
900 mg	[redacted]	[redacted]
1200 + mg	[redacted]	[redacted]

B.3.3. Clinical parameters and variables

The clinical evidence relevant to the economic analysis for ravulizumab consists of:

- ALXN1210-PNH-301 (NCT02946463) Phase III trial: a randomized, open-label, non-inferiority study in complement inhibitor-naïve adult patients with PNH (n=246)
- ALXN1210-PNH-302 (NCT03056040) Phase III trial: a randomized, open-label, non-inferiority study in patients with PNH who were clinically stable after having been treated with eculizumab for a least the past 6 months (n=195)

Data from both trials were used in the economic model to provide clinical data for the different patient cohorts, as summarized in Section B.3.2.1. Specifically, data from both the Randomized Period (Weeks 0–26) and data from the first 26 weeks of the Extension Periods (Weeks 27–52) were used.

The base case analysis is aligned with the trial population and observed outcomes from ALXN1210-PNH-301 and ALXN1210-PNH-302. Given that eculizumab was administered at its licensed dose in the pivotal trials, the efficacies of eculizumab and ravulizumab were taken directly from the respective clinical trials and treatment arms. In contrast, the equal effectiveness scenario aligns with the non-inferiority trial designs and assumes that, when for the management of BTH due to incomplete C5 inhibition patients receive an up-dose of eculizumab as per clinical practice, the efficacy of ravulizumab and eculizumab is equivalent.

The following sections outline how these data were used for the BTH events and transfusion events for both the eculizumab and ravulizumab treatment arms, and how the literature was used to inform the occurrence of spontaneous remission. It is also stated explicitly which efficacy inputs are/are not relevant to the base case and equal effectiveness scenario. This is summarized in Table 21.

Table 21: Differences in efficacy inputs modelled for the base case analysis and equal effectiveness scenario

Model input	***Base case analysis***	**Equal effectiveness scenario**	***Justification***
CAC-related BTH Events	CAC-related BTH events that occurred in Study ALXN1210-PNH-301 and ALXN1210-PNH-302 were modelled per trial.	CAC-related BTH events were assumed to be the same in the eculizumab and ravulizumab arms.	In the base case, given that the population is the same as the populations from the trials, the observed events from the trials were also used. In the equal effectiveness scenario, non-inferiority is assumed when all eculizumab patients are on a clinically stable dose; hence, events are assumed to be equal across arms, as per the ravulizumab arm.
Incomplete C5 inhibition-related BTH events	Incomplete C5 inhibition-related BTH events that occurred in Study ALXN1210-PNH-301 and ALXN1210-PNH-302 were modelled.	Incomplete C5 inhibition-related BTH events were not modelled or assumed to be zero.	In the base case, given that the population was the same as the populations from the trials, the observed events from the trials were also used. In the equal effectiveness scenario, all patients in the eculizumab arm were assumed to receive a clinically stable dose (i.e. UK dosing was used) – and not the licensed dose (900 mg) given in the pivotal trials. At the clinically stable dose, it was assumed that patients would not experience BTH due to incomplete C5 inhibition.
Blood transfusions	Transfusions reported in Study ALXN1210-PNH-301 and ALXN1210-PNH-302 were modelled per trial.	Transfusions were not modelled or assumed to be zero.	In the base case, given that the population is the same as the populations from the trials, the observed events from the trials were also used. In the equal effectiveness scenario, transfusion was not modelled (assumed same on both arms so will cancel out).
Spontaneous remission	Included as a model scenario.	Included as a model scenario.	Evidence of spontaneous remission was derived from the literature; given the uncertainty, this is not considered in the base case.
Key: BTH, breakthrough haemolysis CAC, complement-amplifying condition.			

B.3.3.1. Efficacy – BTH

BTH is a relevant outcome to both the base case analysis and equal effectiveness scenario, due to the treatment required to manage BTH events. Specifically, eculizumab (as a single up-dose) is used in both treatment arms to manage CAC-related BTH events.

Number of BTH events

Table 22 presents the number of BTH events experienced by patients in the Randomized Period of each clinical study as summarized in Section B.2.6.1. Table 23 presents the number of BTH events experienced by patients in the Extension Period of each clinical study, as summarized in Section B.2.6.2. For both incomplete C5 inhibition-related and CAC-related BTH events, numerically lower and non-inferior rates were seen for ravulizumab. These event rates were used to determine the transitions to and from BTH events.

Table 22: Number of BTH events by clinical study (Randomized Period)[45]

	Clinical study ALXN1210-PNH-301			
	Patient (N)	**BTH events**		
		Incomplete C5 inhibition-related	**CAC-related**	**Undetermined**
Eculizumab	121	7	4	4
Ravulizumab	125	0	4	1
	Clinical study ALXN1210-PNH-302			
Eculizumab	98	4	2	1
Ravulizumab	97	0	0	0
Key: BTH, breakthrough haemolysis; CAC, complement-amplifying condition. **Note:** No CAC-related BTH events were observed in the ravulizumab arm of ALXN1210-PNH-302 (during the Randomized Period).				

Table 23: Number of BTH events by clinical study (Extension Period)[67, 69]

	Clinical study ALXN1210-PNH-301			
	Patient (N)	**BTH events**		
		Incomplete C5 inhibition-related	**CAC-related**	**Undetermined**
Eculizumab switch to	119	0	1	1

	Clinical study ALXN1210-PNH-301			
	Patient (N)	BTH events		
		Incomplete C5 inhibition-related	CAC-related	Undetermined
Ravulizumab				
Ravulizumab continue Ravulizumab	124	0	1	4
	Clinical study ALXN1210-PNH-302			
Eculizumab switch to Ravulizumab	98	0	1	0
Ravulizumab continue on Ravulizumab	97	0	2	1

Key: BTH, breakthrough haemolysis; CAC, complement-amplifying condition.
Note: No incomplete C5 inhibition-related BTH events were observed in the extension periods of ALXN1210-PNH-301 and ALXN1210-PNH-302.

Transitions to and from BTH events

BTH events associated with incomplete C5 inhibition and CAC-related events were modelled separately, in alignment with the aetiologies distinguished in ALXN1210-PNH-301 and ALXN1210-PNH-302.[66, 68] Patients with incomplete C5 inhibition-associated BTH events were confirmed in the clinical studies to have elevated C5 levels, indicating suboptimal complement inhibition. CAC-related BTH events were associated with a concomitant infection or other CAC (e.g. trauma, surgery) that resulted in elevated complement activity and intravascular haemolysis.

Undetermined BTH events were a collection of BTH events that investigators failed to determine a true aetiology for. Following clinical guidance, these were classified as CAC-related BTH events for the model.[25]

Transitions to initial CAC-related BTH events

Transition matrices were constructed in three steps:

1. Patient-visit-level data for ALXN1210-PNH-301 and ALXN1210-PNH-302 were organized to determine the probability of a CAC-related BTH event

- Based on the subset of data identified in Step 1, a full-information maximum-likelihood multinomial logit model was estimated to predict the outcome state, conditional on the initial state (‘No BTH’)
- This approach was used to account for censoring from lack of follow-up as well as simultaneous competing risks of transitions to other states
- Adjusted models controlled for the time between initial and follow-up visits, and treatment arm

2. The model estimation produced a transition equation for each (initial state–follow-up state) pair that related the predictors to the probability of transitioning via the estimated coefficients
   - The transition equations developed in Step 2 were used to calculate mean transition probabilities for each (initial state-follow-up state) pair
   - This involved multiplying a vector of covariate values by the corresponding vector of estimated coefficients at the observation level for all possible outcomes from the initial state (’No BTH’), applying the formula for calculating predicted probabilities from a multinomial logit to the products, and then calculating the mean predicted probabilities across observations.
3. In this calculation, the time-between-visits covariate was held constant at a value of 14 days, to generate 2-weekly transition probabilities aligning with the model cycle length

Transition probabilities were calculated for both values of the treatment covariate, a binary indicator for whether the patient received ravulizumab or eculizumab in the Randomized Period (i.e. first 26 weeks) and the Extension Period (Week 27–52) of the clinical study.

Transitions to initial incomplete C5 inhibition-related BTH events

In ALXN1210-PNH-301 and ALXN1210-PNH-302, no incomplete C5 inhibition-related BTH events were experienced in the ravulizumab arm.

In the base case analysis, incomplete C5 inhibition-related BTH events that were experienced in the eculizumab arm were modelled, and the steps outlined above were also applicable for determining the transitions to initial incomplete C5 inhibition-related BTH events.

In the equal effectiveness scenario, it was assumed that the same clinical outcomes would be experienced in both treatment arms when the permanent eculizumab up-dosing as per clinical practice was used. Therefore, no incomplete C5 inhibition-related BTH events were modelled for either eculizumab or ravulizumab.

Transitions to subsequent incomplete C5 inhibition-related BTH events

In the base case analysis, transitions to subsequent incomplete C5 inhibition-related BTH events were modelled. The transition probabilities for subsequent BTH events (incomplete C5 inhibition-related BTH event occurring when there is a history of BTH) differed from those observed for initial BTH events. The below outlines the approach used to derive the transition probabilities for this.

Transition matrices for subsequent incomplete C5 inhibition-related BTH events were determined in the same manner as for the initial incomplete C5 inhibition-related and CAC-related BTH event transitions, with the following exceptions:

- To determine the likelihood of subsequent incomplete C5 inhibition-related BTH events, the sample was restricted to patients with a history of incomplete C5 inhibition-related BTH events
- Only observations that occurred after the first incomplete C5 inhibition-related BTH event were included in the estimation
  - Note that this selection criterion substantially limited the sample for the ALXN1210-PNH-302 clinical study, and thus could only be derived for the ALXN1210-PNH-301 clinical study data
- Since no patient in the ravulizumab arm of either clinical study experienced an incomplete C5 inhibition-related BTH event, the estimation was only performed for patients in the eculizumab arm

This estimation allowed for two initial states, either ‘No BTH’ or ‘Incomplete C5 inhibition-related BTH’ and observed the subsequent health states from either of these starting states

Persistence of incomplete C5 inhibition-related BTH events

Persistence of incomplete C5 inhibition-related BTH events was defined as the probability of an incomplete C5 inhibition-related BTH event in the current cycle of

the model, conditional on having experienced an incomplete C5 inhibition-related BTH event in the previous cycle. This was modelled based on observed persistence in ALXN1210-PNH-301 and ALXN1210-PNH-302.[45]

Occupation of BTH event health state

Duration of BTH (incomplete C5 inhibition-related and CAC-related) symptoms

In the base case analysis, the duration of a BTH event is relevant to health-related quality of life. In modelling the utility impact of incomplete C5 inhibition-related and CAC-related BTH events separately, the model accounts for the duration of each event type within the 2-week cycle. Specifically, it is assumed, based on internal Alexion medical opinion, that symptoms and complications of a CAC-related BTH event would be incurred for the full cycle (14 days), and the duration of an incomplete C5 inhibition-related BTH event may be specified as between 1–14 days. CAC-related BTH events are due to a CAC-related event that requires an additional dose until the infection or CAC has resolved. However, incomplete C5 inhibition-related BTH events occur in patients receiving eculizumab as a result of incomplete C5 inhibition[36], which is normally associated with eculizumab trough levels below 35 µg/ml.[88] This is often observed in the last 1–2 days of the 14-day dosing interval; a pattern that is repeated across dosing cycles.

The duration of an incomplete C5 inhibition-related BTH event due to incomplete C5 inhibition is 2 days. ALXN1210-PNH-301 and ALXN1210-PNH-302 did not report the time from a BTH event at a given visit.[66, 68]; consequently, published literature was consulted to estimate the duration of symptoms and complications of an incomplete C5 inhibition-related BTH event. According to Kelly (2008) and Brodsky (2014), BTH symptoms due to incomplete C5 inhibition often occurred 1–2 days before the next dose in a 14-day dosing schedule.[89, 90] By extrapolation, it was assumed that incomplete C5 inhibition-related BTH symptoms due to incomplete C5 inhibition would last for 2 days in the base case analysis. Variation of the duration was considered in sensitivity analyses.

Excess mortality risk of BTH

In ALXN1210-PNH-301 and ALXN1210-PNH-302, a BTH event was defined as: 'at least 1 new or worsening symptom or sign of intravascular haemolysis (fatigue, haemoglobinuria, abdominal pain, shortness of breath [dyspnoea], anaemia [haemoglobin <10 g/DL], major adverse vascular event, [including thrombosis], dysphagia or erectile dysfunction) in the presence of elevated LDH ≥2 x ULN, after prior LDH reduction to <1.5 x ULN on therapy'. Considering that a BTH event may be accompanied by severe outcomes, such as thrombosis, the model allowed for the specification of excess mortality risk associated with BTH events.

In the base case model analyses, no excess mortality risk of BTH events was specified. The application of higher mortality risk to that of the age- and gender-adjusted background mortality rate was identified in the literature. No evidence is available for a UK population or a comparable disease following a targeted search, therefore data from an alternative source was used. A study of patients enrolled in the Korean PNH registry by Jang et al. (2016) found that the standard mortality ratio associated with LDH ≥1.5 x ULN was 4.81.[16] Given the similarity in LDH threshold to the definition of BTH events in ALXN1210-PNH-301 and ALXN1210-PNH-302, a hazard ratio (HR) of 4.81 applied to patients experiencing BTH events was tested in the scenario analysis. This results in a small incremental life year gain for the ravulizumab arm due to the increased probability of experiencing a BTH event on eculizumab compared to ravulizumab.

Estimated transition probabilities

Transition matrices are presented in Appendix N for the base case analysis. Values were estimated based on all BTH events recorded in ALXN1210-PNH-301 and ALXN1210-PNH-302, including during the Extension Period.

Transition matrices are presented in Appendix O for the equal effectiveness scenario. Values were estimated based on CAC-related BTH events recorded in the ravulizumab arm of studies ALXN1210-PNH-301 and ALXN1210-PNH-302, including during the Extension Period.

Although the use of the Extension Period results in an unbalanced sample (as eculizumab patients switched to ravulizumab after 26 weeks), all data were used given the small number of events observed for ALXN1210-PNH-302.

B.3.3.2. Efficacy – transfusion requirements

Transfusion requirements were included in the base case analysis, due to their impact on HRQL and cost and resource use when differential effectiveness is assumed as per the trials. The economic model allows for the specification of packed red blood cell transfusion requirements, by treatment arm and presence of incomplete C5 inhibition-related or CAC-related BTH event. These transfusion requirements were used to estimate mean transfusion-related cost and utility impacts.

In the equal effectiveness scenario, transfusion requirements were assumed to be equal in the comparison, therefore cancelling each other out; consequently, these were not included in the analysis.

The probabilities of requiring a transfusion in each 2-week cycle, as well as the mean number of units of red blood cells required, were calculated based on patient-level data from ALXN1210-PNH-301 and ALXN1210-PNH-302. Of note, as no patient was observed to require multiple transfusions between visits in the clinical studies, it was assumed that while multiple units of red blood cells may have been required per transfusion, only one transfusion procedure would occur in a model cycle.

In the ‘permanent up-dosing as per clinical practice dose’ scenario, the rate of transfusions and the number of packed red blood cell units required were assumed to be equal to those of the ravulizumab arm.

The methods used to model the transfusion requirements are further described in Appendix P.

B.3.3.3. Spontaneous remission

As discussed in Section B.3.2.6, spontaneous remission was incorporated as a scenario analysis.

To model this scenario, the transition probability of spontaneous remission was calculated from data in Hillmen et al. (1995).[21] Details on the method are provided in Appendix Q.

B.3.3.4. Safety

The safety profile of ravulizumab in the treatment of adults with PNH is similar to that of eculizumab, as discussed in Section B.2.10. Of the adverse events (AEs) that occurred (including headache and nasopharyngitis) in the ALXN1210-PNH-301 and ALXN1210-PNH-302 studies, none were expected to have an impact on the cost-effectiveness analysis and were therefore not modelled.

B.3.4. Measurement and valuation of health effects

As discussed in Section B.1.3, since the use of eculizumab came about in UK clinical practice, much of the disease-related burden of PNH has decreased, and patients generally have a much better quality of life than they did in the pre-eculizumab era. However, at its licensed dose, eculizumab does not eliminate the risk of BTH in all patients, due to incomplete C5 inhibition occurring in a subset of patients.[36] Furthermore, PNH patients treated with eculizumab (or ravulizumab) may also experience CAC-related BTH, which can occur as a result of conditions such as infection or pregnancy.[25, 36]

BTH results in a range of symptoms that can have a significant impact on patient quality of life, making the activities of daily living challenging.[11-19] Typical examples of symptoms resulting from BTH include red or black urine, fatigue, abdominal pain and difficulty swallowing.[36] BTH also results in an increased requirement for blood transfusions[91], which is itself associated with a quality of life decrement.

In addition to the disease-related burden of PNH, treatment with eculizumab, which is administered as an intravenous infusion every 2 weeks, presents as a potential treatment-related burden that may impact the quality of life of both patients and caregivers.[40, 43] The preparation, infusion and post-infusion observance time can take from approximately 25 mins to 45 mins, and patients require 26 infusions per year. Although the majority of patients receive these infusions at home (98%) (data on file), this can still be burdensome; patients have noted anxiety on the day of infusion, an impact on travel and independence, and disruption to work.[43]

Alongside the burden of treatment frequency, a proportion of patients receiving eculizumab require a period of adjustment to determine the dose required to prevent BTH due to incomplete C5 inhibition. Eculizumab at the licenced dose, does not eliminate the risk of BTH in all patients in the UK; approximately 20% of patients with PNH reportedly experience breakthrough haemolysis while receiving label dose of eculizumab (900 mg) treatment (reported range: 5–29%).[26, 33-35] When a patient experiences BTH due to incomplete inhibition of C5, the practice in England is to increase the dose in 300 mg increments to a maximum of 1,800 mg, following two to three occurrences of BTH.[25, 37]

Once the patient's disease is stable on either the licensed or increased dose of eculizumab, the model assumes that only CAC-related BTH events drive HRQL. Patient HRQL is therefore assumed to be related to BTH events (incomplete C5 inhibition-related or CAC-related) and blood transfusions, rather than to changes occurring over time. Consequently, the utility values used in the model are held constant in each health state. Changes to patient HRQL are modelled as the transitions between the different health states.

The sections below present the HRQL data used in the economic model. Note this is not relevant for the equal effectiveness scenario.

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

In the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials, HRQL was measured from baseline to Week 26 using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C-30) and the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue questionnaires, every week for the first 2 weeks (Day 1 and Day 8) followed by a reduced frequency:

- Every 3 weeks, once (Day 29)
- Every 6 weeks, once (Day 71)
- Every 8 weeks from Day 71 to Day 183 (Week 26, end of treatment)

The questionnaires are continuing to be administered in the trial Extension Period, up until Day 911 (Week 130). Throughout this Extension Period, the questionnaires

will be administered four more times (Days 351, 575, 473 and 911). Both questionnaires are validated for use in the PNH patient population.[92] A summary of the EORTC-QLQ-C-30 observations by treatment arm is presented in Table 24 for ALXN1210-PNH-301 and Table 25 for ALXN1210-PNH-302.

Table 24: Summary of EORTC-QLQ-C-30 observations by treatment, ALXN1210-PNH-301

Treatment	Patients in full analysis set	Patients in analysis (%)	Observations	Mean number of observations per patient
All	246	246 (100)	1,452	5.9
Ravulizumab	125	125 (100)	740	5.9
Eculizumab	121	121 (100)	712	5.9

Table 25: Summary of EORTC-QLQ-C-30 observations by treatment, ALXN1210-PNH-302

Treatment	Patients in full analysis set	Patients in analysis (%)	Observations	Mean number of observations per patient
All	195	195 (100)	1,117	5.7
Ravulizumab	97	97 (100)	557	5.7
Eculizumab	98	98 (100)	560	5.7

The EORTC QLQ-C30 Global Health Status (GHS) questionnaire compliance rates from ALXN1210-PNH-301 and ALXN1210-PNH-302 trials were high, as suggested by the mean numbers of observations per patient in Table 24 and Table 25, which are out of a total of six visits/observations. Appendix R provides further detail into the number of EORTC QLQ-C30 observations at each of the six scheduled visits.

In both the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials, compared with eculizumab patients, a greater proportion of ravulizumab patients experienced a ≥3-point improvement in FACIT-Fatigue score and a ≥10-point improvement in the EORTC QLQ-C30 GHS/quality of life score as discussed in Section B.2.6 (Table 8).

As summarized in Section B.2.4 the two pivotal trials were designed to show ravulizumab had a non-inferior efficacy and safety profile to eculizumab; the criteria for non-inferiority for HRQL were met.

The HRQL data collected from the clinical trials are expected to capture the burden of disease (e.g. haemolysis, fatigue, need for transfusions) and the burden of treatment, that is, the need for regular infusions (which may be associated with inconvenience, pain, anxiety, associated AEs, etc.); however, due to the clinical trial designs, the relative benefit of reduced treatment burden was not captured. In ALXN1210-PNH-301 and ALXN1210-PNH-302, regardless of treatment received (i.e. ravulizumab or eculizumab) in the initial 26-week period, patients were required to attend visits on the same schedule. Consequently, in the clinical studies, patients did not experience the potential HRQL benefit of less frequent visits, although they did experience the benefit of less frequent infusions at visits. Additional data were therefore required to capture the benefit of a reduced infusion requirement with ravulizumab. This is detailed in Section B.3.4.3.

Furthermore, the HRQL data captured in the clinical trials do not meet the NICE reference case for cost-effectiveness analysis (three-level EQ-5D® [EQ-5D-3L]). A mapping algorithm (Longworth 2014) was therefore employed to generate utilities for use in the cost-effectiveness analysis.[86]

B.3.4.2. Mapping

Choice of mapping algorithm

EQ-5D data were not collected in the ALXN1210-PNH-301 and ALXN1210-PNH-302 clinical studies, and the SLR identified no published data reporting EQ-5D responses in PNH patients. Therefore, to align with the NICE reference case[83], the EORTC-QLQ-C30 and FACIT-Fatigue data were analysed to determine whether they could be mapped to EQ-5D-3L.

A targeted search was performed to identify published mapping algorithms that could be used to map either the EORTC-QLQ-C30 or FACIT-Fatigue to the EQ-5D. Among the published mappings in the literature, there was one study that had mapped FACIT-Fatigue data to EQ-5D.[93] However, upon further review, it was determined that the mapping could not be done as it required the collection of FACT-G as well

as FACIT-Fatigue data; the former was not collected in the ALXN1210-PNH-301 and ALXN1210-PNH-302 clinical trials.

For the EORTC-QLQ-C30, the Longworth (2014) and McKenzie and van der Pol (2009) mappings were selected for the cost–utility base case and sensitivity analysis, respectively, following an analysis of the literature.[86, 94] Longworth (2014) was published under the HTA programme, as part of the National Institute for Health Research (NIHR); in a recent external validation exercise of the EORTC to EQ-5D mapping algorithms, Doble and Lorgelly (2016) concluded that Longworth (2014), which employed a response-based methodology, was one of two algorithms that performed well on several validation criteria.[95] The other algorithm that was deemed to perform well was an ordinary least-squares regression by Versteegh (2012).[96] Doble and Lorgelly noted that, since Longworth (2014), other studies have reported that the response mapping performed well in new samples. Therefore, the algorithm used in Longworth (2014) was chosen over that of Versteegh (2012) for the base case analysis.[95]

As a sensitivity analysis, it was considered that the linear mappings recommended in Arnold et al. (2015) (another review of mappings study) and Doble and Lorgelly (2016)[95] should be tested.[97] These linear mappings included McKenzie and van der Pol (2009)[94] and Versteegh et al. (2012).[96] McKenzie and van der Pol (2009) estimates a linear model based on the UK EQ-5D-3L value set of Dolan (1997), while Versteegh et al. (2012) estimates were based on the Dutch EQ-5D-3L value set of Lamers et al. (2005).[98, 99] Consequently, the McKenzie and van der Pol (2009) linear model was used in a sensitivity analysis.

The mapping methodology used is detailed in Appendix R.

Regression analyses

For each visit at which EORTC QLQ-C30 data were collected in the ALXN1210-PNH-301 and ALXN1210-PNH-302 clinical trials, EQ-5D-based utility values were estimated using the mapping methods described above. Data from the randomized-treatment periods in the clinical studies were used in regression analyses, to ensure a balanced sample (i.e. to ensure that variations over time could be assessed in both treatment arms).

Regression analysis was then performed to estimate input values for the model, for each clinical study. See Appendix R for a description of the regression specification selection, which yielded the base ordinary least-squares specification:

$$y_{it} = \alpha + \beta_1 BTH_{it} + \beta_3 Trans_{it} + \tau_i + \varepsilon_{it}$$

- y_{it} is the mapped EQ-5D-based utility value for individual *i* at visit *t*
- BTH_{it} is an indicator of whether patient *i* experienced a BTH event since their last visit at visit *t*
- $Trans_{it}$ is an indicator of whether patient *i* met the protocol guidelines for transfusion since their last visit at visit *t*
- τ_t is a patient-level linear time trend, reflecting the counts of visits at which the EORTC QLQ-C30 was assessed (taking values 1–6)

Standard errors were clustered at the patient level.

After the specification selection was performed, ordinary least-squares and mixed-effects models were estimated based on the selected specification. The mixed-effects models were found to have a preferable fit to the underlying data. Finally, a model pooling data from ALXN1210-PNH-301 and ALXN1210-PNH-302 was estimated. The impact of parameters from these variations of the regression models was tested in sensitivity analyses.

Table 26 and Table 27 present the results of these regression models for Longworth et al. (2014) for study ALXN1210-PNH-301 and ALXN1210-PNH-302, respectively.[86, 94]. The results of these regression models for McKenzie et al. (2009) for ALXN1210-PNH-301 and ALXN1210-PNH-302 are in Appendix R.

Table 26: Longworth mapping, mixed-effects specification, study ALXN1210-PNH-301

Covariate	Coefficient	Standard error	z	P>|z|	[95% CI]	
BTH indicator	-0.1143	0.0376	-3.0400	0.0020	-0.1881	-0.0406
Transfusion indicator	-0.0678	0.0131	-5.1700	0.0000	-0.0935	-0.0421
Individual-level linear trend	0.0212	0.0015	14.3000	0.0000	0.0183	0.0241
Constant	0.7592	0.081	93.3500	0.0000	0.7432	0.7751
Notes: BTH, breakthrough-haemolysis event experienced since last visit; individual-level linear trend, time trend (number of visits); transfusion, protocol guidelines for transfusion met since last visit.						

Table 27: Longworth mapping, mixed-effects specification, Study ALXN1210-PNH-302

Covariate	Coefficient	Standard error	z	P>|z|	[95% CI]	
BTH indicator	-0.1828	0.0490	-3.7300	0.0000	-0.2789	-0.0868
Transfusion indicator	-0.0716	0.0189	-3.7800	0.0000	-0.1087	-0.0345
Individual-level linear trend	0.0028	0.0012	2.2800	0.0230	0.0004	0.0052
Constant	0.8471	0.0098	86.5700	0.0000	0.8280	0.8633
Key: CI, confidence interval. **Notes:** BTH, breakthrough-haemolysis event experienced since last visit; individual-level linear trend, time trend (number of visits); transfusion, protocol guidelines for transfusion met since last visit.						

In the base case analysis, different utility values were used for the Cohort 1 and Cohort 2/3 populations (i.e. by study). However, considering the limited number of BTH observations in each clinical study, the pooled data set was tested in the scenario analysis. The results of this were found to be very similar to those of the regression models split by study, suggesting a minimal difference in HRQL between ALXN1210-PNH-301 and ALXN1210-PNH-302. This is reported in Appendix R.

Furthermore, the McKenzie and van der Pol (2009) mapping algorithm was also tested in a scenario and resulted in slightly reduced utilities for both study arms and an increased BTH decrement for ALXN1210-PNH-302. This is reported in Appendix R.

B.3.4.3. Health-related quality of life associated with treatment administration

In addition to the HRQL data derived from ALXN1210-PNH-301 and ALXN1210-PNH-302, an additional utility increment was applied to account for the fact that the relative treatment-related burden of eculizumab and ravulizumab was not captured due to the trial protocols used (as discussed in Section B.1.3.3).

A discrete choice experiment (DCE) was developed to understand the value that people place on differences in treatment administration and consisted of a survey of 507 participants who were broadly representative of UK demographics in terms of age, gender, ethnicity and geography. Of these, 122 failed a simple consistency check in the DCE and so were not included in the final analysis. The aim of the final analysis was to evaluate the relative importance of treatment attributes to the respondents and to establish their willingness to trade attributes against each other. The attributes for inclusion in the DCE survey were identified from a review of the regulatory approvals for eculizumab and based on discussion between clinical experts; the attributes included:

- Reduction in life expectancy (in years)
- Treatment administration

- Risk of infection (e.g. Meningitis)
- Experience of haemolysis
- Need for blood transfusion

Discrete choice data were analyzed using the mixed effects logit regression model, which accounts for preference heterogeneity between respondents. Marginal rates of substitution (MRS) were obtained by taking a ratio of the coefficients for two attributes. MRS represents how individuals trade between attributes. MRS indicates the extent to which participants are willing to forego a unit of one attribute in order to gain a unit in a different attribute. The MRS estimates were then used to estimate utilities for changes in treatment profiles.

The DCE estimated a disutility value of 0.057 for the treatment administration attribute, which compared the 2 weeks dosing schedule of eculizumab with the 8 weeks dosing schedule of ravulizumab, taking into account the longer duration of infusion for ravulizumab.[72] This was applied in the model base case as an annual utility increment of 0.057 for the ravulizumab arm. Note, however, the infusion time of the new 100 mg/mL formulation of ravulizumab is expected to approximate the infusion time of eculizumab, therefore the above utility increment from the DCE may underestimate the HRQL difference.

Previous appraisals were identified that also applied a utility adjustment to account for preferences of different treatment administration modes and frequencies. For example, in a previous NICE highly specialised technology (HST) submission (HST4: migalastat in Fabry disease), an infusion-related utility decrement of -0.025, based on a DCE, was accepted in the base case analysis. This was applied to account for patients' preferences for oral therapy (as opposed to the frequency of dosing schedule). It was argued that patient and clinical experts deemed oral administration of migalastat to be a major advantage of this treatment; the committee agreed that this could result in greater health benefits, albeit with high levels of uncertainty regarding the value used.[100]

Additionally, a treatment frequency and administration related disutility of -0.024 was accepted in a previous NICE STA submission (TA606: lanadelumab in hereditary angioedema) based on the literature. This was applied to account for a patient's preference towards reduced frequency (every 2 to 4 weeks versus twice weekly) and mode of administration (subcutaneous vs intravenous).[101, 102]

Taken together, although neither of the approaches used in HST4 or TA606 align precisely with the dosing regimens of interest (every 8 weeks for ravulizumab and every 2 weeks for eculizumab) estimated in the DCE study, both appraisals support a positive utility difference observed with reduced administration burden.

To test the robustness of the results to a range of different utility increment values, values of 0, 0.025 and 0.05 were tested in the scenario analysis.

B.3.4.4. Health-related quality-of-life studies

A systematic search for published HRQL studies data in PNH was run alongside the searches for economic evaluation and cost and healthcare resource identification, measurement and valuation data noted in Sections B.3.1 and B.3.5. Full details of the HRQL data SLR are presented in Appendix H. From the identified relevant studies, the most frequently reported HRQL-related feature was fatigue.

- Ten studies used the self-reported FACIT-Fatigue questionnaire to assess patients' level of fatigue
- Another measure used to assess fatigue in addition to the FACIT-Fatigue questionnaire was the fatigue symptom scale of the EORTC-QLQ-C30 questionnaire, which was reported in five studies.

A full description of these studies is outlined in Appendix H.

While the information available in these studies provides a good level of information on the change in HRQL for patients receiving eculizumab in the longer term, these data cannot be mapped to utilities using the information

reported in the publications and the data are less relevant than the information from the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials.

Furthermore, of the five cost-effectiveness studies reviewed that reported utility values, aside from the studies by O'Connell et al. (which reported on the same model as our submitted model), none provided utility information for the health states relevant to this analysis.

B.3.4.5. Adverse reactions

As discussed in Section B.2.10, ravulizumab was well tolerated in patients with PNH and the profile and types of AEs reported in the ALXN1210-PNH-301 and ALXN1210-PNH-302 clinical trials were similar in the eculizumab and ravulizumab arms. AEs were not modelled due to the very small numbers (both ravulizumab and eculizumab are generally well tolerated) and similar safety profiles of ravulizumab and eculizumab.

B.3.4.6. Health-related quality-of-life data used in the cost-effectiveness analysis

Table 28 summarizes the inputs used to calculate the utility values applied in the base case cost-effectiveness analysis.

Table 28: Base case analysis inputs for health-utility estimates

Inputs to health-utility estimates		
Input	**Base case value**	**Source**
Constant (annual) (i.e. eculizumab baseline utility)	Study ALXN1210-PNH-301: 0.82 Study ALXN1210-PNH-302: 0.86	Analysis of clinical trials EORTC-QLQ-C30 data (using Longworth mapping algorithm to EQ-5D) Sensitivity: McKenzie mapping, pooled patient population
Utility increment due to reduction in infusions (annual), (ravulizumab versus eculizumab)	Both studies ALXN1210-PNH-301 and ALXN1210-PNH-302: 0.057	Lloyd et al. (2019).[72]

Inputs to health-utility estimates		
Input	**Base case value**	**Source**
BTH utility decrement (annual)	ALXN1210-PNH-301: -0.11 ALXN1210-PNH-302: -0.18	Analysis of clinical trials EORTC-QLQ-C30 data (using Longworth mapping algorithm to EQ-5D) Sensitivity: McKenzie mapping, pooled patient populations
Transfusion utility decrement (annual)	ALXN1210-PNH-301: -0.07 ALXN1210-PNH-302: -0.07	Analysis of clinical trials EORTC-QLQ-C30 data (using Longworth mapping to EQ-5D) Sensitivity: McKenzie mapping, pooled patient population
Key: BTH, breakthrough haemolysis; EORTC-QLQ-C-30, European Organisation for Research and Treatment of Cancer Quality of Life.		

Of note, the utility decrement applied to the BTH health states (CAC and incomplete C5 inhibition-related BTH) was scaled for the number of days that a BTH event is expected to last, out of 14 days in a model cycle. As detailed in Section B.3.3.1 , it was assumed that the HRQL impact of a CAC-related BTH event would be incurred for the full cycle (14 days), while it was assumed that incomplete C5 inhibition-related BTH symptoms would last for 2 days in the 14 day cycle.

Up-dosing was assumed to offset the utility decrement due to BTH. Consistent with clinical practice in England, up-dosing is only done following the second incomplete C5 inhibition-related BTH event. Therefore, the scaled utility decrement was applied for the first incomplete C5 inhibition-related BTH event but not the second (at which point the patient is up-dosed).

The health utility of patients experiencing spontaneous remission (only included in the scenario analysis) was assumed to be the maximum utility in the ravulizumab arm (no BTH) across studies, with no transfusion utility decrement applied.

To maintain face validity, general population utility values were used to cap the patient utility values, ensuring that these did not exceed the age- and gender-matched population norms. This was done by first, capping the highest utility value (i.e. the spontaneous remission health state utility value). The necessary percentage reduction that was used to cap the highest utility value was calculated, and this was applied to all other health states. This was conducted to retain the clinically important differences between the health states. Additionally, adjustments to utility over time were applied, following the assumption that utility declines in PNH patients with age, in line with general population trends. The regression analysis reported by Ara and Brazier was used to inform this.[103]

The resulting estimates of health utility, by modelled health state, are reflected in Table 29.

Table 29: Summary of utility values for the base case analysis

Health state	Intervention		Justification
	Eculizumab	Ravulizumab†	
Cohort 1			
No BTH	0.79	0.85	Study ALXN1210-PNH-301 EORTC-QLQ-C30 data (using Longworth algorithm mapping to EQ-5D) data, inclusion of a utility increment due to reduction in infusions (ravulizumab only) and general population utility cap.[66, 72, 86, 103].
BTH, CAC-related BTH decrement	0.66	0.73	
BTH, incomplete C5 inhibition-related BTH decrement	0.76	N/A	
BTH, *subsequent incomplete C5 inhibition-related BTH decrement	0.78	N/A	
Spontaneous remission	0.88	0.88	
Cohort 2 and 3			
No BTH	0.82	0.87	Study ALXN1210-PNH-302 EORTC-QLQ-C30 data (using Longworth algorithm mapping to EQ-5D) data, inclusion of a utility increment due to
BTH, CAC-related BTH decrement	0.62	0.70	
BTH, incomplete C5 inhibition-related BTH decrement	0.77	N/A	

BTH, *subsequent incomplete C5 inhibition-related BTH decrement	0.79	N/A	reduction in infusions (ravulizumab only) and a general population utility cap.[68, 72, 86, 103].
Spontaneous remission	0.87	0.87	
Key: BTH, breakthrough haemolysis; CAC, complement-amplifying condition; EORTC-QLQ-C-30, European Organisation for Research and Treatment of Cancer Quality of Life. **Note**: * In the base case, up-dosing after the second incomplete C5 inhibition-related BTH event offsets the BTH symptoms. The utility decrement for transfusion requirement was still applied. † The difference in utility is primarily driven by the utility increment derived from the DCE, due to reduction in infusions, See B.3.4.3 for details.			

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

A systematic search for published cost and healthcare resource identification, measurement and valuation data in PNH was run alongside the searches for economic evaluation and HRQL data noted in Sections B.3.1 and B.3.4.4. The review did not identify studies that were relevant for inclusion in the cost-effectiveness model; however, one study that met the inclusion criteria highlighted the high resource use and costs associated with treating PNH. The findings of the review are further detailed in Appendix I.

The following sections outline the costs and resource use inputs used in the base case analysis or equal effectiveness scenario, based on the efficacy inputs being modelled for each analysis (summarized in Table 21).

Table 30 provides an upfront summary to help distinguish which inputs are relevant to which analysis (base case analysis or equal effectiveness scenario). As discussed in Section B.3.2, the equal effectiveness scenario only considered direct drug-related costs (i.e. only the costs that would be incurred with drug treatment), while the base case analysis includes a more comprehensive range of cost inputs.

Table 30: Differences in cost/resource use inputs modelled for the base case analysis and *equal effectiveness scenario*

Model input	***Base case analysis***	***Equal effectiveness scenario***
Drug acquisition and administration costs	Included	Included – these are direct drug-related costs
Meningococcal vaccine cost	Included	
Prophylactic antibiotics	Included	
Transfusion costs	Included	Not included
BTH event costs	All CAC-related BTH and incomplete C5 inhibition costs included	Only the cost of an additional dose of eculizumab was included after a CAC-related BTH event
Other costs (consultant-led haematology follow-up)	Included	Not included
Key: BTH, break-through haemolysis; CAC, complement amplifying condition.		

B.3.5.1. Intervention and comparators' costs and resource use

A list price for ravulizumab of £4,533 per 300 mg vial has been approved by the Department of Health and Social Care. As outlined in Section B.1.2, regulatory review of two new vial sizes (3 mL and 11 mL) containing 100 mg/mL of ravulizumab is also ongoing with marketing authorization expected to extend to these vial sizes by [redacted]

- £4,533 for 3 mL vial (100 mg/mL)
- £16,621 for 11 mL vial (100 mg/mL)

It is the 100 mg/mL formulation that has been used in the model base case analysis as this formulation is expected to be approved by the time of the first appraisal committee meeting. A scenario has been modelled whereby the currently licensed 10 mg/mL formulation is used.

A PAS price of [redacted] per 300 mg ravulizumab (representing a discount of [redacted]% on the list price) has been submitted to reduce [redacted]

[redacted]

The cost of eculizumab was sourced from the Monthly Index of Medical Specialities (MIMS). Pack costs for ravulizumab and eculizumab are presented in Table 31.

Table 31: Drug unit size, pack size, and pack cost

Treatment	Unit size	Pack size	Cost per pack	Source
Ravulizumab	300 mg	1	List price: £4,533 PAS price: [redacted]	Alexion, data on file
	1,100 mg	1	List price: £16,621 PAS price: [redacted]	Alexion, data on file
Eculizumab	300 mg	1	£3,150	MIMS[104]
Key: MIMs, Monthly Index of Medical Specialities; PAS, patient access scheme.				

Costing of ravulizumab

For ravulizumab, dosing is weight based and different doses are given by weight band (≥100 kg, ≥60 kg to <100 kg, and ≥40 kg to <60 kg). The proportion of patients within each weight band was estimated using age- and gender-specific weights that were derived from the 'NHS Health Survey for England 2017: Adult health tables', detailed in Appendix M.[105] These data was preferred over the data from the clinical trials as the trials had a high proportion of Asian patients and therefore were considered less generalisable. As all patients from the survey fell within the ≥60 kg to <100 kg band, only this is presented in Table 32.

For ravulizumab, the recommended dosing regimen for adult patients (18 years and older) consists of an initial loading dose followed by maintenance doses. Maintenance doses are administered every 8 weeks, starting 2 weeks after the initial loading dose.

Table 32: Ravulizumab dosing schedule by weight

Patient body weight	Loading phase	Maintenance phase	Maintenance dosing frequency
≥60 kg to <100 kg	2,700 mg	3,300 mg	Every 8 weeks

The annual cost of ravulizumab was then calculated. This was done by calculating the number of vials required for the initial loading dose and maintenance phase. Given the dosing frequency for the maintenance phase, the number of doses required each year was calculated and multiplied by the number of vials required per dose, to give the number of vials required annually. In the first year, patients receive the loading dose at Week 0, and commence the maintenance dose at Week 2; this is then given every 8 weeks, which equates to seven doses in the first year of treatment. In subsequent years, the number of doses per year alternates between six and seven; for simplicity, 6.5 doses are presented in the calculations in Table 33.

Table 33: Ravulizumab annual cost calculations by weight

Patient body weight	Loading phase: dose	Maintenance phase: annual dose	Annual cost (first year)	Annual cost (subsequent years)
≥60 kg to <100 kg	9 x 300 mg	First year: 11 x 300 mg X 7 Subsequent years: 11 x 300 mg X 6.5	List: £389,838 PAS: [redacted]	List: £324,110 PAS: [redacted]
Key: PAS, patient access scheme. **Note:** [redacted]				

Costing of eculizumab

For eculizumab, the dosing regimen for adult patients consists of a 4-week initial phase followed by a maintenance phase. In the initial phase, 600 mg of eculizumab is given intravenously every week for the first 4 weeks. In the maintenance phase, 900 mg of eculizumab is administered every 2 weeks starting at Week 5, with higher doses used if patients continue to experience incomplete C5 inhibition-related BTH.

As for ravulizumab, the number of doses required each year was calculated and multiplied by the number of vials required per dose. The annual number of doses required in the first year was calculated by subtracting 4 weeks from the number of weeks per year (52) and dividing by 2 (dosing frequency of maintenance phase), resulting in 24 doses. In subsequent years, the 4-week duration is not subtracted (as the initial phase doses are only given in the first year), resulting in 26 doses.

Given that patients may receive a higher-than-licensed eculizumab dose, the annual cost for a 900 mg or 1200 mg maintenance dose is presented in Table 34. In the treatment-experienced cohorts (Cohort 2 and 3), it was assumed that these patients would not require the initial phase doses, given that they are continuing treatment on eculizumab; therefore, the first-year costs are equal to the subsequent year costs. This assumption was not applied to the ravulizumab arm because treatment-experienced patients would switch from eculizumab and thus a ravulizumab loading dose will still be required.

Note that the distribution between the two doses will change over time as patients require an up-dose if an incomplete C5 inhibition event-related BTH or CAC-related BTH event is experienced.

If patients receive an eculizumab dose of greater than 1200 mg, this is covered by Alexion and is therefore not costed in the model – as such, only 900 mg and 1200 mg doses are included.

Table 34: Eculizumab annual cost calculations

Loading phase: dose received	Maintenance phase: dose received	Maintenance phase: annual dose	Annual cost (first year)[a]	Annual cost (subsequent years)
2 x 4 x 300 mg	900 mg	First year: 3 x 300 mg vials for 24 doses Subsequent years: 3 x 300 mg vials for 26 doses	£252,000	£245,700

Not applicable	1200 mg or over	4 x 300 mg vials for 26 doses	£327,600	£327,600
Note: [a] Cohort 2 and 3 do not require a loading dose (as these are patients continuing treatment on eculizumab), therefore, first year costs are equal to subsequent year costs for these patients.				

Costing of spontaneous remission

Patients achieving spontaneous remission discontinue complement inhibitor therapy, and therefore no drug cost is applied.

B.3.5.2. Administration costs

Ravulizumab and eculizumab are both administered via intravenous infusion. NHS England is only responsible for the infusion costs associated with the first loading dose and first maintenance dose of eculizumab, and the loading dose and first maintenance dose of ravulizumab. Thereafter, patients receive infusions at home through the homecare infusion service funded by Alexion. As such, these NHS-administered infusion costs are the only administration costs included in the model. As detailed in Table 35, however, clinical practice is changing such that the first maintenance dose is also being administered at home.

For the cost of administration, before receipt of the homecare service, the cost per hour of Band 7 pharmacist specialist time (£57) and Band 6 nurse specialist time (£113) was derived from the Personal Social Services Research Unit (PSSRU).[106]

The duration of administration (for both the loading dose and maintenance dose) are derived from the summary of product characteristics (SPCs), as presented in Table 35. Where a range was given, e.g. a 25–45-minute infusion, the mid-point was used. The cost of nurse time was applied over these durations, with an additional 1-hour observation time included.

As discussed in Section B.2.11, marketing authorization of two new vial sizes (3 mL and 11 mL) containing 100 mg/mL of ravulizumab, is expected at the [redacted] The increased drug concentration in these new vial sizes

reduces the infusion times for ravulizumab. With the new vial sizes, the minimum infusion time ranges from 25–45 minutes for the loading dose and 30–55 minutes for maintenance doses, bringing infusion times for ravulizumab generally in line with those of eculizumab.[71] The administration time for each infusion of ravulizumab 100 mg/ml (infused at a 50 mg/ml concentration) is therefore expected to be reduced to approximately the same administration time as each infusion of eculizumab.

The costs of administration are summarized in Table 35.

Table 35: Administration costs by the duration of infusion

	Ravulizumab		Eculizumab	
	Duration	**Cost**	**Duration**	**Cost**
Loading dose	35 minutes + 15 minutes pharmacist time	£193.17	35 minutes + 15 minutes pharmacist time	£193.17
Maintenance dose	35 minutes + 15 minutes pharmacist time	£193.17	35 minutes + 15 minutes pharmacist time	£193.17

For the model scenario whereby the currently licensed 10 mg/mL formulation is used, the following infusion durations were assumed:

- Loading dose: 110 minutes nurse time + 30 minutes pharmacist time
- Maintenance dose: 130 minutes nurse time + 30 minutes pharmacist time

B.3.5.3. Health-state unit costs and resource use

PNH disease management is largely driven by the occurrence of BTH. As discussed in Section B.1.3.3, patients experiencing BTH may have an increased risk of catastrophic thromboembolic events and other debilitating PNH-related symptoms, resulting in greater healthcare resource utilization.

To overcome the lack of applicable resource use derived from the SLR, a survey was developed to estimate inputs relating to rates and causes of BTH and medical management for BTH.[25, 39] The survey was administered in the context of an Advisory Board meeting, to 10 clinicians who were experts in the treatment of PNH with both eculizumab and ravulizumab.

In summary, the questions raised in the survey were regarding the following themes:

- The applicability of stratifying resource use relating to CAC-related BTH events by pregnancy and non-pregnancy related events
- Comparability of BTH rates between clinical trials and clinical practice
- Diagnosis of a BTH event
- Causes of BTH events
- Dose changes due to BTH events
- Resource use required, by BTH type

Regarding resource use, experts were asked to estimate the proportion of patients requiring the resource and average duration of resource for four categories: general ward hospitalization, intensive care unit (ICU) hospitalization, medication and dialysis. The responses to this question were incorporated into the model; while variance was noted across clinical expert responses, the average values have been used (see Table 37).

The disease management costs and estimated resource use are discussed in turn below, and a summary of the modelled health state costs is provided in Table 39.

Please note, all disease management costs presented in this section were set to £0 for the equal effectiveness scenario.

Transfusion costs

PNH patients who have significant haemolysis may require blood transfusions to alleviate signs and symptoms of anaemia where clinically indicated (i.e. in patients with a decrease in haemoglobin level, increased dyspnoea or extreme fatigue).The economic model allows for the specification of packed red blood cell transfusion requirements, by treatment arm and presence of incomplete C5 inhibition-related or CAC-related BTH event.

The probabilities of requiring a transfusion in each 2-week cycle, as well as the mean number of units of red blood cells required, were calculated based on patient-level data from ALXN1210-PNH-301 and ALXN1210-PNH-302;

therefore, the estimates from the survey described above in Section B.3.5.3 were not used. However, as discussed in Appendix P these were comparable to the trial data.

The cost of transfusion administration and the cost of packed red blood cells are presented in Table 36. These costs, alongside the transfusion probabilities and mean number of units of red blood cells required were used to calculate the per-cycle transfusion costs in each treatment arm.

Table 36: Red blood cell transfusion unit costs

Resource	Unit cost	Source
Red blood cell transfusion administration	£49.00	Stokes et al. 2018
Packed red blood cells	£128.99	NHS blood and transplant price list; code: BC001[107]

BTH event costs

PNH patients can experience BTH events throughout complement-inhibitor treatment. This can occur as a result of incomplete C5 inhibition or in patients with CACs (CAC-related BTH). BTH is associated with a risk of catastrophic thromboembolic events and various other symptoms such as haemoglobinuria, dysphagia, abdominal pain and fatigue. Such symptoms require additional patient monitoring and treatment, i.e. transfusions, resulting in higher resource use and associated costs.

Based on the expert survey element of the cost analysis of breakthrough haemolysis[39] discussed previously, the resource use associated with a BTH event is presented in Table 37.

Table 37: Resource use associated with BTH

	BTH due to incomplete C5 inhibition		BTH due to CAC	
	First event*	Subsequent event*	First event*	Subsequent event*
Hospital stays				
General ward (days)	15%/1	15%/1	23%/3	23%/3

	BTH due to incomplete C5 inhibition		BTH due to CAC	
	First event*	**Subsequent event***	**First event***	**Subsequent event***
Intensive care (days)	1%/1	1%/1	1%/1	1%/1
Dialysis				
Dialysis (days)	4%/7	4%/7	4%/7	4%/7
Key: BTH, breakthrough haemolysis; CAC, complement-amplifying condition. **Notes:** *Frequency of management strategy (%) / number of units used per treated episode.				

The costs associated with each resource item used to manage a BTH event are discussed in turn below.

Hospital stay costs

Dependent on the severity of the patient's symptoms, hospitalization in the general ward or the ICU may be required.

The costs associated with hospital stay were derived from NHS reference costs. Specifically, the cost of a general ward day for patients with incomplete C5 inhibition-related or CAC-related BTH was assumed to be equal to a per-day cost for haemolytic anaemia.[108] A cost of £554.59 was derived using an average of the non-elective short stay costs for haemolytic anaemia with complication and comorbidity (CC) Score 3+ and haemolytic anaemia with CC Score 0–2 (currency codes SA03G and SA03H, respectively), divided by the respective average length of stay. This is summarized in Appendix S.

The cost of an ICU hospitalization was calculated as the weighted average of healthcare resource groups for non-specific, general adult critical care, as summarized in Appendix S. The calculated weighted average ICU cost per day used in the model was £1,504.47.

Dialysis

The costs of haemodialysis and peritoneal dialysis were included in the model to account for reduced renal function. As discussed in Section B.1.3.2, one of the most common complications associated with haemolysis is renal failure.

Dialysis is used to manage reduced renal function/renal failure and was, therefore accounted for in the model.

NHS reference costs were used to estimate a cost of £134.82 per dialysis, using the renal code.[108] Specifically, all currency descriptions for haemodialysis and peritoneal dialysis in adults (19 years and over) were used to derive the unit costs and number of sessions. This is presented in Appendix S.

Consultant-led haematology follow-up

Follow-up visits with a consultant were also costed in the model and applied to all patients. The costs for this were derived from the NHS reference costs and were assumed to be equal to the cost of a 'non-admitted face-to-face attendance, follow-up' for clinical haematology.[108] This is presented in Table 38.

Table 38: Clinical haematology follow-up attendance

Currency code	Currency description	Unit cost
WF01C	Non-admitted face-to-face attendance, follow-up	£110.61

It was assumed that the follow-up would be required twice per year, resulting in a cost per cycle of £8.48. This was assumed to be the same for both eculizumab and ravulizumab, as suggested by a clinical expert at the December Advisory Board Meeting.[25]

Summary of health state costs applied in the model

Table 39 presents the per cycle (2-weekly) costs associated with each health state applied to each cohort, taking into account the unit costs and resource use described above.

Table 39: List of health states and associated costs in the model

Health states	Items	Value	
No BTH	Haematology specialist visit	£8.48	
	Transfusion - Cohort 1; Ravulizumab| Eculizumab	£14.00	£20.61

Health states	Items	Value	
	Transfusion – Cohort 2 & 3; Ravulizumab| Eculizumab	£5.46	£4.59
CAC-related BTH	General ward admission	£364.00	
	Intensive care admission	£14.67	
	Dialysis	£37.41	
	Haematology specialist visit	£164.80	
	Transfusion - Cohort 1; Ravulizumab| Eculizumab	£40.41	£85.64
	Transfusion – Cohort 2 and 3; Ravulizumab| Eculizumab	N/A	£131.24
Incomplete C5 inhibition-related BTH	General ward admission	£79.13	
	Intensive care admission	£14.67	
	Dialysis	£37.41	
	Haematology specialist visit	£164.80	
	Transfusion - Cohort 1; Ravulizumab| Eculizumab	£40.41	£85.64
	Transfusion – Cohort 2 and 3; Ravulizumab‡| Eculizumab	N/A	£131.24
History of Incomplete C5 inhibition-related BTH, No BTH	Haematology specialist visit	£12.63	
	Transfusion - Cohort 1; Ravulizumab| Eculizumab	£14.00	£20.61
	Transfusion – Cohort 2 and 3; Ravulizumab| Eculizumab	£5.46	£4.59
Subsequent Incomplete C5 inhibition-related BTH	General ward admission	£79.13	
	Intensive care admission	£14.67	
	Dialysis	£37.41	
	Haematology specialist visit	£164.80	
	Transfusion - Cohort 1; Ravulizumab| Eculizumab	£40.41	£85.64
	Transfusion – Cohort 2 and 3; Ravulizumab‡| Eculizumab	N/A	£131.24
History of incomplete C5 inhibition-related BTH, CAC-related BTH	General ward admission	£364.00	
	Intensive care admission	£14.67	
	Dialysis	£37.41	
	Haematology specialist visit	£164.80	
	Transfusion - Cohort 1; Ravulizumab| Eculizumab	£40.41	£85.64

Health states	Items	Value	
	Transfusion – Cohort 2 and 3; Ravulizumab‡| Eculizumab	N/A	£131.24
History of incomplete C5 inhibition-related BTH, Cont. up-dose	Haematology specialist visit	£12.63	
	Transfusion - Cohort 1; Ravulizumab| Eculizumab	£14.00	£20.61
	Transfusion – Cohort 2 and 3; Ravulizumab| Eculizumab	£5.46	£4.59
Cont. up-dose, CAC-related BTH	General ward admission	£364.00	
	Intensive care admission	£14.67	
	Dialysis	£37.41	
	Haematology specialist visit	£164.80	
	Transfusion - Cohort 1; Ravulizumab| Eculizumab	£40.41	£85.64
	Transfusion – Cohort 2 and 3; Ravulizumab‡| Eculizumab	N/A	£131.24
Spontaneous remission	Haematology specialist visit	£12.63	

Key: BTH, breakthrough haemolysis; CAC, complement-amplifying condition; Cont, continuous.
Note: * Health state costs relevant to the equal effectiveness scenario; ‡ no BTH events were observed in the ravulizumab arm of ALXN1210-PNH-302, therefore no transfusion costs were estimated for Cohort 2 and Cohort 3.

B.3.5.4. Adverse reaction unit costs and resource use

As detailed in Section B.3.3.4, AEs, and therefore associated costs, were not included in this analysis due to the similarity in the AE profiles of ravulizumab and eculizumab.

B.3.5.5. Miscellaneous unit costs and resource use

As discussed in Section B.2.10.3, the most important risk associated with C5 complement inhibition is increased susceptibility to infections caused by *Neisseria meningitidis*. To reduce the risk of infection, all patients must be vaccinated against meningococcal infections and receive additional prophylactic antibiotics, the costs of which are detailed below. These costs were applied in both the base case analysis and equal efficacy scenario.

Meningococcal vaccine cost

Complement-inhibitor therapy may increase the risk of meningococcal infection. To minimize this risk, patients must be vaccinated at least 2 weeks before receiving eculizumab or ravulizumab.

Costs and dosing for the two necessary vaccines, MenACWY and MenB, were derived from information from Hampstead Health Pharmacy.[109] Additionally, the PNH National service in Leeds recommends that a booster vaccination of MenACWY is given every 5 years for patients receiving complement-inhibitor treatment.[110] Given that no specific advice was identified for MenB, the same was assumed.

Table 40: Meningococcal vaccination cost and dose frequency

	Cost per dose	Number of doses required	Source	Frequency of booster doses	Source
MenACWY vaccine	£60	1	Hampstead Health Pharmacy	Every 5 years	PNH Service Leeds[110]
MenB vaccine	£115	2		Every 5 years (1 dose only)	PNH Service Leeds[110]

Key: PNH, paroxysmal nocturnal haemoglobinuria.
Note: As the vaccination history is assumed unknown for treatment experienced patients, a booster vaccine is given at the start of model for Cohorts 2 and 3 and thereafter every 5 years.

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

Prophylactic antibiotics

Prophylactic antibiotics, specifically penicillin, are required in all treated patients, while on treatment. The drug cost was derived from the drugs and pharmaceutical electronic market information tool (eMIT).[111] Multiple price options were presented at differing doses; therefore, it was assumed that the pack providing the cheapest cost per mg would be used.

Table 41: Penicillin cost per pack

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

It was assumed that prophylactic penicillin would 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.3.6. Summary of base-case analysis inputs and assumptions

Summary of base-case analysis inputs

A summary of the inputs used in the base case are summarized in Appendix T, including references to the corresponding sections in the submission where each is explained in more detail.

Summary of key model assumptions

Table 42 details the key assumptions used in the economic model and provides a justification for each one, as well as the references to the corresponding sections in the submission where each is explained in more detail.

Table 42: Summary of assumptions applied in the cost-effectiveness analysis

Category	Base case analysis assumptions	Equal effectiveness scenario	Justification/Impact	Reference in submission
Time horizon	Lifetime		A lifetime horizon was used to capture all differences in costs and outcomes for all patients.	B.3.2.6
Population	Patients start on the licensed dose of eculizumab in line with the clinical trial. Up-dosing to clinically stable eculizumab dose was modelled.	Patients who were treated with the licensed dose of 900 mg and who were on a higher-than-licensed dose of eculizumab were included from the model start.	In the base case analysis, dosing was reflective of the ALXN1210-PNH-301 and ALXN1210-PNH-302 populations. Following two incomplete C5 inhibition-related BTH events, continuous up-dosing was modelled. In the equal effectiveness scenario base case, the dosing distribution used was derived from information provided by the PNH National service, reflective of English clinical practice.	B.3.2.1
CAC-related BTH events	BTH events reported as having 'undetermined' cause in ALXN1210-PNH-301 and ALXN1210-PNH-302[66, 68] were assumed to represent CAC-related BTH events.		This was based on internal Alexion expert clinical opinion. Please see Section B.3.2.6 for detailed justification.	B.3.2.6

Category	Base case analysis assumptions	Equal effectiveness scenario	Justification/Impact	Reference in submission
	CAC-related BTH events that occurred in ALXN1210-PNH-301 and ALXN1210-PNH-302 and the transfusions associated with these were modelled per trial. CAC-related BTH events were treated with single up-dosing.	CAC-related BTH events were assumed to be the same in the eculizumab and ravulizumab arms. CAC-related BTH events were treated with single up-dosing.	In the base case analysis, given that the population is the same as the populations from the trials, the observed events from the trials were also used. In the equal effectiveness scenario, non-inferiority was assumed when all eculizumab patients would be on a clinically stable dose; hence, events were assumed to be equal between arms, as per the ravulizumab arm. In line with a clinical opinion, the model assumes one single up-dose would be required in the eculizumab arm to re-establish blockade.[36] Where a CAC-related BTH event occurs in the ravulizumab arm, no data are currently available on the effectiveness or safety of the up-dosing of ravulizumab; thus, there is no informed clinical rationale for giving ravulizumab, so clinicians suggested that instead eculizumab would be given.[25]	B.3.2.6

Category	Base case analysis assumptions	Equal effectiveness scenario	Justification/Impact	Reference in submission
	The probability of CAC-related BTH remains constant throughout the model time horizon.		Given that CAC-related BTH events occur as a result of a CAC such as pregnancy or infection, this was not dependent on the prior health state.	
Incomplete C5 inhibition-related BTH events	Incomplete C5 inhibition-related BTH events that occurred in ALXN1210-PNH-301 and ALXN1210-PNH-302 were modelled. Where an incomplete C5 inhibition-related BTH event occurs, it was assumed that the duration of symptoms would be 2 days out of a 14-day cycle. Incomplete C5 inhibition-related BTH events were treated with continuous up-dosing.	Incomplete C5 inhibition-related BTH events were not modelled/assumed to be zero.	In the base case analysis, given that the population was the same as the populations from the trials, the observed events from the trials were also used. In the equal effectiveness scenario base case, for all patients in the eculizumab arm, English dosing data were used – and not the licensed dose (900 mg) given in the pivotal trials. It was therefore assumed that patients do not experience incomplete C5 inhibition. The assumed duration of an incomplete C5 inhibition-related BTH event was based on findings from the literature (based on Brodsky, 2014 and Kelly, 2008)[89, 90] and was varied in the sensitivity analysis.	B.3.2.6

Category	Base case analysis assumptions	Equal effectiveness scenario	Justification/Impact	Reference in submission
Mortality	There was no excess mortality risk associated with PNH or BTH events – only background mortality was modelled.		Eculizumab has transformed the outlook for PNH patients, significantly reducing progressive morbidity and aligning the life expectancy of patients to that of the general population.[16, 20, 23, 26-32] Ravulizumab has demonstrated non-inferiority to eculizumab and is expected to provide the same impact. The impact of increased mortality due to PNH was tested in scenario analysis.	B.3.2.6
Transition probabilities	It was assumed that the treatment effect remains constant over time.		Ravulizumab has demonstrated non-inferiority to eculizumab, which has been shown to provide a long-term treatment effect. The use of constant post-trial event rates was deemed appropriate at the December 2018 Advisory Board Meeting.[25]	Appendix N

Category	Base case analysis assumptions	Equal effectiveness scenario	Justification/Impact	Reference in submission
Adverse events	Adverse events were not included in this analysis.		Adverse event profiles were similar for ravulizumab and eculizumab. Where differences were seen, none of the adverse events experienced in ALXN1210-PNH-301 or ALXN1210-PNH-302 were expected to have an impact on the analysis (on either costs or QALYs) and were therefore not modelled.	B.3.3.4
Costs and resource use	Meningococcal vaccine		All patients in either treatment arm receive a vaccine in the first cycle as per the SPC indications and a follow up booster dose at 5 years as per guidance from the PNH Service Leeds.[110]	B.3.5.5
	Prophylactic antibiotics		All patients in either treatment arm receive prophylactic antibiotics as per the local treatment practice guidance.	B.3.5.5

Category	Base case analysis assumptions	Equal effectiveness scenario	Justification/Impact	Reference in submission
	Administration cost was a one-time cost per treatment, following the first loading and maintenance doses.		At present, 98% of UK patients receive eculizumab via the Alexion-funded homecare service (data on file); this would also be the case for ravulizumab if approved. This service covers the cost of administration, which would therefore not be charged to the NHS.	B.3.5.2
Health-related quality of life	HRQL was linked to the health status: decrements for BTH events and transfusions were applied.	Not included	Covariate selection deemed these to have been a significant impact on HRQL.	B.3.4.2
	Lower treatment burden due to reduced frequency of administration with ravulizumab was accounted for as a utility decrement of 0.057 applied to the eculizumab arm.[72]		The trials did not capture the benefits of the improved dosing schedule of ravulizumab (less frequent administrations). The assumption of applying a utility increment has been used in a previous HST submission[100], and expert clinical opinion deemed this appropriate.[25]	B.3.4.3

Category	Base case analysis assumptions	Equal effectiveness scenario	Justification/Impact	Reference in submission
	Health utility for patients experiencing spontaneous remission was assumed to be the highest utility estimate based on ALXN1210-PNH-301 and ALXN1210-PNH-302 (i.e. omitting any decrements of BTH and transfusions), plus the increment associated with reduced treatment burden.		When in remission, no treatment burden is experienced.	B.3.4.6

Key: BTH, breakthrough haemolysis; CAC, complement-amplifying condition; HRQL, health-related quality of life; HST, highly specialised technology; SPC, summary of product characteristics.

B.3.7. Base case results

B.3.7.1. Base-case cost–utility results

Base-case incremental cost–utility analysis results

As detailed in Section B.3.5, a confidential patient access scheme (PAS) has been approved. This arrangement provides ravulizumab to NHS patients at a [redacted] discount on the list price. Therefore, this PAS has been applied and the results presented reflect this discount.

The key results of the base-case analysis are presented in Table 43. The results demonstrate that ravulizumab is a cost-effective use of NHS resources for adults with PNH who meet the criteria for complement-inhibitor treatment as outlined in the NHS England Paroxysmal Nocturnal Haemoglobinuria Service (Adults and Adolescents) – Service Specification.[24] Not only does ravulizumab result in a QALY gain but it is also a cost-saving treatment relative to eculizumab.

Table 43: Base-case cost utility results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Eculizumab	[redacted]	35.08	[redacted]				
Ravulizumab	[redacted]	35.08	[redacted]	[redacted]	0.00	[redacted]	Dominant
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.							

Markov traces and disaggregated results are presented in Appendix J.

B.3.8. Sensitivity analyses

B.3.8.1. Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was conducted in which all inputs were varied simultaneously over 1,000 iterations, based upon their distributional information. The

results are summarized in Table 44 and are also presented on a cost-effectiveness plane in Figure 15 and cost-effectiveness acceptability curves in Figure 16.

The mean PSA results are consistent with the deterministic analysis and show that ravulizumab is a cost-effective use of NHS resources and provides a large positive net monetary benefit at a willingness-to-pay threshold of £30,000 per QALY. As shown in Figure 15, every PSA iteration indicates that ravulizumab offers an incremental QALY benefit versus eculizumab at a negative incremental cost. Furthermore, as illustrated in Figure 16, the estimated probability that ravulizumab is a cost-effective alternative to eculizumab is 100% at willingness-to-pay thresholds of £20,000 and £30,000 per QALY gained.

Table 44: Mean probabilistic sensitivity analysis results

Technologies	Mean costs	Mean QALYs	Incremental		ICER	NMB[a]
			Mean costs	Mean QALYs		
Eculizumab	[redacted]	[redacted]				
Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.
Notes: [a]£30,000 willingness-to-pay threshold used.

Figure 15: Probabilistic sensitivity analysis cost-effectiveness plane

Key: QALY, quality-adjusted life year.

Figure 16: Probabilistic sensitivity analysis cost-effectiveness acceptability curve

B.3.8.2. Deterministic sensitivity analysis

A series of one-way sensitivity analyses were performed to evaluate the sensitivity of the model ICER to individual inputs, holding all else constant. In the deterministic sensitivity analysis, the upper and lower bounds of a parameter were taken from their 95% confidence intervals if these were available from the data source. When such information was not available, the upper and lower bounds were assumed to be within ±25% for cost values and ±10% of the other base-case values. These are reported in Appendix T.

In this analysis, the net monetary benefit was most sensitive to the probability of an incomplete C5 inhibition in eculizumab patient with no history of incomplete C5 inhibition BTH events, followed by the utility for ravulizumab and eculizumab patients with no history of BTH, the probability of a subsequent incomplete C5 inhibition BTH event in eculizumab patients with a history of incomplete C5 inhibition BTH event and the utility related to transfusion burden for patients on treatment.

Figure 17: Cost-utility analysis – tornado diagram (PAS price)

Key: BTH, break-through haemolysis; CH, cohort; NMB, Net Monetary Benefit; PAS, patient access scheme; Prob., probability; RBC, red blood cells.
Notes: £30,000 willingness to pay threshold used

B.3.8.3. Scenario analysis

The scenario analyses reported here together test the sensitivity of cost-effectiveness results to methodological, parameter and structural uncertainties in the economic analysis, and form an important element of this submission.

A key scenario was the assumption of equal effectiveness of ravulizumab and eculizumab. This analysis is consistent with the non-inferiority trial designs and provides a more conservative viewpoint, given that all endpoints in the trial were numerically in favour of ravulizumab. We report the detailed results of this analysis first in and provide a summary of all other scenarios tested in Section B.3.8.3.

Equal effectiveness scenario

The results of the equal efficacy scenario are presented below in Table 45. At PAS price, ravulizumab is associated with incremental cost savings of [redacted]. The

lower predicted savings estimated in this scenario compared to the base case analysis are largely due to the assumed constant proportion of patients who receive the higher than licensed dose of eculizumab ([redacted]). In the base case analysis, patients can transition into the continuous up-dosing health state at each model cycle, which results in a greater proportion of patients receiving the higher (and thus more costly) eculizumab dose over the total model time horizon.

Table 45: Equal effectiveness scenario results

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

One-way sensitivity analysis was conducted to explore the sensitivity in the equal effectiveness scenario results when one parameter is varied at a time. Each parameter was set to its lower and upper bound, and the deterministic model results were recorded. A summary of the parameters varied in the analysis is presented in Appendix T.

The top ten influential parameters on the incremental costs are presented as a tornado diagram in Figure 18 at the ravulizumab PAS price. These results demonstrate that the equal effectiveness scenario is relatively insensitive to the majority of parameters with CAC events rates and the cost of the initial NHS treatment administrations the only cost drivers, with ravulizumab offering a consistent cost saving and the upper and lower variation for each sampled parameter.

Figure 18: Equal effectiveness scenario – tornado diagram (PAS price)

Key: CAC, complement-amplifying condition; CH, cohort; IncC5Inhib, incomplete C5 inhibition; No. BTH, no breakthrough haemolysis; NoHx, no history; PAS, patient access scheme.
Notes: £30,000 willingness to pay threshold used

All other scenarios

The results of all other scenarios are presented below in Table 46 at the ravulizumab PAS price. The results were relatively insensitive in most of these analyses with ravulizumab remaining cost saving in all. The scenarios that resulted in the largest impact on the results were time horizon, however ravulizumab remained cost-effective even as the time horizon reduced from lifetime to 10 years. Additionally, changes to the discount rate, and the inclusion of different spontaneous remission rates led to changes in the net monetary benefit. Finally, the inclusion of English clinical practice dosing and no incomplete C5 inhibition BTH events led to consistent saving with the equal efficacy scenario, and a dominant ICER and positive net monetary benefit consistent with the base case analysis.

Table 46: Base case analysis: scenario results (PAS price)

Scenario	Base case	Scenario	Incremental costs	Incremental QALYs	ICER	NMB	% change from base case NMB
Base case			[redacted]	[redacted]	Dominant	[redacted]	0.0%
Time horizon	Lifetime	10 years	[redacted]	[redacted]	Dominant	[redacted]	-84.7%
Time horizon	Lifetime	20 years	[redacted]	[redacted]	Dominant	[redacted]	-54.1%
Discount rate (costs and QALYs)	3.50%	0.00%	[redacted]	[redacted]	Dominant	[redacted]	127.2%
Discount rate (costs and QALYs)	3.50%	6.00%	[redacted]	[redacted]	Dominant	[redacted]	-39.4%
Utility increment of ravulizumab vs eculizumab	0.0570	0.000	[redacted]	[redacted]	Dominant	[redacted]	-5.8%
Utility increment of ravulizumab vs eculizumab	0.0570	0.025	[redacted]	[redacted]	Dominant	[redacted]	-3.1%
Utility increment of ravulizumab vs eculizumab	0.0570	0.050	[redacted]	[redacted]	Dominant	[redacted]	-0.7%
EORTC to EQ-5D mapping (value set)	Longworth et al. (2014)	McKenzie and van der Pol. (2009)	[redacted]	[redacted]	Dominant	[redacted]	0.1%
HRQL regression population	Separate	Pooled	[redacted]	[redacted]	Dominant	[redacted]	0.0%
Utility: general population age adjustment	Applied	Not applied	[redacted]	[redacted]	Dominant	[redacted]	0.5%
Utility: general population cap	Applied	Not applied	[redacted]	[redacted]	Dominant	[redacted]	0.3%

Scenario	Base case	Scenario	Incremental costs	Incremental QALYs	ICER	NMB	% change from base case NMB
BTH excess mortality (HR) vs background	1.00	4.81	[redacted]	[redacted]	Dominant	[redacted]	-1.7%
CAC BTH up-dosing	Yes	No	[redacted]	[redacted]	Dominant	[redacted]	-1.1%
Spontaneous remission rate (per cycle)	0.0000	0.0005	[redacted]	[redacted]	Dominant	[redacted]	-24.4%
Spontaneous remission rate (per cycle)	0.0000	0.0006	[redacted]	[redacted]	Dominant	[redacted]	-28.8%
Spontaneous remission rate(per cycle)	0.0000	0.0010	[redacted]	[redacted]	Dominant	[redacted]	-42.1%
Incomplete C5 inhibition BTH duration (days)	2	3	[redacted]	[redacted]	Dominant	[redacted]	0.0%
Incomplete C5 inhibition BTH duration (days)	2	7	[redacted]	[redacted]	Dominant	[redacted]	0.0%
Ravulizumab formulation	100 mg/ml	10 mg/ml	[redacted]	[redacted]	Dominant	[redacted]	-0.1%
Permanent eculizumab up-dosing per clinical practice dose	Licensed dose at model entry	English clinical practice dosing and no incomplete C5 inhibition BTH events	[redacted]	[redacted]	Dominant	[redacted]	-37.5%

Key: BTH, breakthrough haemolysis; CAC, complement-amplifying condition; EORTC, European Organisation for Research and Treatment of Cancer; HR, hazard ratio; HRQL, health-related quality of life; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALY, quality-adjusted life year.

B.3.8.4. Summary of sensitivity analyses results

The results were robust to changes in the parameters and the key model assumptions. The one-way sensitivity analyses highlight that ravulizumab provides a highly positive net monetary benefit even with variations in each parameter. The equal efficacy scenario, considering the non-inferiority design of the trials and NHS England clinical practice, highlights substantial cost savings. The scenario analyses demonstrate that the model is also robust to changes in key modelling assumptions.

B.3.9. Subgroup analysis

Subgroup analysis was not relevant to the decision problem.

B.3.10. Validation

B.3.10.1. Validation of the cost-effectiveness analysis

All of the parameters and assumptions applied in the economic model were validated by three clinicians and one health economics expert at an Advisory Board meeting.[25] Once the model was finalized, internal modellers validated it. A programmer (other than the one who built the model) reviewed all formulae and labelling in the model.

Based on the analysis of patient-level data from ALXN1210-PNH-301 and ALXN1210-PNH-302, across the model time horizon of 20 years patients spend 24.3% of their time in the up-dosed states which broadly aligns with UK experience described below, providing a measure of external validation.

In the UK population of the PNH National service [redacted]% of patients required eculizumab maintenance dosing higher than the labelled 900 mg every 2 weeks to achieve and maintain efficacy.[38] This estimate aligns with a rate of [redacted]% derived from UK data from the International PNH Registry which was tested in a scenario analysis (data on file).

In addition to BTH, the modelled rate of transfusion, derived from the ALXN1210-PNH-301 and ALXN1210-PNH-302 studies, was validated by an external source. In a survey on BTH and medical management strategies administered by Alexion to a group of 10 clinicians who were experts in treating PNH, the experts indicated that patients would likely receive a transfusion in 30–35% of incomplete C5 inhibition-

related BTH events and 15% of CAC-related BTH events. These frequencies closely align with the probabilities derived from the clinical studies.

In the model, survival was assumed to be equal to that of the age- and gender-matched general population. This is supported by studies identified from the literature, the first being a study by Socie et al. whereby survival in 2,356 patients enrolled in the International PNH registry was assessed to determine the prognosis of patients with aplastic anaemia, an underlying bone marrow disorder. Only 16% (n=375) of patients had aplastic anaemia, and of these, 1% (n=26) died of causes related to aplastic anaemia in the follow-up period, showing that patients with a worse prognosis due to an underlying bone marrow disorder make up a small minority of PNH patients. A second study by Kelly et al. reported that in a study of 79 patients in the Leeds, UK patient cohort, despite the presence of bone marrow disorders in a minority of patients, the survival of patients treated with eculizumab was not different from age- and sex-matched normal controls.[28]

The utilities were derived from EQ-5D data mapped from EORTC-QLQ-C30 data collected in the ALXN1210-PNH-301 and ALXN1210-PNH-302 studies. The resulting utilities were compared with utilities reported in a study by Coyle et al., which was identified in the economic SLR.[112] In the study, three utilities were reported based on transfusion requirement; these were:

- Transfusion independent: 0.84
- Reduced transfusion requirement: 0.77
- Transfusion dependent: 0.60

The mapped utilities from the trial data resulted in a baseline utility of 0.82 in ALXN1210-PNH-301 and 0.86 in ALXN1210-PNH-302. A decrement of -0.07 for Study ALXN1210-PNH-301 and ALXN1210-PNH-302 was applied to account for the need for transfusion. This decrement aligns with the difference in the utilities for reduced transfusion requirement and transfusion-independent (-0.07), suggesting the mapped utilities are consistent with previous findings.

Regarding the incremental QALY benefit of ravulizumab that the base case model predicts, this can be compared to the results reported in the O'Connell et al. studies introduced in Section B.3.1, which based their analyses (US and German) on the

same model as our submitted analysis. The incremental QALYs reported were 1.67 and 0.53 in the US and German analyses, respectively. Our submitted base case predicted QALY gains of [redacted]. This direction of change is expected. The use of a smaller utility benefit due to the reduced dosing frequency of ravulizumab is used in the German analysis, as this was published prior to the availability of the DCE results; this largely explains the smaller incremental QALYs observed compared to our base case. In the US analysis (and also in the German analysis), no age-adjustment to the utility values or utility capping has been applied. In addition, the US analysis uses a different mapping algorithm (McKenzie et al.) and includes treatment arm as a covariate in the utility regression, both of which lead to increased incremental QALYs. These findings therefore help support the face validity of our model results.

The health state costs used in the model were based on the results of a survey of 10 clinicians who were experts in the treatment of PNH with both eculizumab and ravulizumab. The results of this survey was also used to inform a separate cost analysis of breakthrough haemolysis in patients with PNH in the US. The analysis estimated that the total annual cost of BTH management was $386 for ravulizumab-treated patients compared to the $3,472 BTH management cost for eculizumab-treated patients, excluding pregnant women[39]; in essence, the BTH management costs for patients treated with ravulizumab were only ~11% of the BTH management costs for patients treated with eculizumab. As reported in Appendix J2, Table 16 (Summary of costs by health state), our submitted analysis shows that the total cost associated with ravulizumab patients entering any one of the breakthrough haemolysis health states is only ~9% of that accrued in the eculizumab arm. This comparison therefore helps to show that the modelled costs are consistent with the direction of change and relative difference across arms reported previously.

B.3.11. Interpretation and conclusions of economic evidence

PNH is a progressive haematological disorder characterized by uncontrolled activation of the terminal complement pathway leading to intravascular haemolysis.[90, 113] Untreated, this uncontrolled haemolysis, which in turn leads to a prothrombotic state, is the underlying cause of progressive morbidity, impaired quality of life, and premature mortality.[16, 80, 90, 114] Introduced in 2007, eculizumab (Soliris®) represented

a step change in managing PNH, however, it is associated with a high treatment administration burden due to its relatively short half-life.[21]

Ravulizumab has demonstrated non-inferiority to eculizumab in two Phase III trials with numerically greater outcomes in both studies. Across the Phase III trial programme for ravulizumab, all patients treated with ravulizumab achieved complete terminal complement inhibition (defined as serum free C5 <0.5 ug/mL) by the end of the first infusion and this was sustained up to Week 52 (no longer term follow-up data available at this time). Ravulizumab also provides to patients and carers a reduced frequency of regular infusions from 26 to 6-7 per year in the treatment maintenance phase (with a similar infusion time, given the new vial sizes).

Ravulizumab is associated with an incremental gain of [redacted] QALYs per patient and cost savings of [redacted] per patient. These results indicate that ravulizumab is a dominant treatment option as it both increases QALYs and lowers costs. In addition, the probability of ravulizumab being a cost-effective treatment option versus eculizumab is 100% at willingness-to-pay thresholds of £20,000 or £30,000 per QALY.

The ICER was largely insensitive to parameters and assumptions tested in one-way sensitivity analyses and scenario analysis, with ravulizumab remaining a cost-saving treatment in all instances. The assumptions implemented in the base-case analysis have been validated by both the clinical trial data and UK clinical expert opinion.

[redacted]

Limitations of the analysis include the fact that the model is primarily based on 52 weeks of clinical trial data as this was the length of observation for which balanced samples were available, note an extension periods of both trials (ALXN1210-PNH-301 and ALXN1210-PNH-302) are ongoing. Further data reporting up to 104 weeks are expected [redacted]. It is therefore difficult to project long-term outcomes, such as the incidence of CAC-related or incomplete C5 inhibition BTH and transfusions required over time. There are, however, long-term data available for eculizumab,

which show that the rate of such events remains reasonably constant over time.[26, 88, 115]

Additionally, given the trial designs, the treatment-related burden of eculizumab compared with ravulizumab was not collected. Therefore, data from a DCE were used instead to derive a utility decrement applied to the eculizumab arm.

In determining the relevant set of outcomes to capture in the model, several sources were consulted. Literature identifying clinical outcomes that remain relevant to patients receiving complement-inhibitor therapy [36, 90, 116] aligned with feedback from clinical experts in PNH received at the July 2018 advisory board meeting. As such, the conceptualization of the decision problem, and resulting model developed, aligns with the treatment of the disease in the UK.

Finally, during the December 2018 advisory board, the management of patients who experience BTH on ravulizumab was discussed. Up-dosing of ravulizumab as a management strategy, as is done with eculizumab, was not captured within the ALXN1210-PNH-301 and ALXN1210-PNH-302 studies; therefore, evidence to support this strategy was needed. The model therefore allows ravulizumab patients experiencing CAC-related BTH to receive one vial of eculizumab in model cycles where CAC-related BTH is experienced. It is not currently known if this would be reflective of clinical practice.

The cost-effectiveness analysis of ravulizumab versus eculizumab for PNH features several strengths, including [redacted], incorporation of patient-level data from the clinical studies, incorporation of UK clinical practice and alignment with external evidence.

There are no additional resource use considerations associated with ravulizumab treatment. Alexion provides a homecare service to patients with PNH to help minimize their treatment burden, and this will be extended to include PNH patients on ravulizumab.

The clinical data from Study ALXN1210-PNH-301 and ALXN1210-PNH-302 and modelled outcomes were found to be broadly consistent with published data sources, emphasizing the external validity of this economic analysis.

Additionally, the availability of English patient data allowed the English patient experience to be reflected in the equal efficacy scenario and considerable consultation was done to gain clinical experience to understand the experiences of patients treated in England with it being possible to talk to the majority of the experts involved given the low number of patients treated each year and concentration of those patients in two main centres, Leeds and London.

The study data from ALXN1210-PNH-301 and ALXN1210-PNH-302 showed all outcomes were in favour of ravulizumab. Alongside the potential benefit ravulizumab may offer to patients on high dose eculizumab treatment subject to positive results of ALXN1210-PNH-401 due in 2022, this submission provides evidence to support the use of ravulizumab in treating PNH in English clinical practice.[76]

Ravulizumab presents savings for NHS England and offers a well-tolerated convenient alternative to eculizumab for treating adults with PNH who meet the criteria for complement-inhibitor treatment as outlined in the NHS England Service Specification for Paroxysmal Nocturnal Haemoglobinuria Service (Adults and Adolescents).[24]

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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: Weight by age

Appendix N: Base case analysis: transition matrices

Appendix O: Equal effectiveness scenario: transition matrices

Appendix P: Identification of transfusion events

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Appendix S: NHS reference costing of resource use

Appendix T: Base case analysis: summary of variables

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ravulizumab for treating paroxysmal nocturnal haemoglobinuria [ID1457]

Clarification questions

ALEXION RESPONSES

October 2020

File name	Version	Contains confidential information	Date
ID1457 ALEXION Responses to ravulizumab clarification questions	**v1.0**	**Yes**	**20 October 2020**

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Literature searching

A1. Please provide full details for the searches of conference proceedings referred to in Appendix D1.1 (page 7) including URLs, search terms and results for each resource.

American Society for Hematology (ASH) abstracts for 2017–2019 were searched via blood journal supplements:

https://ashpublications.org/blood/issue/130/Supplement%201

https://ashpublications.org/blood/issue/132/Supplement%201

https://ashpublications.org/blood/issue/134/Supplement_1

Abstracts were screened under the search term “Red cells and erythropoiesis, structure and function, metabolism, and survival, excluding iron”.

European Hematology Association (EHA) abstracts for 2017–2019 were searches via the EHA open access library:

https://library.ehaweb.org/eha/#!*menu=5*browseby=8*sortby=2*media=6*label=15847

https://library.ehaweb.org/eha/#!*menu=5*browseby=8*sortby=2*media=6*label=18567

https://library.ehaweb.org/eha/#!*menu=5*browseby=8*sortby=2*media=6*label=19379

Abstracts were screened under the search term “paroxysmal nocturnal hemoglobinuria/haemoglobinuria”.

Relevant citations identified through hand-searching of conference proceedings are detailed in Appendix A1/B1.

A2. Please clarify which study design filters were used for clinical effectiveness searches and, if possible, provide a reference to the filters.

Study design filters for clinical effectiveness were applied using the InterTASC Information Specialists' Sub-Group (ISSG) Search Filter Resource as a reference:

https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home/search-filters-by-design

A3. Please report the database date spans for clinical effectiveness searches of Medline, Embase and Cochrane Library (Table 1).

The database date spans for the clinical effectiveness searches were as follows:

Medline: 1946 to 2020

Embase: 1974 to 2020

Cochrane Library: 2005 to 2020

A4. Please provide justification for the restriction to English language studies.

We acknowledge that restriction to English language studies could introduce bias in evaluating treatment effects; however, given the level of collaboration across the international medical community in PNH, particularly with the International PNH Registry, we expect that the majority of relevant studies for inclusion in this SLR are in English.

Clinical effectiveness

A5. Priority question: In document B (page 68) it states: "The lack of 'up-dosing' in the pivotal clinical trial programme compared with clinical practice may also result in slightly worse clinical outcomes for patients in the eculizumab arm of ALXN1210-PNH-301 and ALXN1210-PNH-302." Given that

eculizumab was not administered in either of the trials according to UK clinical practice i.e. with an up-dose, could the company please:

a) **Justify why eculizumab administered at a dose that would be observed in UK clinical practice might not be more effective than ravulizumab.**

UK clinical practice demonstrates that the majority of PNH patients (~ [redacted]%) are managed at the standard dose of eculizumab as per the marketing authorisation, i.e. 900mg every 2 weeks.{PNH National Service, 2019 #994} This is also the dosing schedule that was applied in the pivotal clinical trial programme comparing ravulizumab with eculizumab. However, approximately [redacted]% of UK PNH patients require an eculizumab dosing adjustment to achieve complete terminal complement inhibition and prevent the symptoms of their PNH and accompanying haemolysis to recur.{PNH National Service, 2019 #994} In some patients this was historically achieved by reducing the eculizumab dosing interval from 14 days to 12 days[1], whereas now the dose is adjusted incrementally until the optimal dose for a specific patient is reached. Terminal complement inhibition is usually controlled with 1200mg dosing, although a small proportion may require 1500mg or 1800mg per infusion.

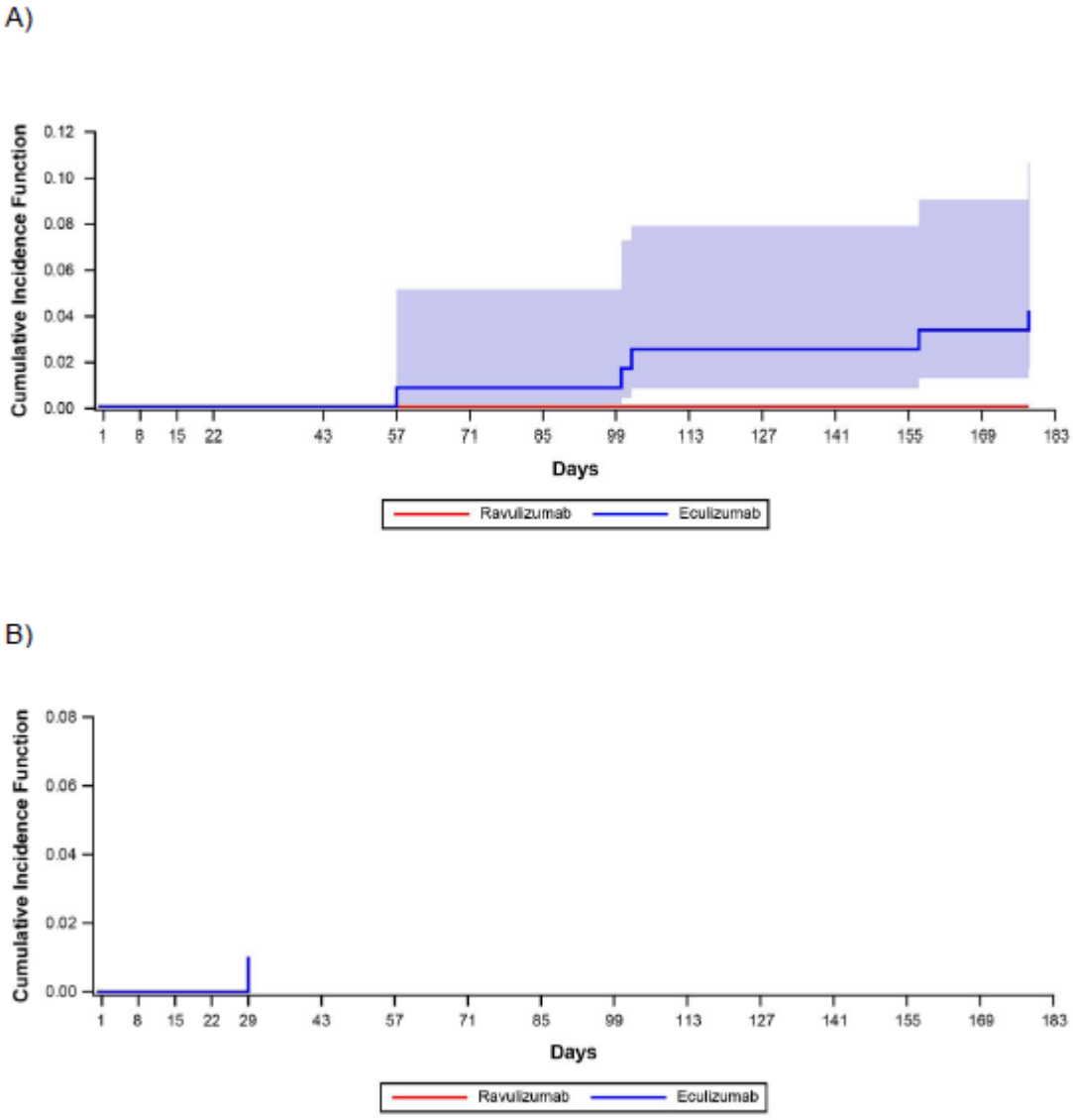
Therefore, eculizumab administered at higher doses than the standard dose would not be more effective than ravulizumab, but would likely prevent the breakthrough haemolysis due to incomplete C5 inhibition events observed in the eculizumab arm of the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials.

It should be noted that while up-dosing of eculizumab was not permitted in the clinical trials, the patients in the ALXN1210-PNH-302 study had been clinically stable for more than 6 months on standard dose eculizumab, which therefore represented the optimised dose of eculizumab for these patients at study entry, thus allowing for a true comparison of ravulizumab and eculizumab.

The mean free C5 concentration over time in the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials are provided in the company submission (see Figures 8, 11, 12 and 13). These data show incomplete terminal complement inhibition (defined as serum free C5 ≥ 0.5 ug/mL) with eculizumab 900 mg every 2 weeks, versus complete terminal complement inhibition (defined as serum free C5 < 0.5 ug/mL) with ravulizumab weight-based dosing every 8 weeks.

Details of breakthrough haemolysis events in the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials are also provided in the company submission (see Section B.2.6.1 and B.2.6.2). The data for the randomized period of the trials show 7 patients in the eculizumab arm of ALXN1210-PNH-301 and 4 patients in the eculizumab arm of ALXN1210-PNH-302 experienced breakthrough haemolysis events due to incomplete C5 inhibition, compared to 0 patients in the ravulizumab arm of each trial (see **Table 1**). The time to first event of breakthrough haemolysis due to incomplete C5 inhibition is depicted in **Figure 1**.

Figure 1: Time to first event of breakthrough haemolysis due to incomplete C5 inhibition in (A) ALXN1210-PNH-301 and (B) ALXN1210-PNH-302



Notes: adjustment for competing risk of complement-amplifying conditions or undetermined causality included.
Source: Brodsky et al. 2020.[2]

If the ‘up-dosing’ practice had been permitted in the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials, the magnitude of mean free C5 concentration variability and breakthrough haemolysis events due to incomplete C5 inhibition would likely have been reduced as patients would have quickly been given additional or increased eculizumab dosing to restore complete terminal complement inhibition. This is acknowledged in the company submission and addressed in the economic analyses with equivalent effectiveness for breakthrough haemolysis due to incomplete C5 inhibition modelled when dosing of eculizumab is adopted as per UK clinical practice; that is, no breakthrough haemolysis due to incomplete C5 inhibition for eculizumab or ravulizumab.

b) Provide additional evidence of the effectiveness of eculizumab at a dose at or closer to one that would be observed in UK clinical practice.

There are no published data that provide an overview of the effectiveness of the current practice of up-dosing of eculizumab as currently observed in the UK and there are no clinical trials underway that will provide these data.

One UK study has been published that evaluated the long term safety and efficacy of the 900mg maintenance dose of eculizumab in 11 patients with PNH during an open-label 52 week extension trial. [1] The study included 2 patients who did not sustain levels of eculizumab necessary to consistently block complement across all 14 days of the dosing interval, and experienced serum haemolytic activity on days 13 and 14 after dosing; a pattern that was repeated between multiple doses.

Adjustment of the eculizumab dosing interval in these two patients from every 14 days to every 12 days successfully sustained eculizumab at sufficient levels to consistently blocked serum haemolytic activity for the remainder of the study. The effective and consistent blockade of complement achieved with the 12 day dosing interval was supported by the resolution of symptoms, including haemoglobinuria and dysphagia, and lower levels of LDH and AST.

This paper supports ongoing clinical practice in the UK where the majority are stable at the labelled dose but approximately [redacted]% require a dose adjustment for complete terminal complement blockade.{PNH National Service, 2019 #994}

A6. The numbers of patients experiencing breakthrough haemolysis are low in both arms of both studies. Is there any data on the presence or absence of compliment amplifying conditions (CAC) in these patients?

Breakthrough haemolysis events for the Randomized Period of the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials are summarized in **Table 1**.

These data show that 4/5 events in the ravulizumab arm and 4/15 events in the eculizumab arm of the ALXN1210-PNH-301 trial were temporally associated with complement-amplifying conditions (CAC), all infections. Concomitant infection was also observed in 2/7 events with free C5 elevation in the eculizumab arm of the ALXN1210-PNH-301 trial. In the ALXN1210-PNH-302 trial, 2/7 events in the eculizumab arm were temporally associated with CAC (infections) and concomitant infection was observed in 1/4 events with free C5 elevation.

Table 1: Incidence of breakthrough haemolysis and overall temporal association in ALXN1210-PNH-301 and ALXN1210-PNH-302: Randomized Period

	ALXN1210-PNH-301		ALXN1210-PNH-302	
	Ravulizumab (n=125)	Eculizumab (n=121)	Ravulizumab (n=97)	Eculizumab (n=98)
Patients with BTH, n (%)	5 (4.0)	13 (10.7)	0	5 (5.1)
BTH events, n	5	15	0	7
BTH events with free C5 elevation (≥ 0.5 ug/mL), n	0	7[a]	0	4[b]
BTH events with infection (and no free C5 elevation), n	4	4	0	2
BTH events unrelated to free C5 elevation or infection, n	1	4	0	1

Key: BTH, breakthrough haemolysis.
Notes: [a], two patients with free C5 elevation also had concomitant infection; [b], one patient with free C5 elevation also had concomitant infection.
Source: Brodsky et al. 2020.[2]

Breakthrough haemolysis events for the Extension Period of the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials are summarized in **Table 2**.

These data show that 1/4 events in the ravulizumab-ravulizumab arm and 1/2 events in the eculizumab-ravulizumab arm of the ALXN1210-PNH-301 trial were temporally associated with CAC, both infections. In the ALXN1210-PNH-302 trial, 2/3 events in the ravulizumab-ravulizumab arm and 1/1 event in the eculizumab-ravulizumab arm were temporally associated with CAC (infections). The patient experiencing

breakthrough haemolysis with infection in the eculizumab-ravulizumab arm had also experienced breakthrough haemolysis with infection in the randomized treatment period while receiving eculizumab.

Table 2: Incidence of breakthrough haemolysis and overall temporal association in ALXN1210-PNH-301 and ALXN1210-PNH-302: Extension Period

	ALXN1210-PNH-301		ALXN1210-PNH-302	
	Ravulizumab-ravulizumab (n=124)	Eculizumab-ravulizumab (n=119)	Ravulizumab-ravulizumab (n=96)	Eculizumab-ravulizumab (n=95)
Patients with BTH, n (%)	4 (3.2)	2 (1.7)	3 (3.1)	1 (1.1)
BTH events, n	4	2	3	1
BTH events with free C5 elevation (≥ 0.5 ug/mL), n	0	0	0	0
BTH events with infection (and no free C5 elevation), n	1	1	2	1[a]
BTH events unrelated to free C5 elevation or infection, n	3	1	1	0

Key: BTH, breakthrough haemolysis.
Notes: [a], this patient also experience BTH with infection during the randomized treatment period.
Source: Kulasekararaj et al. 2019.[3]; Schrezenmeier et al. 2019.[4]

For more detail on breakthrough haemolysis events observed in the Randomized Period of the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials, please see patient narratives provided in Appendix A6.

A7. Given the importance of the clinical consequences of breakthrough haemolysis, is there any data on the rates of MAVE/thrombolytic events during the extension phase of the included studies?

[redacted] in the ravulizumab-ravulizumab arm and [redacted] in the eculizumab-ravulizumab arm experienced a major adverse vascular event (MAVE) during the Extension Period of the ALXN1210-PNH-301 trial ([redacted]).{Alexion Pharmaceuticals, 2018 #310} [redacted] in the ravulizumab-ravulizumab arm and [redacted] in the eculizumab-ravulizumab arm experienced a MAVE during the Extension Period of the ALXN1210-PNH-302 trial ([redacted]).{Alexion Pharmaceuticals, 2018 #311}

A8. Given the emphasis placed on the ability of ravulizumab treatment to achieve complete complement inhibition (compared with eculizumab), please provide evidence that breakthrough haemolysis events associated with elevated free C5 (at

the frequency and severity seen in patients treated with eculizumab) are associated with increases in adverse clinical outcomes (MAVE/thrombolytic events).

The tight relationship between complement blockade, haemolysis and symptoms in PNH was demonstrated by Anita Hill and Peter Hillmen (Department of Haematology, Leeds Teaching Hospitals NHS Trust) in an open label extension trial of 11 PNH patients.[1] Here, breakthrough patients experienced paroxysms evidenced by severe haemoglobinuria, dysphagia and significant increases in LDH and AST levels that correlated with insufficient levels of eculizumab (PK) and the return of serum haemolytic activity (PD).

It is well recorded in the literature that inhibiting terminal complement, will relieve the symptoms and complications of PNH, including breakthrough haemolysis and MAVE/ thrombotic events:

Brodsky has characterized the breakthrough haemolysis events observed in the two largest international phase 3 clinical studies conducted to date in PNH patients (ALXN-PNH 301 and 302) and noted that a breakthrough haemolysis event represents loss of disease control, is manifested by classical PNH symptoms and can necessitate blood transfusion, but more critically can be associated with the morbidity associated with PNH, including potentially life-threatening thromboembolic events.[2] He concluded that weight-based dosing of ravulizumab administered every 8 weeks was associated with numerically fewer episodes of breakthrough haemolysis versus eculizumab administered 900mg every 2 weeks over 26 weeks of complement inhibitor therapy in PNH patients with high disease activity, He also concluded that the observed differences in breakthrough haemolysis rates for ravulizumab versus eculizumab may be attributable to the ability of ravulizumab to completely inhibit free C5 over the entire 8-week dosing interval.

Further evidence that breakthrough haemolysis events associated with elevated free C5 are associated with clinical outcomes can be found in:

- Hill et al. Thrombosis in paroxysmal nocturnal hemoglobinuria. Blood. 2013;121(25):4985-4996.[5]

- Lee et al. Clinical signs and symptoms associated with increased risk for thrombosis in patients with paroxysmal nocturnal hemoglobinuria from a Korean Registry. Int J Hematol. 2013;97(6):749-757.[6]

- Yenerel et al. Clinical course and disease burden in patients with paroxysmal nocturnal hemoglobinuria by hemolytic status. Blood Cells Mol Dis. 2017;65:29-34.[7]

It is evident from UK clinical practice, that the National PNH Service team take considerable precautions in avoiding any breakthrough haemolysis event by the actions of additional doses of treatment during conditions that may amplify complement activity, such as infections, surgery and pregnancy. This practice appears to highlight their concern through experience of thrombosis or acute renal failure during times of breakthrough haemolysis in patients with PNH so all measures are taken to avoid these events (personal communication, Dr Anita Hill, MBChB (Hons), PhD, MRCP, FRCPath).

A9. Section B.2.12 of the company submission (Innovation) includes the statement: "Ravulizumab provides immediate, complete and sustained terminal complement inhibition across an 8-week dosing interval: alleviating the risk of breakthrough haemolysis due to incomplete C5 inhibition observed with eculizumab, and reducing the frequency of regular infusions to 6–7 per year in the treatment maintenance phase, compared with the 26 needed for effective eculizumab treatment." Please provide a source/reference for this statement.

Source/references for this statement are the pivotal trial data for ravulizumab (ALXN1210-PNH-301 and ALXN1210-PNH-302) that clearly show immediate, complete and sustained terminal complement inhibition with the 8-week dosing interval and no breakthrough haemolysis events due to incomplete C5 inhibition.[8, 9]

The frequency of regular infusions data are based on the recommended dosing for ravulizumab and eculizumab as per their respective summary of product characteristics: eculizumab dosing is every 2 weeks in the maintenance treatment

phase, equating to 26 infusions per year and ravulizumab dosing is every 8 weeks in the maintenance treatment phase, equating to 6–7 infusions per year.[10, 11]

A10. Section B.2.13.2 (generalizability of the included trials to UK clinical practice) includes the statement: “Although there are some differences in baseline LDH levels, transfusion history and a history of MAVE or aplastic anaemia (all generally higher in the UK population), these are likely due to differences in the management pathway at the time of study initiation/registry enrolment. There are no clear clinical indications that the clinical characteristics of patients enrolled in ALXN1210-PNH-301 and ALXN1210-PNH-302 are not generalizable to UK patients.” The acknowledged differences appear to indicate more severe disease in the UK treated population. Please provide evidence to support the assertion that the trial data are generalisable to UK clinical practice.

Eligibility for entry into the clinical trial programme was purely based on the inclusion and exclusion criteria set out in the protocol, and UK patients contributed the largest single country cohort in the ALXN-PNH-302 study.

The differences are not indicative of more severe disease in one population than another, hence why we conclude there are no clear clinical indications that the characteristics of patients enrolled are not generalizable to UK patients. For example, although there are more patients with a history of MAVE in the UK treated population compared to the ravulizumab trial populations; there are more patients with transfusion within the last 12 months in the ravulizumab trial populations compared to the UK treated population.

More recent data for UK patients ever treated are provided in the response to A16, alongside the previously reported data. For the characteristic of history of MAVE, there are [redacted] additional patients included in the more recent data set of which [redacted] patients had a history of MAVE (data on file); this proportion is much more closely aligned with the proportion of patients with a history of MAVE enrolled to ALXN1210-PNH-301 ([redacted]% vs 17.1%), supporting the suspicion that some differences are due to the time periods over which patients presented and evolutions in the management pathway over this time.

A11. Please provide a list of excluded studies for the systematic literature review.

Please see Appendix A11 for a list of excluded studies for the clinical review.

A12. Are both of the included trials representative of clinical practice in the UK, given the higher doses of eculizumab used (pages 67 and 68 of the company submission)?

Please see the company submission for full discussion of how the included trials reflect and differ from clinical practice in the UK. It is acknowledged that the 'up-dosing' practice adopted in the UK was not adopted in the clinical trials and the potential impact of this is fully detailed and addressed in the economic analyses with equivalent effectiveness for breakthrough haemolysis due to incomplete C5 inhibition modelled when dosing of eculizumab is adopted as per UK clinical practice.

Please also note that approximately [redacted]% of the UK population are receiving the standard recommended dose of eculizumab 900 mg every 2 weeks in clinical practice{PNH National Service, 2019 #994}, in line with the clinical trial dosing schedule, and thus the 'higher doses of eculizumab used' is only for a minority of patients.

A13. What were the doses of eculizumab used amongst participants in ALXN1210-PNH-302?

As per the inclusion criteria (see Table 5 of the company submission), patients enrolled to ALXN1210-PNH-302 were treated with eculizumab according to the labelled dosing recommendation for PNH for at least 6 months i.e. they were receiving eculizumab 900 mg every 2 weeks at enrolment.

A14. Please provide a full list of the countries across which the 2 included trials were conducted.

Please see Table 3 for the final list of the countries and number of sites per country across which the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials were conducted. In total, there were 126 sites across 25 countries for ALXN1210-PNH-301 and 49 sites across 11 countries for ALXN1210-PNH-302 (please note summary data for ALXN1210-PNH-302 presented in Table 5 of the company submission was screened rather than final sites).

Table 3: Locations of trial sites for ALXN1210-PNH-301 and ALXN1210-PNH-302

	Country	Number of sites
ALXN1210-PNH-301	Argentina	3
	Australia	1
	Austria	2
	Belgium	2
	Brazil	5
	Canada	2
	Czechia	2
	Estonia	1
	France	6
	Germany	2
	Italy	5
	Japan	25
	Korea	18
	Malaysia	11
	Mexico	1
	Poland	2
	Russia	18
	Singapore	1
	Spain	3
	Sweden	1
	Taiwan	6
	Thailand	3
	Turkey	1
	UK	2
	USA	3
ALXN1210-PNH-302	Australia	5
	Canada	3
	France	6
	Germany	3
	Italy	5
	Japan	5
	Korea	9
	Netherlands	2
	Spain	3
	UK	3
	USA	5

A15. Please provide the full list of approved concomitant medication used in both of the included trials.

As noted in Table 5 of the company submission, any concomitant medication deemed necessary for the patient's standard of care, or for the treatment of any AE, was given at the discretion of the investigator. Concomitant medications used by ≥5% of patients during the Randomized Period of ALXN1210-PNH-301 and ALXN1210-PNH-302 are provided in Appendix A15.

A16. Is there more recent data from the International PNH Registry regarding the UK patients ever treated (as presented in Table 16 of the company submission - up to 8 July 2019)? Could this please be made available?

More recent data (up to 29 June 2020) for UK patients ever treated are presented alongside the original data presented in Table 4 (for characteristics that more recent data were available).

Table 4: Characteristics of UK patients enrolled in the International PNH Registry up to 8 July 2019 versus up to 29 June 2020

	July 2019 data (n=[redacted])	**June 2020 data (n=[redacted])**
Male, n (%)	[redacted]	[redacted]
Race, n (%) Asian White/Caucasian Black/African Other/Unknown	[redacted]	[redacted]
Age at diagnosis Mean years (SD)	[redacted]	[redacted]
LDH Mean U/L (SD)[a]	[redacted]	[redacted]
LDH ratio, n (%)[a] < 1.5 ≥ 1.5 x ULN	[redacted]	[redacted]
pRBC units received within 1 year of study entry or RBC transfusions, n (%) 0 ≥ 1	[redacted]	[redacted]
History of MAVE, n (%)	[redacted]	[redacted]
History of aplastic anaemia (or hypoplastic anaemia in registry), n (%)	[redacted]	[redacted]

Key: GPI, glycophosphatidylinositol; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal haemoglobinuria; pRBC, packed red blood cell; RBC, red blood cell; SD, standard deviation.
Notes: [a], Normal range defined as 120–246 U/L.

Section B: Clarification on cost-effectiveness data

Literature searching

B1. Please provide full details for the searches of conference proceedings referred to in Appendix G.1.1 (page 38) including URLs, search terms and results for each resource.

Please see the response to A1 for full details of the conference proceedings searches and Appendix A1/B1 for results of conference proceedings searches.

B2. Please provide details of the search strategy, date span and results for EconLit (EBSCO) which is listed as a resource searched in Appendix G.1.1 (page 37)

A search for “paroxysmal nocturnal hemoglobinuria” yielded no results in EconLit (accessed via EBSCO). This search was initially run on 3 February 2020 and then again on 2 July 2020. No date restrictions were applied to the search so the date span was equivalent to the coverage of the EconLit database (1969 to present).

B3. Please clarify which filters were used for cost-effectiveness searches and, if possible, provide a reference to the filters.

Study design filters for cost-effectiveness were applied using the InterTASC ISSG Search Filter Resource as a reference:

https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home/search-filters-by-design

B4. Please report the database date spans for Medline, Embase and Cochrane Library searches for economics, HRQL and resource use outcomes (Table 8).

The database date spans for the economic, HRQL and resource use outcome searches were as follows:

Medline: 1946 to 2020

Embase: 1974 to 2020

Cochrane Library: 2005 to 2020

Model structure and implementation

B5. Priority question. In document B (pages 79 and 80) it is mentioned that "a recently published case study has confirmed that a patient on twice the standard eculizumab dose was switched to ravulizumab treatment with no loss of disease control.[75] The patient experienced no breakthrough haemolysis events following switch to ravulizumab, as observed in 52-week data from ALXN1210-PNH-301, in which no patient switching to ravulizumab from eculizumab at 26 weeks experienced an incomplete C5 inhibition-related BTH event while on ravulizumab (including those who experienced an incomplete BTH event while on eculizumab). This provides evidence that patients who experience BTH on eculizumab due to incomplete C5 inhibition (i.e. those who require a higher dose of eculizumab) will not experience BTH due to incomplete C5 inhibition on ravulizumab. We have therefore assumed that when patients are treated with the labelled dose of ravulizumab, patients do not experience incomplete C5 inhibition-related BTH. We have also assumed that patients who receive a higher dose of eculizumab in clinical practice do not experience incomplete C5 inhibition-related BTH when on ravulizumab".

a) **Please clarify whether the 2 above-mentioned assumptions were based on evidence obtained from a single patient in the above-mentioned case study.**

The two above-mentioned assumptions are based on the following sources of evidence: (1) the 26-week data from the ravulizumab arm of ALXN1210-PNH-301 and ALXN1210-PNH-302 (2) the 52-week data from ALXN1210-PNH-301 and ALXN1210-PNH-302 and (4) the recently published case study (Füreder et al. 2020).

To clarify, the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials enrolled complement-inhibitor naïve and complement-inhibitor stable patients, respectively. Both trials consisted of a 26-week Randomized Period in which patients were treated with eculizumab or ravulizumab at their labelled dose. At the end of the 26 week Randomized Period, all patients were invited to enter an Extension Period where they would either continue to receive ravulizumab or switch from eculizumab to

ravulizumab (dependent on their randomized treatment group). Data are currently available for up to 52 weeks of ravulizumab or eculizumab–ravulizumab treatment.

Of the patients who received ravulizumab treatment throughout the 52-week treatment period in both ALXN1210-PNH-301 (n=124) and ALXN1210-PNH-302 (n=96), all achieved complete terminal complement inhibition (defined as serum free C5 < 0.5 ug/mL) and no patients experienced BTH due to incomplete C5 inhibition. These data are provided in the company submission (see Section B.2.6.1 and B.2.6.2) and further clarified in responses to clarification questions A5 and A6 earlier in this document. The trial data therefore provide direct evidence to support the assumption that when patients are treated with the labelled dose of ravulizumab, patients do not experience incomplete C5 inhibition-related BTH.

The ALXN1210-PNH-301 and ALXN1210-PNH-302 trial data also show that patients who switch from eculizumab to ravulizumab achieve complete terminal complement inhibition and do not experience incomplete C5 inhibition-related BTH. Please see the response to B5b for further details on incomplete C5 inhibition-related BTH events for these ‘switch’ patients. The mean free C5 concentration of patients both prior to and following the switch to ravulizumab in the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials are provided in the company submission (see Figures 12 and 13). These data show complete terminal complement inhibition with ravulizumab for all patients initially treated with eculizumab. This includes some patients who had not achieved complete terminal complement inhibition with standard dose eculizumab in the Randomized Period. In UK clinical practice, these patients would be up-dosed to a higher-than-standard eculizumab dose. These data serve to support the second assumption.

As acknowledged in our company submission (Section B.2.13.2), there is an evidence gap from the clinical trials conducted to date in terms of the efficacy and safety of switching patients currently receiving eculizumab ≥ 1,200 mg to ravulizumab. However, there is no clinical rationale as to why these patients would respond differently to the patients who switch from standard dose eculizumab, and therefore we assume they would achieve complete terminal complement inhibition and do not experience incomplete C5 inhibition-related BTH, as observed across the relevant periods of the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials. The

recently published case study (of one patient) by Füreder et al. supports this assumption, recording that a patient, who was on twice the standard eculizumab dose, experienced no loss of disease control and no BTH events following a switch to ravulizumab treatment.[13] The case study is by no means, however, our primary source of evidence. The primary evidence comes from the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials, which are the two largest RCTs conducted in the PNH patient population to date.

b) Please indicate how many patients switched to ravulizumab from eculizumab at 26 weeks without experiencing an incomplete C5 inhibition-related BTH event while on ravulizumab.

As reported in the company submission and further detailed in the response to clarification question A6, the ALXN1210-PNH-301 Extension Period data show that, of the patients who switched from eculizumab to ravulizumab at 26 weeks (n=119), only two patients experienced a BTH event; neither of these events was associated with elevated free C5 levels. For comparison, the number of BTH events associated with elevated free C5 levels experienced by patients receiving eculizumab during the Randomized Period (n=121) was seven.

Similar findings were observed in the ALXN1210-PNH-302 trial. Patients initially randomized to ravulizumab and patients who switched from eculizumab to ravulizumab at Week 26 achieved complete terminal complement inhibition by the end of the first infusion of ravulizumab and this was sustained through Week 52. No patients experienced a BTH event associated with elevated free C5 levels while receiving ravulizumab treatment. For comparison, the number of BTH events associated with elevated free C5 levels experienced by patients receiving eculizumab during the Randomized Period (n=98) was four.

c) Please test the 2 above-mentioned assumptions in scenario analyses.

As discussed during the ERG clarification call, it was agreed that with the responses provided above, scenario analyses to test these assumptions are not required.

d) Based on the 2 above-mentioned assumptions, some of the ravulizumab transition probabilities are equal to 1 (or 0). In order to assess the

uncertainty associated with these assumptions, please allow these transition probabilities to vary in the PSA (i.e. not fixed to 1 or 0).

The only transitions which are 0 (or 1) in the model are those relating to the probability of an incomplete C5 inhibition-related BTH event in patients with a history of an incomplete C5 BTH events in the ravulizumab arm of both trials. The transition to an incomplete C5 BTH event for those with no history of previous incomplete C5 BTH events is not zero in the model (despite 0 events being observed in the trial). This is because the transition is calculated from a full-information maximum-likelihood multinomial logit model fitted to the data pooled across ravulizumab and eculizumab where ravulizumab is included as a covariate (see NICE Document B Section 3.3.1 of the submission for further details).

There is no available information to support the transitions requested, as there were no observed incomplete C5 inhibition BTH events in the ravulizumab arm of either the ALXN1210-PNH-301 or ALXN1210-PNH-302 trials. Therefore, as suggested on the clarification call a Bayesian prior was used to create a theoretical transition. As detailed in Briggs et al, 2003, a minimally informative prior distribution is used.[14] No information is available to inform this prior distribution, therefore 1 is added to both the number of patients in the trial and the event in question.

For the purpose of the PSA an option is added in the updated model to use a prior distribution, see the “Inputs” sheet under BTH events

B6. Priority question. In document B (page 75) it is mentioned that the “analysis modelled the observed clinical trial outcomes while also incorporating English clinical practice dosing; this assumed that after two incomplete C5 inhibition events, patients would be treated with eculizumab at a continuously higher dose than the licensed dose”. Please answer the following questions:

a) **Please clarify whether changing the dose of eculizumab (to reflect clinical practice) would affect the clinical effectiveness as observed in the trial.**

Changing the dose of eculizumab to reflect UK up-dosing clinical practice would be expected to affect the clinical effectiveness as observed in the trial, allowing more

patients in the eculizumab arm to achieve complete and sustained inhibition of terminal complement and thereby avoid associated BTH events.

b) If the answer to a) is "yes", please indicate to what extent changing the dose of eculizumab would affect the clinical effectiveness as observed in the trial.

As detailed in our response to clarification question A5 a), had the 'up-dosing' practice been permitted in the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials, the magnitude of mean free C5 concentration variability and BTH events in the eculizumab arm due to incomplete C5 inhibition are likely to have been reduced, that is, patients would have quickly been given additional or increased eculizumab dose to restore complete terminal complement inhibition.

This would not be expected to impact on the conclusion of the clinical trial (non-inferiority criteria met) as no patients in the ravulizumab arm of either trial experienced BTH due to incomplete C5 inhibition.

Of note, 'up-dosing' is only necessary in [redacted] of the population, based on data provided by the PNH National Service; the majority of patients achieve adequate terminal complement inhibition on the licensed eculizumab dose (900 mg).[12]

c) If the answer to a) is "yes", please explain in which cohorts of patients changing the dose of eculizumab would affect the clinical effectiveness as observed in the trial.

Changing the dose of eculizumab would alter the clinical effectiveness in the 11 eculizumab arm patients who experienced incomplete C5 inhibition related BTH events across the clinical trials; 7 patients in ALXN1210-PNH-301 and 4 patients in ALXN1210-PNH-302.

d) If the answer to any of the previous questions is "yes", please explain whether these changes in clinical effectiveness are captured in the current analyses.

Yes, the pharmacoeconomic analyses presented in the submission both capture the UK clinical practice of up-dosing and the consequent effects on clinical effectiveness.

The cost-utility analysis accounts for changes in clinical effectiveness due to eculizumab 'up-dosing' by assuming that once patients are permanently 'up-dosed' on eculizumab, they no longer experience BTH events due to incomplete C5 inhibition.

This is further addressed in the equivalent effectiveness scenario which assumes that incomplete C5 inhibition-related BTH events in the eculizumab arm are equal to those observed for ravulizumab when dosing of eculizumab is adopted as per UK clinical practice. In essence, no BTH events due to incomplete C5 inhibition are assumed for either eculizumab or ravulizumab.

The results of both analyses are presented in the company submission. The cost-utility analysis demonstrated that ravulizumab is dominant (i.e. more effective [providing more QALYs] and cost saving) versus eculizumab, and the equal effectiveness scenario demonstrated that ravulizumab is cost saving when compared with eculizumab in English clinical practice.

B7. Priority question. In document B (page 90) it states: "The base case analysis is aligned with the trial population and observed outcomes from ALXN1210-PNH-301 and ALXN1210-PNH-302. Given that eculizumab was administered at its licensed dose in the pivotal trials, the efficacies of eculizumab and ravulizumab were taken directly from the respective clinical trials and treatment arms. In contrast, the equal effectiveness scenario aligns with the non-inferiority trial designs and assumes that, when for the management of BTH due to incomplete C5 inhibition patients receive an up-dose of eculizumab as per clinical practice, the efficacy of ravulizumab and eculizumab is equivalent."

a) **Please clarify the clinical plausibility of the base-case and the equal effectiveness scenario analyses and which scenario provides a better representation of UK clinical practice.**

Both pharmacoeconomic analyses incorporate the clinical practice of up-dosing and are therefore reflective of the disease pathway and clinical management of PNH patients who meet the criteria for complement-inhibitor treatment in the UK. As such, both analyses are equally clinically plausible.

The cost-utility analysis base case models the observed clinical trial outcomes whilst also incorporating UK clinical practice by assuming that after two incomplete C5 inhibition events, patients are treated with eculizumab at a continuously higher dose than the licensed dose. While this analysis is based on the most robust clinical evidence available (data from randomised controlled clinical trials), it assumes that all patients are on the licensed dose of eculizumab at the start of the model, in line with the pivotal trial protocols. This is not, however, reflective of the known dosing distribution in UK clinical practice, whereby [redacted] of eculizumab-treated patients are permanently 'up-dosed'.{PNH National Service, 2019 #994}

The equal effectiveness scenario models a world where, due to up-dosing of eculizumab patients as per UK clinical practice, effectiveness is assumed to be the same for both ravulizumab and eculizumab arms. In this analysis, the proportion of patients up-dosed on eculizumab from the model start is [redacted], in line with the percentage of up-dosed patients as reported by the PNH National Service.{PNH National Service, 2019 #994} As discussed in our response to clarification question A5 a), the assumption of equal effectiveness when dosing of eculizumab is adopted as per UK clinical practice (i.e. no incomplete C5 inhibition-related BTH events in either arm) is clinically plausible.

b) Given that eculizumab was not administered in either of the trials according to UK clinical practice (i.e. with an up-dose), please justify why a scenario could not be included where eculizumab given according to UK clinical practice is more effective than ravulizumab.

Please see our response to clarification question A5 a) where we have explained why eculizumab administered at a dose that would be observed in UK clinical practice would not be more effective than ravulizumab.

In summary, the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials show that while incomplete C5 inhibition-related BTH events were observed in patients treated with standard dose eculizumab, zero events were observed in those receiving ravulizumab. In UK clinical practice, the 'up-dosing' of eculizumab is adopted to achieve complete terminal complement inhibition so that affected eculizumab patients stop experiencing BTH due to incomplete C5 inhibition. There is no clinical

rationale to support the assumption that ‘up-dosing’ eculizumab is more effective than ravulizumab given that zero events due to incomplete C5 inhibition have been observed with ravulizumab.

The assumption that BTH events due to incomplete C5 inhibition are likely to be reduced if patients are quickly given additional or increased eculizumab dosing to restore complete terminal complement inhibition, per UK clinical practice, is addressed in the economic analyses. We explain how in our response to clarification question B6 d). In essence, equivalent effectiveness, in terms of BTH due to incomplete C5 inhibition, is modelled when dosing of eculizumab is adopted as per UK clinical practice. Specifically, no incomplete C5 inhibition-related BTH events are modelled for either eculizumab or ravulizumab.

B8. Please explain the appropriateness of combining results for cohorts with different starting age (e.g. life expectancy might be different for cohort 1 compared to cohorts 2 and 3).

In the economic analyses, the mean age at first infusion from the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials was used to inform the starting age of Cohort 1 and Cohort 2, respectively. For Cohort 3, the mean age is assumed to be the same as Cohort 2 – this was considered appropriate given both cohorts represent treatment experienced patients currently treated with eculizumab.

The difference in life expectancy of patients included in the model is accounted for by applying age-adjusted background mortality (as represented by Health Survey for England data modelled by Ara and Brazier) separately to each cohort. The model outcomes for the total population (“aggregated results”) are then combined as the last step; these outcomes were calculated as an average of all cohorts, weighted by the proportion of patients starting in each cohort.

Patient population

B9. Please provide the characteristics of the UK patients who received an up-dose of eculizumab.

As discussed during the clarification TC, no biomarkers and no specific patient characteristics have been identified that correlate with the need for up-dosing and it

is therefore not possible to determine which patients may require up-dosing in advance of the development of BTH events. In UK clinical practice, patients who are treated with standard dose eculizumab are considered for up-dosing if, over two eculizumab dosing intervals, they:

- develop a recurrence of one or more PNH symptoms together with;
- reactivation of haemolytic activity, as evidenced by an increase in LDH of more than twice the upper limit of normal (ULN), after having previously normalised LDH.

Treatment effectiveness

B10. In document B (page 80), the “Base case analysis” section reports that 44 patients received ravulizumab through the ALXN1210-PNH-301 extension or ALXN1210-PNH-302 extension. Please clarify whether these patients were originally randomized to ravulizumab or if they switched treatment.

All 44 UK patients who participated in the ravulizumab clinical trial programme were recruited into the ALXN1210-PNH-302 trial. Of these 44 patients, 23 were initially randomized to ravulizumab with the remaining 21 patients randomized to eculizumab. All 44 patients participated in the Extension Phase of the study, receiving ravulizumab.

B11. In document B, Table 23 (page 92) reports for the study ALXN1210-PNH-301, 1 CAC-related and 1 undetermined BTH event among patients who switched from eculizumab to ravulizumab. Also, among patients continuing to ravulizumab, 1 CAC-related and 4 undetermined BTH events happened. Similarly, CAC-related and undetermined BTH events happened for patients in study ALXN1210-PNH-302. This indicates that these events are still occurring when patients are using ravulizumab. Please provide the time-to-event for both switchers and non-switchers and explain how the events were resolved.

Breakthrough haemolysis (BTH), characterized by the return of intravascular haemolysis and reappearance of classical PNH symptoms may occur due to suboptimal C5 inhibition, and/or complement-amplifying conditions (CACs) such as infection, surgery, or pregnancy that may lead to increased complement activation

resulting from higher C3b density. In some patients with suboptimal C5 inhibition or complement-amplifying conditions, BTH may be ameliorated by shortening the 2-week dosing interval and/or increasing the dose of eculizumab. Where a CAC is driving the BTH (e.g. an infection), there may not be suboptimal C5 inhibition and the underlying condition should primarily be managed – i.e. the infection treated. It has been shown that exposure of host red blood cells to infectious pathogen cells can cause haemolysis independent of complement activity, suggesting that the complement system may not be the sole cause of infection-triggered haemolysis.

The focus in the clinical trial programme has been on the extent to which ravulizumab and eculizumab could inhibit BTH caused by insufficient C5 inhibition, and not the prevention of BTH caused by infections and other CACs.

In the non-clinical trial setting the BTH caused by insufficient C5 inhibition would have been treated by temporarily increasing the dose of eculizumab, or shortening the dosing interval, while BTH caused by a CAC would have required the infection to be treated. However, in the clinical trial setting neither of these were allowed and if a BTH persisted, the patient had to leave the study in order to receive up dosing of his/her complement inhibitor or treatment for the infection.

For more detail on the breakthrough haemolysis events observed in the Extension Period of the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials, please see Appendix B11.

B12. Even though overall survival was not a pre-specified endpoint in the ravulizumab trial programme (deaths were captured as a safety outcome) the company assumed equal mortality as eculizumab (which aligns to that of the general population). Please provide further evidence to justify the assumption that mortality with ravulizumab equals mortality with eculizumab. Also, please include in the model the option to select different mortality per treatment arm, including the possibility of including the mortality data from the ravulizumab trials.

The results of clinical trials ALXN1210-PNH-301 and ALXN1210-PNH-302 demonstrated ravulizumab met non-inferiority versus eculizumab across all disease markers, including those associated with mortality (e.g. LDH, terminal complement inhibition and BTH events). Indeed, all comparisons across endpoints measured

were numerically in favour of ravulizumab. Based on the non-inferiority observed in the trials and the fact that ravulizumab was derived from eculizumab and the technologies share over 99% homology, there is no clinical rationale as to why mortality should differ across the treatments.

As you have acknowledged in your question, overall survival was not a pre-specified endpoint in the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials, although deaths were captured as a safety outcome. Across both trials, the 52-week data did not capture any mortality related to treatment in either the ravulizumab arm or in ravulizumab patients who switched from eculizumab. Only one death was observed, and this was a patient in the eculizumab arm of the ALXN1210-PNH-301 trial who died of lung adenocarcinoma, unrelated to treatment.

As stated in the company submission, further data from the ALXN1210-PNH-301 and ALXN1210-PNH-302 trial Extension Phases reporting outcomes up to 104 weeks are expected to be available in [redacted]. An analysis of overall survival will also be conducted. Although not available at this time, it is anticipated that the data will provide longer-term evidence to support the outcomes observed over the 52-week period.

In the economic analyses, it is assumed that patients who are treated with either eculizumab or ravulizumab have a life expectancy equal to that of the age-matched general population. This is consistent with the reported outlook of PNH patients treated with eculizumab. As discussed in the company submission (Section B.1.3.2), eculizumab has transformed the course of the disease, significantly reducing progressive morbidity and aligning the life expectancy of patients to that of the general population. [10, 15-23] As there is no clinical rationale to expect differential mortality between eculizumab and ravulizumab, this is not included in the model.

B13. The company has assumed a constant treatment effect over time. In document A (Table 8) it is mentioned that “ravulizumab has demonstrated non-inferiority to eculizumab, which has been shown to provide a long-term treatment effect”. However, it could be argued that 1) non-inferiority in the short-term, does not necessarily imply it in the long-term and 2) a long-term treatment effect of

eculizumab (compared to no treatment), does not necessarily imply a long-term effect of ravulizumab compared to eculizumab.

a) Please provide additional evidence to justify this assumption.

NICE Document B Section 2.6.2, Table 9 and Table 10 of the company submission provide an overview of efficacy results for the Extension Period of ALXN1210-PNH-301 and ALXN1210-PNH-302, respectively. These results show that similar proportions of patients avoided transfusion, achieved LDH normalization, achieved haemoglobin stabilization and maintained HRQL in both study periods (0–26 Weeks and 27–52 Weeks) across both treatment arms. The 52-week trial data therefore demonstrate a sustained treatment effect with ravulizumab, with no evidence of a decline or change in treatment effect over this time. As mentioned in response to clarification question B12 above, it is anticipated that the 104-week data from the ALXN1210-PNH-301 and ALXN1210-PNH-302 trial Extension Phase will provide longer-term evidence to support these outcomes.

Although we acknowledge that data for ravulizumab outside of the 52-week ALXN1210-PNH-301 and ALXN1210-PNH-302 trial periods do not currently exist, we would expect longer-term outcomes with ravulizumab to remain similar to eculizumab given non-inferiority was demonstrated and given the technologies share over 99% homology. As stated in the company submission (Section B.3.11), there are long-term data available for eculizumab from over 10 years of use in clinical practice, which show no evidence of treatment waning over time. Indeed, the rate of events such as the incidence of CAC-related or incomplete C5 inhibition-related BTH and transfusions required have remained reasonably constant over time.[1, 15, 24]

b) Furthermore, even though use of constant post-trial event rates was deemed appropriate at the December 2018 Advisory Board meeting, please include in the model the option to select a decline in treatment effect and the option to select the maximum duration for the treatment effect.

As reasoned in our response to part a), clinical rationale and evidence from the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials support a constant treatment effect with ravulizumab, in accordance with the advice received from experts at the advisory board meeting in 2018. Data from over 10 years of eculizumab use in

clinical practice also show that a constant treatment effect is maintained; therefore, a decline in treatment effect over time is not considered clinically plausible and has not been modelled for either treatment arm.

HRQoL

B14. The company has used a mapping to estimate EQ-5D-3L utilities, in line with TSD10 and TSD11. The selected base-case mapping algorithm (Longworth et al 2014) has been consistently tested to be one of the best performing mapping algorithms. However, mapping algorithms are known to be very sensitive to the severity of the population in which they are estimated. The Longworth algorithm was estimated on a dataset in which patients had a global quality of life score of 53. Please clarify whether the mean value reported in Appendix R, Table 31 and 32 represent the global quality of life score of the QLQ-C30, i.e. about 57 at baseline in ALXN1210-PNH-301 and about 75 at baseline in ALXN1210-PNH-302.

To confirm the data presented in Table 31 and Table 32, reports include the mean, median, minimum and maximum EORTC QLQ-C30 Global Health Status subscale scores by treatment arm and observation date. To confirm, as reported in Table 31, the baseline mean for ravulizumab is 56.13 and for eculizumab 57.51. In Table 32, the baseline mean for ravulizumab is 75.25. Relooking at the data in response to this question we noticed the incorrect data as reported in Table 32 for eculizumab. Please see below the corrected data for eculizumab in red. The baseline mean for eculizumab is 69.47.

Table 5: ALXN1210-PNH-302 EORTC-QLQ-C30 observations

Primary evaluation period		**Baseline**	**Day 8**	**Day 29**	**Day 71**	**Day 127**	**Day 183**
Ravulizumab (N=125)	**n**	97	95	92	94	94	95
	Mean (SD)	75.25 (17.237)	75.69 (17.762)	77.25 (15.179)	75.61 (17.068)	74.91 (18.669)	76.57 (15.576)
	Median	83.3	83.3	83.3	83.3	83.3	83.3
	Min, Max	16.7, 100.0	0.0, 100.0	33.3, 100.0	0.0, 100.0	0.0, 100.0	33.3, 100.0
	n	98	90	95	94	96	95

Primary evaluation period		Baseline	Day 8	Day 29	Day 71	Day 127	Day 183
Eculizumab (N=121)	Mean (SD)	69.47 (16.488)	68.98 (18.099)	70.00 (19.983)	68.88 (19.556)	68.83 (21.085)	67.71 (22.147)
	Median	66.7	66.7	66.7	75	75	75
	Min, Max	33.3, 100.0	25.0, 100.0	25.0, 100.0	16.7, 100.0	0.0, 100.0	8.3, 100.0

B15. Following the calculation of utility values, several regression models were fitted to the data to explore the impact of a BTH event. The models of choice took the panel structure of the data into account (mixed model) and are reported to have a better fit than OLS models with clustered standard errors. However, a difference between the mixed-models and the OLS models is that the mixed models no longer include a treatment arm (specified as 'arm_1210' in Table 33 and 34 for OLS but missing from table 39 and 40). Please include the treatment arm parameter 'arm_1210' in the regressions specified in Table 39 and 40. Also, please include in the model the option to select different utilities per treatment arm**.**

As detailed in Appendix R, the treatment arm covariate was excluded from the final model specification. Table 6 and Table 7 present the results of the exploratory regression models including a treatment arm covariate for Longworth et al. (2014) for study ALXN1210-PNH-301 and ALXN1210-PNH-302, respectively.[25, 26] The option to include this parameter as a scenario is in the updated model.

Table 6: Longworth mapping, mixed-effects specification, study ALXN1210-PNH-301

Covariate	Coefficient	Standard error	z	P>|z|	[95% CI]	
BTH indicator	-0.1142	0.0376	-3.0300	0.0020	-0.1880	-0.0404
Treatment*	0.0103	0.0128	0.8100	0.4210	-0.0147	0.0353
Transfusion indicator	-0.0674	0.0131	-5.1500	0.0000	-0.0931	-0.0418
Individual-level linear trend	0.0212	0.0015	14.3000	0.0000	0.0183	0.0241
Constant	0.7540	0.0104	72.5900	0.0000	0.7336	0.7743
Notes: BTH, breakthrough-haemolysis event experienced since last visit; individual-level linear trend, time trend (number of visits); transfusion, protocol guidelines for transfusion met since last visit. Treatment, ravulizumab =1, eculizumab = 0						

Table 7: Longworth mapping, mixed-effects specification, Study ALXN1210-PNH-302

Covariate	Coefficient	Standard error	z	P>|z|	[95% CI]	
BTH indicator	-0.1816	0.0490	-3.7100	0.0000	-0.2777	-0.0856
Treatment*	0.0197	0.0176	1.1200	0.2630	-0.0148	0.0543
Transfusion indicator	-0.0717	0.0189	-3.7800	0.0000	-0.1088	-0.0345
Individual-level linear trend	0.0028	0.0012	2.2800	0.0230	0.0004	0.0052
Constant	0.8373	0.0131	63.8400	0.0000	0.8116	0.8630

Key: CI, confidence interval.
Notes: BTH, breakthrough-haemolysis event experienced since last visit; individual-level linear trend, time trend (number of visits); transfusion, protocol guidelines for transfusion met since last visit. Treatment, ravulizumab =1, eculizumab = 0

B16. Please include an interaction term between arm_1210 and BTH in the regressions specified in Table 39 and 40. Also, please include in the model the option to select the utilities estimated using this approach.

The utility analysis as detailed in Section B3.4.2 and Appendix R of the NICE submission, explored prognostic variables based on discussions with internal Alexion clinicians. These included BTH, transfusion, treatment, baseline utility and LDH level. As detailed in Appendix R, treatment arm was excluded as it was non-significant in all analyses. BTH events were also pooled due to the small number of events, and to provide sufficient estimate of the utility decrement.

Within the dataset there are only a low number of BTH events observed at the visits when EORTC was collected (Appendix R):

- ALXN1210-PNH-301 – one incomplete C5 inhibition (eculizumab) and three CAC (one eculizumab, two ravulizumab)
- ALXN1210-PNH-302 – two incomplete C5 inhibition (eculizumab) and one CAC (eculizumab)

These event numbers are not sufficient to estimate a treatment effect interaction with BTH. An exploratory analysis which includes an interaction term between arm_1210 and BTH therefore cannot be conducted.

B17. Priority question. In the cost effectiveness analyses, the majority of the utility effect is achieved by a difference in mean annual utility derived from an ISPOR poster of a discrete choice experiment (DCE) indexed in Value in Health in 2019 (Lloyd et al, 2019). Please provide the full study report of the Lloyd et al. study.

Please, see attached a copy of the full technical report, that accompanies the study reported by Lloyd et al, 2019. A manuscript of this study is currently under review with Value and Health.

DCE survey report_all countries_

B18. The disutility of -0.057 presented in the Lloyd et al. study was applied annually in the model. The poster reports that marginal rates of substitution were used between the parameters of life expectancy and the outcome of interest (8 weeks versus 2 weeks). However, it is unclear how this DCE was scaled. In order to apply the disutility annually, the parameter for life expectancy has to represent a difference between scenarios of 1 year. Please explain why the attribute levels of life expectancy in the DCE reported by Lloyd et al. warrant an annual application of the disutility value.

The marginal rates of substitution (MRS) were estimated so that it is possible to determine the extent to which participants were willing to trade years of life for avoidance of severe levels on the other attributes (administration frequency, infection risk, haemolysis, and need for transfusions). The numbers in Table 8 represent the number of units of attributes that is equivalent to one year of additional life.

To estimate utilities that could be used to potentially estimate QALYs we make the following assumption: If we have 2 treatments and one is associated with severe haemolysis which requires treatment in hospital while the other has no haemolysis and the treatments are the same in all other regards then the MRS tells us how many years of additional life they will consider equivalent to having to also endure severe haemolysis. This is based on the assumption that they have severe haemolysis each year for the rest of their life (and there are no other external influences on HRQL).

The MRS data (Table 8), indicates that the impact of severe haemolysis is the same weight as 4.93 years of life. Our general population sample has a mean age of 49.8 years. UK average life expectancy in 2015 was 80.97 years (ONS). We have estimated therefore that our sample had 31.17 years of life left on average. The utility loss associated with experiencing severe haemolysis is thus estimated as 4.93/31.17 = 0.158. Applying this rationale utility weights were estimated for differences in attribute levels (Table 8).

Table 8 UK: Calculated marginal utilities (expressed as a disutility) for differences in attribute levels (passed logic choice question)

	MRS	Disutility
Treatment administration	1.789	-0.057
Patient receives an infusion every 2 weeks which takes 1 hour (compared with an infusion every 8 weeks which takes 3 hour)		
Risk of infection	1.242	-0.040
1 additional patient per 1000 will develop meningitis type infection		
Severe RBC destruction, treated in hospital	4.926	-0.158
Patient can expect to develop severe hemolysis requiring hospital treatment in the next two years		
Need for transfusion every year	2.280	-0.073
Patient requires a blood transfusion every year		

B19. The study by Lloyd et al. also reports a disutility for 'severe haemolysis' of -0.158. Please explain how this value relates to the results of the regression analysis which presents a BTH disutility of -0.11 and -0.18 for all types of severity of the event.

The definition of severe haemolysis in the Lloyd et al study was of severe haemolysis which required admission to hospital, which was not preferred by respondents to the study. In contrast, the majority of patients in study ALXN1210-PNH-301 and ALXN1210-PNH-302 had moderate symptoms, which included anaemia, dyspnoea, haemoglobinuria, and fatigue. A detailed narrative of the BTH events observed in study ALXN1210-PNH-301 and ALXN1210-PNH-302 during the Randomized Period is provided in the Brodsky 2020 publication.[2]

The Lloyd et al, study evaluation is based upon a simple description of the impact of BTH, so a comparison of these may not fully capture the patient nuance associated

with BTH observed in the clinical studies. In line with the NICE reference case we would recommend utilising the EQ-5D data from the clinical trial (which were mapped from the EORTC-QLQ-C30 scores captured) where this data is able to capture the event of interest (this is the case for BTH but not for the impact of reduced visits – see the response below).

It is important to note that in the model, the disutility associated with a BTH event is applied only for a short period of time during the model cycle (2 days until the next dose of eculizumab is administered) and therefore has little overall impact on the model results.

B20. In document B (page 102) it is mentioned that "patients did not experience the potential HRQL benefit of less frequent visits, although they did experience the benefit of less frequent infusion visits". Hence, since the clinical trial design allows the estimation of the benefit of difference in infusions, please clarify whether it is possible:

a) to estimate the difference in the benefit of infusions in terms of utility;

To confirm, an analysis of the ALXN1210-PNH-301 and ALXN1210-PNH-302 clinical trials, attempted to estimate this benefit. The treatment effect indicator for ravulizumab can be interpreted as the effort to estimate the difference in the benefit in terms of utility. Ravulizumab infusions are given every 8 weeks compared to every two weeks for eculizumab infusions. However, the clinical trial schedules meant that patients in both treatment arms were seen on the same schedule, every two weeks, either for an infusion of treatment (either ravulizumab or eculizumab) or on weeks in between ravulizumab dosing for a regular check-up. At every visit, patients in each arm received the same regular check-up.

The treatment indicator is therefore likely to be an underestimate of the true benefit associated with fewer infusions, as patients were inconvenienced by the visit to the clinical trial centre even when they didn’t receive an infusion. Despite this, a small utility benefit in favour of ravulizumab can be observed (0.0103 and 0.0197 in ALXN1210-PNH-301 and ALXN1210-PNH-302 respectively), although non-significant (see response to question B15).

b) to incorporate this estimate in the model as a substitute for the estimates derived from the DCE;

Please see response B15, for information on the treatment effect indicator, this has been included in the updated model.

c) to provide another estimate for the HRQoL benefit related only to the time benefit of the frequency of visits.

An estimate related only to the time benefit of the frequency of visits is unavailable from the trial evidence as the visit frequency was the same for each arm as required by the clinical trial protocol.

Cost and Resource use

B21. In Appendix G.2.1, it was indicated that 2 economic models published by O'Connell et al., 2019/2020 specifically assessed the cost effectiveness of ravulizumab compared with eculizumab for the treatment of PNH, and that these models are basically the same as the company's model but with different base case settings. In the models by O'Connell et al., one-way sensitivity analyses showed that the results were most sensitive to eculizumab dosing and that the variation in the level of cost savings were driven by using higher-than-labelled eculizumab dosing for the management of BTH. Please provide the variation in the level of cost-savings (e.g. in a tabular format) that is expected to be driven by using higher-than-labelled eculizumab dosing.

In response to the request for cross-validation of the submitted cost-effectiveness model following discussions with the ERG, the O'Connell et al. 2020 (full-text article) publication was considered as a useful source. However, the O'Connell model and the submitted model differ in the application of specific parameters and also the relevance of others to the NICE decision problem. The differences between the O'Connell study and the submitted cost-effectiveness analysis include:

- Perspective: A US perspective was used in the study
- Mapping algorithm: The analysis applied the McKenzie and van der Pol (2009) mapping

- Treatment effect indicator: The analysis included a treatment effect applied to the ravulizumab arm, this was applied in addition to the utility increment due to the reduction in infusions derived by Lloyd et al. (2019).[72]
- Cohort transition: The analysis assumed treatment naive patients' risk of BTH events would match that of treatment experienced patients after 6 months.
- General population utility: The analysis didn't include any adjustment for general population utility
- Costs: All costs in the analysis are for a US healthcare perspective

Based upon this we concluded that the O'Connell study is too different from the submitted cost effectiveness analysis and not an appropriate comparison in the UK.

Therefore to fully explore the variation in the level of cost savings that is expected to be driven by using higher-than-labelled eculizumab dosing using relevant UK data, a OWSA was explored (see Figure *2*), using the equal efficacy scenario, where the proportion in Cohort 3 at the start of the model is [redacted]. This scenario explores the impact of using the upper and lower bounds of the 95% CI around the % receiving eculizumab dosing based upon the UK registry data ([redacted]%, [redacted]%). As might be expected when this information is included in the OWSA it becomes the key model driver, however, ravulizumab remains considerably cost saving even at the lower bound of the 95% CI.

Figure 2: Equal efficacy scenario – tornado diagram (PAS price) – incremental cost

Key: BTH, break-through haemolysis; CH, cohort; NMB, Net Monetary Benefit; PAS, patient access scheme; Prob., probability; RBC, red blood cells.

Section B.3.1 and Appendix G in the company submission compare the differences between our submitted analysis and the published O'Connell et al. studies; the differences noted make any comparison between the two limited.

B22. Please confirm that all costs (i.e., costs associated with drug acquisition and administration, BTH event management and blood transfusions) included in the model are inflated to the same year according to the standard methods.

An overview of all costs included in the economic model and the associated cost years is provided in Table 9. As presented, all costs have been taken from the most up to date source – either from 2018/2019 or 2020 – except for the costs associated with transfusion administration. This was derived from a publication by Stokes et al.

2018, which reports costs that were collected in 2014/15 British pounds (as indicated using red text in Table 9 below). Thank you for bringing this to our attention.

We have updated the model with the transfusion administration cost inflated to a 2019 cost year using healthcare indices published in Unit Costs of Health and Social Care.

$$\frac{£49.00}{290.5} * 312.9 = £52.77$$

The impact of this change on the model results is presented in response to clarification B27.

Table 9: Overview of costs included in the model and associated cost year

Cost category		Source	Cost year
Treatment acquisition: eculizumab		MIMS	2020
Treatment acquisition: ravulizumab		Alexion, data on file	
Treatment administration		PSSRU 2019	2018/2019
Meningococcal vaccine		Hampstead Health Pharmacy	2020
Prophylactic antibiotics		eMIT 2020	2019
Transfusion administration		Stokes et al. 2018	2014/2015
Packed red blood cells		NHS blood and transplant price list; code: BC001	2018/2019
BTH event resource use	General ward admission (day)	NHS reference costs	2018/2019
	Intensive care admission (day)		
	Dialysis (session)		
	Haematology specialist visit		

Key: BTH, breakthrough haemolysis; eMIT, electronic market information tool; MIMS, Monthly Index of Medical Specialities; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

Cost effectiveness analyses and results

B23. Priority question. Please include half-cycle correction in the economic model.

The purpose of half-cycle correction is to acknowledge and account for the fact that events/transitions do not necessarily occur at the beginning or end of the cycle, but somewhere in between. Half-cycle correction is not part of the NICE reference case[28]; therefore, judgement has been used as to whether it is appropriate. In a publication by Naimark et al. 2013, the authors discuss the limitations of the standard approach to half-cycle correction and discuss alternative approaches.[29] Of note, the authors suggest that "for less complex decision models in which the computational burden is not large, reducing the cycle length to a month or less and using no correction should result in small estimation biases".[29]

We do not believe it is appropriate to apply half-cycle correction in the economic model. A 2-week cycle length is used in the economic model which corresponds with the dosing schedule of eculizumab (in the maintenance phase) and is shorter than the 8-week dosing schedule of ravulizumab.

The biggest costs accrued in the model and biggest driver of the model results are the eculizumab and ravulizumab drug costs. The model cycle length was selected with the dosing frequencies in mind, and patients will receive the treatment at the start of the cycle. Assuming these treatment costs are incurred at the mid-point of the cycle is incorrect and would underestimate the true costs.

Furthermore, given a short cycle length of 2-weeks is used in the economic model, for other costs (non-drug costs) and health outcomes where it may be more reasonable to assume these are spread across time, adjusting these to account for half-cycle correction is likely to have a minimal impact.

B24. Priority question. Several potentially important parameters were not included in the deterministic and probabilistic sensitivity analyses (sheet "Analysis parameters"). Please include the following parameters in the OWSA and the PSA: all weight (for age) parameters, the proportion of patients in each cohort (including cohort 3, which is currently 0), all transition probabilities that

are assumed to be equal to 0 (or 1) as per question B5 and the utility regression coefficients from the 301 and 302 clinical trials.

The model has been updated to include the requested parameters in the OWSA (where appropriate) and PSA. Weight and age were not originally included as inclusion is non-standard in the; the decision problem population is assumed fixed. Additionally, the health state utilities were varied in the OWSA and PSA, in the submitted model The utility regression coefficients from the 301 and 302 clinical trials are not included in the OWSA, as it is not recommended to assess joint uncertainties in OWSA. Therefore, the health state utilities are still varied in the OWSA and utility regression coefficient are varied in the PSA. Note the weight for age parameters were not included in the original submission as it is not standard to vary these parameters

The base case cost utility analysis PSA in Figure 3 (Figure 15, Document B) and OWSA in Figure 4, (Figure 17, Document B) are provided below for reference.

The addition of each parameter (except the transition probabilities as per question B5 and impact of the utility regression coefficients) is tested below, in OWSA in Figure 5 and in PSA in Figure 6. An additional PSA is run to test the addition of the transition probabilities as per question B5 and impact of the utility regression coefficients in Figure 7. For the purpose of the PSA, an option is added in the updated model to include or exclude joint variance parameters and test their impact (see the “PSA” sheet).

As detailed above, the utility coefficients are not varied in the OWSA. However, heath state utilities are varied, and the results as shown in Figure 5 show no change in the top eight parameters, with the addition of the proportion of cohort 1 and 2. The inclusion of parameter uncertainty for weight for age and the cohort distribution has increased the uncertainty mostly in terms of cost as shown in the cost effectiveness plane, as shown in Figure 6 .The addition of the transition probabilities as per question B5 and impact of the utility regression coefficients is shown in Figure 7, and shows little impact on top of the uncertainty associated with the weight for age and the cohort distribution

Figure 3: Base case cost utility analysis probabilistic sensitivity analysis cost-effectiveness plane

Key: QALY, quality-adjusted life year.

Figure 4: Base case cost utility analysis– tornado diagram (PAS price)

Key: BTH, break-through haemolysis; CH, cohort; NMB, Net Monetary Benefit; PAS, patient access scheme; Prob., probability; RBC, red blood cells.
Notes: £30,000 willingness to pay threshold used

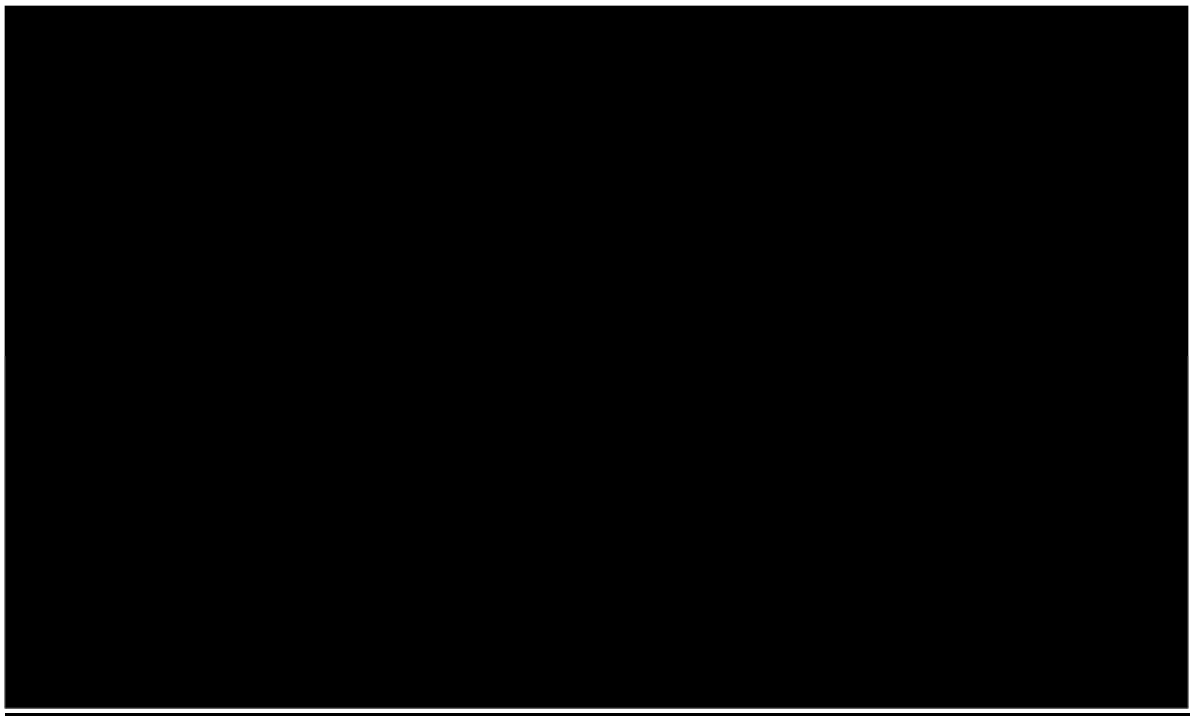
Figure 5: Cost utility analysis– tornado diagram (PAS price) –(additional parameters)

Key: BTH, break-through haemolysis; CH, cohort; NMB, Net Monetary Benefit; PAS, patient access scheme; Prob., probability; RBC, red blood cells.
Notes: £30,000 willingness to pay threshold used

Figure 6: Updated cost utility analysis probabilistic sensitivity analysis cost-effectiveness plane (additional parameters – except Bayesian prior and joint variance parameters)

Key: QALY, quality-adjusted life year.

Figure 7: Updated cost utility analysis probabilistic sensitivity analysis cost-effectiveness plane (including all additional parameters)



Key: QALY, quality-adjusted life year.

Model validation

B25. Priority question: Please provide details about what validation efforts were performed in Section B.3.10 of the company submission and the results of these validation efforts. This could be presented for example (but not necessarily) with the help of the validation tool AdViSHE (https://advishe.wordpress.com/author/advishe/).

The AdViSHE validation tool has been completed to detail the validation efforts performed.


ID1457 AdViSHE tool.docx

B26. Priority question: Please provide all details of the communication between the company and the clinical experts. Please include anonymised information about the clinical experts, detailed minutes of the face-to-face meeting and/or teleconference, list of expert recommendations and justifications for clinical assumptions and inputs used in the model.

Two advisory boards were held to incorporate clinical and economic expert opinion into the design and validation of the economic model.

The first was held in July 2018[30] and was attended by five experts from the following backgrounds:

- Two consultant clinicians with specialisms in haematology, both of whom are from the only two nationally commissioned centres for the treatment of PNH
- Three health economists, one of whom is based in a key academic centre for health economics and two who are independent (consultancy-based) health economists

The economic experts provided feedback on HRQL specifically advice regarding mapping and the application of a treatment-related burden, on the cost-effectiveness modelling approach and also relevant parameters, including predictors of disease prognosis, current management of PNH patients, spontaneous remission and relevant clinical outcomes: BTH, thrombotic events and pulmonary hypertension.

The second advisory board meeting was held in December 2018[31], and had six attendees from the following backgrounds:

- Four consultant clinicians with specialisms in haematology, from the two nationally commissioned centres for the treatment of PNH
- Two health economists, one based in a key academic centre for health economics and one being an independent health economist

The topics that were covered at the meeting included understanding the current treatment pathway for patients with PNH, the impact of introducing ravulizumab based on the clinical trial data, the cost-effectiveness modelling approach and relevant parameters.

Following each of the advisory board meetings, the minutes taken were formally written up and circulated for approval. The approved minutes are provided in the NICE dossier. In the company submission (Document B) these minutes are referenced as:

- Reference 25 “Alexion Pharmaceuticals. Ravulizumab advisory board (December 2018). 13 December 2018. Data on File”
- Reference 36 “Alexion Pharmaceuticals. Haematology reimbursement advisory board UK (July 2018). 6 July 2018. Data on File”

B27. Priority question: If any changes are made to the model originally submitted in the company submission, please provide a clear list of these changes, the appropriate justification, and the impact on the model results.

As discussed in the answers below, the majority of changes made have impacted either OWSA and/or PSA, with the exception of a minor cost update detailed in B22. A list of changes is provided below.

Table 10: Summary of model changes and impact on the base case cost utility analysis

Change	Model change (sheetname:cellname)	Impact on basecase ICER
Inclusion of Bayesian prior distribution option in response to question B5	Inputs:H67 [IO]_Model_BayesPrior Addition of model option to include Bayesian prior in response to question B5	No change (not included in base case analysis)
Inclusion of a treatment arm utility option in response to question B15	Input:H160 [IO]_HU_InclTxArm	No change

	Addition of model option to include treatment arm in response to question B15	(not included in base case analysis)
Update of the cost for transfusion administration	Inputs:H259 Update on cost in response to question B22	ICER remains dominant
Inclusion of parameters into OSWA and PSA • Weight for age • Cohort proportions • Utility regression coefficients • Bayesian priors in response to question B5	Analysis parameters: K17:K123, N17:N123, K206:K217 K206,K212 – text change to Yes Analysis parameters:N175:N185 – text change to No Updated in response to question B 24	No change (not included in base case analysis)
Inclusion of option to model joint variance	PSA:K8 PSA_Jointvar_include Updated to include option to test joint variance in the PSA (applies to utility covariates and Ara and Brazier general population utility variance)	No change (not included in base case analysis)

Section C: Textual clarification and additional points

C1. Please explain what parameters were changed (and where in the model) to reproduce all results presented in Document B Table 46.

The scenarios as presented in Document B Table 46 are created on the sheet “ScenSA”. The scenario results are presented on the left side of the sheet, column C:U. Each scenario is run for each cohort with the result presented for Cohort 1 in columns F:I, for Cohort 2 in columns J:M, for Cohort N:Q and for the aggregate population in R:U. The scenario names start from Row 17.

The scenario set up is found in columns W:AT. In columns W:AN, the base case settings are saved These follow a sheet, range, value naming convention. The scenario values are found in columns AD:AT. These follow a value naming convention.

For example, to test a 10-year time horizon in a scenario, only one parameter is changed. The parameters sheet name is inputted into column W Sheet (1), “inputs”, the range name is inputted into column X Range (1), “[IO]_Time_Horizon”, the base case value is inputted into column Y Value(1), “101”. The scenario value is then is

inputted in column AO Value (1), 10. To validate the base case setting of each scenario, follow the sheet.range name to navigate to the relevant range. If any scenario is changed, press the “Run Scenarios” button to update the results. Note old results are overwritten.

The model allows for a total of 6 parameters to change to model a scenario. No scenario currently set in the model, exceeds 5 scenario inputs.

The formatted tables which inform the cost utility analysis and are presented in Table 46 of Document B can be found in Rows 53:76.

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Appendix A1/B1

Table 11: Citations identified through hand-searching of conference proceedings

Clinical/economic review	Reference	Conference proceeding
Clinical review	Hanes et al. Clinical characteristics of patients with paroxysmal nocturnal hemoglobinuria (PNH): A retrospective chart review study. Blood Conference: 61st Annual Meeting of the American Society of Hematology, ASH. 2019;134 (S1).	ASH 2019
Clinical review	Kang et al. Real-world efficacy of eculizumab for paroxysmal nocturnal hemoglobinuria in South Korea: Paradox of eculizumab. Blood Conference: 61st Annual Meeting of the American Society of Hematology, ASH. 2019;134 (S1).	ASH 2019
Clinical review	Karadag et al. Evaluation of patients with PNH treated by eculizumab: Real world data from Turkey. Blood Conference: 61st Annual Meeting of the American Society of Hematology, ASH. 2019;134 (S1).	ASH 2019
Clinical review	Kulagin et al. Phase III clinical trial of Elizaria and Soliris in adult patients with paroxysmal nocturnal hemoglobinuria: Results of comparative analysis of efficacy, safety, and pharmacological data. Blood Conference: 61st Annual Meeting of the American Society of Hematology, ASH. 2019;134 (S1).	ASH 2019
Economic review	Levy A et al. Comparison of lost productivity due to eculizumab and ravulizumab treatments for paroxysmal nocturnal hemoglobinuria in France, Germany, Italy, Russia, Spain, the United Kingdom, and the United States. Blood Conference: 61st Annual Meeting of the American Society of Hematology, ASH. 2019;134(Supplement 1).	ASH 2019
Clinical review	Liu et al. Outcomes of haploidentical haematopoietic stem cell transplantation for paroxysmal nocturnal haemoglobinuria. Blood Conference: 61st Annual Meeting of the American Society of Hematology, ASH. 2019;134 (S1).	ASH 2019
Clinical review	Yamakawa et al. Clinical characteristics of Brazilian patients with paroxysmal nocturnal hemoglobinuria and changing prognosis with eculizumab. Blood Conference: 61st Annual Meeting of the American Society of Hematology, ASH. 2019;134 (S1).	ASH 2019

Clinical review	Urbano-Ispizua et al. Efficacy of eculizumab in pediatric patients with paroxysmal nocturnal hemoglobinuria in the international PNH registry. Blood Conference: 60th Annual Meeting of the American Society of Hematology, ASH. 2018;132 (S1).	ASH 2018
Clinical review	Yenerel et al. The importance of eculizumab in paroxysmal nocturnal hemoglobinuria: A cohort study. Blood Conference: 60th Annual Meeting of the American Society of Hematology, ASH. 2018;132 (S1).	ASH 2018
Clinical review	Hill et al. Interim analysis of safety outcomes during treatment with eculizumab: Results from the international paroxysmal nocturnal hemoglobinuria registry. Blood Conference: 59th Annual Meeting of the American Society of Hematology, ASH. 2017;130 (S1).	ASH 2017
Clinical review	Lee et al. Efficacy of eculizumab in patients with paroxysmal nocturnal hemoglobinuria (PNH) and high disease activity with or without history of aplastic anemia in the international PNH registry. Blood Conference: 59th Annual Meeting of the American Society of Hematology, ASH. 2017;130 (S1).	ASH 2017
Clinical review	McKinley et al. Extravascular hemolysis due to C3-loading in patients with PNH treated with eculizumab: Defining the clinical syndrome. Blood Conference: 59th Annual Meeting of the American Society of Hematology, ASH. 2017;130 (S1).	ASH 2017
HRQL review	Hochsmann B et al. Effect of eculizumab in paroxysmal nocturnal hemoglobinuria (PNH) patients with or without high disease activity: Results from the international pnh registry. Haematologica. 2017;102 (Supplement 2):188-189.	EHA 2017
Clinical review	Markiewicz et al. ALLO-HCT for paroxysmal nocturnal hemoglobinuria-12 years of experience. Haematologica. 2017;102 (S2):300.	EHA 2017
Cost & resource review	Muus P et al. Patient-reported outcomes and healthcare resource utilization before and during treatment with eculizumab: Results from the international paroxysmal nocturnal hemoglobinuria registry. Haematologica. 2017;102 (Supplement 2):125-126.	EHA 2017

Appendix A6

Table 12: Patient narratives for breakthrough haemolysis events observed in the Randomized Period of the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials

Trial / treatment arm	Characteristics: Sex / age / body weight	BTH event; symptoms	Study day	LDH, U/L	Free C5, ug/mL	RBC transfusion, U	Possible CAC	Association
ALXN1210-PNH-301 Ravulizumab	Female / 34 years / 115 kg	First; fatigue, abdominal pain, dyspnoea	155 169	593 511	0.105 0.101	None	Giardiasis	CAC
ALXN1210-PNH-301 Ravulizumab	Female / 30 years / 57 kg	First; haemoglobinuria	71	687	0.0787	None	Viral infection	CAC
ALXN1210-PNH-301 Ravulizumab	Female / 24 years / 57 kg	First; haemoglobinuria, anaemia	113 127 155 169 183	517 773 513 926 555	0.0602 0.0768 0.0428 0.0896 0.0909	2	Influenza, URI	CAC
0ALXN1210-PNH-301 Ravulizumab	Male / 37 years / 66 kg	First; anaemia	71 85 99	544 525 827	0.0623 0.0414 0.0505	2	Gum infection	CAC
ALXN1210-PNH-301 Ravulizumab	Male / 43 years / 70 kg	First; anaemia	99	615	0.0766	3	None	Unexplained
ALXN1210-PNH-301 Eculizumab	Male / 25 years / 92 kg	First; anaemia	99	866	55.9	2	None	Free C5 ≥ 0.5 ug/mL
ALXN1210-PNH-301 Eculizumab	Male / 45 years / 74 kg	First; haemoglobinuria	155	933	34.4	None	None	Free C5 ≥ 0.5 ug/mL

Trial / treatment arm	Characteristics: Sex / age / body weight	BTH event; symptoms	Study day	LDH, U/L	Free C5, ug/mL	RBC transfusion, U	Possible CAC	Association
ALXN1210-PNH-301 Eculizumab	Female / 35 years / 88 kg	First; fatigue, dyspnoea, anaemia	57 71	571 1,164	24.2 80.0	2	None	Free C5 ≥ 0.5 ug/mL
		Second: fatigue, haemoglobinuria, dyspnoea, anaemia	169 183	890 865	58.6 64.4	None	URI	Free C5 ≥ 0.5 ug/mL; CAC
ALXN1210-PNH-301 Eculizumab	Male / 39 years / 94 kg	First; fatigue, anaemia	183	3,720	86.1	2	None	Free C5 ≥ 0.5 ug/mL (missed day 169 dose)
ALXN1210-PNH-301 Eculizumab	Male / 39 years / 70 kg	First; fatigue, haemoglobinuria, abdominal pain, dyspnoea, anaemia, erectile dysfunction	43	506	0.0445	None	Common cold	CAC
ALXN1210-PNH-301 Eculizumab	Female / 49 years / 56 kg	First; fatigue, dyspnoea, anaemia	99	529	0.0644	2	URI	CAC
ALXN1210-PNH-301 Eculizumab	Male / 35 years / 93 kg	First; anaemia	43	700	0.148	None	Non-specific infection	CAC
ALXN1210-PNH-301 Eculizumab	Male / 57 years / 89 kg	First; dyspnoea, anaemia	141	524	0.189	None	Influenza Bronchitis	CAC

Trial / treatment arm	Characteristics: Sex / age / body weight	BTH event; symptoms	Study day	LDH, U/L	Free C5, ug/mL	RBC transfusion, U	Possible CAC	Association
ALXN1210-PNH-301 Eculizumab	Male / 52 years / 73 kg	First: fatigue, haemoglobinuria, anaemia	99 113	1,242 1,088	18.2 1.46	1	None	Free C5 ≥ 0.5 ug/mL
		Second: haemoglobinuria, anaemia	155 169 183 US	1,172 653 4,080 >4,200	17.6 1.41 90.9 -	2	URI Acalculous cholecystitis	Free C5 ≥ 0.5 ug/mL; CAC
ALXN1210-PNH-301 Eculizumab	Female / 50 years / 72 kg	First; dyspnoea	57	524	-	None	None	Unexplained
ALXN1210-PNH-301 Eculizumab	Male / 28 years / 55 kg	First; anaemia	71	597	0.03	None	None	Unexplained
ALXN1210-PNH-301 Eculizumab	Female / 64 years / 82 kg	First; fatigue, anaemia	141	520	0.0748	None	None	Unexplained
ALXN1210-PNH-301 Eculizumab	Female / 29 years / 48 kg	First; abdominal pain	169	579	0.0411	None	None	Unexplained
ALXN1210-PNH-302 Eculizumab	Male / 29 years / 95 kg	First; haemoglobinuria	29	1,257	24.1	None	None	Free C5 ≥ 0.5 ug/mL
		Second; haemoglobinuria	57	1,037	24.8	None	None	Free C5 ≥ 0.5 ug/mL
		Third; haemoglobinuria	99 113	811 3,846	19.3 91.9	1	None	Free C5 ≥ 0.5 ug/mL
ALXN1210-PNH-302 Eculizumab	Male / 34 years / 71 kg	First; haemoglobinuria	141	618	0.1	None	Flu-like symptoms	CAC
ALXN1210-PNH-302 Eculizumab	Female / 47 years / 75 kg	First; fatigue, haemoglobinuria, dyspnoea, anaemia	176	515	0.1	4	Acute pyeonephritis	CAC

Trial / treatment arm	Characteristics: Sex / age / body weight	BTH event; symptoms	Study day	LDH, U/L	Free C5, ug/mL	RBC transfusion, U	Possible CAC	Association
ALXN1210-PNH-302 Eculizumab	Male / 60 years / 79 kg	First; fatigue, haemoglobinuria, anaemia	127	1,846	2.1	2	Gastroenteritis	CAC
ALXN1210-PNH-302 Eculizumab	Male / 60 years / 84 kg	First: fatigue, dyspnoea	155	799	0.1	None	None	Unexplained

Key: BTH, breakthrough haemolysis; CAC, complement-amplifying condition; LDH, lactate dehydrogenase; RBC, red blood cell.
Notes: the upper limit of normal for LDH is 246 U/L; complete terminal complement inhibition defined as free C5 < 0.5 ug/mL.
Source: Brodsky et al. 2020.[2]

Appendix A11

Table 13: Citations excluded at secondary screening phase for the clinical systematic literature review

Author	Year	Title	Reason
Alashkar et al	2018	The Role of Whole-Body Magnetic Resonance Imaging (WB-MRI) in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH)	Outcomes
Alashkar et al	2017	Serologic response to meningococcal vaccination in patients with paroxysmal nocturnal hemoglobinuria (PNH) chronically treated with the terminal complement inhibitor eculizumab	Outcomes
Boschetti et al	2004	Clinical and molecular aspects of 23 patients affected by paroxysmal nocturnal hemoglobinuria	Outcomes
Brodsky et al	2006	Effect of the terminal complement inhibitor eculizumab on patient reported outcomes in paroxysmal nocturnal hemoglobinuria (PNH): phase III triumph study results	Duplicate Publication
Burroughs et al	2017	Allogeneic Hematopoietic Cell Transplantation Using Treosulfan-Based Conditioning for Treatment of Marrow Failure Disorders	Other
Carrion Madronal et al	2018	Analysis of expenditure on orphan drugs according to the diagnosis	Outcomes
Centre for Reviews and Dissemination	2015	Prevalence and prognosis of paroxysmal nocturnal haemoglobinuria and the clinical and cost-effectiveness of eculizumab (Structured abstract)	Duplicate Publication

Author	Year	Title	Reason
Choi et al	2017	Efficacy of eculizumab in paroxysmal nocturnal hemoglobinuria (PNH) patients with or without aplastic anemia; Prospective study of Korean PNH cohort	Duplicate Publication
Colado et al	2017	Clinical impact of age and comorbidity in PNH patients	Outcomes
Connock et al	2016	Prevalence and prognosis of paroxysmal nocturnal haemoglobinurea and the clinical and cost-effectiveness of eculizumab (Structured abstract)	Duplicate Publication
Coyle et al	2014	Opportunity cost of funding drugs for rare diseases: the cost-effectiveness of eculizumab in paroxysmal nocturnal hemoglobinuria	Duplicate Publication
De Latour et al	2011	Influence of nucleated cell dose on overall survival of unrelated cord blood transplantation for patients with severe acquired aplastic anemia: A study by eurocord and the aplastic anemia working party of the european group for blood and marrow transplantation	Outcomes
DeZern et al	2018	Eculizumab Bridging Before Bone Marrow Transplant for Marrow Failure Disorders is Safe and Does Not Limit Engraftment	Other
Fattizzo et al	2018	Clinical significance of PNH clones in 3085 patients with cytopenia: A large single-center experience	Outcomes
Fattizzo et al	2019	Prognostic and predictive impact of small PNH clones in a large cohort of patients with myelodysplastic syndromes and aplastic anemia: A single-center experience	Outcomes
Fattizzo et al	2018	Prevalence of PNH clones and their clinical and prognostic significance in 3085 patients with cytopenia: A twenty-year single center experience	Outcomes

Author	Year	Title	Reason
Griffin et al	2016	Concurrent treatment of aplastic anemia (AA) with immunosuppressive therapy and paroxysmal nocturnal hemoglobinuria (PNH) with eculizumab	Intervention/Comparator
Griffin et al	2016	Concurrent treatment of aplastic anaemia (AA) with immunosuppressive therapy and paroxysmal nocturnal hemoglobinuria (PNH) with eculizumab: A UK experience	Outcomes
Halder et al	2018	Paroxysmal nocturnal hemoglobinuria in childhood and adolescence-a 5-year retrospective analysis from a single tertiary care center from North India	Population
Hallstensen et al	2015	Eculizumab treatment during pregnancy does not affect the complement system activity of the newborn	Study Design
Hill et al	2016	A subcutaneously administered investigational RNAi therapeutic (ALN-CC5) targeting complement C5 for treatment of PNH and complement-mediated diseases: Interim phase 1 study results	Population
Hill et al	2017	An investigational RNAi therapeutic (ALN-CC5) targeting complement C5 for treatment of PNH and complement-mediated diseases: Exploratory analysis of interim phase 1/2 study results supports reduced eculizumab dosing in patients with PNH	Outcomes
Hill et al	2007	TRIUMPH, a randomized placebo-controlled phase III trial, demonstrates that the terminal complement inhibitor eculizumab improves anaemia in PNH	Duplicate Publication
Hill et al	2017	Coversin, a novel C5 complement inhibitor, for the treatment of PNH: Results of a phase 2 clinical trial	Outcomes

Author	Year	Title	Reason
Hill et al	2017	Coversin, a novel C5 complement inhibitor, is safe and effective in the treatment of PNH: Results of a phase ii clinical trial	Outcomes
Ho et al	2008	Eculizumab for paroxysmal nocturnal hemoglobinuria: a review of clinical and cost-effectiveness (Structured abstract)	Study Design
Hoekstra et al	2009	Paroxysmal nocturnal hemoglobinuria in Budd-Chiari Syndrome: Findings from a cohort study	Other
Jalbert et al	2019	Epidemiology of PNH and real-world treatment patterns following an incident PNH diagnosis in the us	Outcomes
Jang et al	2017	Comparison of baseline clinical characteristics between asian vs. non-asian patients with paroxysmal nocturnal hemoglobinuria (PNH) from international PNH registry	Outcomes
Jovic et al	2016	Rare clonal blood disorders in childhood-single center experience	Study Design
Kelly et al	4576	Successful pregnancy outcomes in paroxysmal nocturnal hemoglobinuria with long-term eculizumab treatment	Study Design
Kelly et al	2010	The management of pregnancy in paroxysmal nocturnal haemoglobinuria on long term eculizumab	Study Design
Kruatrachue et al	1974	Pattern of "paroxysmal nocturnal hemoglobinuria" red blood cell in aplastic anemia	Intervention/Comparator

Author	Year	Title	Reason
Kulagin et al	2014	Prognostic value of paroxysmal nocturnal haemoglobinuria clone presence in aplastic anaemia patients treated with combined immunosuppression: Results of two-centre prospective study	Outcomes
Kulasekararaj et al	2016	Feasibility and optimal schedule of eculizumab in patients with haemolytic paroxysmal nocturnal hemoglobinuria (hPNH) with severe aplastic anaemia (SAA) prior to haemopoietic stem cell transplant (HSCT)	Intervention/Comparator
Lachmann et al	2016	Further studies of the down-regulation by Factor I of the C3b feedback cycle using endotoxin as a soluble activator and red cells as a source of CR1 on sera of different complotype	Study Design
Lee et al	2016	Immediate, complete, and sustained inhibition of C5 with ALXN1210 reduces complement-mediated hemolysis in patients with paroxysmal nocturnal hemoglobinuria (PNH): interim analysis of a dose-escalation study	Duplicate Publication
Lee et al	2016	ALXN1210, A long-acting C5 inhibitor, results in rapid and sustained reduction of LDH with a monthly dosing interval in patients with PNH: Preliminary data from a dose-escalation study	Duplicate Publication
Lukina et al	2018	Tissue iron overload assessment in patients with paroxysmal nocturnal hemoglobinuria	Study Design
Mercuri et al	2017	A retrospective study of paroxysmal nocturnal hemoglobinuria in pediatric and adolescent patients	Outcomes
Munir et al	2018	Anabolic steroids are effective in treatment of aplastic anaemia; Careful withdrawal is possible with no evidence of relapse hence reducing the long term toxicity	Intervention/Comparator

Author	Year	Title	Reason
Naithani et al	2008	Paroxysmal nocturnal hemoglobinuria in childhood and adolescence - A retrospective analysis of 18 cases	Outcomes
Nakayama et al	2016	Eculizumab Dosing Intervals Longer than 17 Days May Be Associated with Greater Risk of Breakthrough Hemolysis in Patients with Paroxysmal Nocturnal Hemoglobinuria	Outcomes
Narita et al	2015	Paroxysmal nocturnal hemoglobinuria and telomere length predicts response to immunosuppressive therapy in pediatric aplastic anemia	Population
National Horizon Scanning Centre	2016	Eculizumab (Soliris) for paroxysmal nocturnal haemoglobinuria: horizon scanning technology briefing (Structured abstract)	Study Design
Nevill et al	2016	The presence of a PNH clone influences the kinetics of response to immunosuppressive therapy (IST) in aplastic anemia (AA) patients	Outcomes
Nevill et al	2017	Aplastic anemia patients with monocyte-dominant PNH clones have a unique presentation and are less responsive to immunosuppressive therapy	Outcomes
Nissen-Meyer et al	2015	Paroxysmal nocturnal haemoglobinuria at Oslo University Hospital 2000-2010	Other

Author	Year	Title	Reason
Noguera et al	2000	Aplastic anemia and paroxysmal nocturnal hemoglobinuria: a follow-up study of the glycosylphosphatidylinositol-anchored proteins defect	Outcomes
Pagliuca et al	2016	Aplastic anemia in the context of hemolytic paroxysmal nocturnal hemoglobinuria: Feasibility of antibody-based intensive immunosuppression during eculizumab treatment	Outcomes
Pagliuca et al	2016	Long-term follow up of patients with immune-mediated bone marrow failure syndromes treated with alemtuzumab-based immunosuppression	Outcomes
Pagliuca et al	2017	Aplastic anemia in the context of hemolytic paroxysmal nocturnal hemoglobinuria: Intensive immunosuppression and eculizumab treatment. A retrospective analysis from two reference centers	Outcomes
Paquette et al	1997	Clinical characteristics predict response to antithymocyte globulin in paroxysmal nocturnal haemoglobinuria	Study Design
Parab et al	1990	Paroxysmal nocturnal hemoglobinuria: a study of 17 cases	Intervention/Comparator
Peffault De Latour et al	2019	Prognostic value of clone size in paroxysmal nocturnal hemoglobinuria (PNH) for thrombotic events in untreated patients in the International PNH Registry	Intervention/Comparator
Pichon Riviere et al	2016	Effectiveness of eculizumab in the treatment of paroxysmal nocturnal hemoglobinuria (Structured abstract)	Other

Author	Year	Title	Reason
Plessier et al	2019	Paroxysmal nocturnal hemoglobinuria and Budd Chiari syndrome: Impact of Eculizumab therapy on survival and liver outcome in 54 patients: A multicentric valdig study	Outcomes
Ramos Santana et al	2018	Budgetary impact of ultra-rare diseases in a third-level hospital	Outcomes
Roeth et al	2017	Optimization of dose regimen for ALXN1210, a novel complement C5 inhibitor, in patients with paroxysmal nocturnal hemoglobinuria (PNH): Results of 2 phase 1/2 studies	Duplicate Publication
Rogers et al	2017	Outcomes of immunosuppressive therapy for pediatric aplastic anemia: A north american pediatric aplastic anemia consortium (napaac) study	Population
Roth et al	2018	Effect of eculizumab on transfusion needs in PNH patients with and without transfusion history	Other
Roth et al	2007	Treatment with the terminal complement inhibitor eculizumab improves anaemia in patients with paroxysmal nocturnal haemoglobinuria: phase III TRIUMPH-study results	Other
Sahin et al	2019	The evaluation of paroxismal nocturnal hemoglobinuria patients who underwent eculizumab therapy	Outcomes

Author	Year	Title	Reason
Saito et al	2016	Hypomegakaryocytic thrombocytopenia (HMT): an immune-mediated bone marrow failure characterized by an increased number of PNH-phenotype cells and high plasma thrombopoietin levels	Population
Sallerfors et al	2016	Eculizumab treatment in paroxysmal nocturnal hemoglobinuria (Structured abstract)	Study Design
Schrezenmeier et al	2007	Safety and efficacy of the terminal complement inhibitor eculizumab in patients with paroxysmal nocturnal hemoglobinuria: shepherd phase III clinical study results	Other
Schrezenmeier et al	2017	Analysis of baseline clinical characteristics and disease burden in patients enrolled in the international paroxysmal nocturnal hemoglobinuria registry	Outcomes
Schrezenmeier et al	2014	Baseline characteristics and disease burden in patients in the international paroxysmal nocturnal hemoglobinuria registry	Outcomes
Schubert et al	2006	Treatment with the terminal complement inhibitor eculizumab improves anemia in patients with paroxysmal nocturnal hemoglobinuria: phase III Triumph study results	Duplicate Publication
Shaw et al	1999	Hematopoietic stem-cell transplantation using unrelated cord-blood versus matched sibling marrow in pediatric bone marrow failure syndrome: one center's experience	Other

Author	Year	Title	Reason
Socie et al	1996	Paroxysmal nocturnal haemoglobinuria: long-term follow-up and prognostic factors. French Society of Haematology	Outcomes
Socie et al	2016	Changing prognosis in paroxysmal nocturnal haemoglobinuria disease subcategories: an analysis of the International PNH Registry	Outcomes
Stebler et al	1990	High-dose recombinant human erythropoietin for treatment of anemia in myelodysplastic syndromes and paroxysmal nocturnal hemoglobinuria: a pilot study	Other
Sun et al	2002	Clinical analysis of 78 cases of paroxysmal nocturnal hemoglobinuria diagnosed in the past ten years	Duplicate Publication
Sutton et al	2013	Immune markers of disease severity and treatment response in pediatric acquired aplastic anemia	Population
Tisdale et al	2002	Late complications following treatment for severe aplastic anemia (SAA) with high-dose cyclophosphamide (CY): Follow-up of a randomized trial	Population
Ueda et al	2016	The first follow-up data analysis of patients with acquired bone marrow failure harboring a small population of PNH-type cells in the japanese, multicenter, prospective study optima	Outcomes
Ueda et al	2017	Effects of eculizumab treatment on the quality of life in patients with paroxysmal nocturnal hemoglobinuria treated in Japan	Duplicate Publication

Author	Year	Title	Reason
Urbano-Ispizua et al	2018	Efficacy of eculizumab in pediatric patients with paroxysmal nocturnal hemoglobinuria in the international PNH registry	Population
Vernon et al	2018	Excellence in PNH in Canada (EPIC): A single centre pilot project evaluating disease trajectory for PNH patients receiving eculizumab	Outcomes
Vinogradova et al	2016	The pregnancy course and outcomes during targeted therapy of paroxysmal nocturnal hemoglobinuria	Duplicate Publication
Vinogradova et al	2017	Paroxysmal nocturnal hemoglobinuria treatment during pregnancy	Duplicate Publication
Wilson et al	2017	Paroxysmal nocturnal hemoglobinuria: A 5-year institutional review	Other
Young et al	2006	Safety and efficacy of the terminal complement inhibitor eculizumab in patients with paroxysmal nocturnal hemoglobinuria: interim shepherd phase III clinical study	Duplicate Publication
Zanichelli et al	2016	Paroxysmal nocturnal hemoglobinuria: Clinical features and outcome in 124 patients evaluated in a single center	Outcomes
Zhao et al	2002	Clinical analysis of 78 cases of paroxysmal nocturnal hemoglobinuria diagnosed in the past ten years	Outcomes

Appendix A15

Table 14: Concomitant medications used by ≥ 5% of patients in the Randomized Period of ALXN1210-PNH-301

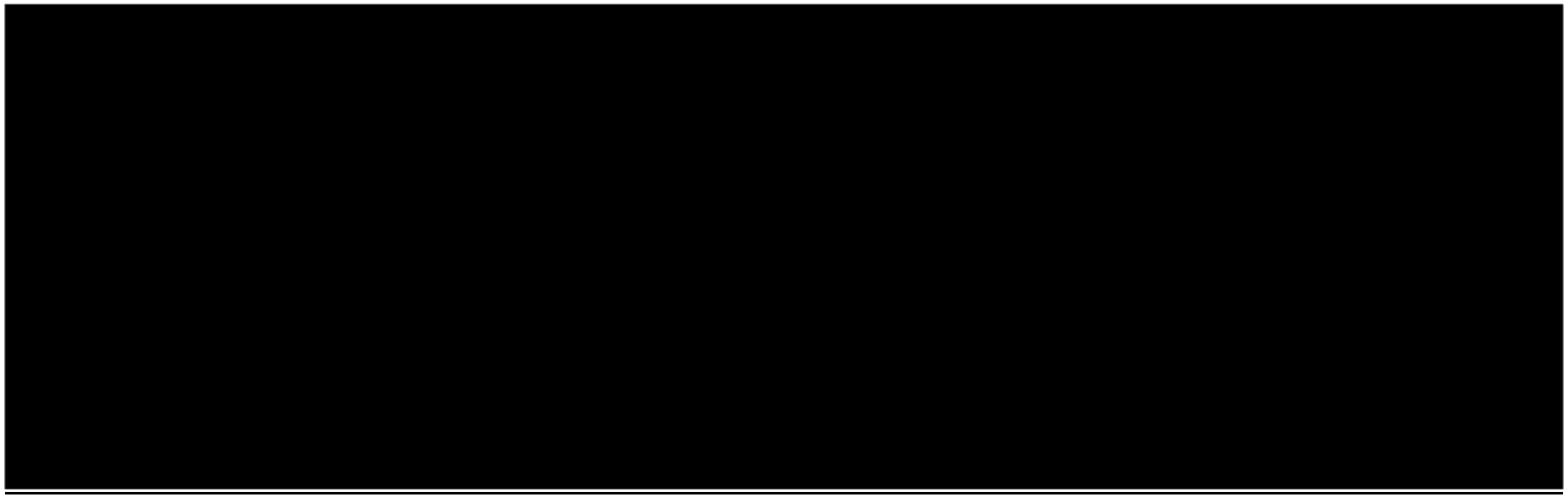
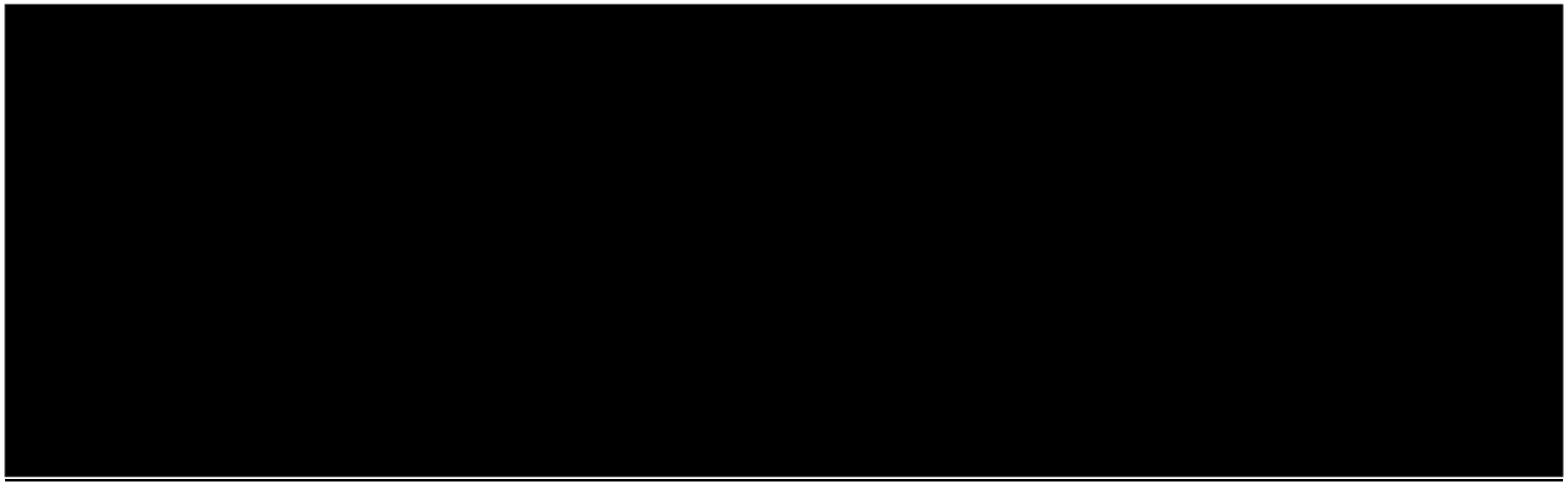


Table 15: Concomitant medications used by ≥ 5% of patients in the Randomized Period of ALXN1210-PNH-302



[redacted]

Appendix B11

Table 16: Breakthrough haemolysis events observed in the Extension Period of the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials

Trial / treatment arm	Characteristics: Sex / age / body weight	BTH event; symptoms	Visit/ Analysis visit	Visit Date	Date of Breakthrough	LDH Level (U/L)
ALXN1210-PNH-301 Eculizumab - Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ALXN1210-PNH-301 Eculizumab - Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ALXN1210-PNH-301 Ravulizumab - Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ALXN1210-PNH-301 Ravulizumab - Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ALXN1210-PNH-301 Ravulizumab - Ravulizumab		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ALXN1210-PNH-301 Ravulizumab - Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ALXN1210-PNH-301 Ravulizumab - Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Trial / treatment arm	Characteristics: Sex / age / body weight	BTH event; symptoms	Visit/ Analysis visit	Visit Date	Date of Breakthrough	LDH Level (U/L)
ALXN1210-PNH-302 Eculizumab - Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ALXN1210-PNH-302 Ravulizumab - Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ALXN1210-PNH-302 Ravulizumab - Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ALXN1210-PNH-302 Ravulizumab - Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: BTH, breakthrough haemolysis; LDH, lactate dehydrogenase.
Notes: the upper limit of normal for LDH is 246 U/L.
Source: Alexion data on file.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Ravulizumab for treating paroxysmal nocturnal haemoglobinuria [ID1457]

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	AAT
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	AAT (www.theaat.org.uk) is a charity registered with the Charities Commission of England and Wales (no. 1107539) as well as with OSCE in Scotland (SC049810). AAT currently has 1700 members. Membership is open to patients (and their families/carers) living with Aplastic Anaemia ("AA") living in England, Scotland, Wales and Northern Ireland. **Around 50% of AA patients have a PNH clone.** Our MISSION is to enable vital research into the causes of aplastic anaemia and other rare bone marrow failures that ultimately leads to finding a cure, and to support everyone affected by them, so they can lead healthy and fulfilling lives. We work to achieve this by: 1. Providing a moderated ONLINE COMMUNITY via a closed Facebook group. 2. Providing people with reliable and up-to-date INFORMATION resources that answer practical and treatment related questions.

	3. ADVOCATING on the patients' behalf across care providers in the UK for better quality care and support. 4. Providing a HELPLINE 5. Organising EVENTS, face to face or digitally, to get AA patients and their families together, for mutual support. 6. Raising funds for RESEARCH to find a cure that works for all, working with leading AA scientists and research centres 7. Delivering AWARENESS campaigns about AA and the support provided by the AAT. The AAT receives no funding from government or statutory sources. Last year we received funding from the following sources: 29% - donations and legacies; 60% - grant income (restricted); 11% - fundraising events.
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.	Yes. Alexion Pharma UK Ltd grant of £10,000 towards Patient Support and Outreach Programme (May 2019) and £8,000 towards an emergency programme of focussed information and support during Covid-19 crisis (May 2020).
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?	PNH Support undertook a survey (of primarily open ended questions) of PNH patients and carers which was disseminated via the following routes: • Via email and post to PNH Support members • Survey link posted on PNH Support and the Aplastic Anaemia Trust closed Facebook groups • Via email by the PNH National Service (Kings College Hospital) to patients for which they held email addresses 54 patients and 20 carers provided their experiences via survey responses. Of the 54 patients who responded, 16 are being treated with ravulizumab and 34 are being treated with eculizumab or not currently receiving treatment. Of the 20 carers who responded, 6 are carers of patients receiving ravulizumab and 14 are carers of patients being treated with eculizumab or not currently receiving treatment. 69 responses were received from patients (50) and carers (19) living in England, 4 were received from patients (3) and carers (1) living in Wales. One was received from a patient living in Northern Ireland. Graphs representing the respondents and the themes identified in the open ended survey question responses are set out as an Appendix to this document.

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?	**Patients** Of the 54 responses by patients to the question "Please describe what it is like to live with PNH", the 4 main categories into which responses fell are: 1) symptoms; 2) psychological impact; 3) quality of life with PNH; and 4) impact of treatment **1. Symptoms** The following symptoms were referred to by patients: Anaemia – 10 responses mentioned anaemia, 4 referred to the need for regular blood transfusions and 2 specified breathlessness. Two responses mentioned dizziness and "unbalanced movements". Cognitive problems – Three responses related to this e.g. "*the 'brain fog' can affect my attention span, my ability to understand when people are talking to me, and it slows down my ability to finish simple tasks."* Fatigue – 27 responses mention fatigue. "*The worst thing about PNH is probably the relentless fatigue. Some weeks are worse than others but it never goes away."* Breakthrough haemolysis – one response. Muscle pain – 4 responses mentioned muscle and joint aching, pain and general discomfort. **2. Psychological Impact** In terms of psychological impact, comments about fear featured most prominently including fear of: deterioration of the disease; blood clots; and fear of contracting an infection due to increased susceptibility and the consequential increase in symptoms/deterioration "*Also, there is always the niggling worry that one might pick up a virus when even a common cold can land one in hospital."* There were also comments about anxiety, frustration, worry, depression, negative mood and a reduction in confidence: "*Living with PNH affects me physically & mentally hugely*." **3. Quality of Life with PNH** In the quality of life with PNH category, the unpredictability of the disease was mentioned most often (7 times). "*The real difficulty with PNH is the unknown times you will be hit hard. There is no time frame, it isn't days before treatment or after. I don't know when I will have a bad day. That is the major difficulty with living with PNH*." Restriction on activities was also mentioned (5 times) i.e. physical activities have been curtailed to accommodate PNH related limitations especially fatigue and reduced energy. The impact of infections on patients was mentioned twice with this resulting in the return of PNH symptoms, the length of time taken to recover and the impact on general wellbeing. "*The other main concern is how carefully you have to monitor your health if you become unwell, as a simple virus on infection can often cause PNH symptoms to recur, and even if it doesn't, your ability to recover still takes longer and impacts your blood counts and general well-being*." The lack of understanding of PNH by people generally as a result of it being an invisible condition was commented on 4 times. *"It's difficult being a PNH patient, reasons been the majority of the population have no idea what it is and how it impacts our lives.".* This lack of knowledge also extends to the medical profession generally leaving patients needing to educate them on what PNH is "*The fact that PNH is so rare means that when one is seeing a consultant of another speciality he/she does not know the details of the illness and one has to explain the implications*." The length of time to diagnosis was mentioned by 2 patients including the burden of feeling "*mistaken with you [sic] symptoms and [you[begin to believe what people are saying that you are 'making it up*". Four patients commented that they essentially have a normal quality of life "*I am very fortunate that I live a fairly normal life as PNH affects everyone differently*."

4. Impact of Treatment

Under the impact of treatment category, the most comments (11) related to the improvement of symptom control and quality of life generally since treatment with eculizumab including patients who no longer need regular blood transfusions. "*Living with PNH is very debilitating (if not on medication), my quality of life became very poor - I was extremely tired, felt constantly nauseous, haemolysing was very unpleasant and left me feeling sick and weak. I also had severe bouts of extreme abdominal pain which left me bed bound for days at a time. I also suffered from jaundice and my sleep suffered hugely*". There were an equal number of comments (9) centred around: a) the improvement of symptom control and quality of life generally since treatment with ravulizumab and b) the burden of fortnightly infusions of eculizumab. "*But on ravulizumab I have been able to lead a normal life with little or no side effects and I don't think about my condition as my energy levels seem to be fairly constant*". The benefit of a longer period of time between infusions i.e. 8 weeks: "*Having treatment every 8 weeks instead of every 2 is helpful in organising one's life keeping things more normal*".

The burden of fortnightly infusions included not being able to be flexible with making plans or going on holiday outside the 14 day treatment period. It also included: anxiety caused by logistics of receiving the fortnightly treatment i.e. deliveries, scheduling of homecare visits; the impact of fortnightly treatment on employment with some employers not being accommodating; the impact on family life with the whole family's schedule being ruled by the fortnightly infusions; and caring duties being disrupted by infusions. Two patients mentioned the negative impact treatment with warfarin has had on them including the inconvenience and monitoring requirements which impacted their choice of employment and employment generally.

Carers

Of the 19 responses given by carers to the question "As a carer, please tell us what it is like for you to care for someone with PNH", there was a prevalence of comments about the negative psychological impact on carers including the fear of the patient getting an infection or having a crisis and needing hospitalisation: "*To some degree, we live on a "knife edge" never knowing when the next crisis will come. As soon as the patient has a high temperature or any kind of infection, we immediately shift into crisis mode, which can result in trips to the A&E department, antibiotics administered (often IV) and transfusions required*". These comments also included the stress of the diagnosis process, the difficulty of seeing a loved one suffer, the burden of treatment on the patient, the stress of infusions on the carer, being worried about the onset of symptoms or the impact of an infection. The impact on the carer of needing to provide support was also mentioned: "*Bit of a roller coaster... obviously have to offer support, both physical and emotional at what can be quite trying times."* One carer felt isolated as support groups were too far to travel.

Some carers commented on the impact on family life including: needing to provide support to the patient; infusions being intrusive; there being less energy for home life; and the need for the carer to take on more of the burden of running the home i.e. "*The impact on me as his partner has been that I have had to maintain the family home and take almost complete responsibility for housework, cooking, gardening, DIY and maintaining extended family relationships over many years."* One mentioned that the impact of PNH on the patient had been a reason why they had decided not to have children. One carer commented on their improved quality of life as a result of treatment with eculizumab "Seeing my husband stabilise on Soliris and leaving a normal life is a huge relief." Some also mentioned the impact which the lack of knowledge of PNH by healthcare professionals generally had on them as it increased the responsibility of the carer to educate them/ensure the PNH was being addressed. "*Given how rare PNH is, as carers, we often find that we know more about the illness and how it should be treated than the local health professionals we meet. Most have never heard of PNH, much less know how it should be treated. This places additional strain on carers and family members at what is already a stressful time. This strain becomes unbearable if the local doctors are unwilling to listen to the carers or to take advice on how the patient should be treated from the PNH specialist centres*". Two carers said no care was required to be provided by them to

	the patient, and one commented that it was "OK". One carer had reduced their work commitments to be able to assist the patient if required.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	**Patients** Of the 54 responses by patients to the question "What do you think of the current PNH treatments (not including Ravulizumab) and care available on the NHS?", most comments related to treatment related to eculizumab: the majority of which (21 comments) related to the burden of fortnightly infusions including the restrictions this places on making plans, travelling, work (including the ability to work), social and family life and the constant reminder of the illness. Many comments (17) concerned the positive impact of eculizumab on symptom control and the ability to have an improved quality of life: "*Sorlis [sic] is a great treatment and enables me to have good quality of life*." Patients also commented (13 comments) on the limitations of eculizumab including patients who had unmet need despite being treated with it including onset of fatigue and symptoms between fortnightly treatments "*The treatment is every 14 days, but for me, it doesn't last the full 14 days. From day 9, I get fatigued and out of breath. This means I have to ration my activities. I can't work full-time, socialise as well as exercise. I have to choose what I do. If I do all three, I get fatigued even earlier than day 9. Normally I can't do anything the last few days, so I schedule my treatment for Mondays, so that I can just rest over the week-end before treatment, when my symptoms are at their worst."* 5 of the 13 responses concerned being negatively impacted by the regular cannulation required for the fortnightly infusions: "*Treatment is an infusion which means having to be cannulated every 14 days. If the nurses don't succeed first time round, it could hurt and even bruise*." 12 responses expressed satisfaction with being able to receive the treatment at home or work "*Being able to have the treatment at home or at work, and not in hospital, saves time and is very convenient*" with one of those responses noting the stress involved in organising the homecare visits. One comment mentioned that being able to have infusions at home during COVID 19 meant being able to be treated without fear. A number (9) of comments expressed a desire for more treatment choices to be available including ones with different delivery methods including sub-cutaneous injection and longer periods between treatments "*To have a variety of drugs would allow patients to find the best option for their personal circumstances. Be that trying a mixture of drugs, different dosages, different timings and delivery options e.g. via IV, tablet, subcutaneous injection*." 5 responses related to the fact that eculizumab was available to them and at no cost. In relation to care, the majority of comments (24) considered the care of the NHS to be excellent, many (7) said very good, equal numbers (3) said good and not good (2 comments related to care outside the PNH National Service), 5 didn't know (with one not receiving treatment). One expressed that there was no cure. One expressed problems communicating recently with the PNH National Service. **Carers** Of the 21 responses by carers to this question, most comments (8)related to treatment with eculizumab including 6 responses referring to improved quality of life and symptom control after treatment with eculizumab: "*Soliris is undoubtedly an excellent treatment and provides patients with a degree of stability in managing a life limiting condition. It does reduce the reliance on regular transfusions and provides a level of "normal life."* 6 comments also mentioned the burden of fortnightly infusions including the restrictions this places on quality of life generally including making plans, travelling, work (including the ability to work) and general independence and 2 commented on the fact that eculizumab was available to them, and at no cost. Equal numbers of comments (3) expressed satisfaction with the homecare service i.e. being able to receive the treatment at home and reduction in hospital visits "*The fortnightly treatment at home is very welcome, in reducing the number of hospital visits and appointments"* and to the limitations of eculizumab including patients who experienced unmet need including fatigue and other symptoms despite treatment, One carer commented that taking daily (prophylactic) antibiotics and carrying emergency antibiotics whilst on eculizumab affected the patient's

	quality of life. In relation to care, 6 considered the care of the NHS to be excellent, 5 said very good, 2 said good, one didn't know as was only aware of blood transfusions and warfarin as treatments. One expressed problems communicating with the NHS. One carer expressed the desire for her son to move to ravulizumab and one carer expressed that being able to live closer to a specialist PNH centre would be preferable as local care was not the same.
8. Is there an unmet need for patients with this condition?	**Patients** Of the 54 responses by patients to the question "Do you think there is an unmet need for patients with PNH (i.e. something that is not addressed by current care or treatment)?", equal numbers of comments (12) considered there was no unmet need and were satisfied with the care and support provided and expressed a desire for more treatment choices with alternative delivery methods e.g. non-intravenous and longer periods between treatment "*Whilst Soliris has been a life changing drug for me, relying on a 12 day cycle has become increasingly difficult. It can effectively feel like a ball and chain weighing you down. As Soliris is currently the only drug available I feel that that in itself is an unmet need. With no other possible options you are limited in how you fully engage with work, family, travel, exercise, to name a few... The list feels endless."* 2 patients considered a cure to be an unmet need. Many (10) responses identified the burden of fortnightly eculizumab infusions to be an unmet need referring to the negative impact on planning, holidays, working and general disruption. "*It would be good for if intervals can be longer i.e. more than a month or so. Having treatment every two weeks is very disruptive especially when you work*". One patient wanted to minimise the time spent at hospital receiving fortnightly infusions (Northern Ireland). Six patients consider that healthcare professionals generally needed education about PNH: "*Again the condition is not taken seriously by all medical personnel. In my case it took 21 months for a diagnosis and a further 12 months before anyone bothered to explain in detail and simply so that I and my family could have greater understanding of what I had to learn to live with.".* Four patients considered that primary and secondary care needs to be more joined up or care is inconsistent between personnel. Three patients felt that more of a holistic approach to their care needed to be taken rather than care being limited to review of standard symptoms or blood results. Three patients felt that addressing the psychological impact of PNH to be an unmet need and one suggested that counselling should be offered as part of standard treatment. Two patients thought more information could be provided generally, and about living with PNH e.g. on obtaining disability cards or benefits and one considered transparency about new treatment and drugs to be lacking. One patient considered fatigue to be an unmet need and another considered pain to be one. **Carers** Of the 21 responses by carers to this question, most comments considered that the burden of the fortnightly eculizumab infusion was an unmet need referring to the negative impact on planning, holidays, working (including the ability to work), general disruption and intrusiveness (including the psychological impact and stress of a fortnightly infusion) and the effect of regular cannulation on veins and the fact that the timing of the homecare visits cannot be guaranteed. "*The need for a 2 - 3 hour treatment in the patient's home every two weeks and the fact that the healthcare provider cannot guarantee the time that the treatment will be provided, means that patients lose 0.5 - 1 day every 2 weeks from their working life which can make it challenging to maintain full time work*". 3 considered there to be no unmet need. 8 responses expressed a desire for more treatment choices with alternative delivery methods and longer periods between treatment and one carer commented that there was no cure, merely a maintenance of patients "*in a relatively stable state*." Two carers considered addressing the psychological impact of PNH to be an unmet need including recognition of this by the medical professional and local authorities and having accessible support groups to relieve isolation. Three carers considered that treatment with eculizumab resulted in unmet need in terms of prevalence of symptoms and stability of PNH. One carer considered side effects to be an unmet need and another considered there needed to be more information about new drugs and when they will be available. One didn't know.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	**Patients** Of the 16 responses **by patients being treated with ravulizumab** to the question "What do you think the advantages are of being treated with Ravulizumb (e.g. symptom control, ability to work, psychological impact, impact on relationships, family life, quality of life etc)?", most (13) comments related to the positive psychological impact of taking ravulizumab including being able to work full time "*My whole outlook on life has changed since being on Ravulizumab and I feel like a normal member of the population making a full contribution*." It reduces the stress related to employment which patients face when having fortnightly infusions. An 8 weekly infusion means not having to think about it every 2 weeks which improves quality of life and wellbeing and is "*psychologically less intrusive."* 9 comments specifically related to how patients identify with the disease i.e. forgetting they have PNH or not considering themselves defined by it any more. "*I can actually forget I have PNH*." 10 responses addressed improved symptom control: "*Since being on Ravulizumab I have had really good symptom control - I have not had any infections or any breakthrough haemolysis in 3 years".* Two patients commented that their symptom control was the same as with eculizumab. 8 patients commented that their quality of life generally had improved, 9 patients commented that the 8 weekly infusion allowed them greater independence in relation to planning, holidays, working, activities, family and social life. "*The treatment is every 2 months: a. This means fewer cannulations and therefore less anxiety b. Less disruption to my work schedule c. Being able to go on holiday more easily d. I don't have to tell my employer when my treatment is and can simply take holiday on the day of treatment. The treatment makes me feel more free and almost as if I am not ill, as I don't have to arrange my whole life around a bi-weekly treatment*." Equal numbers of comments (6) were provided on the positive impact on family life including being able to take holidays, less disruption and stress to partners and relationships: "*My family life is now normal, with me able to do work around the house and do all the normal day to day things like shopping and cooking, i also have no worries about going out and I can book ticket for an event in the future with the almost, certain knowledge that I will be able to attend*" and on the positive impact on employment including being able to work full time, treatment being less disruptive of work and not requiring them to take sick days. Of the 37 responses **by patients not being treated with ravulizumab** to the question "What do you think the advantages would be to you of being treated with Ravulizumb (e.g. symptom control, ability to work, psychological impact, impact on relationships, family life, quality of life etc)?" Most (20) comments concerned the increased independence that would be provided by 8 weekly infusions due to it being less intrusive and being able to plan more freely, travel and take holidays. 13 comments referred to an improvement in quality of life in general. Equal numbers of comments (12) considered that it would have: a positive effect on their employment including treatment being less disruptive, not needing to take sick days to have treatment, being able to work full time: "*Ravulizumb would open up a new chapter in my life. The restrictions of fortnightly infusion, have at times impacted on my working life. Generally I have found companies do not tolerate employees requiring time off on a regular basis";* a positive effect on their family life including less disruption to family arrangements and caregiving duties, family members not having to witness the fortnightly treatment and having more energy and time for family; a positive psychological impact including the relief provided to the general psychological impact of living with, managing and adapting to a chronic illness "*The psychological burden of beginning to understand that you have an incurable disease takes a long time to process and adjust to. Add to that the daily management of looking after yourself, taking note of your symptoms, diarising your IV treatments, liaising [sic] with drug deliveries, hospital staff, nurses etc. Not only does this effectively 'fill your brain' but it drains you and wears you down. To live in a mental state where a lot of these daily concerns are removed or minimised would have an incredibly positive effect on my mental health*." 4 comments regarding psychological impact were specifically about the patients' identification with PNH and the fact that 8 weekly infusions meant they would not be reminded of the disease as often, they could forget they have PNH for periods of time and wanting to feel "*like a normal person between*

	treatments." 10 responses considered anticipated improved symptom control would be an advantage. 5 responses considered the reduced number of cannulations to be an advantage due to damage to veins or being anxious about needles. one patient was hoping for a permanent treatment option and one thought life expectancy to be an advantage. 4 patients did not know about ravulizumab to be able to answer this question. One patient said "*feeling better about the future would be a great feeling to have".* **Carers** Of the 6 responses **by carers (of patients being treated with ravulizumab)** to the question "As a carer /family member of a PNH patient, what do you think the advantages are (to you/your family) of your loved one being treated with Ravulizumb (e.g. symptom, control, your ability to work, psychological impact, impact on your relationship/family life etc)?", equal numbers of comments (5) related to: a positive impact on family life due to improved energy levels**,** ability to plan and less disruption **"***Life has become much more relaxing knowing that she feels a lot better and it bouces [sic] off. The household has become a happier place. She is not as tired as use to be, more responsive to life. Not always tired when gets home from work - has some energy left for me & the family. She wishes to socialise more and is more caring with homelife* ; and positive psychological impact and less anxiety for the carer caused by fortnightly infusions: "*Every eight weeks normalises her life and is beneficial to her overall well being and mental health".* Two of these 5 comments related specifically to being able to forget for 8 weeks at a time that the patient is ill or on treatment. Many responses (4) referred to the increased independence provided by 8 weekly infusions being an advantage due to being less intrusive and having the ability to plan more freely, travel and take holidays and give the patient independence. 2 responses considered improved symptom control to be an advantage. One carer commented that the patient's energy levels were the same as with eculizumab. One comment referred to the positive impact on the patient's employment where an 8 week infusion made work easier to manage. Of the 14 responses **by carers (of patients not being treated with ravulizumab)** to the question "As a carer/family member of a PNH patient, what do you think the advantages would be (to you/your family) of your loved one being able to be treated with Ravulizumb (e.g. your ability to work, psychological impact, impact on your relationship/family life etc)?", the majority (13) of comments related to the independence provided by 8 weekly infusions due to life being less disrupted and the ability to plan more freely, travel (including to other countries to see family), take holidays, a reduced amount of time at hospital and having less treatments: **"***it would be amazing to space the infusions out to 8 weeks. it would be life changing*". The positive psychological impact of 8 weekly infusions was commented on by 7 carers due to their current level of worry and "*psychological distress*", and it would provide a patient with more confidence and improve mental health and wellbeing. "*This would then have a positive effect on his psychological wellbeing and give him greater confidence and assurance."* Six comments referred to patients' ability to work and have a full time job and the economic benefits of this: "*From an economic perspective, the longer treatment cycle would enable patients of working age to hold down full time jobs in line with their professional qualifications and experience. We have evidence that employers are reticent to employ someone who needs half a day off work on medical grounds every 2 weeks. Reducing this to half a day every 8 weeks would make a material difference to patients' job prospects and the wider UK economy*." 5 comments referred to an improved quality of life generally due to the 8 weekly infusions, 4 comments related to the positive impact of 8 weekly infusions on family life e.g. so children are not impacted by seeing parents receive treatment and the impact of treatment schedules on caregiving and family relationships: "*I do not want our baby to grow up watching her dad having to go through this infusion very often. If it is once in two months, I will make arrangements to keep her away, it's just much easier to manage things when it is not that often*." Three responses hoped for improved symptom control. One carer had no information about ravulizumab and one was not sure what the advantages would be. One carer commented that the 8 weekly infusion would enable the patient to spend more time in education.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	**Patients** Of the 16 responses by **patients being treated with ravulizumab** to the question "What do you think the disadvantages are of being treated with Ravulizumab?", 5 patients said there were no disadvantages, 5 comments related to the delivery mode of ravulizumab being a disadvantage i.e. intravenous infusion, that it can't be self-administered and veins aren't good or are difficult to find, 3 comments related to unmet need despite treatment i.e. still needing blood transfusions and experiencing fatigue. Two patients considered the longer infusion time a disadvantage. One patient had experienced joint pain since receiving this treatment, one had experienced mouth ulcers and one patient would prefer not to attend a hospital to receive the infusion. One patient preferred the oversight provided by nurses when having fortnightly infusions "*As an older person I quite liked having the care of nurses every 2 weeks. I felt they were able to keep a check on my health.".* One was concerned about unknown possible long term side effects of a new drug and one considered having to take daily prophylactic antibiotics to be annoying. Of the 37 responses by **patients not being treated with ravulizumab** to the question "What do you think the advantages would be to you of being treated with Ravulizumb (e.g. symptom control, ability to work, psychological impact, impact on relationships, family life, quality of life etc)?", 10 patients commented that there were no disadvantages, 9 patients commented that they didn't know, 8 comments related to concern they may have unmet need despite treatment e.g. if they don't respond well to the drug. 6 patients stated that possible side effects could be a disadvantage, 2 commented on the negative impact of changing from one drug to another including increased monitoring and "*Changing to a different drug can sometimes take a while and can drain your energy*." one said that if the 8 weekly treatment was delayed, this would be a disadvantage. One patient considered no medical contact for 8 weeks to be a disadvantage, one said that if the infusion was not delivered at home this would be a disadvantage, one considered the longer infusion time to be a disadvantage and one considered the delivery method to be a disadvantage: "*Still an infusion and for me medicalises my treatment a little, not in my control*". One patient considered that having blood tests with the infusion to be a disadvantage **Carers** Of the 6 responses **by carers (of patients being treated with ravulizumab)** to the question "As a carer/family member of a PNH patient, what do you think the disadvantages are (to you/your family) of your loved one being treated with Ravulizumb?", most (4) carers said there were none, one commented on the delivery method i.e. "*the physical canulation [sic] into veins which are difficult to find*" and one commented on the stress involved "*where this new and much better treatment may not be paid for in the UK and we will have to go back to the old version*". Of the 14 responses **by carers (of patients not being treated with ravulizumab)** to the question "As a carer/family member of a PNH patient, what do you think the disadvantages would be (to you/your family) of your loved one being able to be treated with Ravulizumb?"**,** 5 comments stated there were no disadvantages, 4 stated they didn't know about ravulizumab, two were concerned about remaining unmet need despite treatment. One carer expressed that it was a disadvantage to have less healthcare professional (HCP) oversight i.e. "*It is quite reassuring to have a health Professional visit our home fortnightly*." One was not sure, one was concerned about possible side effects, one was concerned with possible long term effects of a new medicine and one stated that it was not a cure and still only "*maintained patients*".

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	PNH affects patients very differently. Ravulizumab may be more appropriate for treating patients who respond well to C5 inhibitors and don't have additional unmet need despite treatment with them i.e. anaemia and extra-vascular haemolysis.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	We are not aware of any equality issues.
Other issues	
13. Are there any other issues that you would like the committee to consider?	• Surveyed patients treated with ravulizumab have experience of receiving ravulizumab since 2017 until the present (both during the trial and after the trial completed) and therefore their experiences of the therapy extend beyond the trial period. • Ravulizumab is innovative is the frequency of its delivery (i.e. 8 weekly) which represents significant increased independence from a fortnightly infusion and the negative consequences of that (on employment, family and social life and psychological impact) and an improvement in quality of life for both patients and their families. Reduced treatment frequency also requires less oversight by the overburdened NHS. Less contact between patients and medical personnel also reduced the risk of infection with COVID 19 to patients already vulnerable to infection. • Patients currently receiving ravulizumab and their carers were also surveyed about the impact to them of having to revert to treatment with eculizumab, should ravulizumab not be approved for treatment. Of the 16 responses by **patients**, the burden of fortnightly infusions including the negative affect of cannulation every 2 weeks and concern about deterioration in their current symptom control were the most significant impacts. These were followed by the negative effect on their quality of life generally including family life their employment (and the ability to be able to work/work full time). The negative psychological impact was also identified: "*My overall mental health & wellbeing would greatly suffer and I would be afraid of going back into depression" and the* loss of recently found independence: " *I am sure that there would be a deterioration in my mental health as my life would be dominated by treatment again*" , "*I have tasted freedom and normality for 3 years and going back to treatment with the two weekly Eculizumab, will take that away from me*." Of the 6 responses by **carers** of patients currently receiving ravulizumab, many referred to the burden of the fortnightly infusions: "*would mean that your life becomes a 2 week cycle and everything has to be planned around that*" and the impact on employment would also be negative: "*they would have their independence lessened considerably and would struggle to lead a normal and*

	economically productive life." They also identified the negative impact on quality of life generally including family life and the loss of a "*normal life*": "*A normal life would ge [sic] gone - the general well being of the family would be affected"* together with negative psychological impact: "*A grave impact as family as a whole with tension in the house 80% of the time. It would make all our lives miserable."* • Patients who are currently not on treatment or are currently being treated with eculizumab were also asked "If you qualified for treatment (i.e. 18 years plus and have haemolysis with clinical symptom(s) indicative of high disease activity or your PNH is clinically stable after having eculizumab for at least 6 months) and Ravulizumab was available, would you want to be treated with it?" Of the 37 responses received, 28 responded "Yes", one responded "No" (due to concern that the infusion would not relieve symptoms for the whole 8 week period) and 8 responded "I don't know" due to needing more information, medical advice, wanting an alternative treatment option and not needing treatment.
14. To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] if there are none delete highlighted rows and renumber below	

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- PNH is a serious condition which, without treatment, carries a heavy symptom and complications burden. This burden has been mitigated significantly in many patients by the intravenous fortnightly treatment, eculizumab, requiring contact with medical personnel every 14 days +/- 2 days.
- The unmet needs prioritised by surveyed patients and carers are: the need for more treatment choices with alternative delivery methods; and the burden of fortnightly eculizumab infusions. The fortnightly infusions have a negative impact on many elements of a patient and their family's quality of life especially their independence to be able to make plans, socialise, spend time with their family, go on holiday and work.
- The frequency of ravulizumab infusions (i.e. 8 weekly) is innovative in that it offers PNH patients and their families independence from the fortnightly treatment regime (and the associated negative impact on their quality of life mentioned above). Ravulizumab also provided improved symptom control for most patients surveyed, increasing their quality of life. Reduced treatment frequency also requires less oversight by the NHS.
- An essential element of the independence arising from treatment with ravulizumab to both patients, their families and society is the impact on a patient's ability to work: either at all or full time as a result of the absence of a fortnightly infusion disruptions and/or improved symptom control.
- The psychological benefit to patients (and their families) of being able to forget their incurable chronic disease for 8 weeks at a time contributes significantly to increased: mental health; overall wellbeing; productivity; and identification as full members of society.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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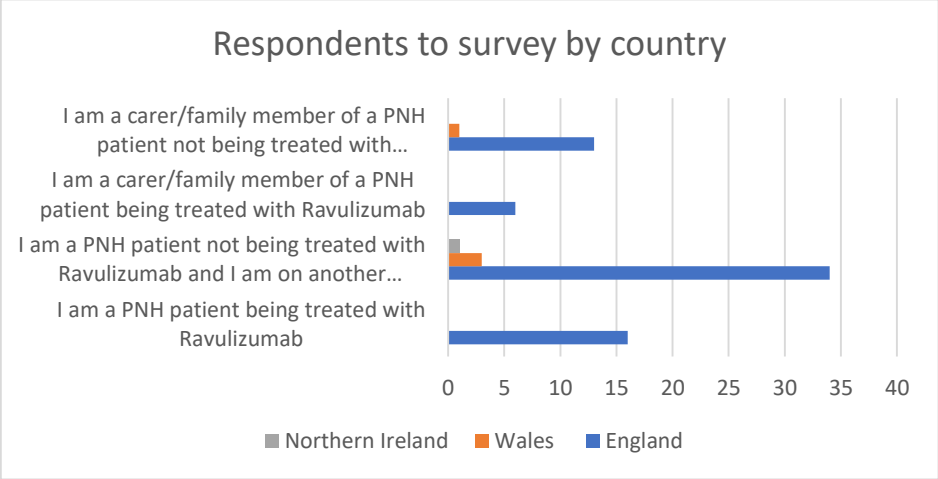
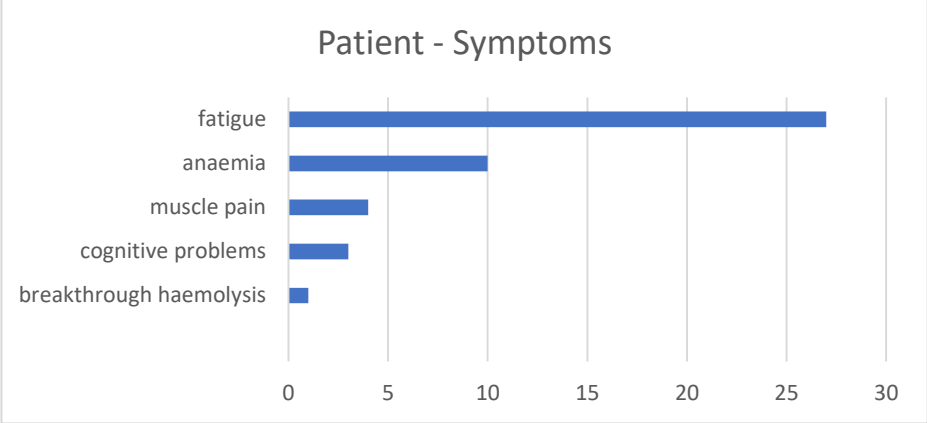
Appendix to AAT Support patient organisation submission re ravulizumab for treating PNH [ID 1457]

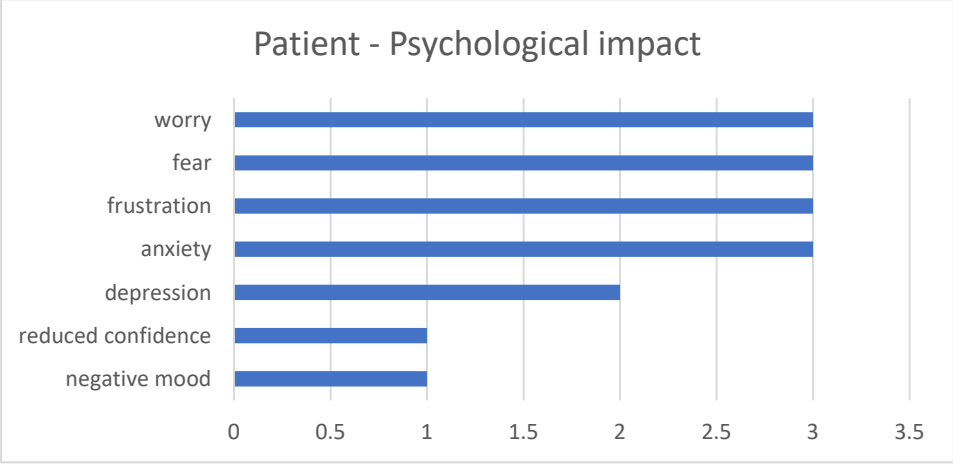
The numbers and headings referred to below relate to the NICE "Patient organisation submission" template document.

5. How did you gather information about the experiences of patients and carers to include in your submission?



6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?





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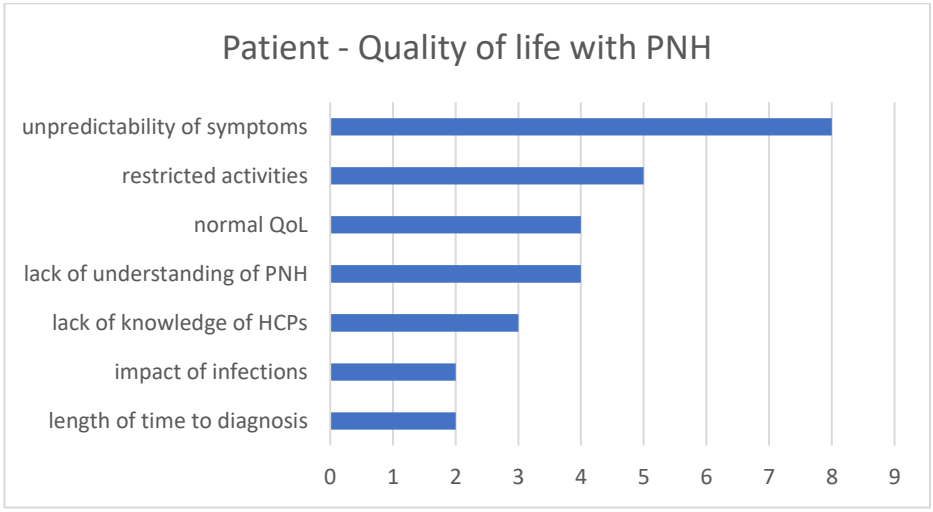
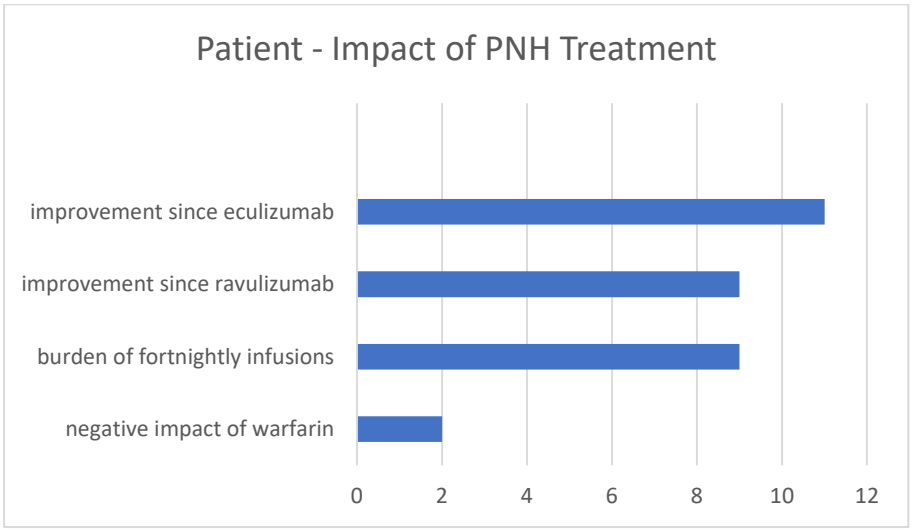
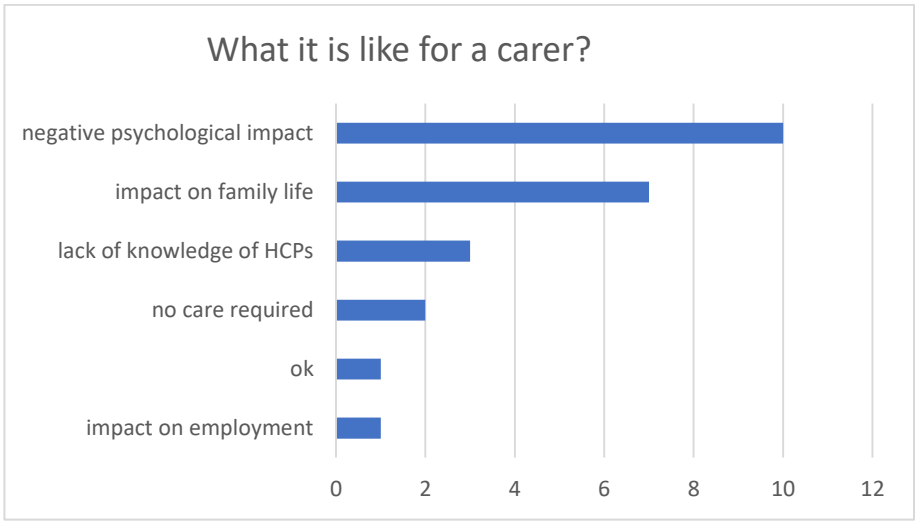
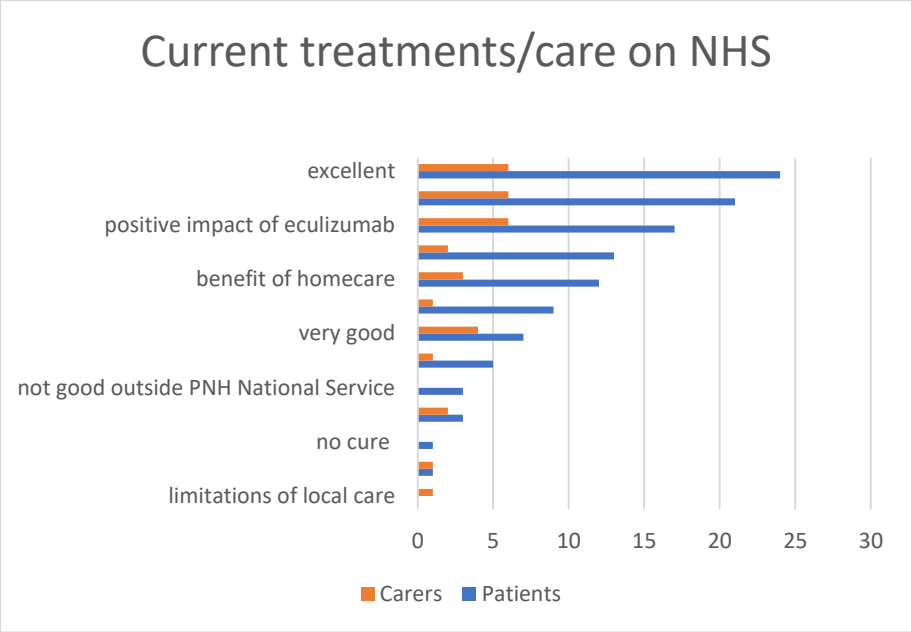


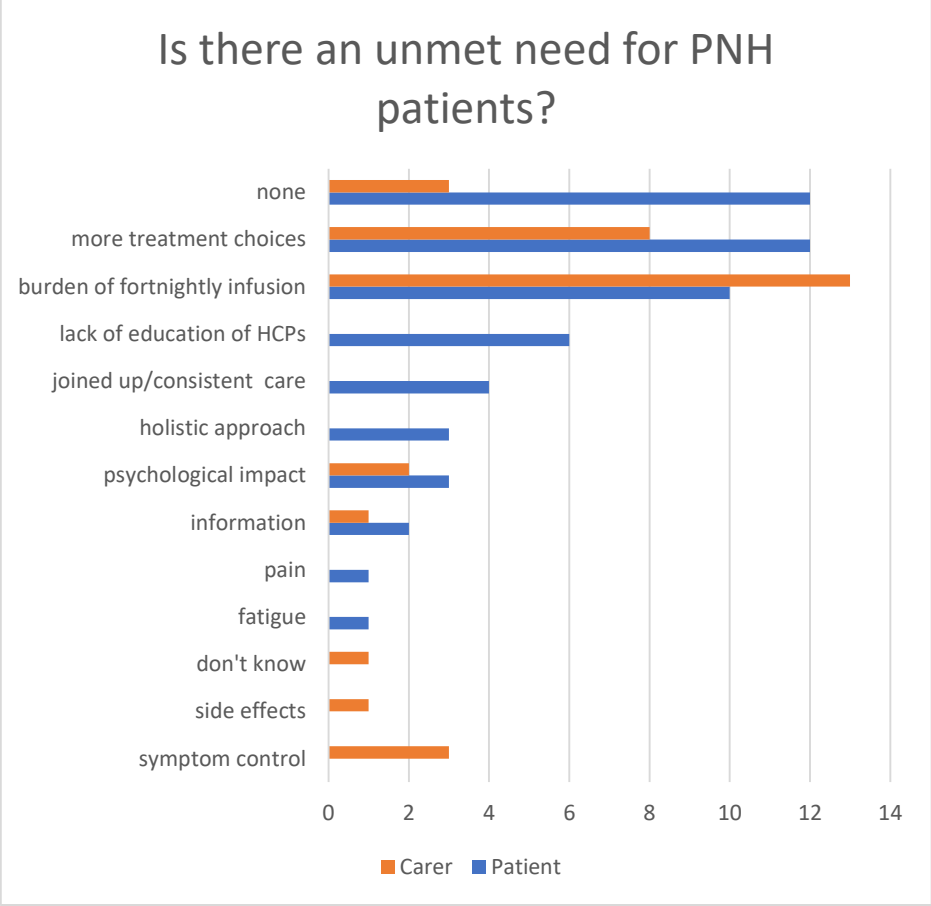




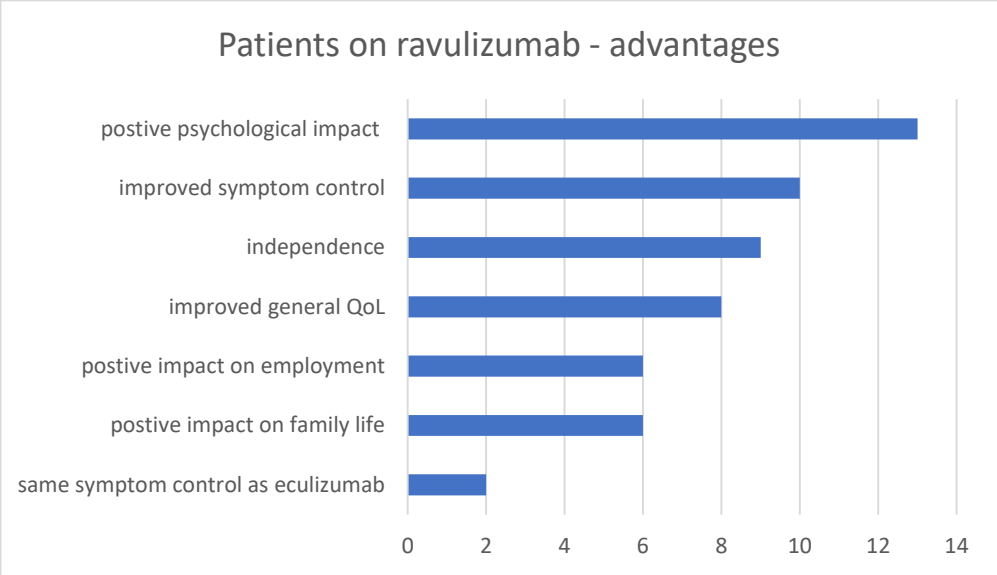
7. What do patients or carers think of current treatments and care available on the NHS?

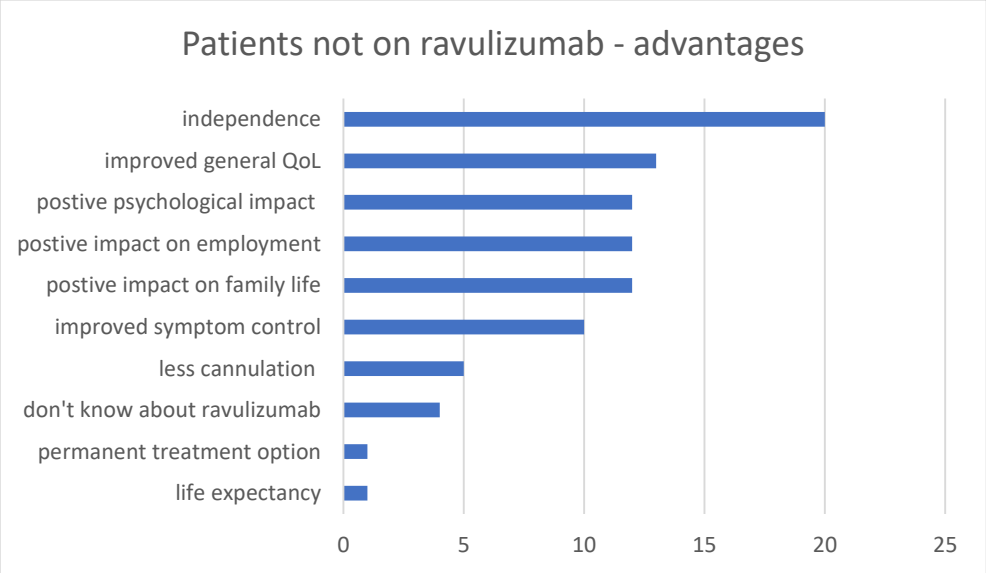


8. Is there an unmet need for patients with this condition?



9. What do patients or carers think are the advantages of the technology?





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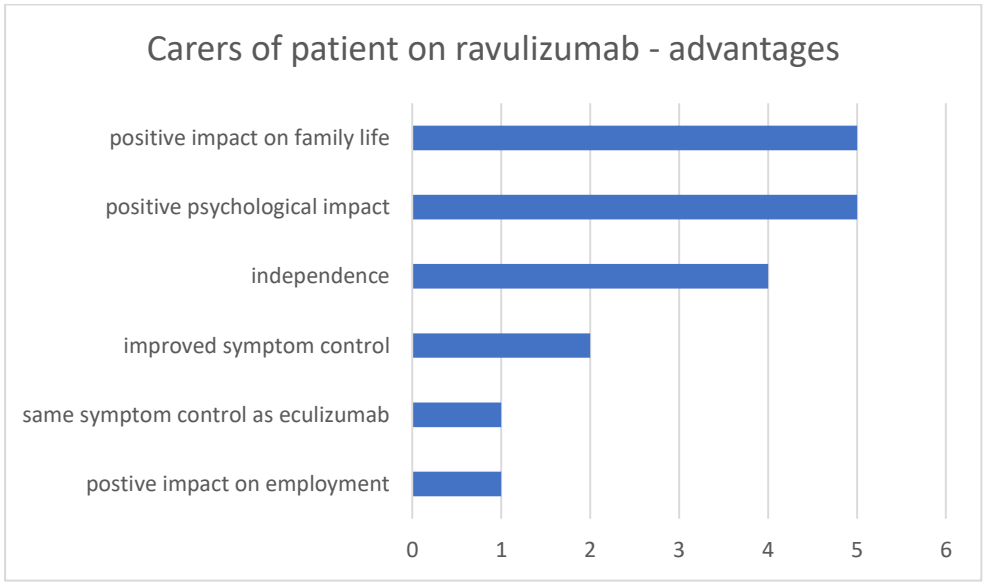
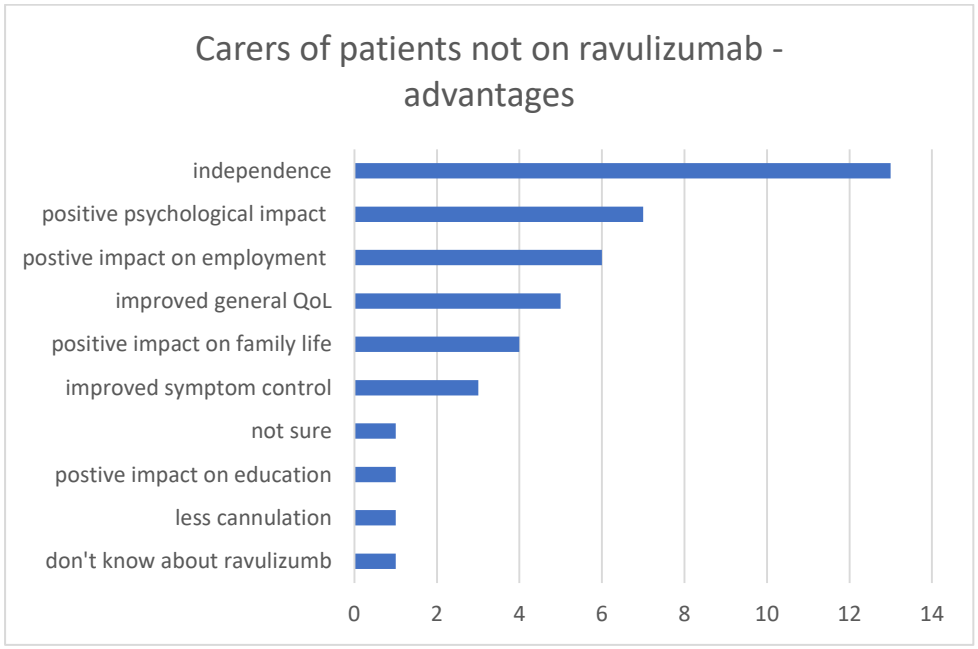
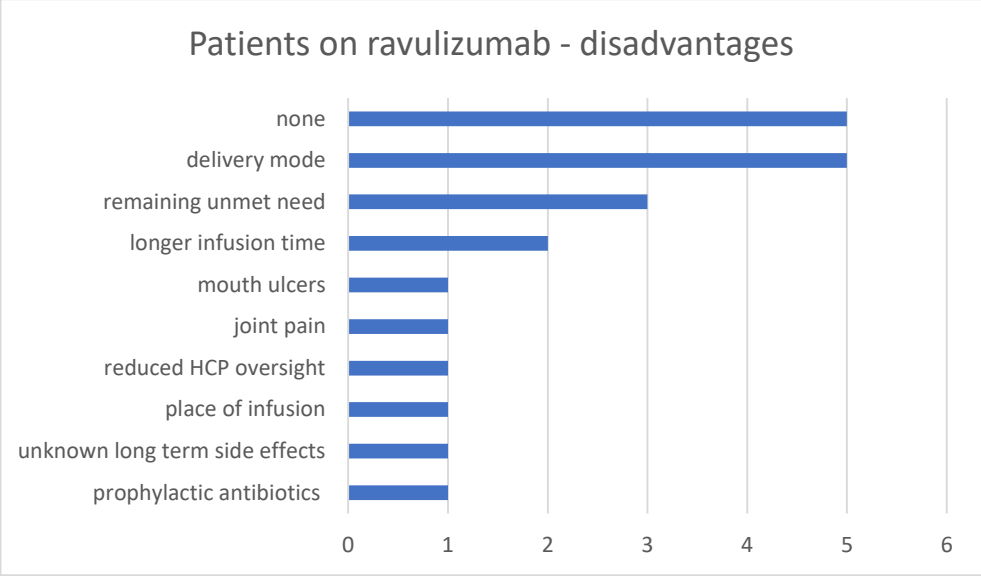
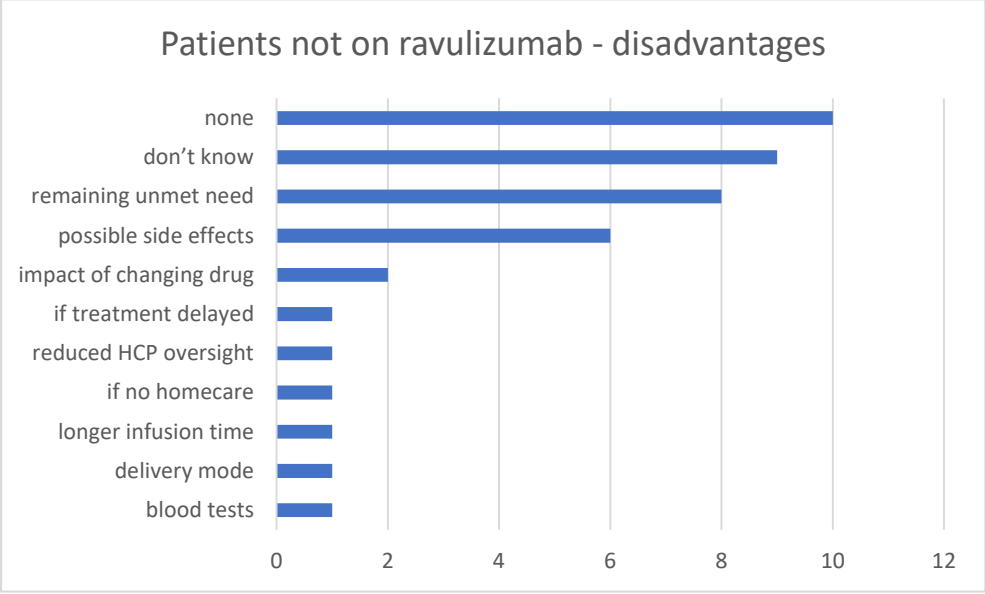




10. What do patients or carers think are the disadvantages of the technology?





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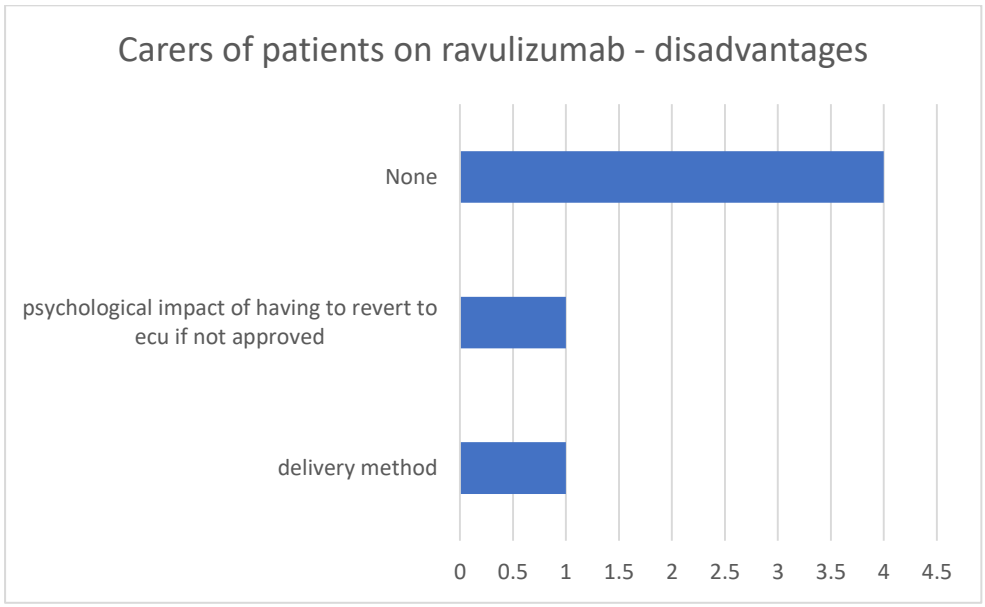
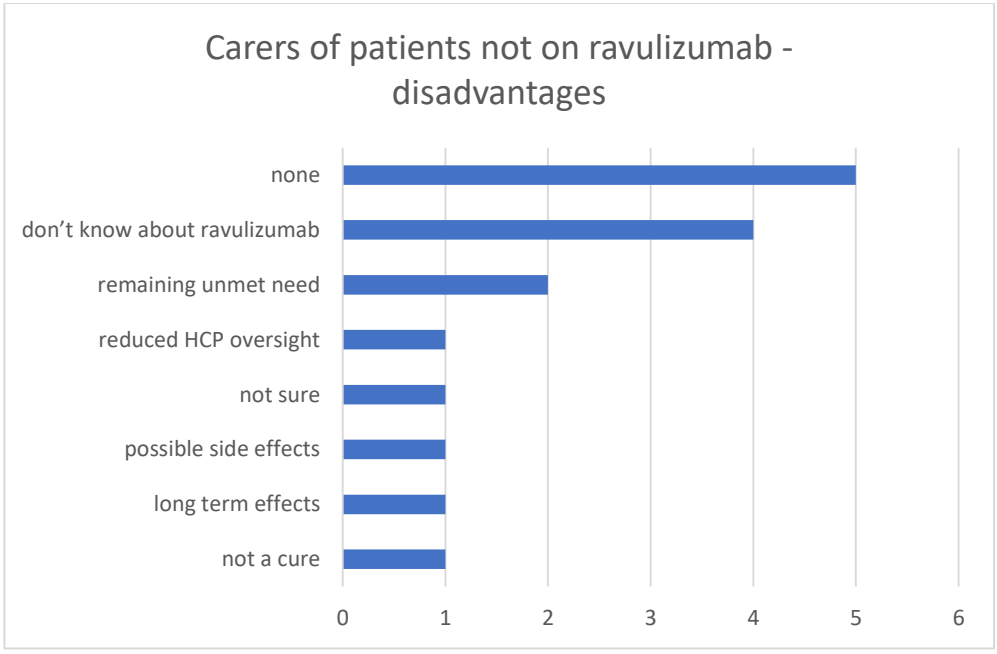
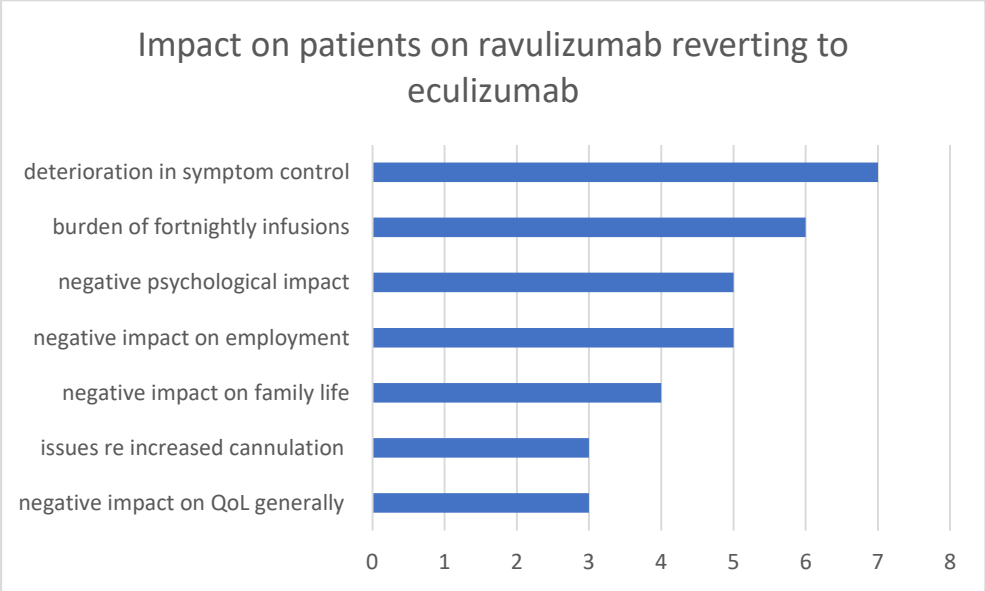
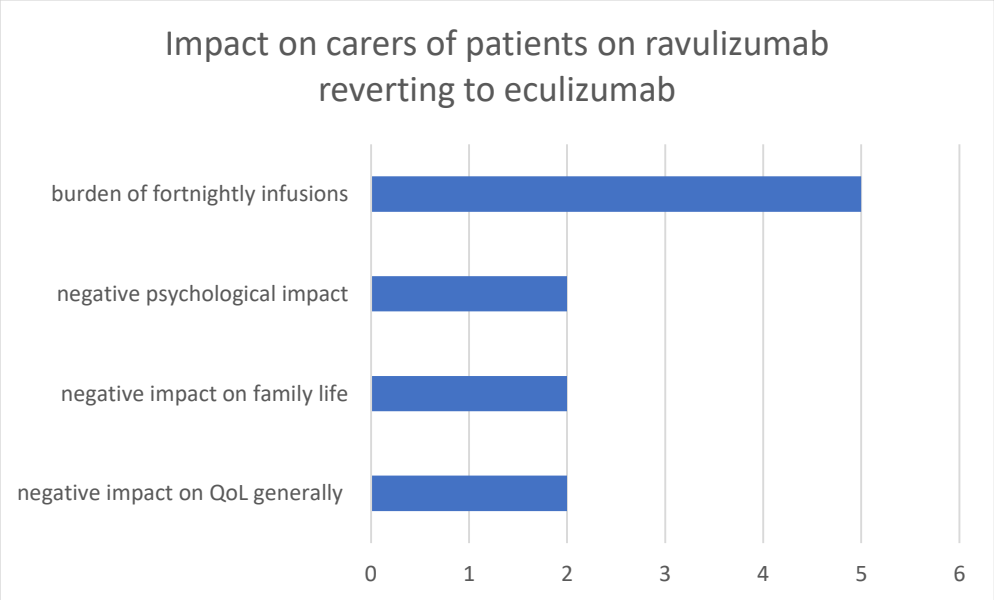




13. Are there any other issues that you would like the committee to consider?





NICE National Institute for Health and Care Excellence

Patient organisation submission

Ravulizumab for treating paroxysmal nocturnal haemoglobinuria [ID1457]

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	PNH Support
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	PNH Support (www.pnhuk.org) is a Charitable Incorporated Organisation registered with the Charities Commission of England and Wales (no.1161518). The trustees operate within PNH Support's constitution dated 30 April 2015 (the "Constitution"). The Constitution is an 'Association' model and has voting members other than its trustees. PNH Support currently has 117 members. Membership is open to patients (and their families/carers) living with Paroxysmal Nocturnal Haemoglobinuria ("PNH") living in England, Wales and Northern Ireland. The objects of PNH Support (as set out in its Constitution) are as follows: 1)To promote, protect and preserve the physical and mental health of those diagnosed with Paroxysmal Nocturnal Haemoglobinuria who reside in England, Wales and Northern Ireland (either permanently or temporarily) through the provision of support, education, advocacy and practical advice; 2)To advance the education of patients with PNH who reside in England, Wales and Northern Ireland, in particular but not exclusively by the provision of advice and a point of contact for newly diagnosed PNH patients, in England, Wales and Northern Ireland. We moderate a closed Facebook group, send email updates to

	members, produce a 6 monthly newsletter, hold regional patient and family meetings, hold a biennial patient and family conference and most since the onset of COVID 19, host Zoom calls. PNH Support is currently funded by donations but has received grants from pharmaceutical companies in the past together with honoraria and consultancy fees for provision of advice to pharmaceutical companies.
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.	Yes. Alexion Pharma UK Ltd, £180 – honoraria for advice provided subject to an agreement dated 4 December 2019.
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?	We undertook a survey (of primarily open ended questions) of PNH patients and carers which was disseminated via the following routes: • Via email and post to PNH Support members • Survey link posted on PNH Support and the Aplastic Anaemia Trust closed Facebook groups • Via email by the PNH National Service (Kings College Hospital) to patients for which they held email addresses 54 patients and 20 carers provided their experiences via survey responses. Of the 54 patients who responded, 16 are being treated with ravulizumab and 34 are being treated with eculizumab or not currently receiving treatment. Of the 20 carers who responded, 6 are carers of patients receiving ravulizumab and 14 are carers of patients being treated with eculizumab or not currently receiving treatment. 69 responses were received from patients (50) and carers (19) living in England, 4 were received from patients (3) and carers (1) living in Wales. One was received from a patient living in Northern Ireland. Graphs representing the respondents and the themes identified in the open ended survey question responses are set out as an Appendix to this document.

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?	**Patients** Of the 54 responses by patients to the question "Please describe what it is like to live with PNH", the 4 main categories into which responses fell are: 1) symptoms; 2) psychological impact; 3) quality of life with PNH; and 4) impact of treatment **1. Symptoms** The following symptoms were referred to by patients: Anaemia – 10 responses mentioned anaemia, 4 referred to the need for regular blood transfusions and 2 specified breathlessness. Two responses mentioned dizziness and "unbalanced movements". Cognitive problems – Three responses related to this e.g. "*the 'brain fog' can affect my attention span, my ability to understand when people are talking to me, and it slows down my ability to finish simple tasks."* Fatigue – 27 responses mention fatigue. "*The worst thing about PNH is probably the relentless fatigue. Some weeks are worse than others but it never goes away."* Breakthrough haemolysis – one response. Muscle pain – 4 responses mentioned muscle and joint aching, pain and general discomfort. **2. Psychological Impact** In terms of psychological impact, comments about fear featured most prominently including fear of: deterioration of the disease; blood clots; and fear of contracting an infection due to increased susceptibility and the consequential increase in symptoms/deterioration "*Also, there is always the niggling worry that one might pick up a virus when even a common cold can land one in hospital."* There were also comments about anxiety, frustration, worry, depression, negative mood and a reduction in confidence: "*Living with PNH affects me physically & mentally hugely*." **3. Quality of Life with PNH** In the quality of life with PNH category, the unpredictability of the disease was mentioned most often (7 times). "*The real difficulty with PNH is the unknown times you will be hit hard. There is no time frame, it isn't days before treatment or after. I don't know when I will have a bad day. That is the major difficulty with living with PNH*." Restriction on activities was also mentioned (5 times) i.e. physical activities have been curtailed to accommodate PNH related limitations especially fatigue and reduced energy. The impact of infections on patients was mentioned twice with this resulting in the return of PNH symptoms, the length of time taken to recover and the impact on general wellbeing. "*The other main concern is how carefully you have to monitor your health if you become unwell, as a simple virus on infection can often cause PNH symptoms to recur, and even if it doesn't, your ability to recover still takes longer and impacts your blood counts and general well-being*." The lack of understanding of PNH by people generally as a result of it being an invisible condition was commented on 4 times. *"It's difficult being a PNH patient, reasons been the majority of the population have no idea what it is and how it impacts our lives.".* This lack of knowledge also extends to the medical profession generally leaving patients needing to educate them on what PNH is "*The fact that PNH is so rare means that when one is seeing a consultant of another speciality he/she does not know the details of the illness and one has to explain the implications*." The length of time to diagnosis was mentioned by 2 patients including the burden of feeling "*mistaken with you [sic] symptoms and [you[begin to believe what people are saying that you are 'making it up*". Four patients commented that they essentially have a normal quality of life "*I am very fortunate that I live a fairly normal life as PNH affects everyone differently*."

4. Impact of Treatment

Under the impact of treatment category, the most comments (11) related to the improvement of symptom control and quality of life generally since treatment with eculizumab including patients who no longer need regular blood transfusions. "*Living with PNH is very debilitating (if not on medication), my quality of life became very poor - I was extremely tired, felt constantly nauseous, haemolysing was very unpleasant and left me feeling sick and weak. I also had severe bouts of extreme abdominal pain which left me bed bound for days at a time. I also suffered from jaundice and my sleep suffered hugely*". There were an equal number of comments (9) centred around: a) the improvement of symptom control and quality of life generally since treatment with ravulizumab and b) the burden of fortnightly infusions of eculizumab. "*But on ravulizumab I have been able to lead a normal life with little or no side effects and I don't think about my condition as my energy levels seem to be fairly constant*". The benefit of a longer period of time between infusions i.e. 8 weeks: "*Having treatment every 8 weeks instead of every 2 is helpful in organising one's life keeping things more normal*".

The burden of fortnightly infusions included not being able to be flexible with making plans or going on holiday outside the 14 day treatment period. It also included: anxiety caused by logistics of receiving the fortnightly treatment i.e. deliveries, scheduling of homecare visits; the impact of fortnightly treatment on employment with some employers not being accommodating; the impact on family life with the whole family's schedule being ruled by the fortnightly infusions; and caring duties being disrupted by infusions. Two patients mentioned the negative impact treatment with warfarin has had on them including the inconvenience and monitoring requirements which impacted their choice of employment and employment generally.

Carers

Of the 19 responses given by carers to the question "As a carer, please tell us what it is like for you to care for someone with PNH", there was a prevalence of comments about the negative psychological impact on carers including the fear of the patient getting an infection or having a crisis and needing hospitalisation: "*To some degree, we live on a "knife edge" never knowing when the next crisis will come. As soon as the patient has a high temperature or any kind of infection, we immediately shift into crisis mode, which can result in trips to the A&E department, antibiotics administered (often IV) and transfusions required*". These comments also included the stress of the diagnosis process, the difficulty of seeing a loved one suffer, the burden of treatment on the patient, the stress of infusions on the carer, being worried about the onset of symptoms or the impact of an infection. The impact on the carer of needing to provide support was also mentioned: "*Bit of a roller coaster... obviously have to offer support, both physical and emotional at what can be quite trying times."* One carer felt isolated as support groups were too far to travel.

Some carers commented on the impact on family life including: needing to provide support to the patient; infusions being intrusive; there being less energy for home life; and the need for the carer to take on more of the burden of running the home i.e. "*The impact on me as his partner has been that I have had to maintain the family home and take almost complete responsibility for housework, cooking, gardening, DIY and maintaining extended family relationships over many years."* One mentioned that the impact of PNH on the patient had been a reason why they had decided not to have children. One carer commented on their improved quality of life as a result of treatment with eculizumab "Seeing my husband stabilise on Soliris and leaving a normal life is a huge relief." Some also mentioned the impact which the lack of knowledge of PNH by healthcare professionals generally had on them as it increased the responsibility of the carer to educate them/ensure the PNH was being addressed. "*Given how rare PNH is, as carers, we often find that we know more about the illness and how it should be treated than the local health professionals we meet. Most have never heard of PNH, much less know how it should be treated. This places additional strain on carers and family members at what is already a stressful time. This strain becomes unbearable if the local doctors are unwilling to listen to the carers or to take advice on how the patient should be treated from the PNH specialist centres*". Two carers said no care was required to be provided by them to

	the patient, and one commented that it was "OK". One carer had reduced their work commitments to be able to assist the patient if required.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	**Patients** Of the 54 responses by patients to the question "What do you think of the current PNH treatments (not including Ravulizumab) and care available on the NHS?", most comments related to treatment related to eculizumab: the majority of which (21 comments) related to the burden of fortnightly infusions including the restrictions this places on making plans, travelling, work (including the ability to work), social and family life and the constant reminder of the illness. Many comments (17) concerned the positive impact of eculizumab on symptom control and the ability to have an improved quality of life: "*Sorlis [sic] is a great treatment and enables me to have good quality of life.*" Patients also commented (13 comments) on the limitations of eculizumab including patients who had unmet need despite being treated with it including onset of fatigue and symptoms between fortnightly treatments "*The treatment is every 14 days, but for me, it doesn't last the full 14 days. From day 9, I get fatigued and out of breath. This means I have to ration my activities. I can't work full-time, socialise as well as exercise. I have to choose what I do. If I do all three, I get fatigued even earlier than day 9. Normally I can't do anything the last few days, so I schedule my treatment for Mondays, so that I can just rest over the week-end before treatment, when my symptoms are at their worst."* 5 of the 13 responses concerned being negatively impacted by the regular cannulation required for the fortnightly infusions: "*Treatment is an infusion which means having to be cannulated every 14 days. If the nurses don't succeed first time round, it could hurt and even bruise*." 12 responses expressed satisfaction with being able to receive the treatment at home or work "*Being able to have the treatment at home or at work, and not in hospital, saves time and is very convenient*" with one of those responses noting the stress involved in organising the homecare visits. One comment mentioned that being able to have infusions at home during COVID 19 meant being able to be treated without fear. A number (9) of comments expressed a desire for more treatment choices to be available including ones with different delivery methods including sub-cutaneous injection and longer periods between treatments "*To have a variety of drugs would allow patients to find the best option for their personal circumstances. Be that trying a mixture of drugs, different dosages, different timings and delivery options e.g. via IV, tablet, subcutaneous injection*." 5 responses related to the fact that eculizumab was available to them and at no cost. In relation to care, the majority of comments (24) considered the care of the NHS to be excellent, many (7) said very good, equal numbers (3) said good and not good (2 comments related to care outside the PNH National Service), 5 didn't know (with one not receiving treatment). One expressed that there was no cure. One expressed problems communicating recently with the PNH National Service. **Carers** Of the 21 responses by carers to this question, most comments (8)related to treatment with eculizumab including 6 responses referring to improved quality of life and symptom control after treatment with eculizumab: "*Soliris is undoubtedly an excellent treatment and provides patients with a degree of stability in managing a life limiting condition. It does reduce the reliance on regular transfusions and provides a level of "normal life."* 6 comments also mentioned the burden of fortnightly infusions including the restrictions this places on quality of life generally including making plans, travelling, work (including the ability to work) and general independence and 2 commented on the fact that eculizumab was available to them, and at no cost. Equal numbers of comments (3) expressed satisfaction with the homecare service i.e. being able to receive the treatment at home and reduction in hospital visits "*The fortnightly treatment at home is very welcome, in reducing the number of hospital visits and appointments"* and to the limitations of eculizumab including patients who experienced unmet need including fatigue and other symptoms despite treatment, One carer commented that taking daily (prophylactic) antibiotics and carrying emergency antibiotics whilst on eculizumab affected the patient's

	quality of life. In relation to care, 6 considered the care of the NHS to be excellent, 5 said very good, 2 said good, one didn't know as was only aware of blood transfusions and warfarin as treatments. One expressed problems communicating with the NHS. One carer expressed the desire for her son to move to ravulizumab and one carer expressed that being able to live closer to a specialist PNH centre would be preferable as local care was not the same.
8. Is there an unmet need for patients with this condition?	**Patients** Of the 54 responses by patients to the question "Do you think there is an unmet need for patients with PNH (i.e. something that is not addressed by current care or treatment)?", equal numbers of comments (12) considered there was no unmet need and were satisfied with the care and support provided and expressed a desire for more treatment choices with alternative delivery methods e.g. non-intravenous and longer periods between treatment "*Whilst Soliris has been a life changing drug for me, relying on a 12 day cycle has become increasingly difficult. It can effectively feel like a ball and chain weighing you down. As Soliris is currently the only drug available I feel that that in itself is an unmet need. With no other possible options you are limited in how you fully engage with work, family, travel, exercise, to name a few... The list feels endless."* 2 patients considered a cure to be an unmet need. Many (10) responses identified the burden of fortnightly eculizumab infusions to be an unmet need referring to the negative impact on planning, holidays, working and general disruption. "*It would be good for if intervals can be longer i.e. more than a month or so. Having treatment every two weeks is very disruptive especially when you work*". One patient wanted to minimise the time spent at hospital receiving fortnightly infusions (Northern Ireland). Six patients consider that healthcare professionals generally needed education about PNH: "*Again the condition is not taken seriously by all medical personnel. In my case it took 21 months for a diagnosis and a further 12 months before anyone bothered to explain in detail and simply so that I and my family could have greater understanding of what I had to learn to live with.".* Four patients considered that primary and secondary care needs to be more joined up or care is inconsistent between personnel. Three patients felt that more of a holistic approach to their care needed to be taken rather than care being limited to review of standard symptoms or blood results. Three patients felt that addressing the psychological impact of PNH to be an unmet need and one suggested that counselling should be offered as part of standard treatment. Two patients thought more information could be provided generally, and about living with PNH e.g. on obtaining disability cards or benefits and one considered transparency about new treatment and drugs to be lacking. One patient considered fatigue to be an unmet need and another considered pain to be one. **Carers** Of the 21 responses by carers to this question, most comments considered that the burden of the fortnightly eculizumab infusion was an unmet need referring to the negative impact on planning, holidays, working (including the ability to work), general disruption and intrusiveness (including the psychological impact and stress of a fortnightly infusion) and the effect of regular cannulation on veins and the fact that the timing of the homecare visits cannot be guaranteed. "*The need for a 2 - 3 hour treatment in the patient's home every two weeks and the fact that the healthcare provider cannot guarantee the time that the treatment will be provided, means that patients lose 0.5 - 1 day every 2 weeks from their working life which can make it challenging to maintain full time work*". 3 considered there to be no unmet need. 8 responses expressed a desire for more treatment choices with alternative delivery methods and longer periods between treatment and one carer commented that there was no cure, merely a maintenance of patients "*in a relatively stable state.*" Two carers considered addressing the psychological impact of PNH to be an unmet need including recognition of this by the medical professional and local authorities and having accessible support groups to relieve isolation. Three carers considered that treatment with eculizumab resulted in unmet need in terms of prevalence of symptoms and stability of PNH. One carer considered side effects to be an unmet need and another considered there needed to be more information about new drugs and when they will be available. One didn't know.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	**Patients** Of the 16 responses **by patients being treated with ravulizumab** to the question "What do you think the advantages are of being treated with Ravulizumb (e.g. symptom control, ability to work, psychological impact, impact on relationships, family life, quality of life etc)?", most (13) comments related to the positive psychological impact of taking ravulizumab including being able to work full time "*My whole outlook on life has changed since being on Ravulizumab and I feel like a normal member of the population making a full contribution*." It reduces the stress related to employment which patients face when having fortnightly infusions. An 8 weekly infusion means not having to think about it every 2 weeks which improves quality of life and wellbeing and is "*psychologically less intrusive."* 9 comments specifically related to how patients identify with the disease i.e. forgetting they have PNH or not considering themselves defined by it any more. "*I can actually forget I have PNH*." 10 responses addressed improved symptom control: "*Since being on Ravulizumab I have had really good symptom control - I have not had any infections or any breakthrough haemolysis in 3 years".* Two patients commented that their symptom control was the same as with eculizumab. 8 patients commented that their quality of life generally had improved, 9 patients commented that the 8 weekly infusion allowed them greater independence in relation to planning, holidays, working, activities, family and social life. "*The treatment is every 2 months: a. This means fewer cannulations and therefore less anxiety b. Less disruption to my work schedule c. Being able to go on holiday more easily d. I don't have to tell my employer when my treatment is and can simply take holiday on the day of treatment. The treatment makes me feel more free and almost as if I am not ill, as I don't have to arrange my whole life around a bi-weekly treatment*." Equal numbers of comments (6) were provided on the positive impact on family life including being able to take holidays, less disruption and stress to partners and relationships: "*My family life is now normal, with me able to do work around the house and do all the normal day to day things like shopping and cooking, i also have no worries about going out and I can book ticket for an event in the future with the almost, certain knowledge that I will be able to attend*" and on the positive impact on employment including being able to work full time, treatment being less disruptive of work and not requiring them to take sick days. Of the 37 responses **by patients not being treated with ravulizumab** to the question "What do you think the advantages would be to you of being treated with Ravulizumb (e.g. symptom control, ability to work, psychological impact, impact on relationships, family life, quality of life etc)?" Most (20) comments concerned the increased independence that would be provided by 8 weekly infusions due to it being less intrusive and being able to plan more freely, travel and take holidays. 13 comments referred to an improvement in quality of life in general. Equal numbers of comments (12) considered that it would have: a positive effect on their employment including treatment being less disruptive, not needing to take sick days to have treatment, being able to work full time: "*Ravulizumb would open up a new chapter in my life. The restrictions of fortnightly infusion, have at times impacted on my working life. Generally I have found companies do not tolerate employees requiring time off on a regular basis";* a positive effect on their family life including less disruption to family arrangements and caregiving duties, family members not having to witness the fortnightly treatment and having more energy and time for family; a positive psychological impact including the relief provided to the general psychological impact of living with, managing and adapting to a chronic illness "*The psychological burden of beginning to understand that you have an incurable disease takes a long time to process and adjust to. Add to that the daily management of looking after yourself, taking note of your symptoms, diarising your IV treatments, liaising [sic] with drug deliveries, hospital staff, nurses etc. Not only does this effectively 'fill your brain' but it drains you and wears you down. To live in a mental state where a lot of these daily concerns are removed or minimised would have an incredibly positive effect on my mental health*." 4 comments regarding psychological impact were specifically about the patients' identification with PNH and the fact that 8 weekly infusions meant they would not be reminded of the disease as often, they could forget they have PNH for periods of time and wanting to feel "*like a normal person between*

	treatments." 10 responses considered anticipated improved symptom control would be an advantage. 5 responses considered the reduced number of cannulations to be an advantage due to damage to veins or being anxious about needles. one patient was hoping for a permanent treatment option and one thought life expectancy to be an advantage. 4 patients did not know about ravulizumab to be able to answer this question. One patient said "*feeling better about the future would be a great feeling to have".* **Carers** Of the 6 responses **by carers (of patients being treated with ravulizumab)** to the question "As a carer /family member of a PNH patient, what do you think the advantages are (to you/your family) of your loved one being treated with Ravulizumb (e.g. symptom, control, your ability to work, psychological impact, impact on your relationship/family life etc)?", equal numbers of comments (5) related to: a positive impact on family life due to improved energy levels**,** ability to plan and less disruption **"***Life has become much more relaxing knowing that she feels a lot better and it bouces [sic] off. The household has become a happier place. She is not as tired as use to be, more responsive to life. Not always tired when gets home from work - has some energy left for me & the family. She wishes to socialise more and is more caring with homelife* ; and positive psychological impact and less anxiety for the carer caused by fortnightly infusions: "*Every eight weeks normalises her life and is beneficial to her overall well being and mental health".* Two of these 5 comments related specifically to being able to forget for 8 weeks at a time that the patient is ill or on treatment. Many responses (4) referred to the increased independence provided by 8 weekly infusions being an advantage due to being less intrusive and having the ability to plan more freely, travel and take holidays and give the patient independence. 2 responses considered improved symptom control to be an advantage. One carer commented that the patient's energy levels were the same as with eculizumab. One comment referred to the positive impact on the patient's employment where an 8 week infusion made work easier to manage. Of the 14 responses **by carers (of patients not being treated with ravulizumab)** to the question "As a carer/family member of a PNH patient, what do you think the advantages would be (to you/your family) of your loved one being able to be treated with Ravulizumb (e.g. your ability to work, psychological impact, impact on your relationship/family life etc)?", the majority (13) of comments related to the independence provided by 8 weekly infusions due to life being less disrupted and the ability to plan more freely, travel (including to other countries to see family), take holidays, a reduced amount of time at hospital and having less treatments: **"***it would be amazing to space the infusions out to 8 weeks. it would be life changing*". The positive psychological impact of 8 weekly infusions was commented on by 7 carers due to their current level of worry and "*psychological distress*", and it would provide a patient with more confidence and improve mental health and wellbeing. "*This would then have a positive effect on his psychological wellbeing and give him greater confidence and assurance."* Six comments referred to patients' ability to work and have a full time job and the economic benefits of this: "*From an economic perspective, the longer treatment cycle would enable patients of working age to hold down full time jobs in line with their professional qualifications and experience. We have evidence that employers are reticent to employ someone who needs half a day off work on medical grounds every 2 weeks. Reducing this to half a day every 8 weeks would make a material difference to patients' job prospects and the wider UK economy*." 5 comments referred to an improved quality of life generally due to the 8 weekly infusions, 4 comments related to the positive impact of 8 weekly infusions on family life e.g. so children are not impacted by seeing parents receive treatment and the impact of treatment schedules on caregiving and family relationships: "*I do not want our baby to grow up watching her dad having to go through this infusion very often. If it is once in two months, I will make arrangements to keep her away, it's just much easier to manage things when it is not that often*." Three responses hoped for improved symptom control. One carer had no information about ravulizumab and one was not sure what the advantages would be. One carer commented that the 8 weekly infusion would enable the patient to spend more time in education.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	**Patients** Of the 16 responses by **patients being treated with ravulizumab** to the question "What do you think the disadvantages are of being treated with Ravulizumab?", 5 patients said there were no disadvantages, 5 comments related to the delivery mode of ravulizumab being a disadvantage i.e. intravenous infusion, that it can't be self-administered and veins aren't good or are difficult to find, 3 comments related to unmet need despite treatment i.e. still needing blood transfusions and experiencing fatigue. Two patients considered the longer infusion time a disadvantage. One patient had experienced joint pain since receiving this treatment, one had experienced mouth ulcers and one patient would prefer not to attend a hospital to receive the infusion. One patient preferred the oversight provided by nurses when having fortnightly infusions "*As an older person I quite liked having the care of nurses every 2 weeks. I felt they were able to keep a check on my health.".* One was concerned about unknown possible long term side effects of a new drug and one considered having to take daily prophylactic antibiotics to be annoying. Of the 37 responses by **patients not being treated with ravulizumab** to the question "What do you think the advantages would be to you of being treated with Ravulizumb (e.g. symptom control, ability to work, psychological impact, impact on relationships, family life, quality of life etc)?", 10 patients commented that there were no disadvantages, 9 patients commented that they didn't know, 8 comments related to concern they may have unmet need despite treatment e.g. if they don't respond well to the drug. 6 patients stated that possible side effects could be a disadvantage, 2 commented on the negative impact of changing from one drug to another including increased monitoring and "*Changing to a different drug can sometimes take a while and can drain your energy*." one said that if the 8 weekly treatment was delayed, this would be a disadvantage. One patient considered no medical contact for 8 weeks to be a disadvantage, one said that if the infusion was not delivered at home this would be a disadvantage, one considered the longer infusion time to be a disadvantage and one considered the delivery method to be a disadvantage: "*Still an infusion and for me medicalises my treatment a little, not in my control*". One patient considered that having blood tests with the infusion to be a disadvantage **Carers** Of the 6 responses **by carers (of patients being treated with ravulizumab)** to the question "As a carer/family member of a PNH patient, what do you think the disadvantages are (to you/your family) of your loved one being treated with Ravulizumb?", most (4) carers said there were none, one commented on the delivery method i.e. "*the physical canulation [sic] into veins which are difficult to find*" and one commented on the stress involved "*where this new and much better treatment may not be paid for in the UK and we will have to go back to the old version*". Of the 14 responses **by carers (of patients not being treated with ravulizumab)** to the question "As a carer/family member of a PNH patient, what do you think the disadvantages would be (to you/your family) of your loved one being able to be treated with Ravulizumb?"**,** 5 comments stated there were no disadvantages, 4 stated they didn't know about ravulizumab, two were concerned about remaining unmet need despite treatment. One carer expressed that it was a disadvantage to have less healthcare professional (HCP) oversight i.e. "*It is quite reassuring to have a health Professional visit our home fortnightly*." One was not sure, one was concerned about possible side effects, one was concerned with possible long term effects of a new medicine and one stated that it was not a cure and still only "*maintained patients*".

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	PNH affects patients very differently. Ravulizumab may be more appropriate for treating patients who respond well to C5 inhibitors and don't have additional unmet need despite treatment with them i.e. anaemia and extra-vascular haemolysis.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	We are not aware of any equality issues.
Other issues	
13. Are there any other issues that you would like the committee to consider?	• Surveyed patients treated with ravulizumab have experience of receiving ravulizumab since 2017 until the present (both during the trial and after the trial completed) and therefore their experiences of the therapy extend beyond the trial period. • Ravulizumab is innovative is the frequency of its delivery (i.e. 8 weekly) which represents significant increased independence from a fortnightly infusion and the negative consequences of that (on employment, family and social life and psychological impact) and an improvement in quality of life for both patients and their families. Reduced treatment frequency also requires less oversight by the overburdened NHS. Less contact between patients and medical personnel also reduced the risk of infection with COVID 19 to patients already vulnerable to infection. • Patients currently receiving ravulizumab and their carers were also surveyed about the impact to them of having to revert to treatment with eculizumab, should ravulizumab not be approved for treatment. Of the 16 responses by **patients**, the burden of fortnightly infusions including the negative affect of cannulation every 2 weeks and concern about deterioration in their current symptom control were the most significant impacts. These were followed by the negative effect on their quality of life generally including family life their employment (and the ability to be able to work/work full time). The negative psychological impact was also identified: "*My overall mental health & wellbeing would greatly suffer and I would be afraid of going back into depression" and the* loss of recently found independence: " *I am sure that there would be a deterioration in my mental health as my life would be dominated by treatment again*" , "*I have tasted freedom and normality for 3 years and going back to treatment with the two weekly Eculizumab, will take that away from me.*" Of the 6 responses by **carers** of patients currently receiving ravulizumab, many referred to the burden of the fortnightly infusions: "*would mean that your life becomes a 2 week cycle and everything has to be planned around that*" and the impact on employment would also be negative: "*they would have their independence lessened considerably and would struggle to lead a normal and*

	economically productive life." They also identified the negative impact on quality of life generally including family life and the loss of a "*normal life*": "*A normal life would ge [sic] gone - the general well being of the family would be affected"* together with negative psychological impact: "*A grave impact as family as a whole with tension in the house 80% of the time. It would make all our lives miserable."* • Patients who are currently not on treatment or are currently being treated with eculizumab were also asked "If you qualified for treatment (i.e. 18 years plus and have haemolysis with clinical symptom(s) indicative of high disease activity or your PNH is clinically stable after having eculizumab for at least 6 months) and Ravulizumab was available, would you want to be treated with it?" Of the 37 responses received, 28 responded "Yes", one responded "No" (due to concern that the infusion would not relieve symptoms for the whole 8 week period) and 8 responded "I don't know" due to needing more information, medical advice, wanting an alternative treatment option and not needing treatment.
14. To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] if there are none delete highlighted rows and renumber below	

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- PNH is a serious condition which, without treatment, carries a heavy symptom and complications burden. This burden has been mitigated significantly in many patients by the intravenous fortnightly treatment, eculizumab, requiring contact with medical personnel every 14 days +/- 2 days.
- The unmet needs prioritised by surveyed patients and carers are: the need for more treatment choices with alternative delivery methods; and the burden of fortnightly eculizumab infusions. The fortnightly infusions have a negative impact on many elements of a patient and their family's quality of life especially their independence to be able to make plans, socialise, spend time with their family, go on holiday and work.
- The frequency of ravulizumab infusions (i.e. 8 weekly) is innovative in that it offers PNH patients and their families independence from the fortnightly treatment regime (and the associated negative impact on their quality of life mentioned above). Ravulizumab also provided improved symptom control for most patients surveyed, increasing their quality of life. Reduced treatment frequency also requires less oversight by the NHS.
- An essential element of the independence arising from treatment with ravulizumab to both patients, their families and society is the impact on a patient's ability to work: either at all or full time as a result of the absence of a fortnightly infusion disruptions and/or improved symptom control.
- The psychological benefit to patients (and their families) of being able to forget their incurable chronic disease for 8 weeks at a time contributes significantly to increased: mental health; overall wellbeing; productivity; and identification as full members of society.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

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The information that you provide on this form will be used to contact you about the topic above.

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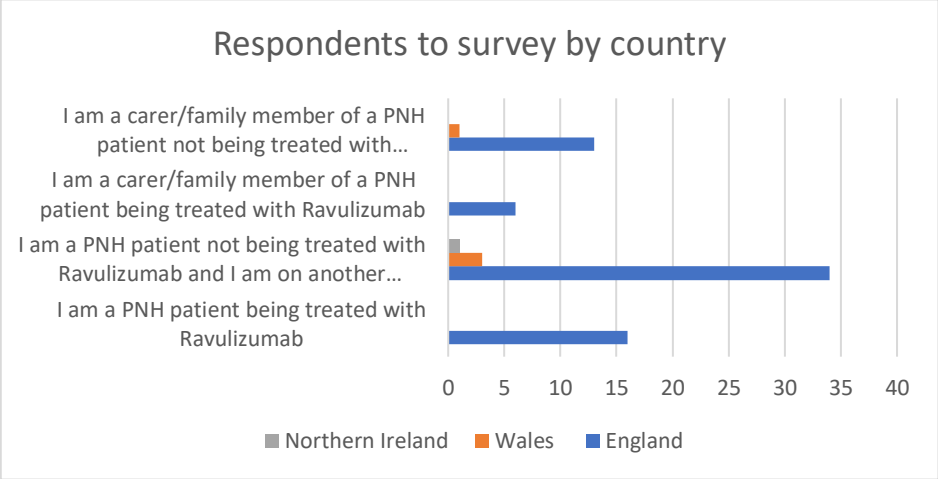
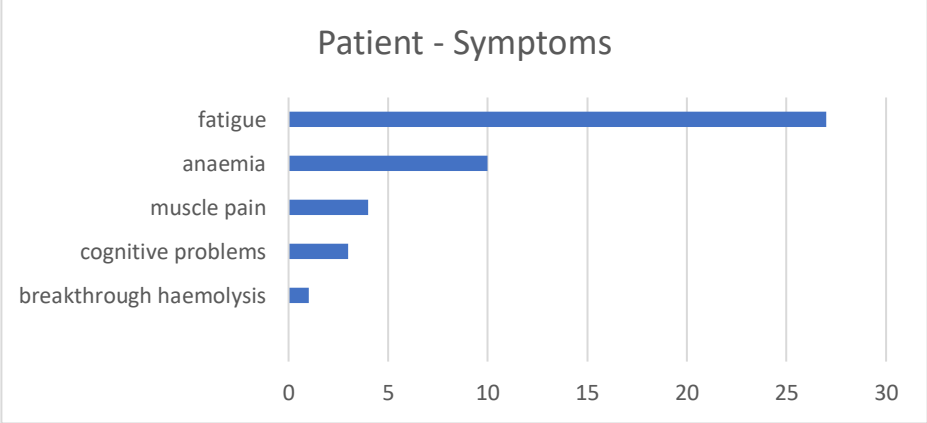
Appendix to PNH Support patient organisation submission re ravulizumab for treating PNH [ID 1457]

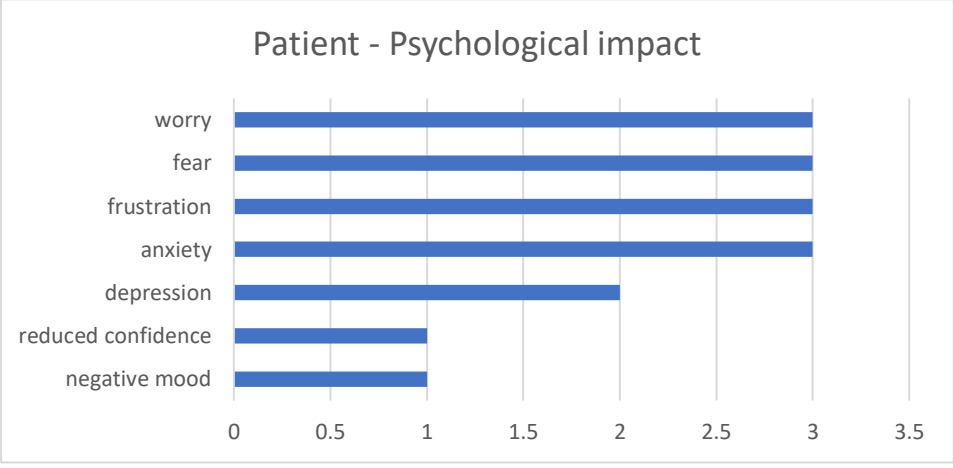
The numbers and headings referred to below relate to the NICE "Patient organisation submission" template document.

5. How did you gather information about the experiences of patients and carers to include in your submission?



6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?





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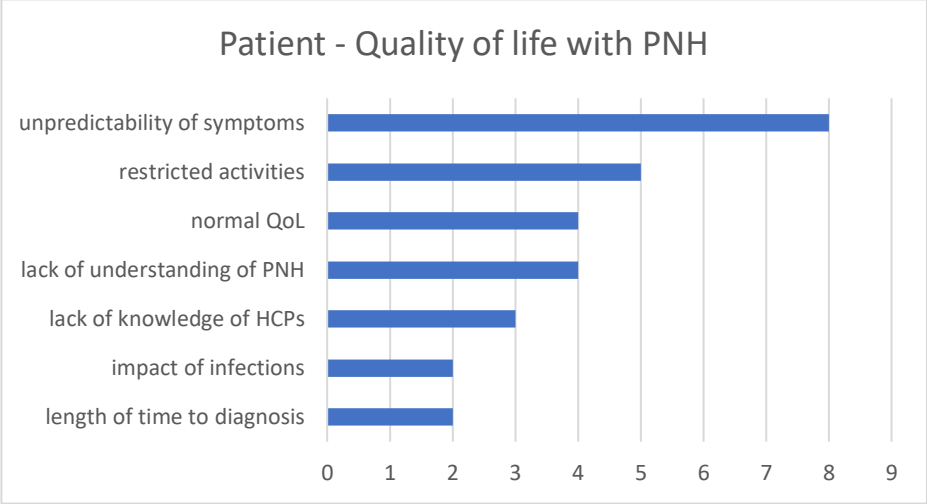
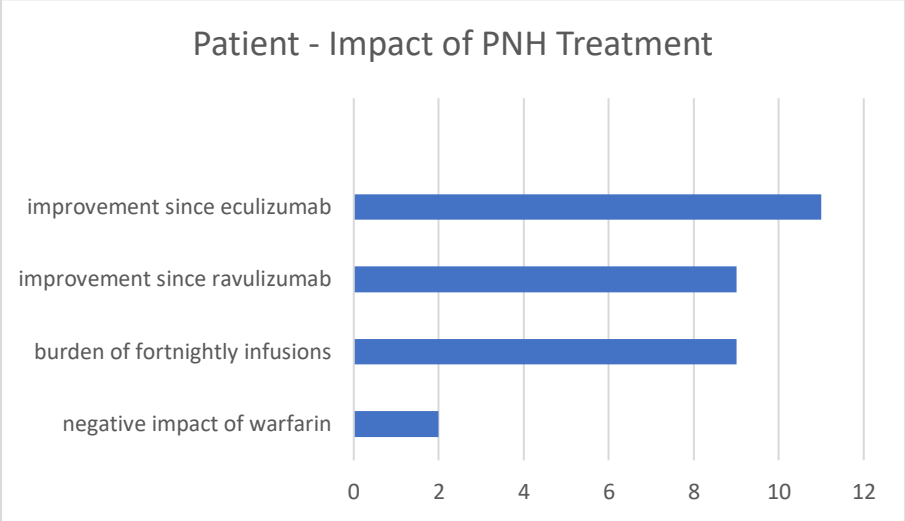
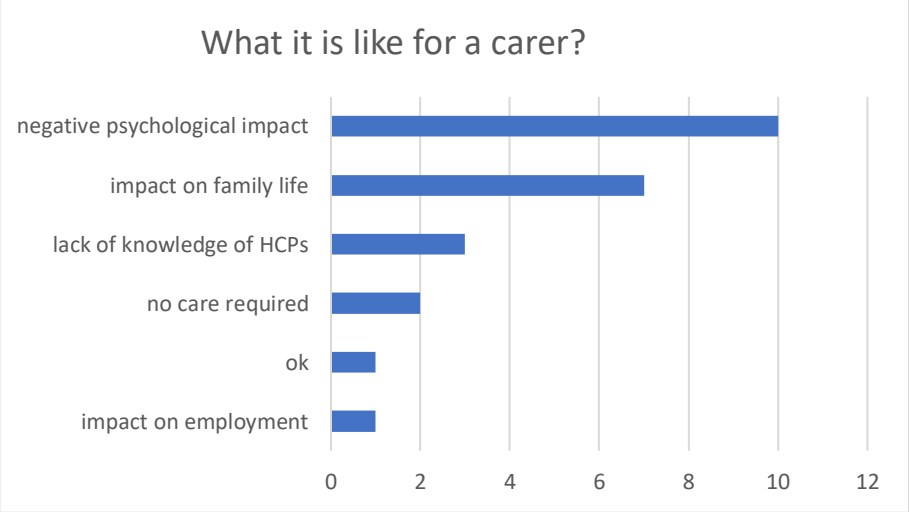
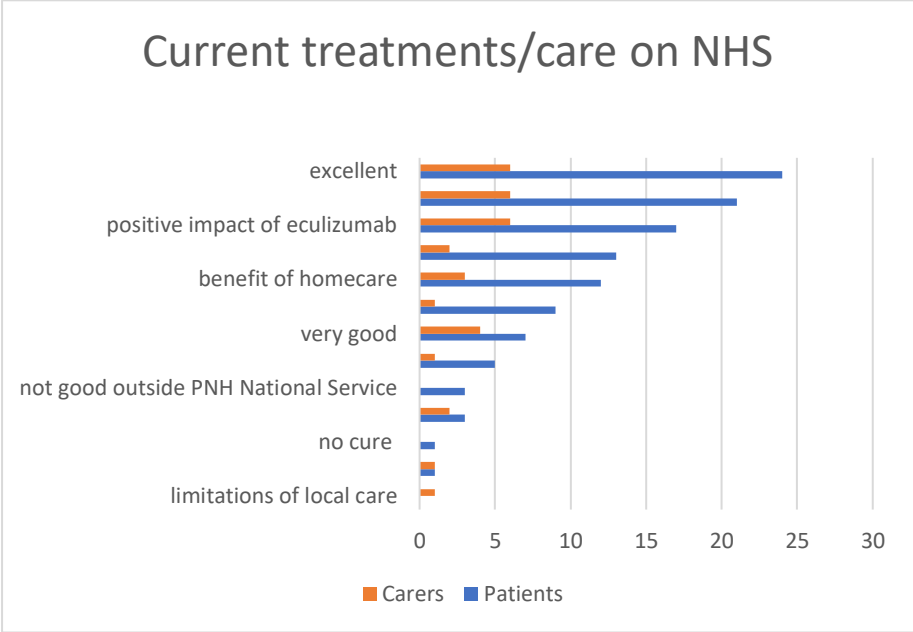


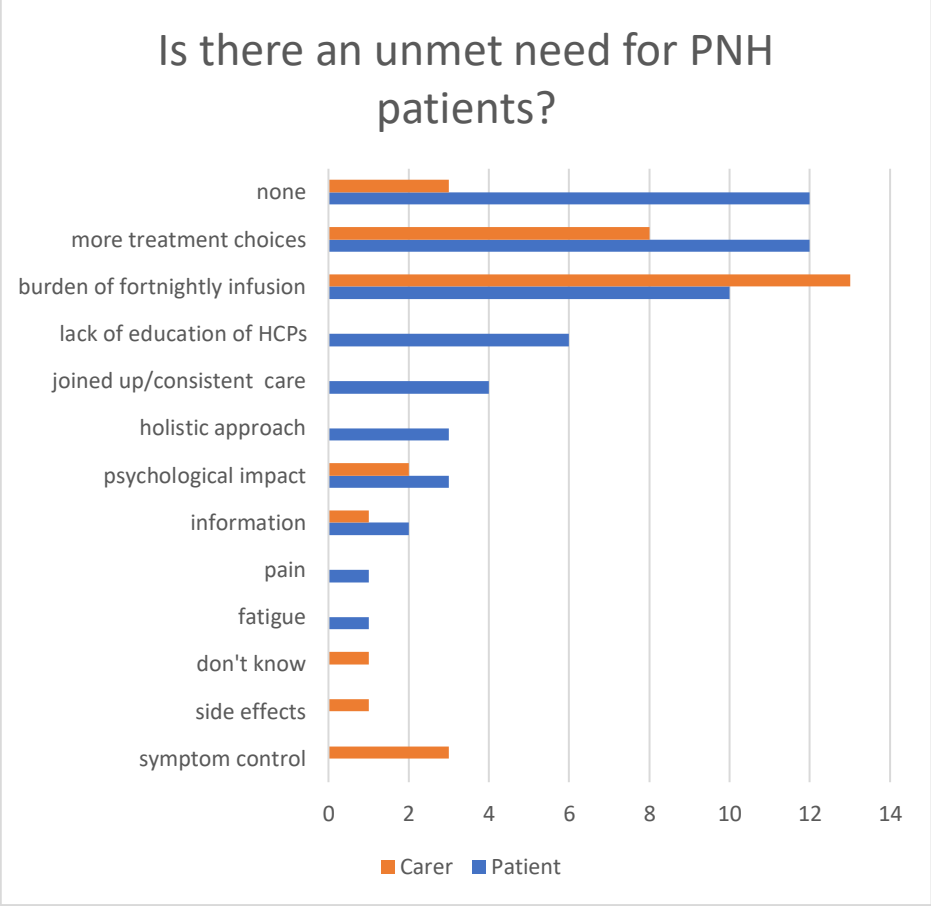




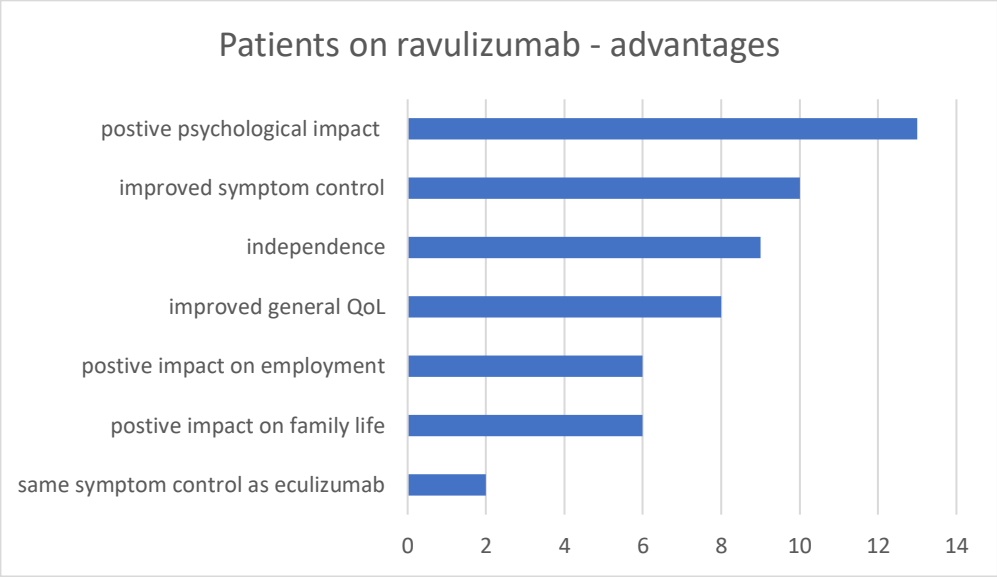
7. What do patients or carers think of current treatments and care available on the NHS?

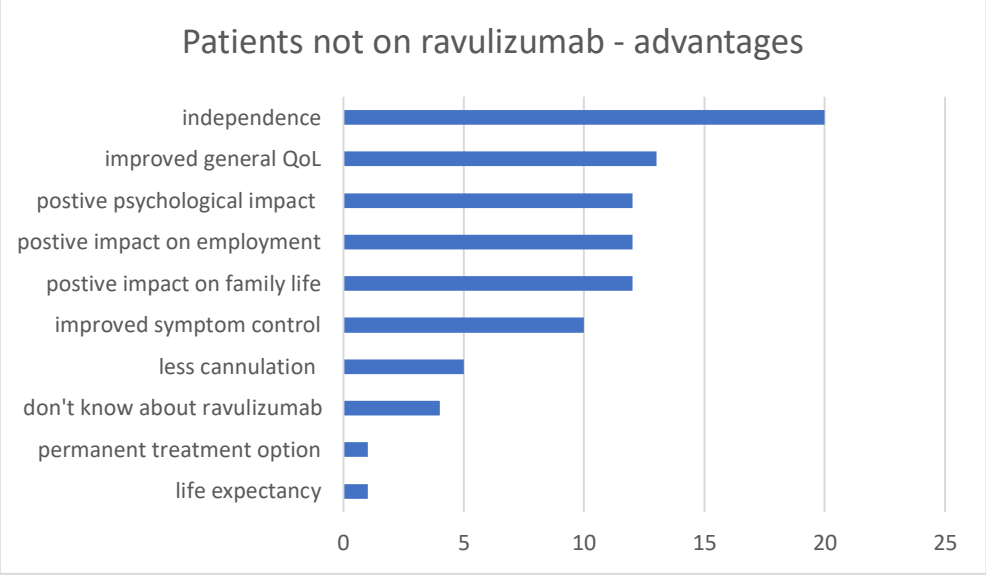


8. Is there an unmet need for patients with this condition?



9. What do patients or carers think are the advantages of the technology?





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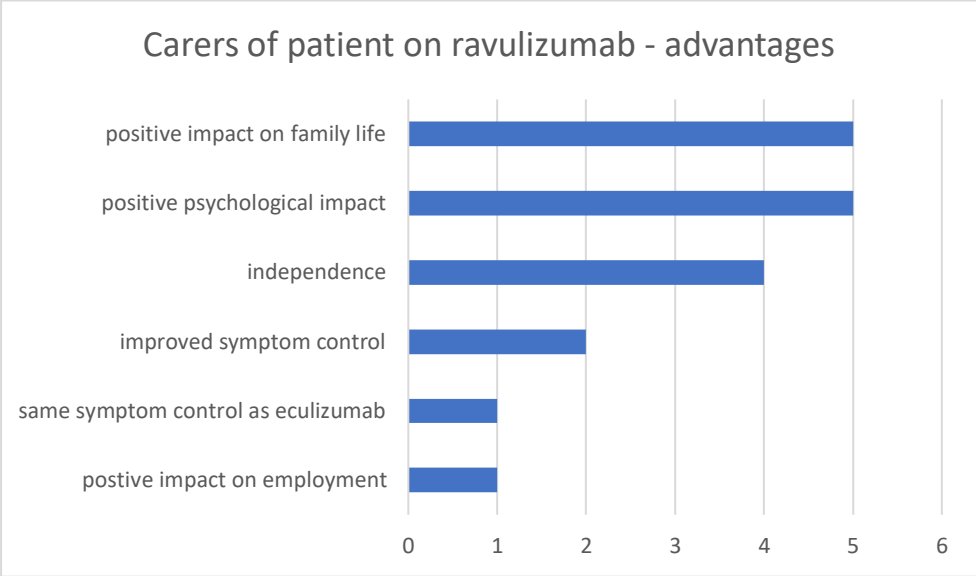
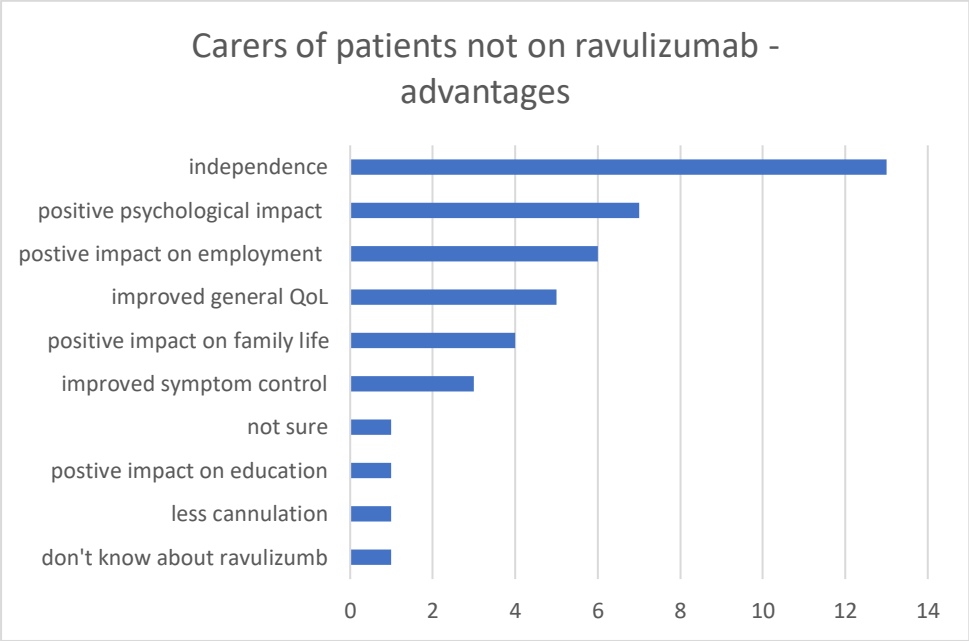
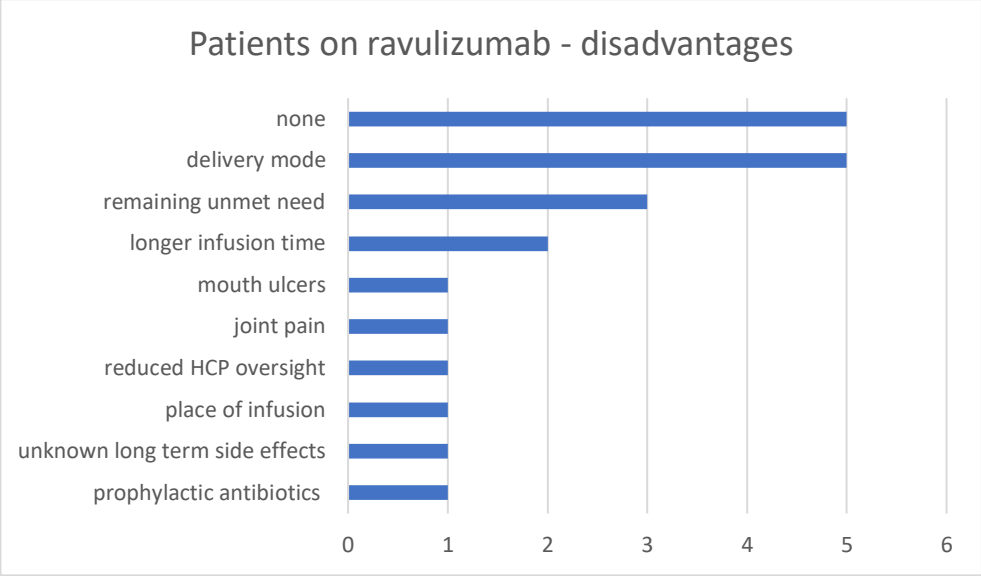
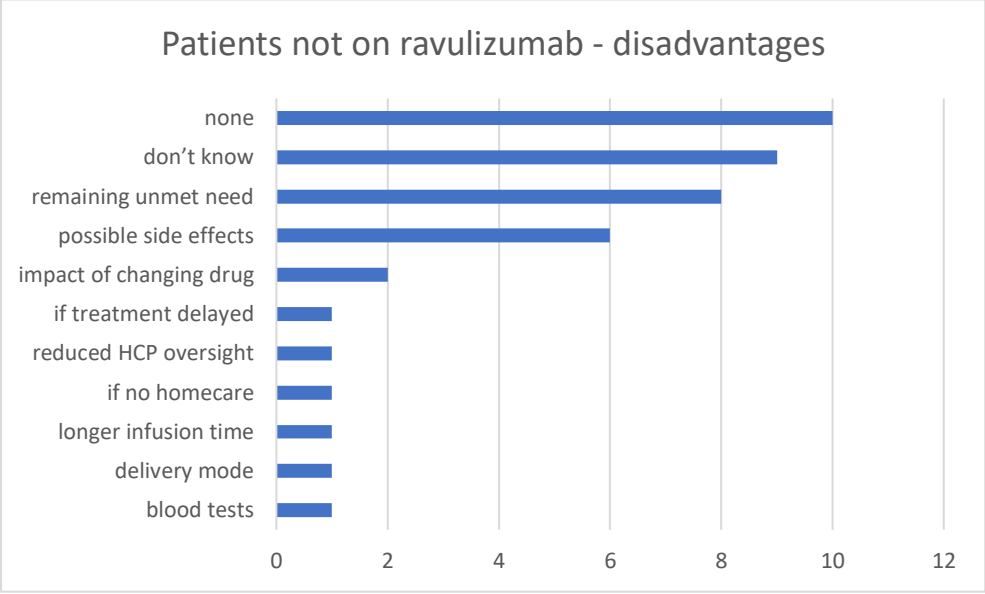




10. What do patients or carers think are the disadvantages of the technology?





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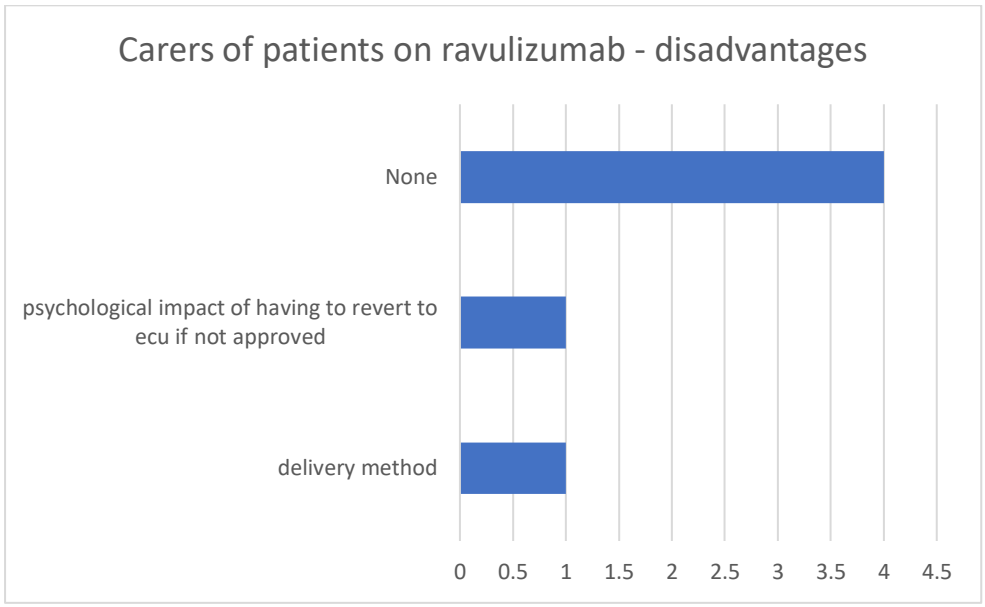
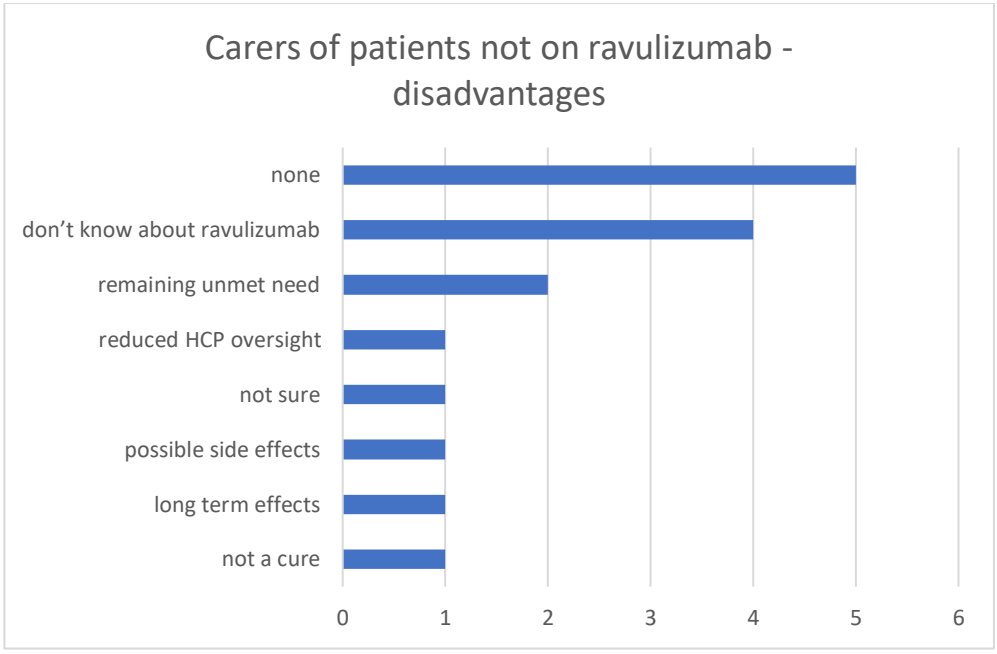
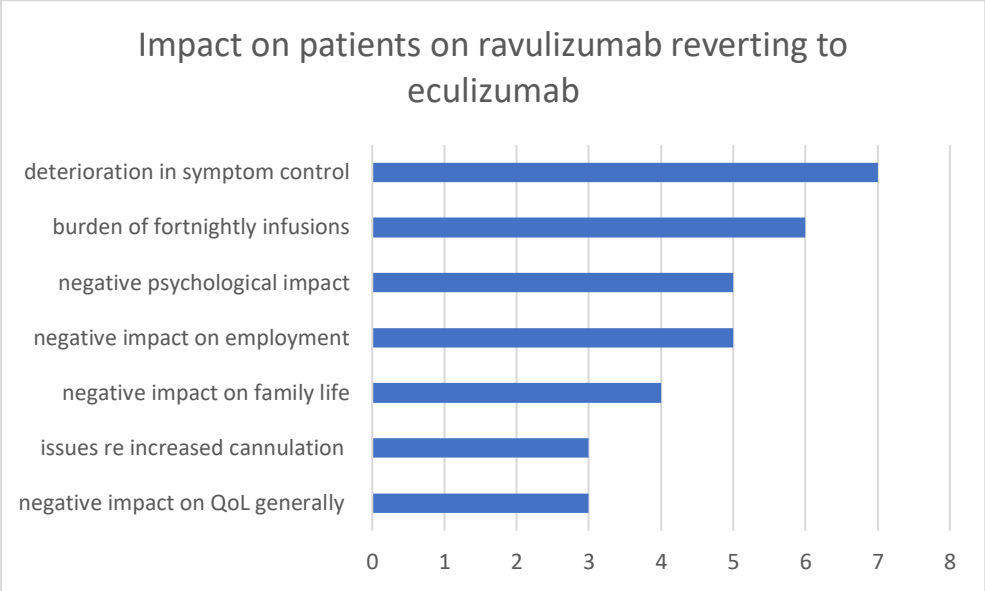
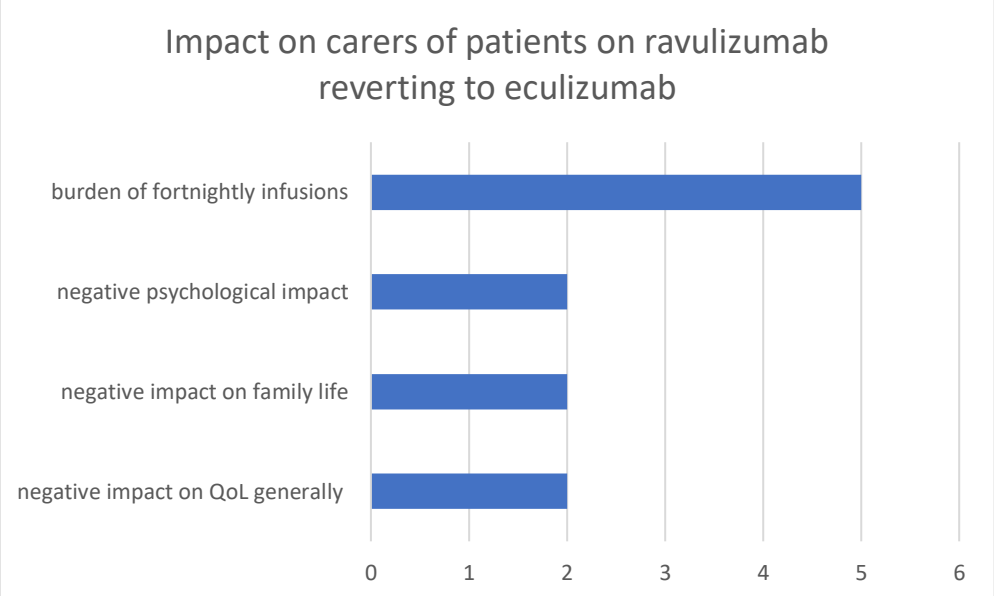




13. Are there any other issues that you would like the committee to consider?





NICE National Institute for Health and Care Excellence

NHS organisation submission (CCG and NHS England)

Ravulizumab for treating paroxysmal nocturnal haemoglobinuria [ID1457]

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 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? ☒ 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?	Patients are treated at two expert centres in Leeds and London. The two expert centres have developed information for both professional and patients, including guidelines, which is available on their website at: https://www.pnhleeds.co.uk/
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.)	The pathway of care is well-defined and there are no significant differences of option between professionals.
8. What impact would the technology have on the current pathway of care?	Ravulizumab would allow those patients with PNH who are being treated with eculizumab (currently administered fortnightly) to have this treatment every eight weeks instead.
The use of the technology	
9. To what extent and in which population(s) is the technology being used in your local health economy?	The only patients receiving this treatment are on clinical trials.

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	If the drug was approved, its use would be managed through the existing treatment pathway by the two designated expert centres.
• How does healthcare resource use differ between the technology and current care?	There would be some reduction is resource use because the drug only needs to be administered every eight weeks instead of every two. There may need to be some additional monitoring to ensure that there is no breakthrough haemolysis.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The use of the drug would be managed through two expert centres with administration generally via home care on a fortnightly basis.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The treatment can be introduced using current clinical pathways and services.
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this	No additional testing is required.

include any additional testing?	
11. What is the outcome of any evaluations or audits of the use of the technology?	To date, there have not been any evaluations or audits of the technology.
Equality	
12a. Are there any potential equality issues that should be taken into account when considering this treatment?	There are no specific equality issues or issues related to protected characteristics. The HST Committee is familiar with issues faced by patients with rare diseases such as the current patient cohort.
12b. Consider whether these issues are different from issues with current care and why.	n/a

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 paroxysmal nocturnal haemoglobinuria [ID1457]

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: Leeds Teaching Hospitals

Please indicate your position in the organisation:

- a specialist in the treatment of people with the condition for which NICE is considering this technology?

- a specialist in the clinical evidence base that is to support the technology (e.g. participation in clinical trials for the 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: NA

What is the expected place of the technology in current practice?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ravulizumab for treating paroxysmal nocturnal haemoglobinuria [ID1457]

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences in opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

1: PNH is a rare life threatening condition, characterised by intravascular haemolysis, and thrombosis. Patients can present at any change but median age of presentation is 30's. Life expectancy prior to the availability of eculizumab was poor, however with eculizumab the life expectancy is near normal
Patients experience symptoms including severe fatigue, anaemia, abdominal pain, dysphagia, erectile dysfunction, renal failure, pulmonary hypertension, life threatening thrombosis
Patients experience reduced quality of life, loss of time spent working/family life etc. Treatment with eculizumab has significantly improved management of PNH into a chronic disease, however treatment is burdensome, with IV infusions every 2 weeks, whereas ravulizumab is given every 8 weeks.

2: There is no geographical variation, PNH is managed in England and Wales through two centres

3: PNH is managed by a small number of Haematologists, centred in Leeds or London. Working collaboratively, there are no differences in opinion between professionals

4: Ravulizumab is given every 8 weeks, compared to eculizumab which is given every two weeks by intravenous infusion. This improves patient's ability to work without frequent interruptions increasing productivity, travel and reduces healthcare staff time.

Patients with issues of venous access will also have improved care, potentially avoiding the requirement for semi-permanent devices such as PICC line or Port

Ravulizumab is equivalent in terms of efficacy (control of PNH parameters) compared to eculizumab, however episodes of breakthrough haemolysis are lower in ravulizumab compared to eculizumab (phase III trial data).

To what extent and in which population(s) is the technology being used in your local health economy?

- is there variation in how it is being used in your local health economy? *No*
- is it always used within its licensed indications? If not, under what circumstances does this occur?
Ravulizumab will be used for the same indications that eculizumab is used for

- what is the impact of the current use of the technology on resources?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ravulizumab for treating paroxysmal nocturnal haemoglobinuria [ID1457]

Patients are currently treated with eculizumab which requires infusion with homecare nurse every 2 weeks; ravulizumab is an infusion every 8 weeks, reducing healthcare attendance. It will also reduce number of calls/rearranged treatments required for patients allowing nurses to have more time.
Patients have fewer episodes of breakthrough haemolysis on ravulizumab which reduces attendance and admissions to hospital, and the requirements for blood transfusions etc.

- what is the outcome of any evaluations or audits of the use of the technology?

Two phase three randomised controlled trials have compared Ravulizumab to eculizumab (treatment naïve and a switch study). Ravulizumab is non-inferior to eculizumab. Disease control with Ravulizumab however is improved compared to eculizumab with improved control of lowering of C5 levels

Reference:
Lee JW, Sicre de Fontbrune F, Wong Lee Lee L, et al. Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study. Blood. 2019;133(6):530-539. doi:10.1182/blood-2018-09-876136

Kulasekararaj AG, Hill A, Rottinghaus ST, et al. Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor-experienced adult patients with PNH: the 302 study. Blood. 2019;133(6):540-549. doi:10.1182/blood-2018-09-876805

- what is your opinion on the appropriate use of the technology?

Ravulizumab, whilst clinically comparable to eculizumab in clinical trials, offers patients a marked improvement in terms of quality of life and reduced frequency of infusions.
Indications for treatment will remain the same as indications for eculizumab.
Fewer infusions allow patients to have more time to work, travel and enjoy family life.
Reduced frequency of treatment also reduces cannulation frequency; some of our patients have very poor venous access and thus require semi-permanent lines inserted the need for this would be reduced

Potential impact on the NHS if NICE recommends the technology

What impact would the guidance have on the delivery of care for patients with this condition?

The delivery of care for patients with indications for treatment would not change from current practice, the main benefit being reduced infusion frequency.
Indications for treatment will remain the same as for eculizumab.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ravulizumab for treating paroxysmal nocturnal haemoglobinuria [ID1457]

If NICE recommends the technology, there will require a period of transition, patients will then continue to receive treatment with homecare services

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional resources (for example, staff, support services, facilities or equipment)?

Ravulizumab should be prescribed as directed by the PNH service Leeds and London, or by the local physicians in Wales with guidance from PNH Leeds and London. All patients requiring treatment with ravulizumab will meet the current agreed indications for treatment for eculizumab.
Patients will receive the first dose in hospital with subsequent doses at home with a home-care service

Can you estimate the likely budget impact? If this is not possible, please comment on what factors should be considered (for example, costs, and epidemiological and clinical assumptions).

Clinical assumptions: Patient's who are eligible for changing from eculizumab to ravulizumab are likely to want to change over to the newer treatment. This would be approximately 166-170 patients in England and 17-20 in Wales currently (data from march 2020)
The PNH service in Leeds treats approximately 15-18 new patients a year who require treatment commencing, who would be eligible if NICE approves the treatment.
Treatment will remain being provided at home through homecare services following the initial dose unless the patient is an inpatient

All patients within the service and those newly referred where eligible are offered entry into clinical trials of new treatments

Would implementing this technology have resource implications for other services (for example, the trade-off between using funds to buy more diabetes nurses versus more insulin pumps, or the loss of funds to other programmes)?

PNH is a very rare disorder, which has significant co-morbidity if untreated. Patients eligible for treatment are currently commenced on eculizumab. If ravulizumab was approved by NICE, it would depend on the cost of Ravulizumab as to whether this would impact on other services
Ravulizumab has less frequent infusions reducing nursing attendance to patients

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ravulizumab for treating paroxysmal nocturnal haemoglobinuria [ID1457]

Would there be any need for education and training of NHS staff?
Education and training of healthcare staff for preparing, infusing and monitoring of patients will be required. This will be done by the PNH service
The PNH service staff are already familiar with treating patients with ravulizumab due to treating patients within the clinical trials and then within the Global Access to medicines Scheme

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.

All patients are treated equally, with respect and without discrimination by the PNH service. Patients who meet indications for treatment are offered treatment

Other Issues

Please include here any other issues you would like the Appraisal Committee to consider when appraising this technology?

……

Your privacy

Appendix G – NHS organisation submission template (DH and WG)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ravulizumab for treating paroxysmal nocturnal haemoglobinuria [ID1457]

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in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Ravulizumab for paroxysmal nocturnal haemoglobinuria

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Declared competing interests of the authors

None.

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None.

Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Academic in confidence (AiC) data are highlighted in yellow throughout the report.

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:

Riemsma R, Corro Ramos I, Zaim R, Westwood M, Chalker A, Armstrong N, Ahmadu C, Santi I, Versteegh M, Worthy G, De Kock S, Al M, Kleijnen J. Ravulizumab for paroxysmal nocturnal haemoglobinuria: a Single Technology Assessment. York: Kleijnen Systematic Reviews Ltd, 2020.

Contributions of authors

Rob Riemsma acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Isaac Corro Ramos acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Remziye Zaim, Irene Santi, Matthijs Versteegh, Charlotte Ahmadu and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Marie Westwood and Annette Chalker acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Shelley de Kock critiqued the search methods in the submission and contributed to the writing of the report. Maiwenn Al acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

ADAs	Antidrug antibodies
AE	Adverse events
AIC	Akaike Information Criterion
ASH	American Society of Hematology
BI	Budget impact
BIC	Bayesian information criterion
BSH	British Society for Haematology
BTH	Breakthrough haemolysis
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
cRBC	Chicken red blood cell
CRD	Centre for Reviews and Dissemination
CS	Company's submission
CSR	Clinical study report
CV	Cardiovascular
DC	Discontinuation
DCE	Discrete choice experiment
DSU	Decision Support Unit
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EPAR	European Public Assessment Report
EQ-5D	European Quality of Life-5 Dimensions
ERG	Evidence Review Group
EUR	Erasmus University Rotterdam
FACIT	Functional Assessment of Chronic Illness Therapy
FAD	Final appraisal document
FAS	Full analysis set
FDA	Food and Drug Administration
GHS	Global health score
GPI	Glycophosphatidylinositol
Hb	Haemoglobin
HGB-S	Haemoglobin stabilisation
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
IC	Indirect comparison
ICER	Incremental cost effectiveness ratio
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
IVRS	Interactive voice response system
KSR	Kleijnen Systematic Reviews
LDH	Lactate dehydrogenase
LDH-N	Normalisation of lactate dehydrogenase levels
LDH-PCHG	Lactate dehydrogenase-percent change
LSM	Least squares mean
LYs	Life years
LYG	Life years gained

MAVE	Major adverse vascular event
MeSH	Medical Subject Headings
MHRA	Medicines and Healthcare Products Regulatory Agency
MTA	Multiple technology appraisal
MTC	Mixed treatment comparison
NA	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NIM	Non-inferiority margin
NMA	Network meta-analysis
NO	Nitric oxide
NR	Not reported
OS	Overall survival
PAS	Patient access scheme
PD	Pharmacodynamics
PFS	Progression-free survival
PK	Pharmacokinetics
PNH	Paroxysmal nocturnal haemoglobinuria
PP	Per protocol
pRBC	Packed red blood cells
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QoL	Quality of life
q8w	Every eight weeks
RBC	Red blood cell
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RR	Relative risk; Risk ratio
SAE	Serious adverse events
ScHARR	School of Health and Related Research
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
STA	Single technology appraisal
TA	Transfusion avoidance
TEAE	Treatment emergent adverse events
TTO	Time trade-off
UK	United Kingdom
ULN	Upper limit of normal
UMC	University Medical Centre
URTI	Upper respiratory tract infection
WBC	White blood cell
WHO	World Health Organization
WRS	Web response system
WTP	Willingness-to-pay

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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. Where possible, 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 discusses the decision problem, Section 1.3 issues related to clinical effectiveness, and Section 1.4 issues related to cost effectiveness. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report, see Sections 2 (background), 3 (decision problem), 4 (clinical effectiveness) and 5 (cost effectiveness) for more details.

All issues identified represent the ERG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the ERG's key issues

Table 1.1: Summary of key issues

ID1457	Summary of issue	Report sections
1	Generalisability of the trial populations to UK patients	Section 4.2.3
2	Dosing of eculizumab	Sections 3.3 and 4.2.2
3	Short follow-up in the trials	Section 4.2.5
4	Appropriateness of the company's base-case analysis	Section 5.2.3, 6.1 and 6.3
5	Appropriateness of the company's "equal effectiveness" scenario	Section 5.2.3
6	Generalisability of the ERG base-case to UK clinical practice	Section 5.2.2 and 5.2.3
7	Health-related quality of life	Section 5.2.8
8	Ravulizumab treatment effect duration	Section 5.2.6
9	Treating undetermined and CAC-related BTH events	Section 5.2.2

The most important deviation from the company's base-case was to assume no eculizumab up-dose to align the cost effectiveness analyses with the clinical trials. As explained below, the ERG acknowledged that this assumption is not completely representative of UK clinical practice. However, as the company stated in the company submission (CS), the majority (about [redacted]%) of PNH patients in UK clinical practice are managed at the standard eculizumab dose for whom an additional eculizumab up-dose is not needed. Additionally, the ERG proposed a different approach to utilities under the assumption that the ravulizumab quality of life benefit due to reduced treatment frequency might be captured by the treatment effect coefficient included in the mixed-effects regression equations used by the company to estimate utilities. This also implied that the additional ravulizumab utility for reducing treatment frequency, which was estimated from an external discrete choice experiment (DCE) and included in the company's base-case, was not used (set equal to 0) in the ERG preferred base-case. Finally, for the cost calculations, the ERG assumed the currently licensed 10mg/ml ravulizumab formulation, as opposed to 100mg/ml assumed by the company.

1.2 Overview of key model outcomes

The company's base-case results indicated that ravulizumab accrued [redacted] incremental quality adjusted life years (QALYs) and was cost saving compared to eculizumab. The largest differences in costs

across treatment arms were due to acquisition costs in the "No BTH" health state, which resulted in [redacted] difference for ravulizumab compared to eculizumab. However, these costs were outweighed by eculizumab due to patients requiring eculizumab up-dose. Thus, in the health state "continuous up-dose with history of incomplete C5 inhibition-related BTH event", the costs for eculizumab are [redacted], while there are no costs for ravulizumab in this health state (no incomplete C5 inhibition-related BTH events and no up-dose in the ravulizumab arm). However, the proportion of time spent in the continuous up-dose health states across the complete model time horizon was [redacted]%, which is approximately twice as much as the [redacted]% reported by the company to be expected to receive an increased dose of eculizumab in UK clinical practice. Consequently, the company's base-case results might be biased against eculizumab.

1.3 The decision problem: summary of the ERG's key issues

The decision problem addressed in the company submission (CS) is broadly in line with the final scope issued by NICE. However, there is uncertainty about the trial population being representative for UK patients (Table 1.2) as well as the dosing of the comparator: eculizumab (Table 1.3).

Table 1.2: Key issue 1: Generalisability of the trial populations to UK patients

Report section	**Section 4.2.3 and 5.2.3**
Description of issue and why the ERG has identified it as important	Both trials were international trials with most patients included from countries other than the UK. Therefore, there is a question about the generalisability of the trial populations to UK clinical practice. In the ALXN1210-PNH-301 trial, 246 patients were included with [redacted] patients treated in England. In the ALXN1210-PNH-302 trial, 195 patients were included with [redacted] patients treated in England and [redacted] patients treated in Scotland. It is possible that patients included in the two trials have less severe disease than UK patients.
What alternative approach has the ERG suggested?	It is unclear how this difference in population characteristics influences results. Therefore, the ERG has no alternative approach.
What is the expected effect on the cost effectiveness estimates?	The expected change to the ICER is unclear.
What additional evidence or analyses might help to resolve this key issue?	The ERG is unclear how this issue can be resolved without new evidence.

Table 1.3: Key issue 2: Dosing of eculizumab

Report section	**Section 3.3, 4.2.2 and 5.2.3**
Description of issue and why the ERG has identified it as important	In UK clinical practice, an increased dose of eculizumab is used to manage breakthrough haemolysis (BTH) due to incomplete C5 inhibition. Data from the Paroxysmal nocturnal haemoglobinuria (PNH) national service indicate this is necessary for [redacted]% of the population (see CS, Section B.3.2.1), with the majority of patients remaining stable on the licensed eculizumab dose (900 mg). However, in the two ravulizumab trials included in the company submission, dose-escalation/up-dosing of eculizumab was not permitted (CS, page 89). This may have resulted in worse clinical outcomes for patients in the eculizumab arms of the two trials. Therefore, the

	effectiveness of ravulizumab may have been overestimated.
What alternative approach has the ERG suggested?	The size of this overestimation is not clear. Therefore, the ERG has no alternative approach.
What is the expected effect on the cost effectiveness estimates?	In the cost effectiveness analysis the company made assumptions regarding up-dosing of eculizumab and assumed equal effectiveness in a scenario analysis, which resulted in a very small increase in the number of QALYs with eculizumab, although ravulizumab was still dominant. However, as discussed more fully below, the ERG has concerns about the assumptions regarding up-dosing, which might have led to the effectiveness of eculizumab still being underestimated and the cost overestimated.
What additional evidence or analyses might help to resolve this key issue?	The company could not present evidence of the effectiveness of eculizumab at a dose at or closer to one that would be observed in UK clinical practice. Therefore, the ERG is unclear how this issue can be resolved without new evidence.

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

The ERG identified one major concern with the evidence presented on the clinical effectiveness, namely the short follow-up of the included randomised controlled trials (RCTs; see Table 1.4).

Table 1.4: Key issue 3: Short follow-up in the trials

Report section	**Section 4.2.5**
Description of issue and why the ERG has identified it as important	Data are relatively immature in that they currently provide data for up to 52 weeks for a chronic condition requiring lifelong treatment. There is uncertainty about the long-term effectiveness of ravulizumab.
What alternative approach has the ERG suggested?	It is unclear how this will affect results. Therefore, the ERG has no alternative approach.
What is the expected effect on the cost effectiveness estimates?	The expected change to the ICER is unclear
What additional evidence or analyses might help to resolve this key issue?	The ERG is unclear how this issue can be resolved without new evidence.

1.5 The cost effectiveness evidence: summary of the ERG's key issues

A full summary of the cost effectiveness evidence review conclusions can be found in Section 7.4 of this report. The company's cost effectiveness results are presented in Section 6, the ERG's summary and detailed critique in Section 5, and the ERG's amendments to the company's model and results are presented in Section 7. The key issues in the cost effectiveness evidence are discussed in Tables 1.5 to 1.10.

Table 1.5: Key issue 4: Appropriateness of the company's base-case analysis

Report section	5.2.3 Population, 6.1 Company's cost effectiveness results and 6.3 Model validation and face validity check
Description of issue and why the ERG has identified it as important	The proportion of time spent in the continuous up-dose health states of the model, across the complete model time horizon, was [redacted]% in the company's base-case analysis. This is approximately twice as much as the [redacted]% reported by the company to be expected to receive an increased dose of eculizumab in UK clinical practice. The ERG is concerned that the company's base-case analysis might overestimate the proportion of time spent in the continuous up-dose health states and consequently the results might be biased against eculizumab.
What alternative approach has the ERG suggested?	In the company's "equal effectiveness" scenario, the proportion of time spent in the continuous up-dose health states *across the complete model time horizon* was assumed to be exactly [redacted]%, matching the PNH National Service estimate of the proportion of patients expected to receive an increased dose of eculizumab in UK clinical practice. This is the main reason why the ERG considers that the "equal effectiveness" scenario may provide a better representation of UK clinical practice than the company's base-case scenario.
What is the expected effect on the cost effectiveness estimates?	Ravulizumab is more effective and cost saving compared to eculizumab, as in the company's base-case. Incremental costs in the "equal effectiveness" scenario are lower than in the company's base-case (i.e. ravulizumab "less" cost saving).
What additional evidence or analyses might help to resolve this key issue?	Clinical expert opinion should help assessing the plausibility of the company's base-case scenario.

Table 1.6: Key issue 5: Appropriateness of the company's "equal effectiveness" scenario

Report section	5.2.3 Population
Description of issue and why the ERG has identified it as important	The ERG is concerned that the sub-population of patients who would require an eculizumab up-dose might be underestimated in the trials. The company explained that approximately 5% of patients in the trial population would need an eculizumab up-dose, which is approximately [redacted] lower than the [redacted]% estimate from the PNH National Service. The ERG wonders whether the conclusions from the trials, in which only 5% of patients would be "eligible" for an eculizumab up-dose, would be the same if there were approximately [redacted]% of patients who would need such an up-dose (as in UK clinical practice).
What alternative approach has the ERG suggested?	The ERG prefers a base-case scenario based completely on the clinical trials, thus, with no eculizumab up-dose included in the model.
What is the expected effect on the cost effectiveness estimates?	Could potentially have a substantial impact on the cost effectiveness.
What additional evidence or analyses might help to resolve this key issue?	Additional data may help reducing the uncertainty regarding this aspect of the analysis.

Table 1.7: Key issue 6: Generalisability of the ERG base-case to UK clinical practice

Report section	5.2.2 Model structure and 5.2.3 Population
Description of issue and why the ERG has identified it as important	The ERG prefers a base-case scenario based on the clinical trials. Thus, with no eculizumab up-dose included in the model. The majority (about [redacted]%) of PNH patients in UK clinical practice are managed at the standard eculizumab dose for whom an additional eculizumab up-dose is not needed. Therefore, the ERG base-case is not completely representative of UK clinical practice.
What alternative approach has the ERG suggested?	No alternative suggested. The ERG considers that, with the current evidence, neither the company base-case nor the equal effectiveness scenario would provide a better representation of UK clinical practice.
What is the expected effect on the cost effectiveness estimates?	Could potentially have a substantial impact on the cost effectiveness.
What additional evidence or analyses might help to resolve this key issue?	Additional data may help reducing the uncertainty regarding this aspect of the analysis.

Table 1.8: Key issue 7: Health-related quality of life

Report section	5.2.8 Health-related quality of life
Description of issue and why the ERG has identified it as important	The ERG disagrees that health-related quality of life (HRQoL) could not be assessed in the trial, as the administration frequency for ravulizumab was lower in the trial and substantial benefits, other than time of the patient, ought to be captured in the trial. Furthermore, the ERG argues that the methodological challenges of the discrete choice experiment outweigh its benefit as an external source for utility values.
What alternative approach has the ERG suggested?	The ERG prefers a non-significant utility benefit of 0.0103 and 0.0197 for ravulizumab, derived from a mixed-effects regression model, as the source of HRQoL benefit in the cost effectiveness model and prefers not to use the utility benefit for treatment frequency of 0.057 as derived from the discrete choice experiment.
What is the expected effect on the cost effectiveness estimates?	Substantial impact on the cost effectiveness under the ERG base-case settings (no eculizumab up-dose).
What additional evidence or analyses might help to resolve this key issue?	The ERG would recommend collecting EQ-5D data in the patient population rather than the cancer oriented QLQ-C30. The ERG would also recommended that the HRQoL benefit, including that related to frequency of administration, is measured in patients with a generic preference-based measure rather than externally through a DCE.

Table 1.9: Key issue 8: Ravulizumab treatment effect duration

Report section	5.2.6 Treatment effectiveness and extrapolation
Description of issue and why the ERG has identified it as important	The ERG is concerned about the company's assumption of a constant lifelong ravulizumab treatment effect. In response to clarification question B13, the company refused to model a decline in treatment effect over time as this was not considered clinical plausible. However, it can be argued that data from over 10 years are available only for eculizumab and the long-term effects of ravulizumab are unknown.
What alternative approach has the ERG suggested?	Given the time constraints associated to this project, the ERG was unable to run a scenario where a decline in treatment effect over time was included in the model.
What is the expected effect on the cost effectiveness estimates?	Could potentially have a substantial impact on the cost effectiveness.
What additional evidence or analyses might help to resolve this key issue?	Additional data may help reducing the uncertainty regarding this aspect of the analysis. Additional scenario analyses may provide an estimation of the impact of this uncertainty on the cost effectiveness results.

Table 1.10: Key issue 9: Treating undetermined and CAC-related BTH events

Report section	5.2.2 Model structure
Description of issue and why the ERG has identified it as important	The ERG is unclear how patients with undetermined BTH events were treated in the clinical trials. Therefore, the ERG was unable to judge the appropriateness of modelling undetermined BTH events as complement-amplifying condition (CAC)-related BTH events. Also, the ERG feels that the rationale to assume to treat all CAC-related events with one single up-dose of eculizumab should have been better justified.
What alternative approach has the ERG suggested?	With the evidence presented in the CS and the response to the clarification letter, the ERG preferred to assume that CAC-related BTH events would not be treated with an eculizumab up-dose, in line with what was observed in the clinical trials in which up-dose was not allowed.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Clinical expert opinion may help reducing the uncertainty regarding this aspect of the analysis.

1.6 Other key issues: summary of the ERG's view

No other key issues were identified by the ERG.

1.7 Summary of the ERG's view

1.7.1 ERG preferred base-case

Fixing errors

1. Error in the model "Output" sheet in the ca1culation of the proportion of time spent in the model health states. This has no impact on the model cost effectiveness results, but it is important for clinical validation.

Fixing violations

2. No violations to the NICE reference case, scope or best practice were identified by the ERG.

Matters of judgement

3. Eculizumab up-dose: based completely on the clinical trials ALXN1210-PNH-301 and ALXN1210-PNH-302. Thus, without modelling eculizumab up-dose.
4. Utilities: ravulizumab utility benefit derived from a mixed-effects regression model with treatment as covariate.
5. Utilities: additional utility benefit for treatment frequency set to 0 (instead of 0.057, as derived from the DCE).
6. Ravulizumab currently licensed 10mg/ml formulation (instead of 100mg/ml).

1.7.2 ERG scenarios

1. Cohort 3 is assumed to reflect UK clinical practice, where a continuous increased dose of eculizumab is used to manage BTH events. The reported range of PNH patients requiring this up-dose is between 5% and 29%, with an estimated mean value of [redacted]%. In this scenario, the impact of assuming a smaller population (5%) in Cohort 3 was explored by the ERG.
2. In this scenario, the ERG assumed [redacted]% of patients in Cohort 3, the ravulizumab utility benefit derived from a mixed-effects regression model with treatment as covariate, the additional utility benefit for treatment frequency set to 0 and the ravulizumab formulation of 10mg/ml.
3. In this scenario, the ERG assumed eculizumab up-dose as in the company's base-case (continuous after second incomplete C5 inhibition-related BTH event), the ravulizumab utility benefit derived from a mixed-effects regression model with treatment as covariate, the additional utility benefit for treatment frequency set to 0 and the ravulizumab formulation of 10mg/ml.
4. The ERG explored the impact of assuming the utility decrement of 0.057 (instead of 0) as in the company base-case, and half of this value (0.029). The remaining ERG preferred assumptions were as in the ERG base-case (no eculizumab up-dose and the ravulizumab formulation of 10mg/ml).
5. In this scenario, the ERG base-case was run with the assumption of BTH excess mortality as reported by Jang et al. (2016). A standard mortality ratio of 4.81 was applied.

1.7.3 Conclusion

The changes made by the ERG led to a situation where ravulizumab was not cost saving compared to eculizumab, unlike the company's base-case. The ICER from the ERG base-case was £38,290, obtained from the estimated [redacted] incremental QALYs gained by ravulizumab at an incremental cost of [redacted] compared to eculizumab. The differences with respect to the company's base-case were mostly explained by the assumption of no eculizumab up-dose. The ERG also conducted a

probabilistic sensitivity analysis (PSA) based on its preferred assumptions. The probabilistic ICER was £46,976 per QALY gained (incremental costs were [redacted] and incremental QALYs were [redacted]), thus, £8,686 larger than the ERG deterministic ICER. The ERG considers that this relatively large difference might be explained because the ERG PSA allows a (small) proportion of patients in the ravulizumab arm to transition to the incomplete C5 inhibition-related BTH events related health states. The cost effectiveness (CE)-plane showed approximately [redacted]% of the simulations in the south eastern quadrant, in which ravulizumab is dominant. The remaining simulations were in the north eastern quadrant. The cost effectiveness acceptability curve (CEAC) showed that the probability of ravulizumab being cost effective was [redacted]% (as opposed to [redacted]% in the company's PSA) at a threshold ICER of £30,000 per QALY gained. The ERG also conducted additional scenario analyses to explore important areas of uncertainty in the model. These key uncertainties were related to the so-called "equal effectiveness" scenario, utilities and BTH mortality. Other sources of uncertainty were deemed less important and were not explored in this section.

The results of these analyses showed that when eculizumab up-dose was included in the analysis, ravulizumab becomes a cost saving (and more effective) option compared to eculizumab. These analyses highlight the large impact that the proportion of patients treated with eculizumab up-dose has on the overall cost effectiveness results, even though this sub-population represents a minority (approximately [redacted]%) of the total PNH patients. The other assumptions tested by the ERG had an impact on the model results only when up-dose was not included in the analyses, thus under the ERG preferred assumption. The choice of non-zero values for the additional ravulizumab utility for reducing treatment frequency, had a relatively large impact on the ERG preferred base-case ICER. When the value estimated from the DCE and used by the company in their base-case, was used (0.057), the ICER decreased to £11,790 and when this utility value was halved (0.029) the ICER was £17,688. Thus, in both cases below the £30,000 threshold ICER. Finally, when excess mortality risk of BTH events was added to the ERG preferred analysis, by applying a hazard ratio of 4.81 to patients experiencing BTH events, sourced from the Korean PNH registry by Jang et al. 2016, the ICER increased to £124,433. This scenario highlights the impact of BTH excess mortality on the ERG base-case results. Additional data from the ALXN1210-PNH-301 and ALXN1210-PNH-302 trial Extension Phases reporting clinical outcomes up to 104 weeks are expected to be available in [redacted]. When the new data become available, the company will conduct an analysis of overall survival, which might be useful in reducing the uncertainty regarding BTH excess mortality.

It should be emphasised that throughout the CS and the responses to the clarification letter, the company have made it clear that eculizumab 'up-dosing' is only necessary in approximately [redacted]% of the PNH population and that most patients would achieve an adequate terminal complement inhibition on the licensed eculizumab dose. However, despite being a minority, the assumptions about patients who would require an eculizumab up-dose are the main driver of the cost effectiveness results. A summary of the ERG's base-case results is presented in Table 1.11.

Table 1.11: Summary of ERG's preferred assumptions and ICER

Scenario	Incremental cost	Incremental QALYs	ICER
Company base-case (after clarification)	[redacted]	[redacted]	Ravulizumab dominates
ERG change 1: no eculizumab up-dose (key issue 6)	[redacted]	[redacted]	£14,798
ERG change 2: utilities treatment arm as	[redacted]	[redacted]	£11,538

Scenario	Incremental cost	Incremental QALYs	ICER
covariate (key issue 7)			
ERG change 3: utilities no additional utility benefit for treatment frequency (key issue 7)	[redacted]	[redacted]	£37,474
ERG's preferred base-case (ravulizumab formulation 10mg/ml)	[redacted]	[redacted]	£38,290

Based on the CS and the electronic model of the CS.
Abbreviations: CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year

2. BACKGROUND

2.1 Introduction

In this report, the Evidence Review Group (ERG) provides a review of the evidence submitted by Alexion Pharmaceuticals in support of ravulizumab, trade name Ultomiris®, for patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolysis with clinical symptoms indicative of high disease activity, or whose disease is clinically stable after receiving eculizumab treatment for a minimum of six months. In this section, the ERG summarises and critiques the company's description of the underlying health problem and the company's overview of the current service provision. The information for this critique is taken from Document B of the company submission (CS).[1]

2.2 Critique of company's description of the underlying health problem

PNH is caused by an acquired mutation in the *PIG-A* gene in haematopoietic stem cells,[1, 2 3] that results in a partial or absolute deficiency in proteins linked to the cell membrane by a glycosylphosphatidylinositol (GPI) anchor. PNH is a rare condition, with an estimated 725 diagnosed cases in the UK (2018 figures).[4]

PNH is a progressive, life-threatening haematological disorder that is characterised by uncontrolled activation of the terminal complement pathway, which can lead to intravascular haemolysis, anaphylaxis, inflammation and thrombosis.[1] The CS states that, '*without complement-inhibitor treatment, the majority of patients (up to 75%) die within 20 years of diagnosis, and the median survival time is estimated at approximately 10 years (from diagnosis).*'[1, 5]

ERG comment: The ERG notes that reference cited, in support of the statements about the life expectancy of patients with PNH who are not treated with complement-inhibitors, refers to a study of patients wo were referred to Hammersmith Hospital, London between 1940 and 1970. It is not clear that whether the life expectancy of patients with PNH had improved, over time, prior to the introduction of compliment-inhibitors.

The clinical course of PNH varies, with some patients experiencing sudden symptom onset with rapid progression to death and others experiencing chronic illness with limited life-threatening complications.[1, 6] Chronic haemolysis is considered to be the underlying cause of morbidity and premature mortality in patients with PNH,[1] and can result in a variety of symptoms and adverse outcomes, including anaemia, fatigue, dyspnoea, haemoglobinuria, pulmonary hypertension, thrombosis.[1] The symptoms of PNH can have a substantial impact on patients' quality of life and functioning. A 2007 multi-national survey of 29 patients with PNH found that 76% were forced to modify their daily activities in order to manage their disease and 17% were unemployed due to PNH; nearly all (96%) patients in the study reported experiencing fatigue and more than half reported abdominal pain, headache and shortness of breath.[7] However, 31% of patients surveyed also reported not receiving any medication for their PNH.[7]

2.3 Critique of company's overview of current service provision

Current service provision for patients with PNH, in NHS England, is managed through a PNH National Service that was initiated in April 2009.[1, 4] This service is provided through two main centres, one at St James' University Hospital in Leeds, and the second at King's College Hospital in London, and a further eight outreach clinics around the UK (Birmingham, Bristol, Lanarkshire, Liverpool, Manchester, Oxford, Peterborough and Southampton).[1] Referrals for suspected PNH are

usually made by haematologists and, on confirmed diagnosis, patients are managed on a shared care basis between the PNH National Service and referring haematologists.[1]

Adult patients with PNH and haemolysis with clinical symptom(s) indicative of high disease activity in the UK are currently treated with eculizumab.[1, 8] In the treatment initiation phase, patients receive eculizumab 600mg via 25 to 45 minute intravenous infusion every week for the first four weeks.[1, 9] In the treatment maintenance phase, patients receive eculizumab 900mg via 25 to 45 minute intravenous infusion every 14 ± 2 days. For patients in England, initial dose(s) are administered at one of the PNH National Service centres, after which most patients choose to have treatment administered at their home through a homecare service.[1, 10, 11]

The criteria used, by the PNH National Service, to determine treatment eligibility are[1]:

- Thrombosis related to PNH
- Complications associated with haemolysis:
    - Renal failure
    - Pulmonary hypertension
- Pregnancy (and for at least three months post-partum)
- Haemolytic (lactate dehydrogenase [LDH] levels > 1.5 times the upper limit of normal [ULN]) PNH with either of the following:
- With anaemia (Hb < 9 g/L) or
- With agreement with Joint Service colleagues at multidisciplinary team (MDT)
- Exceptional cases (not fulfilling the above criteria) with approval across PNH National Service centres and the National Commissioners

With respect to remaining unmet need, the CS notes that approximately 20% of patients experience breakthrough haemolysis while receiving recommended dose of eculizumab (900mg) treatment (reported range: 5–29%),[1, 12-15] and states that experiencing breakthrough haemolysis have an increased risk of potentially fatal thromboembolic events and other debilitating PNH-related symptoms.[1]

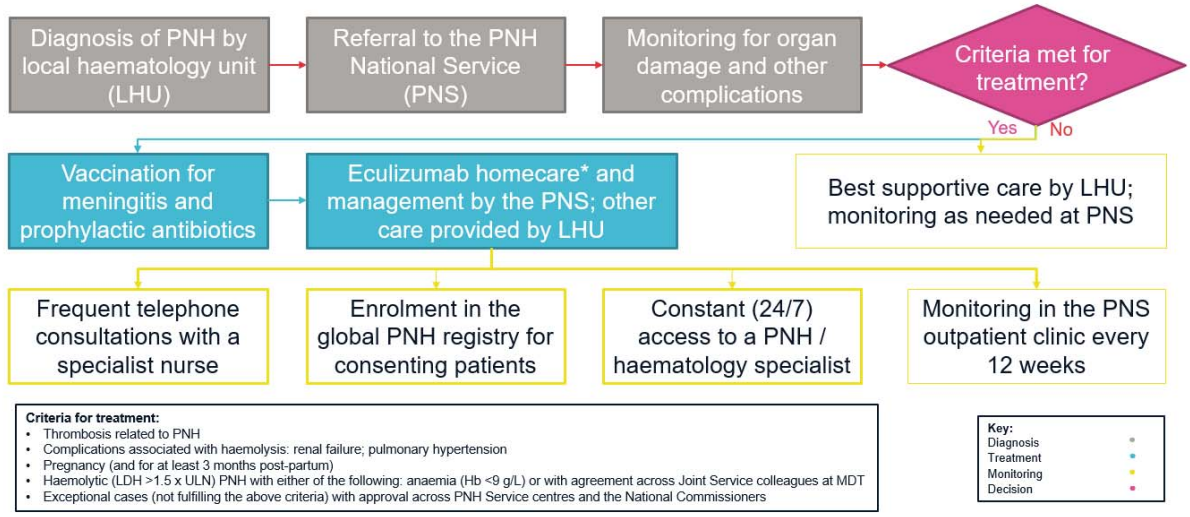
Breakthrough haemolysis can occur when the blood concentration of complement inhibitor is insufficient to provide complete C5 inhibition, or as a result of a concomitant complement-amplifying condition (CAC) such as pregnancy or infection.[1, 14, 16] Treatment with complement-inhibitors cannot prevent breakthrough haemolysis due to a CAC, it should prevent breakthrough haemolysis due to incomplete C5 inhibition. In confirmed cases of incomplete terminal complement inhibition, the PNH National Service recommend permanently increasing the dose of eculizumab to 1,200mg or higher if needed.[1, 17] According to UK data from the International PNH Registry (2 October 2018) and PNH National Service data (March 2019), approximately [redacted]% of patients treated in current practice are receiving a dose of eculizumab that is higher than the recommended 900mg.[1]

ERG comment: The extent to which breakthrough haemolysis occurs on higher doses of eculizumab and the clinical consequences of breakthrough haemolysis (e.g. incidence of thrombosis) remain unclear.

The CS also notes that eculizumab is associated with a high administration burden due to its relatively short half-life, with patients requiring bi-weekly infusions to maintain C5 inhibition.[1]

The proposed position of ravulizumab is as an alternative to eculizumab to address the remaining areas of unmet need described above.[1] Figure 2.1 shows the proposed treatment pathway for adult patients with PNH.[1]

Figure 2.1: The clinical pathway for adult patients with PNH



Source: Figure 1 of Document A

LDH = lactate dehydrogenase; LHU = local haematology unit; PNS = PNH National Service; PNH = paroxysmal nocturnal haemoglobinuria

3. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 3.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
Population	Adults with paroxysmal nocturnal haemoglobinuria: • who have haemolysis with clinical symptom(s) indicative of high disease activity or • whose disease is clinically stable after having eculizumab for at least 6 months	Adults with paroxysmal nocturnal haemoglobinuria: • who have haemolysis with clinical symptom(s) indicative of high disease activity or • whose disease is clinically stable after having been treated with eculizumab for at least 6 months	Not applicable	The population is in line with the NICE scope
Intervention	Ravulizumab	Ravulizumab	Not applicable	The intervention is in line with the NICE scope
Comparator(s)	Eculizumab	Eculizumab	Not applicable	The comparators are in line with the NICE scope.
Outcomes	The outcome measures to be considered include: • overall survival • haemolysis (measured by lactate • dehydrogenase [LDH] level) • breakthrough haemolysis • transfusion avoidance • stabilised haemoglobin • thrombotic events • adverse effects of treatment • health-related quality of life	The outcome measures to be considered include: • overall survival • haemolysis (measured by lactate • dehydrogenase [LDH] level) • breakthrough haemolysis • transfusion avoidance • stabilised haemoglobin • thrombotic events • adverse effects of treatment • health-related quality of life	Overall survival was not a pre-specified endpoint in the ravulizumab trial programme, although deaths were captured as a safety outcome. Eculizumab has aligned the life expectancy of paroxysmal nocturnal haemoglobinuria patients to the general population such that the economic model uses standard mortality estimates. Health-related quality of life data collection was limited to patients in the ravulizumab trial programme. Thus,	The outcomes reported are in line with the NICE scope

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
	(for patients and carers)	(for patients and carers)	health-related quality of life for carers is only considered in a qualitative sense and not captured in the economic model.	
Economic analysis	The cost effectiveness of treatments should be expressed in terms of incremental cost per QALY	Cost effectiveness is expressed in terms of incremental cost per QALY	Not applicable	The cost effectiveness analyses were conducted according to the NICE reference case.
Time horizon	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	A lifetime horizon (100 − mean age at baseline) was adopted to capture costs over a sufficient length of time and consistent with previous analyses in PNH	Not applicable	The time horizon selected by the company 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	Health effects, expressed in QALYs, based on EORTC QLQ-C30 data, mapped to EQ-5D-3L	Not applicable	Health effects are expressed in line with the NICE scope and according to the NICE reference case.

Source: CS, Table 1, page 7 (Document B0 and Table 3, pages 10-12 (Document A).

EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D-3L, three-level EQ-5D; HRQL, health-related quality of life; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal haemoglobinuria; PSS, personal social services; QALY, quality-adjusted life years.

3.1 Population

The population defined in the scope is: Adults with paroxysmal nocturnal haemoglobinuria who have haemolysis with clinical symptom(s) indicative of high disease activity or whose disease is clinically stable after having eculizumab for at least six months.[18] This population is in line with the population in the CS, and with the license indication for ravulizumab (Ultomiris®) (CS, Table 2, page 10).[1]

See also Sections 4.2.2, 4.2.3 and 5.2.3 for the generalisability of the trial populations to UK patients.

3.2 Intervention

The intervention (ravulizumab) is in line with the scope.

Ravulizumab is administered by intravenous infusion. The dosing schedule consists of an initial loading dose, followed by maintenance dosing, starting two weeks after the loading dose. Dosage is determined by weight with a loading dose of 2400mg to 3000mg, and maintenance dose of 3000mg to 3600mg every eight weeks. Treatment is recommended to continue for the patient's lifetime, unless discontinuation is clinically indicated, for example, in the rare circumstance of spontaneous remission or recovery due to bone marrow transplant for underlying bone marrow failure. In trials ALXN1210-PNH-301 and ALXN1210-PNH-302 a loading dose of ravulizumab was given on Day 1 with maintenance doses on Days 15, 71 and 127.

According to the company, no additional tests are required prior to the administration of ravulizumab (CS, page 10).[1]

3.3 Comparators

Eculizumab is the only comparator specified in the NICE scope.[18]

In the treatment initiation phase, patients receive eculizumab 600mg via 25–45 minute intravenous infusion every week for the first four weeks.[9] In the treatment maintenance phase, patients receive eculizumab 900mg via 25–45 minute intravenous infusion every 14 ± 2 days. For patients in England, up to the first five eculizumab doses (often only the first dose) are administered at one of the PNH National Service centres, after which most patients choose to have treatment administered at their home through a homecare service.[10, 11] (CS, page 13-14).[1]

In UK clinical practice, an increased dose of eculizumab is used to manage BTH due to incomplete C5 inhibition. Data from the PNH national service indicate this is necessary for [redacted]% of the population (see CS, Section B.3.2.1), with most patients remaining stable on the licensed eculizumab dose (900mg). However, in the two ravulizumab trials included in the company submission, dose-escalation/up-dosing of eculizumab was not permitted (CS, page 89). According to the company: "[redacted]" (CS, page 145), and "*The lack of 'up-dosing' in the pivotal clinical trial programme compared with clinical practice may also result in slightly worse clinical outcomes for patients in the eculizumab arm of ALXN1210-PNH-301 and ALXN1210-PNH-302"* (CS, page 68).[1]

ERG comment: As the company states the lack of 'up-dosing' in the two trials compared with UK clinical practice may result in worse clinical outcomes for patients in the eculizumab arms. It is not clear how much effect the difference in dosing of eculizumab has. In theory it is possible that eculizumab administered at a dose that would be observed in UK clinical practice might even be more effective than ravulizumab. When asked about this in the clarification letter (Question A5), the company responded: "*UK clinical practice demonstrates that the majority of PNH patients (~ [redacted])*

are managed at the standard dose of eculizumab as per the marketing authorisation, i.e. 900mg every 2 weeks. This is also the dosing schedule that was applied in the pivotal clinical trial programme comparing ravulizumab with eculizumab. However, approximately [redacted]% of UK PNH patients require an eculizumab dosing adjustment to achieve complete terminal complement inhibition and prevent the symptoms of their PNH and accompanying haemolysis to recur….. Therefore, eculizumab administered at higher doses than the standard dose would not be more effective than ravulizumab, but would likely prevent the breakthrough haemolysis due to incomplete C5 inhibition events observed in the eculizumab arm of the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials".[19]

3.4 Outcomes

The NICE final scope lists the following outcome measures:

- Overall survival
- Haemolysis (measured by lactate dehydrogenase [LDH] level)
- Breakthrough haemolysis
- Transfusion avoidance
- Stabilised haemoglobin
- Thrombotic events
- Adverse effects of treatment
- Health-related quality of life (for patients and carers)

These were all assessed in the two included ravulizumab trials ALXN1210-PNH-301 and ALXN1210-PNH-302. Although, health-related quality of life data collection was limited to patients in the ravulizumab trial programme. Thus, health-related quality of life for carers is only considered in a qualitative sense and not captured in the economic model.

3.5 Other relevant factors

Ravulizumab was derived from eculizumab and the technologies share over 99% homology, in that sense ravulizumab is not an innovative technology. Nevertheless, the company states that "*the small differences in their design and administration have a substantial impact: alleviating the risk of breakthrough haemolysis associated with incomplete C5 inhibition, and reducing the frequency of regular infusions to 6–7 per year in the treatment maintenance phase (from 26 per year)*" (CS, Section B.12).[1] In addition, the company claims that health-related benefits are likely to exist outside of the formal QALY calculations, especially for carers.

A Patient Access Scheme (PAS) is in place between the Department of Health and the company (Alexion) for ravulizumab.

[redacted] (representing a discount of [redacted]% on the list price).

This appraisal does not fulfil the End-of-Life criteria as specified by NICE because the life expectancy of patients eligible for ravulizumab is well beyond 24 months. Therefore, treatment is not indicated for patients with a short life expectancy (normally less than 24 months). As stated by the company, "*Eculizumab has transformed the prognosis of patients with haemolytic PNH, significantly reducing progressive morbidity and aligning the life expectancy of patients to that of the general population*" (CS, page 14).[1]

According to the company, no equality issues are anticipated for the appraisal of ravulizumab (CS, Section B.1.4).

4. CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Searches

Appendix D of Document B of the CS details a systematic literature review (SLR) conducted to identify the available clinical evidence for the current treatment options for adult patients with PNH. Searches were conducted on 31 January 2020, with a subsequent update on 2 July 2020. Searches were designed to only include terms relating to the population, study designs and adverse events. No language or publication date limits were reported. Databases were searched from date of inception. A summary of the sources searched is provided in Table 4.1.

Table 4.1: Data sources for the clinical effectiveness systematic review (as reported in CS and response to clarification)

	Resource	Host/source	Date ranges	Dates searched
Electronic databases	MEDLINE and Epub Ahead of Print, In-Process and Daily Versions	Ovid	1946-2020	(i) 31.1.20 (ii)2.7.20
	Embase	Ovid	1974-2020	(i) 31.1.20 (ii)2.7.20
	Cochrane CDSR	Ovid	2005-2020	(i) 31.1.20 (ii)2.7.20
	Cochrane CENTRAL	Ovid	2005-2020	(i) 31.1.20 (ii)2.7.20
	DARE	Ovid	Not provided	(i) 31.1.20 (ii)2.7.20
Conference proceedings	American Society of Hematology Annual Meeting	https://ashpublications.org/blood/issue/134/Supplement_1	2019	
		https://ashpublications.org/blood/issue/132/Supplement%201	2018	
		https://ashpublications.org/blood/issue/130/Supplement%201	2017	
	European Haematology Association Annual Meeting	https://library.ehaweb.org/eha/#!*menu=5*browseby=8*sortby=2*media=6*label=19379	2019	
		https://library.ehaweb.org/eha/#!*menu=5*browseby=8*sortby=2*media=6*label=18567	2018	
		https://library.ehaweb.org/eha/#!*menu=5*browseby=8*sortby=2*media=6*label=15847	2017	

ERG comments:

- Searches were undertaken to identify clinical effectiveness data. The CS provided sufficient details for the ERG to appraise the literature searches. A range of database and conference

proceedings were searched. Both the original and the update searches were overall well conducted and documented, making them transparent and reproducible. In response to clarification, it was confirmed that all databases were searched from inception.

- No date or language limits were unnecessarily applied to the database searches.
- Study design filters were applied but not appropriately referenced. In response to clarification, a link was provided to the ISSG search filters website but it was not clear which filters were used.
- Terms to identify adverse events were included and combined with the population which seemed appropriate.
- Only the population was searched for which seemed appropriate considering the sparsity of literature.
- Although thesaurus terms for the population were searched for, free text terms for the population were limited and it is possible that use of more synonyms, truncation and adjacency may have increased the retrieval of potentially relevant records.
- It was not reported if reference checking had been undertaken. Best practice outlined in the Cochrane Handbook states that, "Checking reference lists within eligible studies supplements other searching approaches and may reveal new studies, or confirm that the topic has been thoroughly searched."[20]

4.1.2 Inclusion criteria

The eligibility criteria used in the search strategy for randomised controlled trials (RCTs) and non-RCTs is presented in Table 4.2.

Table 4.2: Eligibility criteria used in search strategy for RCT and non-RCT evidence

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Adult patients Diagnosis of PNH	Paediatric patients No diagnosis of PNH
Intervention	Ravulizumab Eculizumab Allogenic stem cell transplant Blood or erythrocyte transfusion Iron supplementation Folic acid supplementation Vitamin B12 supplementation Steroid or androgen therapy Anticoagulation Immunosuppressive treatment	Any intervention not listed for inclusion
Comparators	Any comparator	–
Outcomes	Any efficacy outcome Any safety outcome	No efficacy or safety outcomes reported
Study design	Randomised controlled trial Non-randomised controlled trial Single-arm trial Prospective observational study Retrospective observational study	Preclinical studies Case reports/series Editorials Commentaries and letters
Language restrictions	English	Non-English

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Source: CS, Appendix D, Table 2. PNH = paroxysmal nocturnal haemoglobinuria.		

ERG comment: The inclusion criteria are wider than the scope and cover a number of comparators not mentioned in the NICE scope. Therefore, the inclusion criteria are more than appropriate for this appraisal. However, only English language papers were included. This seems adequate for NICE appraisals but is not in line with best practice.

4.1.3 Critique of data extraction

Double data extraction was completed on the eligible studies and clinical study reports. Discrepancies were resolved through discussion until consensus was reached.[21] The extracted data included the study author and year of publication, study design and population, geographic location, baseline demographic characteristics, baseline clinical characteristics, sample size, intervention and comparator information, clinical outcomes, adverse events (AEs), serious adverse events (SAEs), and treatment-related adverse events (TRAEs). Of the clinical characteristics, the extracted information included breakthrough haemolysis, transfusion dependence, lactate dehydrogenase levels, haemoglobin levels, thrombotic events, and renal function.[21]

ERG comment: The ERG has no further comment on this matter.

4.1.4 Quality assessment

According to D.1.3 of the appendices of CS, the Cochrane Risk of Bias assessment tool for randomised trials or Strengthening the Reporting of Observational studies in Epidemiology (STROBE) Statement for observational studies were utilised.

ERG comment: STROBE is not a risk of bias tool; it is a reporting guideline. Therefore, it would not be appropriate. However, as no non-RCTs were included this is not an issue.

4.1.5 Evidence synthesis

An evidence synthesis of ravulizumab studies was not appropriate according to the company, because the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials provide data for distinct populations: complement-inhibitor naïve and eculizumab exposed patients, respectively.

ERG comment: The ERG agrees that it is not appropriate to pool results from the two ravulizumab studies.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Included studies

The company identified two trials providing evidence of the clinical benefits of ravulizumab for the treatment of adult patients with PNH: ALXN1210-PNH-301 and ALXN1210-PNH-302, as summarised in Table 4.3. Both are non-inferiority, randomised controlled trials (RCTs) which were designed to show that ravulizumab was non-inferior to eculizumab. Both trials report outcomes of relevance to the decision problem and are used to populate the subsequent economic modelling.

Table 4.3: Clinical effectiveness evidence

	ALXN1210-PNH-301 NCT02946463	**ALXN1210-PNH-302 NCT03056040**
Study design	Phase III Open-label; parallel assignment. Non-inferiority	Phase III Open-label; parallel assignment. Non-inferiority
Population	Adult patients with PNH who are complement-inhibitor naïve	Adult patients with PNH who are clinically stable following ≥ 6 months treatment with eculizumab
Intervention(s)	Ravulizumab	Ravulizumab
Comparator(s)	Eculizumab	Eculizumab
Reported outcomes specified in the decision problem	Haemolysis (measured by LDH levels) **Breakthrough haemolysis** Transfusion avoidance Stabilised haemoglobin Thrombotic events **Adverse effects of treatment** **HRQL (for patients)**	Haemolysis (measured by LDH levels) **Breakthrough haemolysis** Transfusion avoidance Stabilised haemoglobin Thrombotic events **Adverse effects of treatment** **HRQL (for patients)**
All other reported outcomes	**Transfusion units** PK and PD endpoints	**Transfusion units** PK and PD endpoints
Complete published reports	Lee et al. 2019[22] Brodsky et al. 2020[23]	Kulasekararaj et al. 2019[24] Brodsky et al. 2020[23]
Regulatory materials	European Public Assessment Report[25] Summary of Product Characteristics[26]	European Public Assessment Report[25] Summary of Product Characteristics[26]
Clinical study reports	Clinical study report[27] 52-week data addendum[28]	Clinical study report[29] 52-week data addendum[30]

Source: CS, Table 4, pages 17-18.
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 addition, the company identified two earlier phase ravulizumab trials providing additional safety data on patients with PNH treated with ravulizumab, which are detailed in Section 4.2.6 of this report (see also (Appendix F of the CS).

4.2.2 Methodology of included studies

4.2.2.1 ALXN1210-PNH-301and ALXN1210-PNH-302

ALXN1210-PNH-301 and ALXN1210-PNH-302 were both open-label, multicentre, randomised active-controlled, non-inferiority studies. The populations differed between the two trials in that the ALXN1210-PNH 302 patients had to have been treated with eculizumab for PNH for at least six months, whereas patients in the ALXN1210-PNH-301 trial were complement-inhibitor naïve.

Both trials received the same loading doses of ravulizumab according to body weight. The trials differed in terms of comparator doses of eculizumab, due to the different populations enrolled. ALXN1210-PNH-301 utilised 600mg induction doses on Days 1, 8, 15, and 22 and then increased to 900mg maintenance doses afterwards, while the ALXN1210-PNH-302 trial delivered 900mg of eculizumab all throughout (as patients had received induction doses at least 6 months prior to enrolment). However, the utilised doses of eculizumab in both trials was stated not to fully reflect UK

clinical practice, which according to the CS, recommends a permanent escalation to at least 1200mg for maintenance dosing in the minority of patients for whom the licensed 900mg maintenance dosing does not provide complete complement inhibition. The ERG requested justification of why eculizumab administered at a dose that would be observed in UK clinical practice (i.e. allowing 'up-dosing' in patients with incomplete complement inhibition) might not be more effective than ravulizumab.

The company stated that the majority (about [redacted]%) of PNH patients in UK clinical practice managed at the standard eculizumab dose of 900mg every two weeks. The company noted in their response to clarification that up-dosing was not permitted in either trial. Further noting that patients in the ALXN1210-PNH-302 trial had been clinically stable for more than six months on eculizumab, which then identified the optimised dose for these patients at the study entry. The ERG also requested the company provide additional evidence regarding the effectiveness of eculizumab at a dose at or closer to one observed in UK clinical practice. The company stated that there was no published data available that could provide an overview of the effectiveness of the up-dosing eculizumab observed in the UK.

Details of the trial design, key inclusion criteria and outcomes for both trials are provided in Table 4.4.

The randomised period for both trials was 26 weeks, while the extension period was two years during which all patients were treated with ravulizumab. Both trials received a ravulizumab loading dose that was given on Day 1 (ranging from 2400- 3000mg based on patient body weight) with maintenance doses (ranging from 3000- 3600mg based on patient body weight) on Days 15, 71, and 127. In the ALXN1210-PNH-301 trial, eculizumab was administered as a 600mg induction dose on Days 1, 8, 15, and 22, followed by maintenance doses of 900mg on Days 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, and 169. Whereas the ALXN1210-PNH-302 trial received 900mg doses of eculizumab on Days 1, 15, 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, and 169. Use of complement inhibitors other than the randomised treatment was prohibited.

The co-primary efficacy endpoints of the ALXN1210-PNH-301 trial were transfusion avoidance (the proportion of patients who remained transfusion-free and did not require a transfusion per protocol-specified guidelines to Week 26) and haemolysis, measured by LDH-N (≤ 1 x ULN, from Day 29 to Day 183 (Week 26)). Details of other outcomes measured at Week 26 are shown in Table 4.4.

The primary efficacy endpoint for the ALXN1210-PNH-302 was percent change in LDH from baseline to Week 26. Details of other outcomes measured at Week 26 are shown in Table 4.4.

ERG comment: Multiple clarifications regarding the use of eculizumab as a comparator in either trial against UK clinical practice were required. According to the company the use of eculizumab up-dosing was not permitted in the trials. The company could not present evidence of the effectiveness of eculizumab at a dose at or closer to one that would be observed in UK clinical practice.

Table 4.4: Trial methods

	ALXN1210-PNH-301 **NCT02946463**	**ALXN1210-PNH-302** **NCT03056040**
Centres and randomisation	123 sites across 25 countries including the UK (N=246; [redacted] patients from England). Randomisation was 1:1 using computer-generated sequence (IVRS/IWRS), stratified into six groups based on patient's transfusion history (0, 1 to 14, or > 14 units of pRBCs in year prior to first dose of study drug) and screening LDH levels (1.5 to < 3 or ≥ 3 x ULN).	52 sites across 12 countries including the UK (N=195; [redacted] patients from England; [redacted] patients from Scotland). Randomisation was 1:1 using computer-generated sequence (IVRS/IWRS), stratified into two groups based on patient's transfusion history (received a transfusion of pRBCs in year prior to first dose of study drug, yes or no).
Trial periods	Screening Period: 4 weeks Randomised Period: 26 weeks Extension Period: up to 2 years Primary Evaluation Period includes Screening and Randomised. Extension Period, all patients received ravulizumab.	Screening Period: 4 weeks Randomised Period: 26 weeks Extension Period: up to 2 years Primary Evaluation Period includes Screening and Randomised. Extension Period, all patients received ravulizumab.
Inclusion criteria	1. Male or female, 18 years of age or older 2. Documented diagnosis of PNH, confirmed by high sensitivity flow cytometry evaluation or RBCs and WBCs with granulocyte or monocyte clone size of ≥ 5% 3. Presence of one or more of the following PNH-related signs or symptoms within 3 months of screening: • Fatigue • Haemoglobinuria • Abdominal pain • Shortness of breath (dyspnoea) • Anaemia (haemoglobin < 10 g/dL) • History of major adverse vascular event, including thrombosis • Dysphagia • Erectile dysfunction	1. Male or female, 18 years of age or older 2. Treated with eculizumab according to the labelled dosing recommendation for PNH for at least six months prior to Day 1 3. LDH ≤ 1.5 x ULN at screening 4. Documented diagnosis of PNH, confirmed by high sensitivity flow cytometry evaluation or RBCs and WBCs with granulocyte or monocyte clone size of ≥ 5% 5. Vaccinated against meningococcal infections within three years prior to, or at the time of, initiating study drug. Patients who initiated study drug treatment less than two weeks after receiving a meningococcal vaccine were required to have received treatment with appropriate prophylactic antibiotics until two weeks after vaccination 6. Female patients of childbearing potential and male patients with female partners of childbearing potential must have followed protocol-specified guidance for avoiding pregnancy

	ALXN1210-PNH-301 **NCT02946463**	**ALXN1210-PNH-302** **NCT03056040**
	• History of pRBC transfusion due to PNH 4. LDH ≥ 1.5 x ULN at screening 5. Vaccinated against meningococcal infections within three years prior to, or at the time of, initiating study drug. Patients who initiated study drug treatment less than two weeks after receiving a meningococcal vaccine were required to have received treatment with appropriate prophylactic antibiotics until two weeks after vaccination 6. Female patients of childbearing potential and male patients with female partners of childbearing potential must have followed protocol-specified guidance for avoiding pregnancy while on treatment	while on treatment
Main exclusion criteria	1. Current or previous treatment with a complement inhibitor 2. Platelet count < 30,000/mm^3 at screening 3. Absolute neutrophil count < 500/µl at screening 4. History of bone marrow transplantation 5. Body weight < 40kg at screening 6. History of *N. meningitidis* infection 7. History of unexplained, recurrent infection 8. Active systemic bacterial, viral or fungal infection within 14 days prior to study drug administration on Day 1	1. LDH value > 2 x ULN in the six months prior to Day 1 2. Major adverse vascular event in the six months prior to Day 1 3. Platelet count < 30,000/mm^3 at screening 4. Absolute neutrophil count < 500/µl at screening 5. History of bone marrow transplantation 6. Body weight < 40kg at screening 7. History of *N. meningitidis* infection 8. History of unexplained, recurrent infection 9. Active systemic bacterial, viral or fungal infection within 14 days prior to study drug administration on Day 1.
Primary outcomes	Co-primary efficacy endpoints: 1. Transfusion avoidance, defined as the proportion of patients who remained transfusion-free and did not require a transfusion per protocol-specified guidelines to Day 183 (Week 26) 2. Haemolysis as measured by LDH-N, defined as LDH levels ≤ 1 x ULN, from Days 29 to 183 (Week 26)	Primary efficacy endpoint: Percent change in LDH, from baseline to Day 183 (Week 26)
Secondary outcomes	Key secondary efficacy endpoints tested in a hierarchical manner:	Key secondary efficacy endpoints tested in a hierarchical

	ALXN1210-PNH-301 **NCT02946463**	**ALXN1210-PNH-302** **NCT03056040**
	1. Percentage change in LDH from baseline to Day 183 (Week 26) 2. Change in QoL assessed via the FACTIT-Fatigue Scale from baseline to Day 183 (Week 26) 3. Proportion of patients with BTH, defined as at least one new or worsening symptom or sign of intravascular haemolysis (including fatigue, haemoglobinuria, abdominal pain, shortness of breath, anaemia [Hb < 10 g/dL], major adverse vascular events, dysphagia or rectile dysfunction) in the presence of elevated LDH (defined as ≥ twice the ULN) 4. Proportion of patients with stabilised Hb, defined as avoidance of a ≥ 2 g/dL decrease in haemoglobin level from baseline in the absence of transfusion through Day 183 (Week 26) Safety including AEs, SAEs and ADAs	manner: 1. Proportion of patients with BTH, defined as at least one new or worsening symptom or sign of intravascular haemolysis (including fatigue, haemoglobinuria, abdominal pain, shortness of breath, anaemia [Hb < 10 g/dL], major adverse vascular events, dysphagia or erectile dysfunction) in the presence of elevated LDH (defined as ≥ twice the ULN) 2. Change in QoL assessed via the FACIT-Fatigue Scale from baseline to Day 183 (Week 26) 3. Transfusion avoidance, defined as the proportion of patients who remained transfusion-free and did not require a transfusion as per protocol-specified guidelines from baseline through Day 183 (Week 26) 4. Proportion of patients with stabilised Hb, defined as avoidance of a ≥ 2 g/dL decrease in haemoglobin level from baseline in the absence of transfusion through Day 183 (Week 26) Safety including AEs, SAEs and ADAs

Source: CS, Table 5.
ADA = antidrug antibodies, AE = adverse events, BTH = breakthrough haemolysis; Hb = haemoglobin; IVRS = interactive voice response system; IWRS = interactive web response system; LDH = lactate dehydrogenase; PNH = paroxysmal nocturnal haemoglobinuria; ULN = upper limit of normal.

4.2.3 Baseline characteristics

The baseline characteristics of the two included studies are presented in Table 4.5.

Table 4.5: Baseline patient characteristics

	ALXN1210-PNH-301		ALXN1210-PNH-302	
	Ravulizumab (n=125)	**Eculizumab (n=121)**	**Ravulizumab (n=97)**	**Eculizumab (n=98)**
Male, n (%)	65 (52.0)	69 (57.0)	50 (51.5)	48 (49.0)
Race, n (%)				
Asian	72 (57.6)	57 (47.1)	23 (23.7)	19 (19.4)
White/Caucasian	43 (34.4)	51 (42.1)	50 (51.5)	61 (62.2)
Black/African	2 (1.6)	4 (3.3)	5 (5.2)	3 (3.1)
American Indian/Alaska	1 (0.8)	1 (0.8)	–	–
Other/Unknown	7 (5.6)	8 (6.6)	19 (19.6)	15 (15.3)
Age at diagnosis				
Mean years (SD)	37.9 (14.9)	39.6 (16.7)	34.1 (14.4)	36.8 (14.1)
Age at first infusion				
Mean years (SD)	44.8 (15.2)	46.2 (16.2)	46.6 (14.4)	48.8 (14.0)
Years on eculizumab before study infusion, mean (SD)	NA	NA	6.0 (3.5)	5.6 (3.5)
Weight, mean kg (SD)	68.2 (15.6)	69.2 (14.9)	72.4 (16.8)	73.4 (14.6)
Weight at first infusion, % < 40 kg 40 to < 60 kg 60 to < 100 kg ≥ 100 kg Unknown	[redacted]	[redacted]	[redacted]	[redacted]
LDH, mean U/L (SD)[a]	1633.5 (778.8)	1578.3 (727.1)	228.0 (48.7)	235.2 (49.7)
LDH ratio, n (%) 1.5 to < 3 x ULN[a] ≥ 3 ULN	 18 (14.4) 107 (85.6)	 16 (13.2) 105 (86.6)	NA[b]	NA[b]
pRBC units received within 1 year prior to first dose, n (%)[c]				
0	23 (18.4)	21 (17.4)	84 (86.6)	86 (87.8)
1-14 units	102 (81.6)	100 (82.6)	13 (13.4)	12 (12.2)
>14 units	23 (18.4)	22 (18.2)	–	–
PNH clone size, mean % (SD)				
Type II RBCs[d]	12.4 (20.5)	13.7 (17.7)	14.9 (19.6)	16.3 (23.6)
Type III RBCs[d]	26.3 (17.2)	25.2 (16.9)	44.6 (30.5)	43.5 (29.7)
Total RBCs	38.4 (23.7)	38.7 (23.2)	60.6 (32.5)	59.5 (31.4)
Granulocytes	84.2 (21.0)	85.3 (19.0)	82.6 (23.6)	84.0 (21.4)
Monocytes	86.9 (18.1)	89.2 (15.2)	85.6 (20.5)	86.1 (19.7)
Haemoglobin, mean g/L (SD)[e]	[redacted]	[redacted]	[redacted]	[redacted]

	ALXN1210-PNH-301		ALXN1210-PNH-302	
	Ravulizumab (n=125)	Eculizumab (n=121)	Ravulizumab (n=97)	Eculizumab (n=98)
Haptoglobin, g/L (SD)[f]	[redacted]	[redacted]	[redacted]	[redacted]
History of MAVE, n (%)	17 (13.6)	25 (20.7)	28 (28.9)	22 (22.4)
History of aplastic anaemia, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 6 of the CS
NA = not applicable; GPI = glycophosphatidylinositol; MAVE = major adverse vascular event; PNH = paroxysmal nocturnal haemoglobinuria; SD = standard deviation.
Notes: a) Normal range defined as 120–246 U/L, ULN defined as 246 U/L; b) patients enrolled to Study 302 had stable disease and thus LDH within normal range; c) randomisation strata; d) n = 124 for ravulizumab arm and n = 120 for eculizumab arm of Study 301; e) normal range defined as 11.5–16.0 g/dL for women and 13.0–17.5 g/dL for men; f) normal range defined as 0.4–2.4 g/dL.

Both trials were international trials with the majority of patients included from countries other than the UK. Therefore, there is a question about the generalisability of the trial populations to UK practice. In the ALXN1210-PNH-301 trial, 246 patients were included with [redacted] patients treated in England. In the ALXN1210-PNH-302 trial, 195 patients were included with [redacted] patients treated in England and [redacted] patients treated in Scotland.

To show that the clinical characteristics of patients enrolled in the two trials are generally comparable with those of UK patients, the company provided a comparison with characteristics of UK patients 'ever treated' according to International PNH Registry data. In the response to clarification (Question A16), the company provided the most up-to-date results from the International PNH Registry (June 2020 data (n=[redacted])).[19] However, these data were less complete than the 2019 data, provided in the CS and reproduced in the Table below (Table 4.6).

Table 4.6: Characteristics of patients enrolled in ravulizumab trials versus UK patients 'ever treated' in the International PNH Registry (up to 08 July 2019)

	ALXN1210-PNH-301 (n=246)	ALXN1210-PNH-302 (n=195)	UK patients ever treated (n=[redacted])
Male, n (%)	134 (54.4)	98 (50.3)	[redacted]
Race, n (%) Asian White/Caucasian Black/African American Indian/Alaska Other/Unknown	 129 (52.4) 94 (38.2) 6 (2.4) 2 (0.8) 15 (6.1)	 42 (21.5) 111 (56.9) 8 (4.1) – 34 (17.4)	[redacted]
Age at diagnosis Mean	n=241 38.7 (15.8)	35.5 (14.3)	[redacted]

	ALXN1210-PNH-301 (n=246)	**ALXN1210-PNH-302 (n=195)**	**UK patients ever treated (n=[redacted])**
years (SD)			
Age at first infusion. Mean years (SD)	45.5 (15.7)	47.7 (14.2)	[redacted]
Weight, Mean kg (SD)	68.7 (15.2)	72.9 (15.7)	[redacted]
Weight at first infusion, % 40 to < 60 kg 60 to < 100 kg ≥ 100 kg	[redacted]	[redacted]	[redacted]
LDH Mean U/L (SD)[a]	1606.4 (752.7)	231.6 (49.2)	[redacted]
LDH ratio, n (%)[a] < 1.5 ≥ 1.5 x ULN	0 246 (100)	NA[b]	[redacted]
pRBC units received within 1 year of study entry or RBC transfusions, n (%)[c] 0 ≥ 1	44 (17.9) 202 (82.1)	170 (87.2) 25 (12.8)	[redacted]
History of major adverse vascular event, n (%)	42 (17.1)	50 (25.6)	[redacted]
History of aplastic anaemia (or	[redacted]	[redacted]	[redacted]

	ALXN1210-PNH-301 (n=246)	ALXN1210-PNH-302 (n=195)	UK patients ever treated (n=[redacted])
hypoplastic anaemia in registry), n (%)			
Sources: CS, Table 16, pages 66-67 and Response to Clarification, Question A16. GPI = glycophosphatidylinositol; LDH = lactate dehydrogenase; PNH = paroxysmal nocturnal haemoglobinuria; pRBC = packed red blood cell; RBC = red blood cell; SD = standard deviation. Notes: [a]) Normal range defined as 120–246 U/L = ULN defined as 246 U/L; [b]) patients enrolled to Study 302 had stable disease and thus LDH within normal range; [c]) randomisation strata for Study 301 and Study 302 and RBC transfusions ever received for registry data.			

As can be seen from Table 4.6, there are some differences in baseline LDH levels, transfusion history and a history of MAVE or aplastic anaemia (all generally higher in the UK population). However, according to the company, "*these are likely due to differences in the management pathway at the time of study initiation/registry enrolment. There are no clear clinical indications that the clinical characteristics of patients enrolled in ALXN1210-PNH-301 and ALXN1210-PNH-302 are not generalizable to UK patients*".[1] Nevertheless, it is possible that patients included in the two trials have less severe disease than UK patients.

4.2.4 Statistical analyses

Details of the statistical analysis methods of ALXN1210-PNH-301 and 302 are provided in Table 4.7. Both trials were non-inferiority trials designed to show that ravulizumab was non-inferior (no worse than) eculizumab. ALXN1210-PNH-301 had two co-primary endpoints and both were required to show non-inferiority where the lower limit of the 95% confidence interval (CI) for the difference between ravulizumab and eculizumab lies above a predefined non-inferiority margin (NIM). ALXN1210-PNH-302 had just the one primary endpoint which was also used to demonstrate non-inferiority. The primary population for the efficacy analyses were the full analysis sets (FAS) defined as all randomised patients who received at least one dose of drug and had at least one efficacy assessment. Although this is not the full intention-to-treat (ITT) population, this is a standard dataset commonly used in trials.

Table 4.7: Statistical analysis methods

	ALXN1210-PNH-301 NCT02946463	**ALXN1210-PNH-302 NCT03056040**
Primary objective	To assess the non-inferiority of ravulizumab compared with eculizumab in adult patients with PNH who are complement-inhibitor naïve.	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.
Statistical testing	Non-inferiority was tested for co-primary efficacy endpoints, with a two-sided 95% CI calculated. Ravulizumab was concluded to be non-inferior to eculizumab if (i) the lower bound of the 95% CI for the difference in transfusion avoidance rate (ravulizumab–eculizumab) was greater than the NIM of -20% and (ii) the lower bound of the 95% CI for the odds ratio for LDH-N (ravulizumab vs eculizumab) was greater than 0.39. LDH-N analyses used a GEE model for repeated measures, adjusted for treatment, transfusion history and baseline LDH If non-inferiority was met for both co-primary endpoints, key secondary endpoints were tested using a closed-testing procedure in order of presentation of key secondary endpoints. Point estimates and two-sided 95% CIs were computed.	Non-inferiority was tested for the primary efficacy endpoint, with a two-sided 95% CI calculated. Ravulizumab was concluded to be non-inferior to eculizumab if the lower bound of the 95% CI for the difference (ravulizumab–eculizumab) was greater than the NIM of -15%. Analyses used a mixed-effect repeated measures model, adjusted for treatment, visit, treatment by visit interaction, transfusion history and baseline LDH. If non-inferiority was met for the primary endpoint, key secondary endpoints were tested using a closed-testing procedure in order of presentation of key secondary endpoints. Point estimates and two-sided 95% CIs were computed.
Power calculation	Approximately 214 patients were planned to be randomly assigned to ensure at least 193 evaluable patients (assumes ≤10% dropout). Using a NIM of 0.39 for the co-primary endpoint of LDH-N and a Type I error of 1-sided 2.5%, a minimum of 142 patients would be expected to provide 80% power to demonstrate non-inferiority of ravulizumab to eculizumab. Using a NIM of 20% for the co-primary endpoint of transfusion avoidance, a minimum of 193 patients would be expected to provide 80% power to demonstrate non-inferiority of ravulizumab to eculizumab. The NIMs were based on the TRIUMPH trial	Approximately 192 patients were planned to be randomly assigned to ensure at least 172 evaluable patients (assumes ≤10% dropout). Using a NIM of 15% for the primary endpoint, a Type I error of 1-sided 2.5% and SD of 30%, a minimum of 172 patients would be expected to provide 90% power to demonstrate non-inferiority of ravulizumab to eculizumab. The NIM was based on data from the company's PNH registry.
Analysis sets	**FAS:** all patients who received at least one dose of randomised treatment and had at least one efficacy assessment. **PP:** sensitivity population included patients who:	**FAS:** all patients who received at least one dose of randomised treatment and had at least one efficacy assessment. **PP:** sensitivity population included patients who:

	ALXN1210-PNH-301 NCT02946463	ALXN1210-PNH-302 NCT03056040
	• Missed no doses of ravulizumab or no more than one dose of eculizumab • Met inclusion criteria #2, 3 and 4 • Did not meet exclusion criteria #1, 2, 3 or 4 • Never received the wrong randomised treatment • Followed the protocol-specified transfusion guidelines. **Safety:** patients who received at least one dose of randomised treatment.	• Missed no doses of ravulizumab or no more than one dose of eculizumab • Met inclusion criteria #2, 3 and 4 • Did not meet exclusion criteria #1, 2, 3 or 4 • Never received the wrong randomised treatment • Followed the protocol-specified transfusion guidelines. **Safety:** patients who received at least one dose of randomised treatment.
Missing data	Missing data were not imputed for LDH-N. For transfusion avoidance, patients withdrawing due to lack of efficacy were considered non-responders and counted as requiring transfusion	Missing data were not imputed for percent change in LDH

Source: Table 7 of the CS.
BTH = breakthrough haemolysis; CI = confidence interval; FACIT = Functional Assessment of Chronic Illness Therapy; FAS = full analysis set; GEE = generalised estimating equation; Hb = haemoglobin; LDH-N = normalisation of lactate dehydrogenase levels; NIM = non-inferiority margin; PNH = paroxysmal nocturnal haemoglobinuria; PP = per protocol.

ERG comment: Both trials were designed as non-inferiority trials to show that ravulizumab was non-inferior to eculizumab at the end of the 26-week randomised trial period. They were not designed to show that ravulizumab was superior to eculizumab. The primary analyses of both were based on the effect size and 95% CI for the treatment difference or ratio of ravulizumab compared with eculizumab. If the lower limit of the 95% CI lay above the predefined non-inferiority margin, then it was concluded that ravulizumab was non-inferior to eculizumab. if noninferiority was established for all key secondary endpoints, then superiority was assessed using a closed-testing procedure using a 2-sided 0.05 test of significance for each parameter.

4.2.5 Results

The CS reported the summary of efficacy results from the randomised period for each trial in Table 8 of the CS, see Table 4.8 and Table 4.9 below. The submission also reported summary tables of efficacy results for each trial during the extension periods, which are provided in Table 4.10 and Table 4.11.

Table 4.8: Summary of efficacy results from ALXN1210-PNH-301: randomised period

	ALXN1210-PNH-301		
	Ravulizumab (n=125)	**Eculizumab (n=121)**	**Treatment effect (95% CI)**
Transfusion avoidance rate, % (95% CI)	73.6 (65.87, 81.33)	66.1 (57.68, 74.55)	6.8 (-4.66, 18.14)
LDH-normalisation rate, % (95% CI)	53.6 (45.9, 61.2)	49.4 (41.7, 57.0)	1.19 (0.80, 1.77)
Percent change in LDH, LSM (95% CI)	-76.84 (-79.96, -73.73)	-76.02 (-79.20, -72.83)	0.83 (-3.56, 5.21)
Change in FACIT-Fatigue score, LSM (95% CI)	7.07 (5.55, 8.60)	6.40 (4.85, 7.96)	0.67 (-1.21, 2.55)
≥ 3-point improvement in FACIT-Fatigue score, n (%)	77 (61.6)	71 (58.7)	2.2 (-9.9, 14.3)
Breakthrough haemolysis rate, % (95% CI)	4.0 (0.56, 7.44)	10.7 (5.23, 16.26)	6.7 (-0.18, 14.21)
Haemoglobin stabilisation rate, % (95% CI)	68.0 (59.82, 76.18)	64.5 (55.93, 72.99)	2.9 (-8.80, 14.64)
EORTC QLQ-C30 GHS/QOL Absolute change, mean (SD) ≥ 10-point improvement, n (%)	13.2 (21.4) n = 124 64 (51.2)	12.9 (21.8) n = 118 55 (45.5)	4.8 (-7.7, 17.1)
EORTC QLQ-C30 PF Absolute change, mean (SD) ≥ 10-point improvement, n (%)	13.2 (15.7) 60 (48.0)	11.5 (17.6) n=119 53 (43.8)	3.7 (-8.7, 16.0)
EORTC QLQ-C30 Fatigue Absolute change, mean (SD) ≥ 10-point improvement, n (%)	-20.2 (24.5) 92 (73.6)	-18.6 (24.5) n=119 77 (63.6)	9.1 (-2.5, 20.5)
Number (%) of patients who received any pRBC transfusions	32 (25.6)	40 (33.1)	–

	ALXN1210-PNH-301				
	Ravulizumab (n=125)		**Eculizumab (n=121)**		**Treatment effect (95% CI)**
Number of transfusions per patient, mean (SD)	3.3 (4.2)		3.6 (3.1)		–
Total number of pRBC units transfused per transfusion, mean (SD)	4.8 (5.1)		5.6 (5.9)		–
Patients with MAVE, n (%)	2 (1.6)		1 (0.8)		–
Clinical manifestations of PNH, %	BL	D183	BL n=119	D183 n=119	
Fatigue	64.0	28.8	63.9	30.3	–
Abdominal pain	13.6	4.8	12.6	5.0	
Dyspnoea	33.6	14.4	31.9	14.3	
Dysphagia	10.4	2.4	13.4	0.8	
Chest pain	4.0	2.4	14.3	5.9	
Haemoglobinuria	56.8	10.4	47.5	9.3	
Erectile dysfunction	12.8	8.0	17.6	4.2	

Source: Based on Table 8 of the CS.
BL= baseline; CI = confidence interval; D183 = Day 183; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FACIT = Functional Assessment of Chronic Illness Therapy; FAS = full analysis set; GHS = global health score; LDH = lactate dehydrogenase; LSM = least squares mean; MAVE = major adverse vascular event; PF = physical function; PNH = paroxysmal nocturnal haemoglobinuria; pRBC = packed red blood cells; SD = standard deviation; QOL = quality of life.

Table 4.9: Summary of efficacy results from ALXN1210-PNH-302: randomised period

	ALXN1210-PNH-302		
	Ravulizumab (n=97)	**Eculizumab (n=98)**	**Treatment effect (95% CI)**
Transfusion avoidance rate, % (95% CI)	87.6 (81.1, 94.2)	82.7 (75.2, 90.2)	5.5 (-4.3, 15.7)
LDH-normalisation rate, % (95% CI)	66.0[b]	59.2[b]	–
Percent change in LDH, LSM (95% CI)	-0.82 (-7.8, 6.1)	8.4 (1.5, 15.3)	9.21 (-0.42, 18.8)
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)
≥ 3-point improvement in FACIT-Fatigue score, n (%)	36 (37.1)	33 (33.7)	–
Breakthrough haemolysis rate, % (95% CI)	0 (0, 3.7)	5.1 (1.7, 11.5)	5.1 (-8.9, 19.0)
Haemoglobin stabilisation rate, % (95% CI)	76.3 (67.8, 84.8)	75.5 (67.0, 84.0)	1.4 (-10.4, 13.3)
EORTC QLQ-C30 GHS/QOL Absolute change, mean (SD) ≥ 10-point improvement, n (%)	1.15 (16.51) 18 (18.6)	-1.93 (15.34) 14 (14.3)	4.2 (-6.6, 15.0)
EORTC QLQ-C30 PF Absolute change, mean (SD) ≥ 10-point improvement, n (%)	3.26 (8.71) 21 (21.6)	1.20 (8.89) 12 (12.2)	9.1 (-1.9, 19.7)
EORTC QLQ-C30 Fatigue Absolute change, mean (SD) ≥ 10-point improvement, n (%)	-4.97 (17.26) 41 (42.3)	-0.71 (15.27) 31 (31.6)	9.6 (-4.1, 22.9)
Number (%) of patients who received any pRBC transfusions	10 (10.3)	14 (14.3)	–

	ALXN1210-PNH-302				
	Ravulizumab (n=97)		**Eculizumab (n=98)**		**Treatment effect (95% CI)**
Number of transfusions per patient, mean (SD)	2.7 (2.8)		2.0 (1.3)		–
Total number of pRBC units transfused per transfusion, mean (SD)	4.3 (4.8)		3.4 (3.0)		–
Patients with MAVE, n (%)	0		0		–
Clinical manifestations of PNH, %	BL n=96	D183 n=96	BL n=95	D183 n=95	
Fatigue	30.2	43.8	40.0	37.9	–
Abdominal pain	5.2	5.2	6.3	12.6	
Dyspnoea	6.3	6.3	10.5	17.9	
Dysphagia	2.1	5.2	2.1	5.2	
Chest pain	0	2.1	1.1	5.2	
Haemoglobinuria	4.2	8.3	7.4	9.5	
Erectile dysfunction	10.0	12.0	14.6	12.5	

Source: Based on Table 8 of the CS.
BL = baseline; CI = confidence interval; D183 = Day 183; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FACIT = Functional Assessment of Chronic Illness Therapy; FAS = full analysis set; GHS = global health score; LDH = lactate dehydrogenase; LSM = least squares mean; MAVE = major adverse vascular event; PF = physical function; PNH = paroxysmal nocturnal haemoglobinuria; pRBC = packed red blood cells; SD = standard deviation; QOL = quality of life.

Table 4.10: Summary table of efficacy results from ALXN1210-PNH-301: extension period up to 52 weeks

	ALXN1210-PNH-301			
	Ravulizumab to ravulizumab (n=124)		Eculizumab to ravulizumab (n=119)	
	0–26 weeks	27–52 weeks	0–26 weeks	27–52 weeks
Transfusion avoidance, n (%)	92 (73.6)	95 (76.6)	79 (66.4)	80 (67.2)
LDH-normalisation, n (%)	60 (48.4)	54 (43.6)	50 (42.1)	48 (40.4)
Percent change in LDH, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change in FACIT-Fatigue score, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Breakthrough haemolysis, n (%)	5 (4.0)	4 (3.2)	13 (10.7)	2 (1.7)
Haemoglobin stabilisation, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

FACIT = Functional Assessment of Chronic Illness Therapy; LDH = lactate dehydrogenase.

Table 4.11: Summary table of efficacy results from ALXN1210-PNH-302: extension period up to 52 weeks

	ALXN1210-PNH-302			
	Ravulizumab to ravulizumab		Eculizumab to ravulizumab	
	0–26 weeks (n=97)	27–52 weeks (n=96)	0–26 weeks (n=98)	27–52 weeks (n=95)
Transfusion avoidance, n (%)	85 (87.6)	83 (86.5)	81 (82.7)	79 (83.2)
LDH-normalisation, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Percent change in LDH, Mean (SD)	2.9 (26)	8.8 (29)	6.5 (31)	5.8 (27)
Change in FACIT-Fatigue score, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Breakthrough haemolysis, n (%)	0	3 (3.1)	5 (5.1)	1 (1.1)
Haemoglobin stabilisation, n (%)	74 (76.3)	78 (81.2)	74 (75.5)	77 (81.1)

FACIT = Functional Assessment of Chronic Illness Therapy; LDH = lactate dehydrogenase.

ERG comment: Both trials met their primary objective and demonstrated that ravulizumab was non-inferior to eculizumab in terms of transfusion avoidance rate and LDH-N (ALXN1210-PNH-301) and percentage change in LDH (ALXN1210-PNH-302). Although the point estimates for the primary and secondary outcomes were in favour of ravulizumab none of the results were statistically significant. However, data are relatively immature in that they currently provide randomised data for up to 26 weeks for a chronic condition requiring lifelong treatment. In addition, the lack of 'up-dosing' in the two trials compared with UK clinical practice may result in worse clinical outcomes for patients in the eculizumab arms; the effect of this is unclear.

4.2.6 Adverse events

Both trials reported low infusion interruptions during the randomised period. In the ALXN1210-PNH-301 trial of the 125 ravulizumab patients, 110 experienced an adverse event, whereas of the 121 eculizumab patients, 105 experienced an adverse event. In the ALXN1210-PNH-302 trial, 85 of the 97 ravulizumab patients experienced an adverse event, while 86 of the 98 eculizumab patients experienced an adverse event. The most common reported adverse events for both trials included headache, nasopharyngitis, nausea, upper respiratory tract infection (URTI), and pyrexia. In the ALXN1210-PNH-301 trial, an SAE was experienced by 11 of the ravulizumab patients and nine of the eculizumab patients, whereas in the ALXN1210-PNH-302 trial an SAE was experienced by four of the ravulizumab patients and eight of the eculizumab patients.

In the extension period of the ALXN1210-PNH-301 trial the number of participants in the ravulizumab group who experienced an AE was 79. The number of participants who had experienced an AE who had switched from eculizumab to ravulizumab during the extension period was 89. The most experienced AEs included headache, URTI, pyrexia, and nasopharyngitis. The CS states ravulizumab to be well tolerated among complement-inhibitor naïve patients. In the ALXN1210-PNH-302 trial, 76 patients from the ravulizumab group were noted to have experienced an AE, whereas in the group of patients who switched from eculizumab to ravulizumab 71 patients experienced an AE. In this trial the most commonly experienced AEs during the extension period included headache, URTI, pyrexia, nasopharyngitis, and fatigue. There was one reported death among both trials, which was deemed to be unrelated to treatment. The company emphasised that ravulizumab appeared similar to eculizumab in terms of safety.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

An indirect treatment comparison was not required as the two included trials provide head-to-head data regarding ravulizumab and eculizumab.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

An indirect treatment comparison was not required as the two included trials provide head-to-head data regarding ravulizumab and eculizumab.

4.5 Additional work on clinical effectiveness undertaken by the ERG

No additional work was undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

The considered population of adults with paroxysmal nocturnal haemoglobinuria who have haemolysis with clinical symptoms indicative of high disease activity or whose disease is clinically stable after having eculizumab for at least six months is in line with the scope. The intervention, and

listed outcomes are also in line with the scope. There is, however, a discrepancy between the comparator in the scope and the comparator as delivered in the ravulizumab trials. This is that in the scope eculizumab is as would be delivered in UK clinical practice, which permits up-dosing to manage BTH due to incomplete C5 inhibition, whereas in the trials up-dosing was not permitted. It is unclear what the impact of this would be on the relative effectiveness of ravulizumab versus eculizumab.

The company identified two randomised trials. The ALXN1210-PNH-301 trial was designed to assess the non-inferiority of ravulizumab compared with eculizumab in adult patients with PNH who are complement-inhibitor naïve. The ALXN1210-PNH-302 trial was designed to assess the non-inferiority of ravulizumab compared with eculizumab in adult patients with PNH who are clinically stable following six or more months of treatment with eculizumab.

- ALXN1210-PNH-301: An open-label, randomised, active-controlled, multicentre study, which compared ravulizumab to eculizumab during a 26-week randomisation period followed by an extension period which lasted up to two years. The study was conducted in Argentina, Australia, Austria, Belgium, Brazil, Canada, Czechia, Estonia, France, Germany, Italy, Japan, Korea, Malaysia, Mexico, Poland, Russia, Singapore, Spain, Sweden, Taiwan, Thailand, Turkey, UK, and USA.
- ALXN1210-PNH-302: An open-label, randomised, active-controlled, multicentre study, which compared ravulizumab to eculizumab during a 26-week randomisation period followed by an extension period which lasted up to two years. The study was conducted in Australia, Canada, France, Germany, Italy, Japan, Korea, Netherlands, Spain, UK, and USA.

The ERG notes that the populations of the two trials had distinct differences. The ALXN1210-PNH-301 trial included a population comprised of adult patients with PNH who are complement-inhibitor naïve, whereas the patients in the ALXN1210-PNH-302 trial had PNH who were clinically stable following six or more months of treatment with eculizumab. Due to this, a meta-analysis was not appropriate.

Ravulizumab was found to be non-inferior to eculizumab for the primary outcomes of both the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials. Although the point estimates for the primary and secondary outcomes were in favour of ravulizumab none of the results were statistically significant. However, data are relatively immature in that they currently provide data for up to 26 weeks for a chronic condition requiring lifelong treatment. In addition, the lack of ‘up-dosing’ in the two trials compared with UK clinical practice may result in worse clinical outcomes for patients in the eculizumab arms; the effect of this is unclear. Ravulizumab appeared similar to eculizumab in terms of safety.

5. COST EFFECTIVENESS

5.1 ERG comment on company's review of cost effectiveness evidence

This section pertains mainly to the review of cost effectiveness analysis studies. However, the search section (5.1.1) also contains summaries and critiques of other searches related to cost effectiveness presented in the company submission. Therefore, the following section includes searches for the cost effectiveness analysis review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

5.1.1 Searches performed for cost effectiveness section

Appendix G of Document B detail an SLR conducted to identify all economic, HRQoL and resource use outcomes literature on patients with PNH.[21] Searches were run on 3 February 2020 and updated on 2 July 2020. No language or publication date limits were reported. In response to clarification, it was confirmed that all databases were searched from inception to time of search.[19] A summary of the sources searched is provided in Table 5.1.

Table 5.1: Data sources for the cost effectiveness systematic review (as reported in CS and response to clarification)

	Resource	Host/source	Date range	Date searched
Electronic databases	MEDLINE and Epub Ahead of Print, In-Process and Daily Versions	Ovid	1946-2020	(i)3.2.20 (ii)2.7.20
	Embase	1974-2020	1974-2020	(i)3.2.20 (ii)2.7.20
	Health Technology Assessment Database	Ovid	Not provided	(i)3.2.20 (ii)2.7.20
	NHS EED	Ovid	Not provided	(i)3.2.20 (ii)2.7.20
	EconLit	EBSCO	1969-2020	(i)3.2.20 (ii)2.7.20
	Cochrane Central Register of Controlled Trials	Ovid	2005-2020	(i)3.2.20 (ii)2.7.20
	Cochrane Database of Systematic Reviews	Ovid	2005-2020	(i)3.2.20 (ii)2.7.20
	Database of Abstracts of Reviews of Effects	Ovid	2005-2020	(i)3.2.20 (ii)2.7.20
Conference proceedings	American Society of Hematology Annual Meeting	https://ashpublications.org/blood/issue/134/Supplement_1	2019	
		https://ashpublications.org/blood/issue/132/Supplement%201	2018	
		https://ashpublications.org/blood/iss	2017	

	Resource	Host/source	Date range	Date searched
		ue/130/Supplement%201		
	European Haematology Association Annual Meeting	https://library.ehaweb.org/eha/#!*menu=5*browseby=8*sortby=2*media=6*label=19379	2019	
		https://library.ehaweb.org/eha/#!*menu=5*browseby=8*sortby=2*media=6*label=18567	2018	
		https://library.ehaweb.org/eha/#!*menu=5*browseby=8*sortby=2*media=6*label=15847	2017	
Additional resources	Scottish Medicines Consortium			

ERG comments:

- Individual searches were undertaken for an SLR to identify all cost effectiveness, HRQoL and cost and resource use studies. The CS provided sufficient details for the ERG to appraise the literature searches. A range of databases and conference proceedings were searched and the Scottish Medicines Consortium. The original and the update searches were overall well conducted and were transparent and reproducible.
- No date or language limits were unnecessarily applied to the database searches.
- Study design filters were applied but not appropriately referenced. In response to clarification, a link was provided to the ISSG search filters website but it was not clear which filters were used.[19]
- As with clinical effectiveness searches, more synonyms and use of truncation and adjacency for the population terms may have increased the yield.

5.1.2 Inclusion/exclusion criteria used in the study selection

In- and exclusion criteria for the review on cost effectiveness studies, utilities and costs and resource use are presented in Table 5.2.

Table 5.2: Eligibility criteria used for the systematic literature review

PICOS	Inclusion criteria	Exclusion criteria
Patient population	Individuals with paroxysmal nocturnal haemoglobinuria	Children
Interventions	Eculizumab	Non-interventional
	Ravulizumab	
	Allogeneic stem cell transplantation	
	Blood or erythrocyte transfusion	
	Iron supplementation	
	Folic acid supplementation	
	Vitamin B12 supplementation	
	Steroid or androgen therapy	
	Anticoagulation	

PICOS	Inclusion criteria	Exclusion criteria
	Immunosuppressive treatment	
Comparators	Costs	Clinical outcomes
	Resource use	
	Utilities or HRQoL	
	Cost effectiveness	
Study Design	Economic studies	Animal studies
	Randomised controlled trials	Individual case reports
	Prospective or retrospective observational studies	Letters
		Commentaries
		Abstracts
		Reviews
Language restrictions	English only	Non-English
Abbreviations: HRQL, health-related quality of life; PNH, paroxysmal nocturnal haemoglobinuria.		

ERG comment: The eligibility criteria used by the company provide sufficient detail.

5.1.3 Identified studies

The company identified 339 records in the SLR, of which 21 met the inclusion criteria (Figure 6 of Appendix G of the CS).[21] After considering grey literature, three more studies were included. Of the 24 included, six reported outcomes of cost effectiveness (and met all other inclusion criteria relating to population, intervention, comparator and study design). Of these, two cost effectiveness models were identified that specifically assessed the cost effectiveness of ravulizumab compared with eculizumab for the treatment of PNH.

ERG comment: The company's reasoning for excluding cost effectiveness studies are considered appropriate given the defined in- and exclusion criteria. In the CS, two identified cost effectiveness models[31, 32] assessed the cost effectiveness of ravulizumab compared with eculizumab for the treatment of PNH. In the response to the clarification letter, the company explained that the published models and the company's model differ and that the identified studies do not address the current decision problem.[19]

5.1.4 Interpretation of the review

The CS provided an overview of the included cost effectiveness, utility and resource use and costs studies. None of the identified cost effectiveness studies were directly generalisable to the NICE decision problem.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

A summary of the economic evaluation conducted by the company is presented in Table 5.3.

Table 5.3: Summary of the company submission economic evaluation

	Approach	Source/justification in the company submission	Signpost (location in ERG report)
Model	The company developed in Excel a state transition model with 10 health states. The health states included in the model correspond to eight BTH-related health states, a mortality-related health state, and a spontaneous-remission health state.	The model captures the costs and consequences of the clinical events associated with PNH. The cost effectiveness model used in the studies by O'Connell et al. is similar to the one used in this appraisal.[32] However, the O'Connell model and the submitted model differ in the application of specific parameters and also the relevance of others to the NICE decision problem.	Section 5.2.2.
States and events	The health states included in the model correspond to eight BTH-related health states, one mortality-related health state, and a spontaneous-remission health state. Patients start the simulation in the 'No BTH' health state, from which they may transition to the BTH event health states (CAC-related or incomplete C5 inhibition-related) or die. The model can distinguish between first, second and subsequent incomplete C5 inhibition-related BTH events. After a second subsequent incomplete C5 inhibition-related BTH events, patients may transition to health states where they are treated with continuous eculizumab up-dosing. In the continuous eculizumab up-dose health states, only CAC-related BTH events are possible. Spontaneous remission is included for completeness but only used in scenario analyses.	The model is built in such a way that it is possible to model eculizumab up-dosing, even though this was not allowed in the clinical trials ALXN1210-PNH-301 and ALXN1210-PNH-302, to be more reflective of UK clinical practice. This functionality can be easily 'switched-off' to allow running the model under the clinical trial settings (no eculizumab up-dose).	Section 5.2.2.
Comparators	The comparator is eculizumab. In the company's base-case analysis, all patients start the simulation on the licensed 900mg eculizumab dose. A continuous up-dosing (1200mg and above) following two incomplete C5 inhibition-related BTH events was assumed. In the company's "equal effectiveness" scenario, [redacted]% of the patients start the simulation on a higher than licensed dose (1200mg and above) of eculizumab,	In ALXN1210-PNH-301 and ALXN1210-PNH-302 all patients received the licensed 900mg eculizumab dose and eculizumab dose-escalation/up-dosing was not permitted. In UK clinical practice, an increased dose of eculizumab is used to manage BTH due to incomplete C5 inhibition. The proportion of patients receiving a higher than license dose (1200 mg and above) of eculizumab was estimated as [redacted]% based on PNH national service data.[17]	Section 5.2.4.

	Approach	Source/justification in the company submission	Signpost (location in ERG report)
	while the rest of patients start on the licensed eculizumab dose (900mg).		
Natural history	PNH is caused by an acquired mutation in the *PIG-A* gene in haematopoietic stem cells,[1, 2 3] that results in a partial or absolute deficiency in proteins linked to the cell membrane by a glycosylphosphatidylinositol anchor. PNH is a rare condition, with an estimated 725 diagnosed cases in the UK (2018 figures).[4] PNH is a progressive, life-threatening haematological disorder that is characterised by uncontrolled activation of the terminal complement pathway, which can lead to intravascular haemolysis, anaphylaxis, inflammation and thrombosis.[1] The CS states that, *'without complement-inhibitor treatment, the majority of patients (up to 75%) die within 20 years of diagnosis, and the median survival time is estimated at approximately 10 years (from diagnosis)'.*[1, 5]		Section 2.2
Treatment effectiveness	The company used the data and the outcomes assessed in the pivotal trials ALXN1210-PNH-301 and ALXN1210-PNH-302. Patient-visit-level data was used to estimate the transition probabilities for each health state. A base-case analysis and an equal effectiveness scenario were developed by the company. In the latter, patients in the eculizumab arm receiving a clinically stable dose – and not the licensed dose (900mg) given in the pivotal trials – were assumed not to experience BTH due to incomplete C5 inhibition. Therefore, events other than incomplete C5 inhibitor-related BTH were assumed to be equal across arms, as per the ravulizumab arm.	The outcomes assessed in the trials were chosen as representative of the health-related benefits and potential side-effects expected with ravulizumab treatment in practice. The assumption of equal effectiveness when dosing of eculizumab is adopted as per UK clinical practice (i.e. no incomplete C5 inhibition-related BTH events in either arm) was considered clinically plausible.	Section 5.2.6

	Approach	Source/justification in the company submission	Signpost (location in ERG report)
Adverse events	Adverse events (AEs) were not included in the economic model.	EMA concluded that ravulizumab safety profile appeared to be similar to that of eculizumab. AEs observed in the clinical trials (headache and nasopharyngitis) were not considered for modelling purposes, as it was assumed to have a negligible impact on the cost effectiveness analysis.	Section 5.2.7
Health-related QoL	The company estimated utility values for events from mixed-effects regression models on the trial data. No significant HRQoL/utility benefit was obtained for frequency of administration, but the direction of the coefficient was in favour of ravulizumab. Results from a DCE were used to estimate treatment benefit of ravulizumab due to lower frequency administration.	The company argues that in ALXN1210-PNH-301 and ALXN1210-PNH-302 the benefit of reduced frequency of administration could not be measured as patients were still required, due to the trial protocol, to visit the study site.	Section 5.2.8
Resource utilisation and costs	A survey was developed to estimate inputs about the rates and causes of BTH and medical management for BTH in four categories: general ward hospitalisation, intensive care unit hospitalisation, medication and dialysis. Treatment acquisition costs, monitoring costs, health state costs, and miscellaneous costs for meningococcal infections and prophylactic antibiotics were included.	In the absence of resource use data, it is appropriate to source inputs from the survey. Unit prices were based on the NHS reference prices, British National Formulary, and Personal Social Services Research Unit.	Section 5.2.9
Discount rates	Cost and health outcomes discounted at 3.5%	As per NICE reference case	Section 5.2.5
Sensitivity analysis	Probabilistic, deterministic one-way sensitivity analysis and scenario analyses conducted	As per NICE reference case	Section 6.2

Based on the CS.[1]
AE = adverse event; BTH = breakthrough haemolysis; CS = company submission; DCE = discrete choice experiment; EMA = European Medicines Agency; HRQoL = health-related quality of life; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PNH = paroxysmal nocturnal haemoglobinuria; PSS = Personal Social Services; UK = United Kingdom

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.4: 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.	Direct health effects for patients included.
Perspective on costs	NHS and PSS.	NHS and PSS perspective taken.
Type of economic evaluation	Cost utility analysis with fully incremental analysis.	Cost utility analysis with fully incremental analysis undertaken.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared.	The model time horizon of 55 years for Cohort 1 and 52 years for Cohorts 2 and 3 is appropriate for a lifetime horizon. The average age of patients at the start of the simulation is 45 and 48 years, respectively.
Synthesis of evidence on health effects	Based on systematic review.	Systematic review conducted to identify additional evidence on health effects beyond trial data. However, none of the economic evaluations identified were conducted from a UK perspective.
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.	Health effects were expressed in QALYs. The EORTC QLQ-C30 was used to measure HRQoL in the ALXN1210-PNH-301 and ALXN1210-PNH-302 studies and mapped to EQ-5D-3L using the Longworth (2014) mapping algorithm.[33]
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers.	Obtained through a discrete choice experiment [redacted]

Element of health technology assessment	Reference case	ERG comment on company's submission
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population.	Representative sample of the UK population.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	No equity issues have been identified.
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 model includes the costs that relate to NHS and PSS resources, valued using the prices relevant to the NHS and PSS.
Discounting	The same annual rate for both costs and health effects (currently 3.5%).	Costs and health effects are discounted at 3.5%.

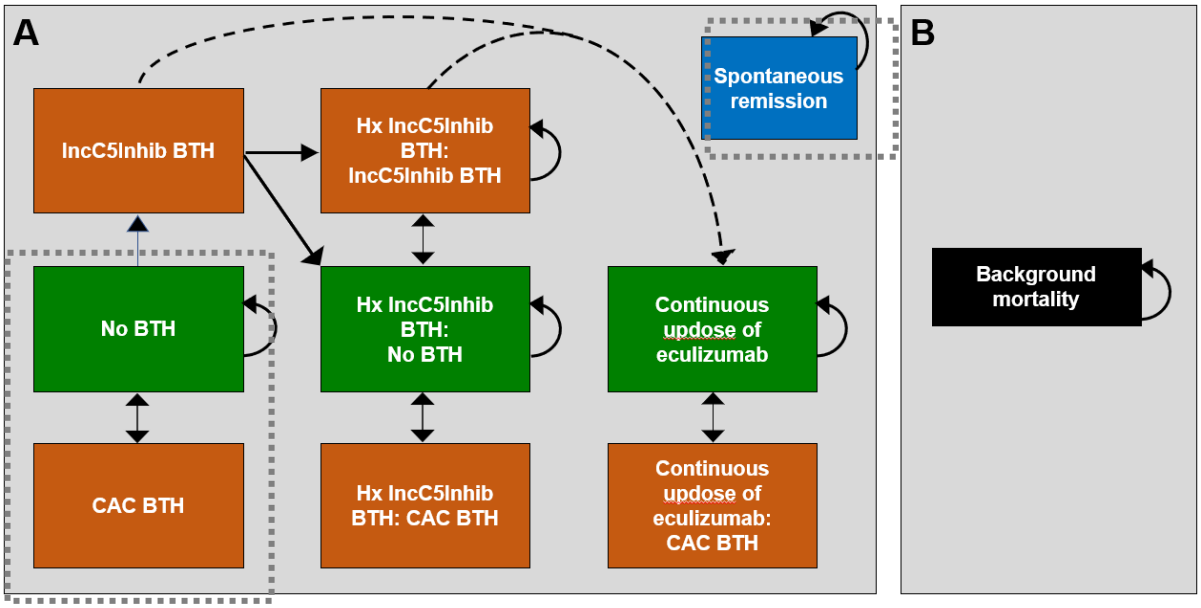
Abbreviations: EQ-5D = European Quality of Life-5 Dimensions; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; ERG = Evidence Review Group; HRQoL = health related quality of life; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; QALY = quality adjusted life year; UK = United Kingdom

5.2.2 Model structure

The company developed a state transition model in Excel with 10 health states. A schematic representation of the model is shown in Figure 5.1. The health states included in the model correspond to eight BTH-related health states, one mortality-related health state, and a spontaneous-remission health state. A detailed description of the health states is provided below. The model uses a cycle length of two weeks, which corresponds to the data collection time points in ALXN1210-PNH-301 and ALXN1210-PNH-302, and the treatment schedule for eculizumab. Given the short cycle length, the company did not apply a half-cycle correction to the model results. Costs and utilities are applied to each health state of the model (except death) to calculate per-cycle costs and quality adjusted life-years (QALYs).

ERG comment: The model captures the costs and consequences of the clinical events associated with PNH and its structure was deemed appropriate by experts consulted by the company at a July 2018 Advisory Board meeting.[16] The cost effectiveness model used in the studies by O'Connell et al. was similar to the one used in this appraisal.[31, 32]

Figure 5.1: Schematic representation of the model structure



Source: Figure 14 in CS.[1]
Abbreviations: BTH = breakthrough haemolysis; CAC = complement-amplifying condition; Hx = history of; IncC5Inhib = incomplete C5 inhibitor.

BTH-related health states

As explained in Section 2.3 of this report, two main types of BTH events were considered in ALXN1210-PNH-301 and ALXN1210-PNH-302: incomplete C5 inhibitor-related BTH and CAC-related BTH. Additionally, an undetermined BTH event was defined as those "*deemed to have neither incomplete C5 inhibition nor concomitant infection*" and, since undetermined events did not show free or high C5 levels, the clinical experts consulted by the company were "*confident that these events were not incomplete C5 inhibition-related BTH events*".[1] Even though a CAC was not reported, the experts considered that the cause of the event might not have been adequately captured and, therefore, a CAC-related cause was not ruled out. Based on this, the company modelled undetermined BTH events as CAC-related BTH events. Transition probabilities were estimated from ALXN1210-PNH-301 and ALXN1210-PNH-302 data. Further details are provided in Section 5.2.6 and Appendix 1.

ERG comment: Based on the information presented in the CS, the ERG is unclear how patients with undetermined BTH events were treated in the clinical trials. This was part of clarification question B11, but no clear answer regarding undetermined BTH events was provided.[19] Therefore, the ERG is unable to judge the appropriateness of modelling undetermined BTH events as CAC-related BTH events. If undetermined BTH events were indeed treated as CAC-related events, then the ERG would agree with this assumption. Otherwise, it would be more appropriate to model undetermined BTH events separately.

Up-dosing due to BTH

As explained in Section 3.3 of this report, in UK clinical practice, an increased dose of eculizumab is used to manage BTH due to incomplete C5 inhibition. However, eculizumab dosing changes were not allowed in ALXN1210-PNH-301 and ALXN1210-PNH-302. In order to include eculizumab up-dosing in the economic model, the following assumptions were made:

- CAC-related BTH events (base-case analysis and "equal effectiveness" scenario):
    - In the eculizumab arm, one single up-dose was required to re-establish the blockade.[16]

  - In the ravulizumab arm, an additional dose of eculizumab, as opposed to ravulizumab, was assumed because there are no available data on the effectiveness or safety of up-dosing ravulizumab. The latter assumption was "*discussed and felt to be appropriate as a potential treatment strategy in the December 2018 Advisory Board meeting*" held by the company.[11]
- Incomplete C5 inhibition-related BTH events (base-case analysis):
  - In the eculizumab arm, a permanent (continuous) eculizumab up-dosing was assumed, as this was considered to be in line with the management algorithm adopted in UK clinical practice by the clinical experts consulted by the company.[11] The continuous up-dosing was assumed for the rest of the model time horizon after a second incomplete C5 inhibition-related BTH event. For the first and second incomplete C5 inhibition-related BTH event, a single up-dose was assumed, similar to the approach used for treating CAC-related BTH events.
  - In the ravulizumab arm, continuous up-dosing to resolve incomplete C5 inhibition-related events was not needed because incomplete C5 inhibition-related events were not observed in the ravulizumab arm in either of the clinical trials. Therefore, in the model it is assumed that these events do not occur in the ravulizumab arm.

ERG comment: In order to model UK clinical practice, where eculizumab up-dosing is used, the company made the assumptions presented above. While the ERG acknowledges the importance of modelling up-dosing to treat BTH events, there are several concerns regarding the way this was operationalised in the model.

The ERG is unclear why the company assumed that CAC-related BTH events were treated with a single eculizumab up-dose in the eculizumab arm, and with an additional dose of eculizumab in the ravulizumab arm. Page 83 of the CS states that "*infection was the most common aetiology of CAC-related BTH events and resolved with treatment of the infection*".[1] This suggests that CAC-related BTH events would be resolved by treating the infection. The same statement also suggests that there were other causes that triggered CAC-related BTH events, but it is not mentioned which ones and how these were treated. Furthermore, in response to clarification question B11, the company indicated that "*BTH may occur due to suboptimal C5 inhibition, and/or complement-amplifying conditions (CACs) such as infection, surgery, or pregnancy that may lead to increased complement activation resulting from higher C3b density*".[19] Therefore, CAC-related events and incomplete C5 inhibition events might also occur simultaneously. The response to clarification question B11 also states that "i*n some patients with suboptimal C5 inhibition or complement-amplifying conditions, BTH may be ameliorated by shortening the 2-week dosing interval and/or increasing the dose of eculizumab*".[19] Furthermore, "*where a CAC is driving the BTH (e.g. an infection), there may not be suboptimal C5 inhibition and the underlying condition should primarily be managed – i.e. the infection treated*".[19] Finally, "i*n the non-clinical trial setting the BTH caused by a CAC would have required the infection to be treated*".[19] Thus, the response to clarification question B11 seems to suggest, even though it is not completely clear to the ERG, that some (but not all) CAC-related events might be treated with an eculizumab up-dose, while some (but not all) might be resolved by treating only the infection. However, it is not mentioned under which circumstances one option would be preferred over the other. The ERG considers that the rationale to assume that all CAC-related events should be treated with an eculizumab up-dose should have been better justified. With the evidence presented in the CS and the response to the clarification letter, the ERG preferred to assume that CAC-related BTH events would not be treated with an eculizumab up-dose, in line with what was observe in the clinical trials in which up-dose was not allowed. The opposite would result in higher costs for the eculizumab arm

of the model since CAC-related events were more frequent in the eculizumab arm than in the ravulizumab arm. Nevertheless, given the low frequency of such events in both arms, the impact on the model results is minor.

Regarding incomplete C5 inhibition-related BTH events, in response to clarification question A5, the company indicated that "*eculizumab administered at higher doses than the standard dose […] would likely prevent the breakthrough haemolysis due to incomplete C5 inhibition events observed in the eculizumab arm of the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials*".[19] Therefore, the ERG is uncertain whether the base-case approach to eculizumab up-dosing would completely capture the additional effects associated with up-dosed eculizumab, as there are no clinical data to validate the base-case results. Furthermore, as will be explained in Section 5.2.3 of this report, this assumption seems to result in an overestimation of the number of patients requiring an up-dose in the eculizumab arm. For these reasons, the ERG does not agree with this assumption. Finally, the model assumes that incomplete C5 inhibition-related events do not occur in the ravulizumab arm. This is in line with the observations of no incomplete C5 inhibition-related in the clinical trials and, therefore, the ERG agrees with this assumption.

In conclusion, the ERG has several concerns regarding how eculizumab up-dosing was implemented in the model. Other concerns regarding up-dosing will be explained in sections "Equal effectiveness scenario" and 5.2.3. Based on all these concerns and the fact that in the two clinical trials up-dosing was not allowed, the ERG prefers a base-case scenario based completely on the clinical trials, thus, no eculizumab up-dose included in the model, even though it is acknowledged that this will not be completely representative of UK clinical practice.

Spontaneous remission

There is some evidence to support that long-term spontaneous remission can occur in PNH patients. The study by Hillmen et al. 1995 reported that, from a cohort of 35 patients who survived 10 years or more, 12 had a spontaneous clinical recovery.[5] The study by Socie et al. 1996 reported a 5% of spontaneous remission on a sample of 220 patients.[34] Finally, the study by Pulini et al. 2011 provided a case report of a male patient who discontinued eculizumab and achieved PNH spontaneous remission.[35] Given the lack of robust evidence, the company did not include spontaneous remission in their base-case analysis. The impact of this assumption was explored in an additional scenario, in which it was assumed that patients achieving spontaneous remission would stop PNH-related treatment (including complement-inhibitor therapy). The same rate of spontaneous remission was assumed in both treatment arms.

ERG comment: The ERG agrees with this approach. The impact of spontaneous remission on the cost effectiveness results was deemed minor and, therefore, was not explored by the ERG in their additional scenario analyses.

Background mortality

Overall survival was not a pre-specified endpoint in ALXN1210-PNH-301 and ALXN1210-PNH-302. Deaths were captured as a safety outcome. In ALXN1210-PNH-301 one death event was reported but this was not treatment-related.[28, 30] The company sought additional evidence around excess mortality associated with PNH from published literature and clinical experts. According to the company, this evidence suggests that "*the clinical consequences of uncontrolled complement activity are diverse, but in severe instances include outcomes such as thrombotic events, endothelial damage, inflammation and ischaemia*".[36] Also, "*persistent BTH events may lead to long-term uncontrolled haemolysis if they are left untreated*".[14] Chronic haemolysis is the underlying cause of premature

mortality in PNH (Page 12, CS).[1] However, eculizumab treatment has aligned the life expectancy of PNH patients to that of the general population (Page 14, CS).[1] Therefore, the company base-case analysis only includes age-adjusted general population mortality risk.[37] In an additional scenario, the company explored the impact of modelling an excess mortality risk associated with BTH events, which is assumed to be equal in both treatment arms.

ERG comment: In clarification question B12, the ERG asked the company to provide further evidence to justify the assumption that mortality with ravulizumab equals mortality with eculizumab. The company referred back to the results from the clinical trials and "*the fact that ravulizumab was derived from eculizumab and the technologies share over 99% homology*".[19] The company concluded that there is no clinical rationale as to why mortality should differ between eculizumab and ravulizumab. Additional data from the ALXN1210-PNH-301 and ALXN1210-PNH-302 trial Extension Phases will report clinical outcomes up to 104 weeks. The company expects these to be available in [redacted]. When the new data become available, the company will conduct an analysis of overall survival. The company also expects that the new data will support the outcomes observed over the 52-week period. With the current evidence, the ERG agrees with the company's approach to mortality.

Equal effectiveness scenario

As discussed in Section 3.3 of this report, the company states in the CS that the lack of "up-dosing" in the two trials compared with UK clinical practice may result in worse clinical outcomes for patients in the eculizumab arms. In response to clarification question A5, the company indicated that "*UK clinical practice demonstrates that the majority of PNH patients (~ [redacted]%) are managed at the standard dose of eculizumab. However, approximately [redacted]% of UK PNH patients require an eculizumab dosing adjustment to achieve complete terminal complement inhibition. Therefore, eculizumab administered at higher doses than the standard dose […] would likely prevent the breakthrough haemolysis due to incomplete C5 inhibition events observed in the eculizumab arm of the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials*".[19] This is the rationale for considering the so-called "equal effectiveness" scenario, in which only CAC-related BTH events (in the three cohorts) were included in the analysis. Thus, this scenario considers a simplified version of the model where only the transitions within the dashed boxes in Figure 5.1 are possible. Also, a cohort of patients (further referred to as Cohort 3) was assumed to be eculizumab up-dosed from the start of the model, to reflect current clinical practice (i.e., approximately 20% of the PNH population as mentioned above). Further details about Cohort 3 and the equal effectiveness scenario are provided in Section 5.2.3 of this report.

ERG comment: The ERG considers that the equal effectiveness scenario provides a better representation of UK clinical practice than the company base-case scenario because it seems to overcome the main ERG concern regarding modelling eculizumab up-dose: the overestimation of the number of patients requiring an up-dose in the eculizumab arm. Nevertheless, as discussed in Section 5.2.3 of this report, the ERG is also concern that the trial population might not be representative of the UK PNH population and, for that reason, the ERG prefers a base-case scenario based completely on the clinical trials, thus, no eculizumab up-dose included in the model, even though it is acknowledged that this will not be completely representative of UK clinical practice.

5.2.3 Population

The population considered in the cost effectiveness analyses is adults with PNH who have haemolysis with clinical symptom(s) indicative of high disease activity or whose disease is clinically stable after

having eculizumab for at least six months. This is the population discussed in Section 3.1 of this report.

Three different cohorts were included in the economic analyses depending on whether patients were either complement inhibitor naïve (or simply treatment – ravulizumab or eculizumab – naïve, referred to as Cohort 1 in the economic analyses) or treatment experienced. Additionally, treatment experienced patients (and clinically stable on eculizumab) were classified as patients on the licensed dose of eculizumab (900 mg – referred to as Cohort 2 in the economic analyses) and patients on a higher-than-labelled dose (1200 mg – referred to as Cohort 3 in the economic analyses).[11] Note that patients in Cohort 3 were not included in ALXN1210-PNH-301 or ALXN1210-PNH-302. The rationale for including Cohort 3 in the economic analyses was already discussed in the "equal effectiveness scenario" section above. In summary, despite eculizumab dosing changes for patients who experienced BTH events not being allowed in ALXN1210-PNH-301 and ALXN1210-PNH-302, PNH National Service data suggests that an increased dose of eculizumab is used in UK clinical practice to achieve complete terminal complement inhibition in [redacted]% of the patients receiving label dose of eculizumab (900mg) treatment (reported range: 5%–29%).[12-15, 38] Thus, Cohort 3 was included in the model to reflect the proportion of patients who receive an eculizumab dose greater than 900mg, which is consistent with UK clinical practice.

The proportion of patients in each cohort was estimated as follows. Based on company data,[38] as of May 2020, eculizumab is being used to treat [redacted] patients in England, [redacted] of whom started treatment in 2019 and, therefore, were classed as treatment naïve. Additionally, [redacted] patients in England are receiving ravulizumab through the ALXN1210-PNH-301 or ALXN1210-PNH-302 extension.[27, 29] This yields a total of [redacted] PNH patients in England. For their base-case analysis, the company assumed a mixture of Cohort 1 and Cohort 2 using a weighted average based on the previous figures. Thus, the proportion of patients in Cohort 1 (treatment naïve patients) was estimated as [redacted] and it was further assumed that that the proportion of patients starting treatment remains the same each year. The proportion of patients in Cohort 2 (treatment experienced and on eculizumab label dose) was estimated as [redacted]. Additionally, the company assumed that eculizumab-treated patients with a history of two incomplete C5 inhibition BTH events, were allowed to "transition" into Cohort 3 during the course of the simulation. In the so-called "equal effectiveness scenario" the company assumed that a proportion of patients in Cohort 2 were allowed to start the simulation on higher-than-labelled eculizumab dose, thus in Cohort 3. Therefore, at the start of the simulation in the equal effectiveness scenario, the proportions of patients in each cohort were [redacted]% in Cohort 1, [redacted]% in Cohort 2 and [redacted]% in Cohort 3. In this scenario, the company additionally assumed that patients receiving their eculizumab dose as per clinical practice, would not experience incomplete C5 inhibition-related BTH events. Therefore, clinical outcomes were assumed to be the same as for the ravulizumab treatment arm in Cohort 2.

ERG comment: Cohorts 1 and 2 were defined to reflect the profiles of patients in ALXN1210-PNH-301 and ALXN1210-PNH-302, respectively. As mentioned above, eculizumab dosing changes to manage BTH events were not allowed in these two studies. Therefore, the lack of "up-dosing" in the two trials compared with UK clinical practice may result in worse clinical outcomes for patients in the eculizumab arms (e.g. Section 4.6).

In order to include eculizumab up-dose in the economic analyses, the company made a number of assumptions as discussed in previous sections. For example, in the company's base-case analysis, patients who experienced a CAC-related BTH event or an incomplete C5 inhibition BTH, were assumed to receive one single up-dose of eculizumab to re-establish the blockade. Additionally,

eculizumab patients with a history of one incomplete C5 BTH event, and who experienced a second incomplete C5 BTH event, transitioned to a continuously higher dose of eculizumab, which according to the company aligning would align to UK clinical practice. However, as shown in Table 6.4 (see Section 6.1 for further details), the proportion of time spent in the continuous up-dose health states across the complete model time horizon is [redacted]%, which is approximately twice as much as the [redacted]% reported by the company to be expected to receive an increased dose of eculizumab in UK clinical practice and, therefore, a large overestimation of the number of patients requiring an up-dose in the eculizumab arm. On pages 81 and 142 of the CS, the company indicated that "*across the model time horizon of 20 years*", patients spend 24.3% of their time in the continuous up-dose health states.[1] The company further concluded that this 24.3% closely aligns with the [redacted]% from the PNH National Service (used for Cohort 3 in the equal effectiveness scenario) which, according to the company, provides a measure of external validation. However, the ERG is unclear why the company has reported the previous comparison "*across the model time horizon of 20 years*" and not across the complete model time horizon (55 years for Cohort 1 and 52 years for Cohorts 2 and 3) where the proportion of time spent in the continuous up-dose health states is approximately two times larger.

In the equal effectiveness scenario, the proportion of time spent in the continuous up-dose health states *across the complete model time horizon* was assumed to be exactly [redacted]% (Cohort 3), thus, matching the PNH National Service estimate of the proportion of patients expected to receive an increased dose of eculizumab in UK clinical practice. The ERG understands, that the proportion of patients expected to receive an increased dose of eculizumab in UK clinical practice refers to the complete time horizon. Therefore, the assumption in the equal effectiveness scenario is in line with the ERG expectations. In clarification question B7, the ERG asked the company to clarify the clinical plausibility of the base-case and the equal effectiveness scenario analyses and which scenario provides a better representation of UK clinical practice.[19] The company answered that "*both pharmacoeconomic analyses incorporate the clinical practice of up-dosing and are therefore reflective of the disease pathway and clinical management of PNH patients who meet the criteria for complement-inhibitor treatment in the UK. As such, both analyses are equally clinically plausible*".[19] The ERG does not agree with the company's interpretation of the plausibility of the scenarios for the reasons explained above and prefers the equal effectiveness scenario over the company's base-case. However, the ERG considers that it is up to the Committee to decide which scenario is clinically more plausible. In any case, the impact of both assumptions on the cost effectiveness results was explored by the ERG in their additional scenario analyses in Section 7.1.3 of this report.

Page 78 of the CS states that "*while the eligibility criteria of the trial were not explicitly matched to the PNH service specification criteria for treatment initiation, they were designed to identify patients requiring active treatment to manage their disease versus those who do not. Patients in the trial were therefore considered representative of the population for whom ravulizumab is intended and for whom eculizumab is currently used*".[1] While the ERG has no reasons to disagree with this statement, the ERG is concerned that the sub-population of patients who would require an eculizumab up-dose might be underestimated in the trials and, therefore, these trial populations might not be representative for the UK. In response to clarification question B6,[19] the company explained that "c*hanging the dose of eculizumab to reflect UK up-dosing clinical practice would be expected to affect the clinical effectiveness as observed in the trial, allowing more patients in the eculizumab arm to achieve complete and sustained inhibition of terminal complement and thereby avoid associated BTH events".* In particular, "*changing the dose of eculizumab would alter the clinical effectiveness in the 11 eculizumab arm patients who experienced incomplete C5 inhibition related BTH events across the clinical trials; 7 patients in ALXN1210-PNH-301 and 4 patients in ALXN1210-PNH-302*.[19] Note that

11 out of a total of 219 patients is approximately 5% of patients in the trial population who would need an eculizumab up-dose, which is approximately [redacted] lower than the [redacted]% estimate from the PNH National Service. While we agree with the company that this "*would not be expected to impact on the conclusion of the clinical trial (non-inferiority criteria met) as no patients in the ravulizumab arm of either trial experienced BTH due to incomplete C5 inhibition*",[19] it might indicate that the population in the trials was not representative of the UK population. Therefore, the ERG wonders whether the conclusions from the trials, in which only 5% of patients would be "eligible" for an eculizumab up-dose, would be the same if there were approximately [redacted]% of patients who would need such an up-dose (as in UK clinical practice). In clarification question A10,[19] the ERG suggested that acknowledged differences between the trial and UK populations, as presented in Section B.2.13.2 of the CS,[1] appear to indicate more severe disease in the UK treated population. In response to the question of the ERG to provide evidence to support the assertion that the trial data are generalisable to UK clinical practice, the company indicated that "*the differences are not indicative of more severe disease in one population than another, hence why we conclude there are no clear clinical indications that the characteristics of patients enrolled are not generalizable to UK patients*".[19] The fact that only 5% of patients would be "eligible" for an eculizumab up-dose in the trials, as opposed to approximately [redacted]% in UK clinical practice might suggest otherwise. Additional data may help reducing the uncertainty regarding this aspect of the analysis. The study ALXN1210-PNH-401 has been designed to investigate the clinical effectiveness of ravulizumab in UK patients who are stable on a higher-than-licensed eculizumab dose, planned to switch to ravulizumab and observed for 52 weeks. The estimated start and completion dates are January 2021 and February 2022, respectively. However, but the study may be delayed due to a pause in recruitment relating to the COVID-19 pandemic.[39].

It is important to emphasise that throughout the CS and the responses to the clarification letter, the company have made it clear that 'up-dosing' is only necessary in approximately [redacted]% of the population and that most patients would achieve an adequate terminal complement inhibition on the licensed eculizumab dose. However, despite being a minority, the assumptions about patients who would require an eculizumab up-dose are crucial for the results of the cost effectiveness analyses. As will be shown in Chapter 7 of this report, this is the main driver of the cost effectiveness results. In conclusion, the ERG prefers a base-case scenario based completely on the clinical trials, without modelling eculizumab up-dose. Even though it is acknowledged that this will not be completely representative of UK clinical practice, the ERG considers that, with the current evidence, neither the company base-case nor the equal effectiveness scenario would provide a better representation of UK clinical practice. The three approaches are explored by the ERG in Chapter 7 of this report.

5.2.4 Interventions and comparators

The intervention considered in this appraisal was ravulizumab. Ravulizumab is administered intravenously in eight week dosing intervals, following a weight-based dosing regimen, as described in Section 3.2 of this report.

As explained in Section 3.3 of this report, the comparator technology is eculizumab. As described in the previous section, in the company's base-case analysis, all patients start the simulation on the licensed 900mg eculizumab dose, which is in line with ALXN1210-PNH-301 and ALXN1210-PNH-302. In UK clinical practice, an increased dose of eculizumab is used to manage BTH due to incomplete C5 inhibition. However, in both ALXN1210-PNH-301 and ALXN1210-PNH-302, eculizumab dose-escalation/up-dosing was not permitted. In the cost effectiveness model, the company assumed a continuous up-dosing (1200mg and above) following two incomplete C5

inhibition-related BTH events, as explained in previous sections. Doses above 1200mg are funded by the company and, therefore, the cost of a 1200mg was assumed for higher doses.

In the company's equal effectiveness scenario, [redacted]% of the patients start the simulation on a higher than licensed dose (1200mg and above) of eculizumab, while the rest of patients start on the licensed eculizumab dose (900mg).

5.2.5 Perspective, time horizon and discounting

The economic analyses were conducted from an NHS and Personal Social Services (PSS) perspective and adopted a lifetime time horizon. Total costs and QALYs were discounted at a 3.5% annual rate, as recommended in the NICE Reference Case.[40]

5.2.6 Treatment effectiveness and extrapolation

The company used the data and the outcomes from the two Phase III trials ALXN1210-PNH-301 (NCT02946463) and ALXN1210-PNH-302 (NCT03056040) to model ravulizumab and eculizumab clinical effectiveness for the three different patient cohorts included in the model, as discussed in Section 5.2.3. The outcomes assessed in the trials were chosen as representative of the health-related benefits and potential side effects expected with ravulizumab treatment in practice. They included BTH events and blood transfusions. **Error! Reference source not found.** shows the source and main assumptions for the model inputs in both the base-case and the equal effectiveness scenario analysis. The company assumed that ravulizumab treatment effect remains constant over time based on opinion from an Advisory Board held in December 2018.[11] This is modelled by assuming the same transition matrices throughout the complete model time horizon.

The company base-case analysis is aligned with the trial population and observed outcomes from ALXN1210-PNH-301 and ALXN1210-PNH-302,[27, 29] with the exception of modelling eculizumab up-dose to treat BTH events, as explained in Sections 5.2.2 and 5.2.3. Given that eculizumab was administered at its licensed dose in the pivotal trials, the efficacies of eculizumab and ravulizumab were taken directly from the respective clinical trials and treatment arms. In contrast, the equal effectiveness scenario aligns with the non-inferiority trial designs and assumes that, when for the management of BTH due to incomplete C5 inhibition patients receive an up-dose of eculizumab as per clinical practice, the efficacy of ravulizumab and eculizumab is equivalent. More details are provided in the following sections.

Table 5.5: Base-case analysis and equal effectiveness scenario - model inputs

Model input	Base-case analysis	Equal effectiveness scenario	Justification
CAC-related BTH Events	CAC-related BTH events that occurred in Study ALXN1210-PNH-301 and ALXN1210-PNH-302 were modelled per trial.	CAC-related BTH events were assumed to be the same in the eculizumab and ravulizumab arms.	In the base-case, given that the population is the same as the populations from the trials, the observed events from the trials were also used. In the equal effectiveness scenario, non-inferiority is assumed when all eculizumab patients are on a clinically stable dose; hence, events are assumed to be equal across arms, as per the ravulizumab arm.
Incomplete C5 inhibition-related BTH events	Incomplete C5 inhibition-related BTH events that occurred in Study ALXN1210-PNH-301 and ALXN1210-PNH-302 were modelled.	Incomplete C5 inhibition-related BTH events were not modelled or assumed to be zero.	In the base-case, given that the population was the same as the populations from the trials, the observed events from the trials were also used. In the equal effectiveness scenario, all patients in the eculizumab arm were assumed to receive a clinically stable dose (i.e. UK dosing was used) – and not the licensed dose (900mg) given in the pivotal trials. At the clinically stable dose, it was assumed that patients would not experience BTH due to incomplete C5 inhibition.
Blood transfusions	Transfusions reported in Study ALXN1210-PNH-301 and ALXN1210-PNH-302 were modelled per trial.	Transfusions were not modelled or assumed to be zero.	In the base-case, given that the population is the same as the populations from the trials, the observed events from the trials were also used. In the equal effectiveness scenario, transfusion was not modelled (assumed same on both arms so will cancel out).
Spontaneous remission	Included as a model scenario.	Included as a model scenario.	Evidence of spontaneous remission was derived from the literature; given the uncertainty, this is not considered in the base-case.

Source: Table 21 in CS.[1]
Abbreviations: BTH = breakthrough haemolysis, CAC = complement-amplifying condition, UK = United Kingdom.

BTH events and transitions probability matrices

BTH event rates from ALXN1210-PNH-301 and ALXN1210-PNH-302 were used to determine the transitions to and from BTH events in the model.[27, 29] In the base-case analysis both incomplete C5 inhibition-related and CAC-related BTH events were modelled. In the equal-effectiveness scenario, only CAC-related BTH events were modelled. **Error! Reference source not found.** to Table 5.9 present the transition probabilities by cohort and by treatment arm for the base-case analysis, and **Error! Reference source not found.** to Table 5.11 for the equal effectiveness scenario. Transition probabilities were based on patient visit-level data from the two clinical studies. The rationale for estimating the transition probabilities is described in Appendix 1.

Table 5.6: Transition matrix Cohort 1 – eculizumab

IncC5Inhib BTH history	No BTH	IncC5Inhib BTH	CAC BTH
No history	[redacted]	[redacted]	[redacted]
History, no current BTH	[redacted]	[redacted]	[redacted]
History, current BTH	[redacted]	[redacted]	[redacted]

Source: economic model.[41]

Abbreviations: IncC5Inhib = incomplete C5 inhibition; BTH = breakthrough haemolysis; CAC, complement-amplifying condition

Table 5.7: Transition matrix Cohort 1 - ravulizumab

IncC5Inhib BTH history	No BTH	IncC5Inhib BTH	CAC BTH
No history	[redacted]	[redacted]	[redacted]
History, no current BTH	[redacted]	[redacted]	[redacted]
History, current BTH	[redacted]	[redacted]	[redacted]

Source: economic model.[41]

Abbreviations: IncC5Inhib = incomplete C5 inhibition; BTH = breakthrough haemolysis; CAC, complement-amplifying condition

Table 5.8: Transition matrix Cohort 2 - eculizumab

IncC5Inhib BTH history	No BTH	IncC5Inhib BTH	CAC BTH
No history	[redacted]	[redacted]	[redacted]
History, no current BTH	[redacted]	[redacted]	[redacted]
History, current BTH	[redacted]	[redacted]	[redacted]

Source: economic model.[41]

Abbreviations: IncC5Inhib = incomplete C5 inhibition; BTH = breakthrough haemolysis; CAC, complement-amplifying condition

Table 5.9: Transition matrix Cohort 2 – ravulizumab

IncC5Inhib BTH history	No BTH	IncC5Inhib BTH	CAC BTH
No history	[redacted]	[redacted]	[redacted]
History, no current BTH	[redacted]	[redacted]	[redacted]
History, current BTH	[redacted]	[redacted]	[redacted]

Source: economic model.[41]

Abbreviations: IncC5Inhib = incomplete C5 inhibition; BTH = breakthrough haemolysis; CAC, complement-amplifying condition

Table 5.10: Transition matrix Cohort 1 – ravulizumab and eculizumab (equal effectiveness scenario)

IncC5Inhib BTH history	No BTH	IncC5Inhib BTH	CAC BTH
No history	[redacted]	[redacted]	[redacted]
History, no current BTH	[redacted]	[redacted]	[redacted]
History, current BTH	[redacted]	[redacted]	[redacted]

Source: economic model.[41]

Abbreviations: IncC5Inhib = incomplete C5 inhibition; BTH = breakthrough haemolysis; CAC, complement-amplifying condition

Table 5.11: Transition matrix Cohort 2 and 3* – ravulizumab and eculizumab (equal effectiveness scenario)

IncC5Inhib BTH history	No BTH	IncC5Inhib BTH	CAC BTH
No history	[redacted]	[redacted]	[redacted]
History, no current BTH	[redacted]	[redacted]	[redacted]
History, current BTH	[redacted]	[redacted]	[redacted]

Source: economic model.[41]

* The same transition probabilities as in Cohort 2 were assumed to model Cohort 3 (higher-than-licensed dose eculizumab patients).

Abbreviations: IncC5Inhib = incomplete C5 inhibition; BTH = breakthrough haemolysis; CAC, complement-amplifying condition

ERG comment: The company derived the transition probabilities from patient-visit-level data from the two clinical studies. Since these data have not been provided in the CS, the ERG could not validate the calculations.

Excess mortality risk of BTH

Considering that a BTH event may be accompanied by severe outcomes, such as thrombosis (see e.g. Section B.3.2.6 of CS [1]), the model allowed for the specification of excess mortality risk associated with BTH events.

In the base-case model analyses, no excess mortality risk of BTH events was specified. The application of higher mortality risk to that of the age- and gender-adjusted background mortality rate was identified in the literature. No evidence was available for a UK population or a comparable disease following a targeted search, therefore, data from an alternative source was used. A study of patients enrolled in the Korean PNH registry by Jang et al. (2016) found that the standard mortality ratio associated with LDH ≥1.5 x ULN was 4.81.[36] Given the similarity in LDH threshold to the definition of BTH events in ALXN1210-PNH-301 and ALXN1210-PNH-302, a hazard ratio (HR) of 4.81 applied to patients experiencing BTH events was tested in the scenario analysis.

Transfusion requirements

Transfusion requirements were included in the base-case analysis, due to their impact on HRQoL and cost and resource use when differential effectiveness is assumed as per the trials. The economic model allows for the specification of packed red blood cell transfusion requirements, by treatment arm and presence of incomplete C5 inhibition-related or CAC-related BTH event. These transfusion requirements were used to estimate mean transfusion-related cost and utility impacts. In the equal effectiveness scenario, transfusion requirements were assumed to be equal in the comparison, therefore cancelling each other out; consequently, these were not included in the analysis.

The probabilities of requiring a transfusion in each two week cycle, as well as the mean number of units of red blood cells required, were calculated based on patient-level data from ALXN1210-PNH-301 and ALXN1210-PNH-302. Details of transfusions requirement are reported in Appendix 2. Of note, as no patient was observed to require multiple transfusions between visits in the clinical studies, it was assumed that while multiple units of red blood cells may have been required per transfusion, only one transfusion procedure would occur in a model cycle.

In the 'permanent up-dosing as per clinical practice dose' scenario, the rate of transfusions and the number of packed red blood cell units required were assumed to be equal to those of the ravulizumab arm.

Spontaneous remission

Spontaneous remission was incorporated as a scenario analysis. To model this scenario, the transition probability of spontaneous remission was calculated from data in Hillmen et al. (1995), which provided patient-level data on 80 PNH patients treated with supportive measures, such as oral anticoagulant therapy after established thromboses, and transfusions in the UK between 1940-1970.[5]

5.2.7 Adverse events

Based on the conclusion from EMA that the safety profile appeared to be similar to that of eculizumab,[25] the company did not model any of the adverse events (AEs) that occurred (including headache and nasopharyngitis) in the two clinical trial studies, as it was assumed not to have an impact on the cost effectiveness analysis.

ERG comment: Adverse events were observed in the clinical trials as shown in Tables 6 and 7 of Appendix F to the CS.[21] These seem to be balanced between the two treatment arms and occurring at

low frequencies. Thus, the ERG agrees with the company that including adverse events in the model is likely to have a minor impact on the model results.

5.2.8 Health-related quality of life

Health related quality of life was measured from baseline to week 26 in the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C-30). Data was collected on Day 1, 8, 29, 71 and then twice between Day 71 and the end of study, resulting in a mean of 5.9 observations per patient in ALXN1210-PNH-301 and 5.7 in ALXN1210-PNH-302. EQ-5D data was not collected (section B3.4.1 CS page 100).[1]

Baseline health on the Global health scale (0 – 100, where 100 is better health) of QLQ-C30 was 56.13 for ravulizumab and 57.51 for eculizumab in ALXN1210-PNH-301. In the ALXN1210-PNH-302 trial, global health in the ravulizumab arm was higher with a mean of 75.25 vs 69.47 in the eculizumab arm (Appendix R of CS, Table 31 page 96 and clarification question B14 Table 5 as amended).[19, 21]

Utility impact of breakthrough haemolysis and transfusion

The QLQ-C30 was mapped to EQ-5D-3L to predict response levels on the five items. using the Longworth et al (2014) response mapping algorithm.[33] The mapped response probabilities were converted to utilities using the 3L UK tariff of Dolan (1997).[42]

In the base-case, utilities from a mixed-effects regression model were used to estimate the impact on utility of BTH events and transfusions. The model was estimated separately on the two trials and the values are presented in the Table 5.12 and Table 5.13 below.

Table 5.12: Mixed-effects model utility input for trial ALXN1210-PNH-301

Covariate	Coefficient	Standard error	Z	P>|z|	[95% CI]	
BTH indicator	-0.1143	0.0376	-3.0400	0.0020	-0.1881	-0.0406
Transfusion indicator	-0.0678	0.0131	-5.1700	0.0000	-0.0935	-0.0421
Individual-level linear trend	0.0212	0.0015	14.3000	0.0000	0.0183	0.0241
Constant	0.7592	0.081	93.3500	0.0000	0.7432	0.7751

Source: Table 26 in CS.[1]
Abbreviations: CI, confidence interval, BTH, breakthrough-haemolysis event experienced since last visit; individual-level linear trend, time trend (number of visits); transfusion, protocol guidelines for transfusion met since last visit.

Table 5.13: Mixed-effects model utility input for trial ALXN1210-PNH-302

Covariate	Coefficient	Standard error	Z	P>|z|	[95% CI]	
BTH indicator	-0.1828	0.0490	-3.7300	0.0000	-0.2789	-0.0868
Transfusion indicator	-0.0716	0.0189	-3.7800	0.0000	-0.1087	-0.0345
Individual-level linear trend	0.0028	0.0012	2.2800	0.0230	0.0004	0.0052

Covariate	Coefficient	Standard error	Z	P>|z|	[95% CI]	
Constant	0.8471	0.0098	86.5700	0.0000	0.8280	0.8633

Source: Table 27 in CS.[1]
Abbreviations: CI, confidence interval, BTH, breakthrough-haemolysis event experienced since last visit; individual-level linear trend, time trend (number of visits); transfusion, protocol guidelines for transfusion met since last visit.

Linear regressions were also estimated where predictor variables included a treatment arm. In those analyses, the treatment arm parameters favoured ravulizumab with utility increments ranging from 0.0098 to 0.0178 (ALXN1210-PNH-301) and 0.0037 to 0.022 (ALXN1210-PNH-302) depending on the selected covariates. None of the treatment arm parameters reach statistical significance in the presented models ($p > 0.1$). In a response to the clarification letter question B15,[19] exploratory mixed-effects models that did include treatment arm parameters were presented that displayed no statistical significance (Table 5.14 and Table 5.15).

Table 5.14: Exploratory mixed-effects model utility input for trial ALXN1210-PNH-301

Covariate	Coefficient	Standard error	Z	P>|z|	[95% CI]	
BTH indicator	-0.1142	0.0376	-3.0300	0.0020	-0.1880	-0.0404
Treatment*	0.0103	0.0128	0.8100	0.4210	-0.0147	0.0353
Transfusion indicator	-0.0674	0.0131	-5.1500	0.0000	-0.0931	-0.0418
Individual-level linear trend	0.0212	0.0015	14.3000	0.0000	0.0183	0.0241
Constant	0.7540	0.0104	72.5900	0.0000	0.7336	0.7743

Source: Table 6 in response to clarification letter.[19]
Abbreviations: CI, confidence interval, BTH, breakthrough-haemolysis event experienced since last visit; individual-level linear trend, time trend (number of visits); transfusion, protocol guidelines for transfusion met since last visit.
*Treatment, ravulizumab =1, eculizumab = 0

Table 5.15: Exploratory mixed-effects model utility input for trial ALXN1210-PNH-302

Covariate	Coefficient	Standard error	Z	P>|z|	[95% CI]	
BTH indicator	-0.1816	0.0490	-3.7100	0.0000	-0.2777	-0.0856
Treatment*	0.0197	0.0176	1.1200	0.2630	-0.0148	0.0543
Transfusion indicator	-0.0717	0.0189	-3.7800	0.0000	-0.1088	-0.0345
Individual-level linear trend	0.0028	0.0012	2.2800	0.0230	0.0004	0.0052
Constant	0.8373	0.0131	63.8400	0.0000	0.8116	0.8630

Source: Table 7 in response to clarification letter.[19]
Abbreviations: CI, confidence interval, BTH, breakthrough-haemolysis event experienced since last visit; individual-level linear trend, time trend (number of visits); transfusion, protocol guidelines for transfusion met since last visit. *Treatment, ravulizumab =1, eculizumab = 0

Utility impact of treatment burden

The majority of the ravulizumab HRQoL benefit is derived from the benefit of the infusion schedule of ravulizumab over eculizumab. It is argued that the impact of ravulizumab on treatment burden could not be fully captured in the trial because patients still needed to attend the research site for other trial protocol obligated reasons. Therefore, the company stated that "*patients did not experience the potential HRQL benefit of less frequent visits, although they did experience the benefit of less frequent infusion visits*".[1] In order to address the benefit of less visits and the benefit of less infusions, data from a discrete choice experiment (DCE) were applied in the model [43].

[redacted]

Adverse event disutilities

Adverse event disutilities were not incorporated in the cost effectiveness model.

ERG comment: NICE Technical Support Document TSD 10 and TSD 11 request the use of EQ-5D unless it is demonstrably insensitive or invalid in a particular condition, which would open the door for alternatives, such as mapping exercises.[45, 46] As no EQ-5D data have been collected in PNH patients, the validity of the instrument in this condition is unknown. However, due to the event related quality of life losses, it is conceivable that the instrument with a recall period of 'today' may not be optimal for capturing events. Hence, the relatively generic QLQ-C30, mapped to EQ-5D is an acceptable alternative due to its longer recall period in the absence of EQ-5D but cannot replace EQ-5D. The utilised mapping algorithm is consistently tested among the best functioning algorithms for estimating EQ-5D-3L UK utility values and is, therefore, a sensible choice.

There is evidence that patients prefer ravulizumab over eculizumab due to the lower treatment frequency.[23] However, that preference did not result in improved quality of life measurable in the trials. There are concerns regarding the validity of the estimated disutility related to treatment frequency. These concerns focus on two elements: the mixed-effect models and the DCE study. Firstly, no significant treatment effect with regards to quality of life could be estimated in any of the ordinary least-squares (OLS) or mixed-effects models (CS appendix R, table 33 and 34, page 99 and

100).[21] The company argued that this is due to the trial design, in which patients could not benefit from differential visit schedule but would benefit from the reduced infusion frequency itself. Hence, the only utility benefit that the trial design could not capture is the reduced burden of visits. The size of such potential disutility is unknown.

Secondly, as the design of the trials could not demonstrate statistically significant health-related quality of life (HRQoL) benefit due to its design, the company resorts to using data external to the trial from a DCE study. Following the reasoning of the company submission, this DCE data would only need to supply disutility data for reduced burden of frequency of visits, as the trial itself shows no statistically significant HRQoL benefit of the infusion frequency, possibly due to the increased length of infusion time with ravulizumab. The DCE, however, has several methodological concerns. [redacted]. Indeed, this time preference can to some extent be observed by the increase in the disutility by using parameters for shorter losses in life expectancy, which would in effect occur closer to the end of life and thus later. Hence, the ERG is of the opinion that the DCE should not be used when trial data on HRQoL are available.

However, the common-sense argument that there is value to patients in having a reduced treatment frequency is substantiated by the fact that patients themselves have indicated that they prefer ravulizumab over eculizumab due mainly to reduced treatment frequency. Therefore, the ERG prefers a base-case that takes this benefit into account, using the non-significant treatment effect from the mixed-effects models. While this point estimate is uncertain, its application in the model including the PSA captures benefit while taking uncertainty into account as well.

5.2.9 Resources and costs

A list price of £4,533 per 300mg vial was approved for ravulizumab by the Department of Health and Social Care. A patient access scheme (PAS) price of [redacted] per 300mg for ravulizumab (representing a discount of [redacted] on the list price) has been submitted by the company to reduce [redacted].[1] The cost of eculizumab was sourced from the Monthly Index of Medical Specialities (MIMS).[47]Pack costs for ravulizumab and eculizumab are listed in Table 5.16.

Table 5.16: Drug unit size, pack size, and pack cost

Treatment	Unit size	Pack size	Cost per pack	Source
Ravulizumab	300mg	1	List price: £4,533 PAS price: [redacted]	Company
	1100mg	1	List price: £16,621 PAS price: [redacted]	Company
Eculizumab	300mg	1	£3,150	MIMS[47]

Source: Table 31 in CS.[1]
Abbreviations: MIMS, Monthly Index of Medical Specialities; PAS, patient access scheme.

For ravulizumab, the recommended dosing regimen for adult patients (≥18 years) consists of an initial loading dose (2700mg) followed by maintenance doses (3300mg). Maintenance doses are administered every eight weeks, starting at two weeks after the initial loading dose. The dosing was weight based and the proportion of patients within each weight band was estimated using age- and gender-specific weights that were derived from the 'NHS Health Survey for England 2017: Adult health tables.[48] All patients from the survey was within the ≥60 kg to <100 kg band. In the first year, patients received the loading dose at Week 0, and commenced the maintenance dose at Week 2; which was given every eight weeks and equated to seven doses in the first year of treatment. In subsequent years, the number of doses per year alternates between six and seven; but for simplicity, 6.5 doses were used. Table 5.17 lists annual costs of ravulizumab by weight.

Table 5.17: Ravulizumab annual cost calculations by weight

Patient body weight	Loading phase: dose	Maintenance phase: annual dose	Annual cost (first year)	Annual cost (subsequent years)
≥60 kg to <100 kg	9 x 300mg	First year: 11 x 300mg X 7	List: £389,838	List: £324,110
		Subsequent years: 11 x 300mg X 6.5	PAS: [redacted]	PAS: [redacted]

Source: Table 33 in CS.[1]
Note: [redacted]
Abbreviations: PAS, patient access scheme.

For eculizumab, the dosing regimen for adult patients consists of a four week initial phase followed by a maintenance phase. In the initial phase, 600mg of eculizumab was given intravenously every week for the first four weeks. In the maintenance phase, 900mg of eculizumab was administered every two weeks starting at Week 5, with higher doses used if patients continue to experience incomplete C5 inhibition-related BTH. Given that patients may receive a higher-than-licensed eculizumab dose, the annual cost for a 900mg or 1200mg maintenance dose was presented in Table 5.18. For Cohort 2 and 3, it was assumed that these patients would not require the initial phase doses; therefore, the first-year costs were equal to the subsequent year costs. This assumption was not applied to the ravulizumab arm because treatment-experienced patients would switch from eculizumab and hence a ravulizumab loading dose would be required.

Table 5.18: Eculizumab annual cost calculations

Loading phase: dose received	Maintenance phase: dose received	Maintenance phase: annual dose	Annual cost (first year)a	Annual cost (subsequent years)
2 x 4 x 300mg	900mg	First year: 3 x 300mg vials for 24 doses Subsequent years: 3 x 300mg vials for 26 doses	£252,000	£245,700
Not applicable	1200mg or over	4 x 300mg vials for 26 doses	£327,600	£327,600

Source: Table 34 in CS.[1]
[a] Cohort 2 and 3 do not require a loading dose (as these are patients continuing treatment on eculizumab), therefore, first year costs are equal to subsequent year costs for these patients.

In the model, no cost of spontaneous remissions was applied given that the patients achieving spontaneous remission discontinue complement inhibitor therapy.

Drug administration costs

The intravenous infusion costs associated with the first loading dose and first maintenance dose of eculizumab, and the loading dose and first maintenance dose of ravulizumab are included within the scheme of NHS England. When patients receive infusions at home through the homecare infusion services, then these costs are funded by the company. Therefore, the NHS-administered infusion costs were the only administration costs included in the model. However, the company indicated that the clinical practice is changing and that the first maintenance dose would also be administered at patients' home. For the cost of administration, before receipt of the homecare service, the cost per hour of Band 7 pharmacist specialist time (£57) and Band 6 nurse specialist time (£113) was derived from the Personal Social Services Research Unit (PSSRU).[49] The duration of administration (for both the loading dose and maintenance dose) were derived from the summary of product characteristics (SPCs).[26] Where a range was given, (i.e., a 25–45-minute infusion), the mid-point was used. The cost of nurse time was applied over these durations, and an additional one-hour observation time was included.

For the company base-case (100 mg/mL formulation), the following infusion durations were assumed for ravulizumab and eculizumab: Loading dose: 35 minutes nurse time + 15 minutes pharmacist time (£193.17), Maintenance dose: 35 minutes nurse time + 15 minutes pharmacist time (£193.17). For the model scenario (10mg/mL formulation), the following infusion durations were assumed: Loading dose: 110 minutes nurse time + 30 minutes pharmacist time, Maintenance dose: 130 minutes nurse time + 30 minutes pharmacist time.

BTH events

PNH patients can experience BTH events throughout complement-inhibitor treatment. This can occur as a result of incomplete C5 inhibition or in patients with CACs. Based on the expert survey, the resource use associated with a BTH event is presented in Table 5.19.

Table 5.19: Resource use associated with BTH

	BTH due to incomplete C5 inhibition		BTH due to CAC	
	First event*	Subsequent event*	First event*	Subsequent event*
Hospital stays				
General ward (days)	15%/1	15%/1	23%/3	23%/3
Intensive care (days)	1%/1	1%/1	1%/1	1%/1
Dialysis				
Dialysis (days)	4%/7	4%/7	4%/7	4%/7

Source: Table 37 in CS.[1]
Abbreviations: BTH, breakthrough haemolysis; CAC, complement-amplifying condition.
Notes: *Frequency of management strategy (%) / number of units used per treated episode.

Health-state costs applied in the model

A survey was developed to estimate inputs about the rates and causes of BTH and medical management for BTH.[11] The survey was administered in the context of an Advisory Board meeting, to 10 clinicians who were experts in the treatment of PNH with both eculizumab and ravulizumab. Clinical experts were asked to estimate the proportion of patients requiring the resource and average duration of resource for four categories: general ward hospitalisation, intensive care unit (ICU) hospitalisation, medication and dialysis. Table 5.20 presents the per cycle (two-weekly) costs associated with each health state applied in the model.

Table 5.20: Health states and associated costs in the model

Health states	Cost Items	Costs	
No BTH	Haematology specialist visit	£8.48	
	Transfusion - Cohort 1; Ravulizumab | Eculizumab	£14.00 Ravulizumab	£20.61 Eculizumab
	Transfusion – Cohort 2 & 3; Ravulizumab | Eculizumab	£5.46 Ravulizumab	£4.59 Eculizumab
CAC-related BTH	General ward admission	£364.00	
	Intensive care admission	£14.67	
	Dialysis	£37.41	
	Haematology specialist visit	£164.80	
	Transfusion - Cohort 1; Ravulizumab | Eculizumab	£40.41 Ravulizumab	£85.64 Eculizumab
	Transfusion – Cohort 2 and 3; Ravulizumab | Eculizumab	N/A Ravulizumab	£131.24 Eculizumab
Incomplete C5 inhibition-related BTH	General ward admission	£79.13	
	Intensive care admission	£14.67	
	Dialysis	£37.41	

Health states	Cost Items	Costs	
	Haematology specialist visit	£164.80	
	Transfusion - Cohort 1;	£40.41 Ravulizumab	£85.64 Eculizumab
	Ravulizumab | Eculizumab		
	Transfusion – Cohort 2 and 3; Ravulizumab‡ | Eculizumab	N/A Ravulizumab	£131.24 Eculizumab
History of Incomplete C5 inhibition-related BTH, No BTH	Haematology specialist visit	£12.63	
	Transfusion - Cohort 1;	£14.00 Ravulizumab	£20.61 Eculizumab
	Ravulizumab | Eculizumab		
	Transfusion – Cohort 2 and 3; Ravulizumab | Eculizumab	£5.46 Ravulizumab	£4.59 Eculizumab
Subsequent Incomplete C5 inhibition-related BTH	General ward admission	£79.13	
	Intensive care admission	£14.67	
	Dialysis	£37.41	
	Haematology specialist visit	£164.80	
	Transfusion - Cohort 1;	£40.41 Ravulizumab	£85.64 Eculizumab
	Ravulizumab | Eculizumab		
	Transfusion – Cohort 2 and 3; Ravulizumab‡ | Eculizumab	N/A Ravulizumab	£131.24 Eculizumab
History of incomplete C5 inhibition-related BTH, CAC-related BTH	General ward admission	£364.00	
	Intensive care admission	£14.67	
	Dialysis	£37.41	
	Haematology specialist visit	£164.80	
	Transfusion - Cohort 1;	£40.41 Ravulizumab	£85.64 Eculizumab
	Ravulizumab | Eculizumab		
	Transfusion – Cohort 2 and 3; Ravulizumab‡ | Eculizumab	N/A Ravulizumab	£131.24 Eculizumab
History of incomplete C5 inhibition-related BTH, Cont. up-dose	Haematology specialist visit	£12.63	
	Transfusion - Cohort 1;	£14.00 Ravulizumab	£20.61 Eculizumab
	Ravulizumab | Eculizumab		
	Transfusion – Cohort 2 and 3; Ravulizumab | Eculizumab	£5.46 Ravulizumab	£4.59 Eculizumab
Cont. up-dose, CAC-related BTH	General ward admission	£364.00	
	Intensive care admission	£14.67	
	Dialysis	£37.41	
	Haematology specialist visit	£164.80	

Health states	Cost Items	Costs	
	Transfusion - Cohort 1; Ravulizumab| Eculizumab	£40.41 Ravulizumab	£85.64 Eculizumab
	Transfusion – Cohort 2 and 3; Ravulizumab‡ | Eculizumab	N/A Ravulizumab	£131.24 Eculizumab
Spontaneous remission	Haematology specialist visit	£12.63	

Source: Table 39 in CS.[1]
* Health state costs relevant to the equal effectiveness scenario; ‡ no BTH events were observed in the ravulizumab arm of ALXN1210-PNH-302, thus no transfusion costs were estimated for Cohort 2 and 3.
Key: BTH, breakthrough haemolysis; CAC, complement-amplifying condition; Cont., continuous.

Adverse reaction unit costs and resource use

No adverse event costs or resource use were included.

Miscellaneous costs and resource use

To reduce the risk of infection, patients must be vaccinated against meningococcal infections and receive additional prophylactic antibiotics, at least two weeks before receiving eculizumab or ravulizumab. Costs and dosing for the two vaccines, MenACWY (£60, one dose) and MenB (£115, two doses) , were derived from information from Hampstead Health Pharmacy.[50] Following the advice of the PNH National Service in Leeds a booster vaccination of MenACWY and MenB (one dose only) are assumed to be given every five years for patients receiving complement-inhibitor treatment.[51] As the vaccination history was assumed unknown for treatment experienced patients, a booster vaccine was given at the start of model for Cohorts 2 and 3 and thereafter every 5 years.

Prophylactic antibiotics, specifically penicillin, are required in all treated patients, while on treatment. The drug cost was derived from the drugs and pharmaceutical electronic market information tool (eMIT). [52] It was assumed that the pack providing the cheapest cost per mg (250mg tablets/pack size 28) would be used. It was assumed that prophylactic penicillin would be given at a dose of 500mg, twice daily. This resulted in a cost per cycle amount of £0.72 and was applied to both treatment arms.

Equal effectiveness scenario

The company only included direct drug-related costs in the equal effectiveness scenario. The differences in cost and resource use inputs modelled for the base-case and equal effectiveness scenario are listed in Table 5.21.

Table 5.21: Differences in cost/resource use inputs modelled for the base-case analysis and equal effectiveness scenario

Model input	Base-case analysis	Equal effectiveness scenario
Drug acquisition and administration costs	Included	Included – these are direct drug-related costs
Meningococcal vaccine cost	Included	
Prophylactic antibiotics	Included	
Transfusion costs	Included	Not included
BTH event costs	All CAC-related BTH and incomplete C5 inhibition costs included	Only the cost of an additional dose of eculizumab was included after a CAC-related BTH event
Other costs (consultant-led haematology follow-up)	Included	Not included

Source: Table 30 in CS.[1]
Key: BTH, break-through haemolysis; CAC, complement amplifying condition.

ERG comment: The company indicated that the regulatory review of two new vial sizes (3mL and 11mL) containing 100mg/mL of ravulizumab is ongoing with marketing authorisation expected to extend to these vial sizes by [redacted]£4,533 for 3mL vial (100 mg/mL), £16,621 for 11mL vial (100mg/mL). 100mg/mL formulation was used in the model base-case analysis as this formulation is expected to be approved by the time of the first appraisal committee meeting. The company also indicated that the increased drug concentration in these new vial sizes reduces the infusion times for ravulizumab. With the new vial sizes, the minimum infusion time is expected to range from 25–45 minutes for the loading dose and 30–55 minutes for maintenance doses.[26] The company assumed that the administration time for each infusion of ravulizumab 100mg/ml (infused at a 50mg/ml concentration) would be reduced to approximately the same administration time as each infusion of eculizumab. A scenario was modelled using the currently licensed 10mg/ml formulation. However, the ERG prefers to use the currently licensed 10mg/mL formulation in the ERG base-case analysis.

In the model, costs were sourced either from year 2018/2019 or 2020, except for the costs associated with transfusion administration. This was derived from a publication which reported costs from year 2014/15.[53] In response to the clarification letter, the company updated the model with the transfusion administration cost, which was inflated to year 2019, using the healthcare indices published in Unit Costs of Health and Social Care.[49]

A survey was developed to estimate inputs about the rates and causes of BTH and medical management for BTH.[11] Ten clinical experts were asked to estimate the proportion of patients requiring the resource use and average duration of resource use for four categories: general ward hospitalisation, intensive care unit (ICU) hospitalisation, medication and dialysis. In the absence of resource use data, the ERG thinks it is appropriate to source inputs from the survey.

6. COST EFFECTIVENESS RESULTS

6.1 Company's cost effectiveness results

Table 6.1 shows the key cost effectiveness results of the company's base-case analysis. Results are reported with the confidential PAS price assumed and discounted. Results indicated that ravulizumab accrued [redacted] incremental QALYs and was cost saving compared to eculizumab.

Table 6.1: Base-case cost effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Eculizumab	[redacted]	35.08	[redacted]	[redacted]	0.00	[redacted]	Ravulizumab dominates
Ravulizumab	[redacted]	35.08	[redacted]				

Source: Table 43 in CS [1]
Abbreviations: ICER, incremental cost effectiveness ratio; Inc., incremental; LYG, life years gained; QALY, quality-adjusted life year.

The disaggregated discounted QALYs by health state are shown in Table 6.2 and the disaggregated discounted costs by cost category are given in Table 6.3. The difference in QALYs between treatment arms is due to modelled ravulizumab benefit over eculizumab. The largest differences in costs across treatment arms are due to acquisition costs in the "No BTH" health state, which resulted in [redacted] difference for ravulizumab compared to eculizumab. However, these costs are outweighed by eculizumab due to patients requiring eculizumab up-dose. Thus, in the health state "continuous up-dose with history of incomplete C5 inhibition-related BTH event", the costs for eculizumab are [redacted], while there are no costs for ravulizumab in this health state (no incomplete C5 inhibition-related BTH events and no up-dose in the ravulizumab arm). This explains why in the company's base-case ravulizumab is cost saving compared to eculizumab.

Table 6.2: Summary of QALY gain by health state (base-case analysis)

Health state	QALY ravulizumab	QALY eculizumab	Increment	Absolute increment	% absolute increment
No BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CAC BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IncC5Inhib BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History of IncC5Inhib BTH, No BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent IncC5Inhib BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History of IncC5Inhib BTH, CAC BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History of IncC5Inhib BTH, Cont. up-dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cont. up-dose, CAC BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spontaneous	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Health state	QALY ravulizumab	QALY eculizumab	Increment	Absolute increment	% absolute increment
remission					
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	100%

Source: Table 15 in Appendix J to the CS.[19]
Abbreviations: BTH, breakthrough haemolysis; CAC, complement amplifying condition; IncC5Inhib, incomplete C5 inhibition; QALY, quality-adjusted life year.

Table 6.3: Summary of costs by health state (base-case analysis)

Health state	Cost ravulizumab	Cost eculizumab	Increment	Absolute increment	% absolute increment
No BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CAC BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IncC5Inhib BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History of IncC5Inhib BTH, No BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent IncC5Inhib BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History of IncC5Inhib BTH, CAC BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History of IncC5Inhib BTH, Cont. up-dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cont. up-dose, CAC BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spontaneous remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	100%

Source: Table 16 in Appendix J to the CS.[19]
Abbreviations: BTH, breakthrough haemolysis; CAC, complement amplifying condition; IncC5Inhib, incomplete C5 inhibition.

Finally, Table 6.4 shows the estimated proportion of time spent in each of the model's health states in the company's base-case analysis. In the ravulizumab arm, since no incomplete C5 inhibition-related BTH events occurred, patients spent most of the time in the "No BTH" health state, with a small proportion of patients ([redacted]%) in the "CAC BTH" health state. In the eculizumab arm, on the contrary, patients may experience incomplete C5 inhibition-related BTH events and, as a consequence, receive eculizumab continuous up-dose. The company's base-case estimated that [redacted]% of patients would require eculizumab continuous up-dose, almost exclusively due to managing incomplete C5 inhibition-related BTH events. The company's base-case also estimated that [redacted]% of eculizumab patients spent their time in the "No BTH" health state. Thus, the "No BTH" and the

continuous up-dose health states account for almost 100% of the time eculizumab patients spent on the company's base-case analysis.

Table 6.4: Proportion of time spent in each health state by treatment arm (base-case analysis)

Health state	Eculizumab	Ravulizumab
No BTH	[redacted]	[redacted]
CAC BTH	[redacted]	[redacted]
IncC5Inhib BTH	[redacted]	[redacted]
Hx IncC5Inhib BTH, No BTH	[redacted]	[redacted]
Subsequent IncC5Inhib BTH	[redacted]	[redacted]
Hx IncC5Inhib BTH, CAC BTH	[redacted]	[redacted]
Hx IncC5Inhib BTH, Cont. up-dose	[redacted]	[redacted]
Cont. up-dose, CAC BTH	[redacted]	[redacted]
Spontaneous remission	[redacted]	[redacted]

Source: economic model.[41]
Abbreviations: BTH, breakthrough haemolysis; CAC, complement amplifying condition; IncC5Inhib, incomplete C5 inhibition.

ERG comment: As previously discussed in Section 5.2.3 of this report and as shown in Table 6.4, the company's base-case seems to result in an overestimation of the number of patients requiring an up-dose in the eculizumab arm. The proportion of time spent in the continuous up-dose health states across the complete model time horizon is [redacted]%, which is approximately twice as much as the [redacted]% reported by the company to be expected to receive an increased dose of eculizumab in UK clinical practice. As a consequence, the company's base-case results might be biased against eculizumab.

6.2 Company's sensitivity analyses

The company conducted a number of sensitivity and scenario analyses. Sensitivity analyses included probabilistic sensitivity analyses (PSA), deterministic one-way sensitivity analyses (DSA) and additional scenario analyses to test the impact of model assumptions on the model results. The results of all these analyses are summarised below. Only discounted results are presented here.

6.2.1 Probabilistic sensitivity analysis

The company conducted a PSA in which all inputs were varied simultaneously over 1,000 iterations, based upon their distributional information. The parameters and the probability distributions used in the PSA are shown in Appendix T to the CS.[21] The PSA results are summarised in Table 6.5**,** and presented on a cost effectiveness (CE) plane in Figure 6.1, from which a cost effectiveness acceptability curve (CEAC) was calculated and plot in Figure 6.2.

The mean PSA results are consistent with the deterministic results shown in Table 6.1 and show that ravulizumab is also dominant compared to eculizumab with a similar QALY gains and cost savings as in the deterministic base-case analysis. As shown in Figure 6.1, every PSA iteration indicated that ravulizumab [redacted]. Therefore, as illustrated in Figure 6.2, the estimated probability that ravulizumab is a cost effective alternative to eculizumab [redacted].

Table 6.5: Mean probabilistic sensitivity analysis results

Technologies	Mean costs	Mean QALYs	Incremental		ICER
			Mean costs	Mean QALYs	
Eculizumab	[redacted]	[redacted]	[redacted]	[redacted]	Ravulizumab dominates
Ravulizumab	[redacted]	[redacted]			

Source: Table 43 in CS.[1]
Key: ICER, incremental cost effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

Figure 6.1: Probabilistic sensitivity analysis cost effectiveness plane

Source: Figure 15 in CS.[1]
Abbreviations: QALY, quality-adjusted life year.

Figure 6.2: Probabilistic sensitivity analysis cost effectiveness acceptability curve

Source: Figure 16 in CS.[1]

ERG comment: Following the ERG request in the clarification letter,[19] additional parameters were included in the model submitted in response to the ERG clarification questions. These are summarised in Table 7.1 of this report. While parameter uncertainty is thus likely to be underestimated in the company's base-case analysis, it is also likely that this would have no impact on decision uncertainty, since all PSA outcomes in the company's base-case analysis are expected to remain in the south eastern quadrant of the CE-plane, even after these additional parameters are included in the PSA.

6.2.2 Deterministic sensitivity analysis

The results of the deterministic one-way sensitivity analysis are presented in Figure 6.3. One-way analyses were performed to evaluate the sensitivity of the ICER to individual inputs, holding all else constant. In the deterministic sensitivity analysis, the upper and lower bounds of a parameter were taken from their 95% confidence intervals if these were available from the data source. When such information was not available, the upper and lower bounds were assumed to be within ±25% for cost values and ±10% of the other base-case values. These are reported in Appendix T of the CS.[21]

In this analysis, conducted in terms of net monetary benefit (NMB), it was shown that the NMB was most sensitive to the probability of an incomplete C5 inhibition in eculizumab patients with no history of incomplete C5 inhibition BTH events. This was followed by the utility for ravulizumab and eculizumab patients with no history of BTH, the probability of a subsequent incomplete C5 inhibition BTH event in eculizumab patients with a history of incomplete C5 inhibition BTH event and the utility related to transfusion burden for patients on treatment. None of them resulted in a situation where the NMB was negative.

Figure 6.3: Cost effectiveness analysis – tornado diagram

Source: Figure 17 in CS.[1]
Abbreviations: BTH, break-through haemolysis; CH, cohort; NMB, Net Monetary Benefit; PAS, patient access scheme; Prob., probability; RBC, red blood cells.
Note: £30,000 willingness to pay threshold used

6.2.3 Scenario analysis

The company ran several scenario analyses to test the sensitivity of the cost effectiveness results to methodological, parameter and structural uncertainties in the economic analysis. A key scenario was built under the assumption of equal effectiveness of ravulizumab and eculizumab, as explained in Section 5.2.2 and 5.2.3 of this report. This analysis is, according to the company, consistent with the non-inferiority trial designs and provides a more conservative viewpoint. Given its importance within the current submission, the equal effectiveness scenario is presented separately below.

Equal effectiveness scenario

The results of the equal efficacy scenario are presented below in Table 6.6. At PAS price, ravulizumab is associated with incremental cost savings of [redacted]. The lower predicted savings estimated in this scenario compared to the base-case analysis are largely due to the assumed constant proportion of patients who receive the higher than licensed dose of eculizumab ([redacted]). In the base-case analysis, patients can transition into the continuous up-dosing health state at each model cycle, which results in a greater proportion of patients receiving the higher (and thus more costly) eculizumab dose over the total model time horizon.

Table 6.6: Equal effectiveness scenario – deterministic results

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Eculizumab	[redacted]	35.08	[redacted]				
Ravulizumab	[redacted]	35.08	[redacted]	[redacted]	0.00	[redacted]	Dominant

Source: economic model.[41]
Abbreviations: ICER, incremental cost effectiveness ratio; Inc., incremental; LYG, life years gained; QALY, quality-adjusted life year.

Since no incomplete C5 inhibition BTH events were modelled in this scenario, all QALYs in the ravulizumab arm correspond to the "No BTH" health state, except for a very small proportion of patients in the "CAC BTH" health state. In the eculizumab arm, there were also no incomplete C5 inhibition BTH events but since continuous up-dose since the start of the simulation is assumed for [redacted]% of patients, [redacted] QALYs are accrued in the continuous up-dose health state, and the remaining QALYs in the "No BTH" health state (and a small proportion in the CAC-related health states). The disaggregated discounted costs by cost category can be interpreted in a similar way as it was done for the costs in the company's base-case presented in Table 6.3. The largest differences in costs across treatment arms are due to acquisition costs in the "No BTH" health state, where ravulizumab resulted in [redacted] additional costs compared to eculizumab. Also, in the equal effectiveness scenario, these costs are outweighed by eculizumab patients requiring an up-dose. Thus, in the health state "continuous up-dose with history of incomplete C5 inhibition-related BTH event", the costs for eculizumab are [redacted], while there are no costs for ravulizumab in this health state. Again, this explains why also in the equal effectiveness scenario ravulizumab is cost saving compared to eculizumab. Note, however, that in the equal effectiveness scenario, ravulizumab is less cost saving ([redacted]) than in the company's base-case ([redacted]). This is because, as shown in Table 6.7, in the equal effectiveness scenario [redacted]% of patients spent their time in the continuous up-dose health state, while in the base-case analysis this was [redacted]%, which is approximately two times larger (and probably an overestimation). Therefore, in the company's base-case analysis, eculizumab is a more expensive option than in the equal effectiveness scenario.

Table 6.7: Proportion of time spent in each health state by treatment arm (equal effectiveness scenario)

Health state	Eculizumab	Ravulizumab
No BTH	[redacted]	[redacted]
CAC BTH	[redacted]	[redacted]
IncC5Inhib BTH	[redacted]	[redacted]
Hx IncC5Inhib BTH, No BTH	[redacted]	[redacted]
Subsequent IncC5Inhib BTH	[redacted]	[redacted]
Hx IncC5Inhib BTH, CAC BTH	[redacted]	[redacted]
Hx IncC5Inhib BTH, Cont. up-dose	[redacted]	[redacted]
Cont. up-dose, CAC BTH	[redacted]	[redacted]
Spontaneous remission	[redacted]	[redacted]

Source: economic model.[41]
Abbreviations: BTH, breakthrough haemolysis; CAC, complement amplifying condition; IncC5Inhib, incomplete C5 inhibition.

ERG comment: The proportion of time spent in the continuous up-dose health states across the complete model time horizon is [redacted]% in the company's base-case, which is approximately twice as much as the [redacted]% assumed in the equal effectiveness scenario and reported by the company to be expected to receive an increased dose of eculizumab in UK clinical practice. For this reason, the ERG prefers the equal effectiveness scenario over the company's base-case. However, for the reasons discussed in Section 5.2.3 regarding the generalisability of the trial populations to UK clinical practice, the ERG prefers a base-case scenario based completely on the clinical trials, without modelling eculizumab up-dose. Even though it is acknowledged that this will not be completely representative of the UK clinical practice.

Company's additional scenario analyses

The results of all other scenarios are presented in **Error! Reference source not found.** at the ravulizumab PAS price. Despite the relatively large number of scenarios run by the company, the results were relatively insensitive in most of these analyses with ravulizumab remaining more effective and cost saving in all.

Table 6.8: Company's additional scenario analyses results

Scenario	Base-case	Scenario	Incremental costs	Incremental QALYs	ICER	NMB	% change from base-case NMB
Base-case			[redacted]	[redacted]	Dominant	[redacted]	0.0%
Time horizon	Lifetime	10 years	[redacted]	[redacted]	Dominant	[redacted]	-84.7%
Time horizon	Lifetime	20 years	[redacted]	[redacted]	Dominant	[redacted]	-54.1%
Discount rate (costs and QALYs)	3.50%	0.00%	[redacted]	[redacted]	Dominant	[redacted]	127.2%
Discount rate (costs and QALYs)	3.50%	6.00%	[redacted]	[redacted]	Dominant	[redacted]	-39.4%
Utility increment of ravulizumab vs eculizumab	0.0570	0.000	[redacted]	[redacted]	Dominant	[redacted]	-5.8%
Utility increment of ravulizumab vs eculizumab	0.0570	0.025	[redacted]	[redacted]	Dominant	[redacted]	-3.1%
Utility increment of ravulizumab vs eculizumab	0.0570	0.050	[redacted]	[redacted]	Dominant	[redacted]	-0.7%
EORTC to EQ-5D mapping (value set)	Longworth et al. (2014)	McKenzie and van der Pol. (2009)	[redacted]	[redacted]	Dominant	[redacted]	0.1%
HRQL regression population	Separate	Pooled	[redacted]	[redacted]	Dominant	[redacted]	0.0%
Utility: general population age adjustment	Applied	Not applied	[redacted]	[redacted]	Dominant	[redacted]	0.5%
Utility: general population cap	Applied	Not applied	[redacted]	[redacted]	Dominant	[redacted]	0.3%
BTH excess mortality (HR) vs background	1.00	4.81	[redacted]	[redacted]	Dominant	[redacted]	-1.7%
CAC BTH up-dosing	Yes	No	[redacted]	[redacted]	Dominant	[redacted]	-1.1%
Spontaneous remission rate (per cycle)	0.0000	0.0005	[redacted]	[redacted]	Dominant	[redacted]	-24.4%

Scenario	Base-case	Scenario	Incremental costs	Incremental QALYs	ICER	NMB	% change from base-case NMB
Spontaneous remission rate (per cycle)	0.0000	0.0006	[redacted]	[redacted]	Dominant	[redacted]	-28.8%
Spontaneous remission rate(per cycle)	0.0000	0.0010	[redacted]	[redacted]	Dominant	[redacted]	-42.1%
Incomplete C5 inhibition BTH duration (days)	2	3	[redacted]	[redacted]	Dominant	[redacted]	0.0%
Incomplete C5 inhibition BTH duration (days)	2	7	[redacted]	[redacted]	Dominant	[redacted]	0.0%
Ravulizumab formulation	100mg/ml	10mg/ml	[redacted]	[redacted]	Dominant	[redacted]	-0.1%
Permanent eculizumab up-dosing per clinical practice dose	Licensed dose at model entry	English clinical practice dosing and no incomplete C5 inhibition BTH events	[redacted]	[redacted]	Dominant	[redacted]	-37.5%

Source: Table 46 in CS.[1]
Abbreviations: BTH, breakthrough haemolysis; CAC, complement-amplifying condition; EORTC, European Organisation for Research and Treatment of Cancer; HR, hazard ratio; HRQL, health-related quality of life; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALY, quality-adjusted life year.

ERG comment: The results of the additional scenarios presented by the company showed that ravulizumab was more effective and cost saving compared to eculizumab in all of them. This is expected given that all scenarios resulted from variations in the company's base-case where proportion of time spent in the continuous up-dose health states across the complete model time horizon was [redacted]%, twice as much as the [redacted]% assumed in the equal effectiveness scenario and reported by the company to be expected in patients receiving an increased dose of eculizumab in UK clinical practice. In previous sections of this report, it has been discussed that the proportion of patients requiring an eculizumab up-dose is the main driver of the cost effectiveness results. This will be further explored by the ERG in Chapter 7 of this report. Since in all scenarios presented in Table 6.8 the assumption about the number of patients requiring an eculizumab up-dose remain unchanged with respect to the company's base-case, it is logical that these scenarios keep showing ravulizumab as a dominant option compared to eculizumab. For this reason, the ERG feels that the impact of some key assumptions on the model results was not sufficiently tested by the company. In particular, a scenario completely based on the trials' settings, where eculizumab up-dose was not allowed seems to be of great importance and it was not explored in the CS. Also, explorations on the equal effectiveness scenario instead of the company's base-case or the duration of ravulizumab treatment effect seem to represent key sources of uncertainty to be addressed in detail. These uncertainties were explored by the ERG in their additional scenario analyses in Section 7.1.3 of this report.

6.3 Model validation and face validity check

Several aspects of validation were discussed by the company in the validation section of the CS (B.3.10).[1] The validation of the conceptual model was assessed by three clinicians and one health economics expert at an Advisory Board meeting conducted by the company.[11] At the same meeting, all input parameters considered in the economic model were also validated.

Additionally, the company discussed in the CS validation regarding overall survival and utilities (as input parameters of the model) in more detail. In particular, the company assumed that (overall) survival was equal to that of the age- and gender-matched general population. To support this assumption the company referred to the studies by Socie et al. (1996) and Kelly et al. (2008).[34, 54] Socie et al. (1996) studied survival of 2,356 PNH patients who were enrolled in the International PNH registry. The study aimed to determine the prognosis of patients with aplastic anaemia, an underlying bone marrow disorder. In total, 16% of the patients included in the study were presented with aplastic anaemia, and 1% of these died of causes that were related to aplastic anaemia in the study follow-up period.[34] Kelly et al. (2008) conducted a study in 79 patients in Leeds, thus, an UK patient cohort. The study reported the presence of bone marrow disorders in a minority of patients. However, the study concluded that "*survival of patients treated with eculizumab was not different from age- and sex-matched normal controls*".[54] The utilities used in the economic analyses were derived from EQ-5D data mapped from EORTC-QLQ-C30 data collected in both ALXN1210-PNH-301 and ALXN1210-PNH-302. The company compared these utilities with the utilities reported in Coyle et al. (2014), a study which was identified in the economic systematic literature review.[55] In this study, the following three utilities were reported based on transfusion requirement: transfusion independent (utility value 0.84), reduced transfusion requirement (utility value 0.77) and transfusion dependent (utility value 0.60). The (mapped) utilities used in the company's economic analyses, resulted in a baseline utility of 0.82 in ALXN1210-PNH-301 and 0.86 in ALXN1210-PNH-302. A utility decrement of -0.07 (estimated from the mixed effects regression in the trial) was applied to account for the need for transfusion. This decrement is the same as the difference in the utilities for reduced transfusion requirement and transfusion independent reported in Coyle et al. (2014).[55]

Regarding the verification of the electronic model, the company indicated that, after the model was finalised, internal modellers (not mentioned how many) undertook its validation. A programmer who was not involved in building the model reviewed all formulae and labelling in the model. Further details on the model verification efforts were not reported.

Finally, the company discussed validation of several model outcomes (both final and intermediate). As mentioned in Section 5.2.3 of this report, across the model time horizon of 20 years, patients spent 24.3% of their time in the eculizumab up-dosed states, which is similar to the [redacted]% reported by the PNH National service and the [redacted]% derived from UK data from the International PNH Registry, of patients who require eculizumab maintenance dosing higher than the labelled 900mg to achieve and maintain efficacy.[38]

The modelled rate of transfusion, which was also derived from ALXN1210-PNH-301 and ALXN1210-PNH-302, was validated using the results of a survey on BTH and medical management strategies conducted by the company with a group of 10 clinicians who were experts in treating PNH. According to the company, the experts indicated that patients would receive a transfusion in approximately 30%–35% of incomplete C5 inhibition-related BTH events and in approximately 15% of CAC-related BTH events. These frequencies are in line with the probabilities derived from ALXN1210-PNH-301 and ALXN1210-PNH-302.

The incremental QALY benefit of ravulizumab compared to eculizumab obtained in the base-case, was compared to the results reported in the O'Connell et al. studies,[31, 32] which were obtained from the same model used in this submission but under the US and Germany settings. The incremental QALYs reported in the US and German studies were 1.67 and 0.53, respectively. The company's base-case resulted in [redacted] incremental QALY, [redacted]. The company explained that this was expected because a smaller utility benefit due to the reduced dosing frequency of ravulizumab was used in the German analysis, which was published prior to the availability of the DCE results used in this submission. In the US and German analyses no age-adjustment to the utility values or utility capping were applied. Additionally, the US analysis used a different mapping algorithm (McKenzie et al. 2009[56]) and included treatment arm as a covariate in the regression equation used to estimate utilities. These two different assumptions led to increased incremental QALYs according to the company.

Health state costs were based on the results of a survey of 10 clinicians, experts in the treatment of PNH with both eculizumab and ravulizumab. The results of this survey were also used to inform a separate cost analysis in the US. This analysis estimated that a total annual cost of BTH management of $386 per ravulizumab-treated patient and $3,472 per eculizumab-treated patient, excluding pregnant women.[57] This shows that BTH management costs for ravulizumab were approximately 11% of BTH management costs for eculizumab. As shown in Table 6.3, in the company's base-case this was approximately 9%, which is in line with what was observed in the US study.

ERG comment: The company discussed important validation aspects in the CS. Furthermore, in response to clarification B25,[19] a filled-in version of the validation tool AdViSHE was included as part of the response.[58] All validation aspects in the tool were covered to some extent.

As discussed, in Section 5.2.3 of this report, the ERG is concerned that the company's base-case analysis overestimates the number of patients in the continuous up-dose health states, which as will be explained in Chapter 7 of this report, has a major impact on the model results. The company indicated that "*across the model time horizon of 20 years*",[1] patients spend 24.3% of their time in the continuous up-dose health states and that this closely aligns with the [redacted]% from the PNH National

Service, which, according to the company, provides a measure of external validation. However, the ERG is unclear why the company has reported the previous comparison "*across the model time horizon of 20 years*" and not across the complete model time horizon where the proportion of time spent in the continuous up-dose health states is [redacted]% (see Table 6.4), which is approximately twice as much as the [redacted]% reported by the company to be expected to receive an increased dose of eculizumab in UK clinical practice and, therefore, a large overestimation of the number of patients requiring an up-dose in the eculizumab arm. In the equal effectiveness scenario, the proportion of time spent in the continuous up-dose health states *across the complete model time horizon* was assumed to be exactly [redacted]%, which is equal to the proportion of patients expected to receive an increased dose of eculizumab in UK clinical practice. The ERG understands that the proportion of patients expected to receive an increased dose of eculizumab in UK clinical practice refers to the complete time horizon. Therefore, the assumption in the equal effectiveness scenario is in line with the ERG expectations. In response to clarification question B7,[19] the company indicated that "*both pharmacoeconomic analyses incorporate the clinical practice of up-dosing and are therefore reflective of the disease pathway and clinical management of PNH patients who meet the criteria for complement-inhibitor treatment in the UK. As such, both analyses are equally clinically plausible*".[19] The ERG does not agree with the company's interpretation of the plausibility of the scenarios seeing that they greatly differ in this very important aspect. However, the ERG considers that it is up to the Committee to decide which scenario is clinically more plausible.

7. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

7.1 Exploratory and sensitivity analyses undertaken by the ERG

7.1.1 Explanation of the company adjustments after the request for clarification

In their response to clarification question B27,[19] the company explained what changes were made in response to the ERG clarification questions. These are summarised in Table 7.1. These changes did not impact the base-case results, except for the update of the cost for transfusion administration. The impact of this change on the overall results was negligible.

Table 7.1: Summary of model changes and impact on the base-case results

Change	Model change (sheetname:cellname)	Impact on base-case ICER
Inclusion of Bayesian prior distribution option in response to question B5	Inputs:H67 [IO]_Model_BayesPrior Addition of model option to include Bayesian prior in response to question B5	No change (not included in base-case analysis)
Inclusion of a treatment arm utility option in response to question B15	Input:H160 [IO]_HU_InclTxArm Addition of model option to include treatment arm in response to question B15	No change (not included in base-case analysis)
Update of the cost for transfusion administration	Inputs:H259 Update on cost in response to question B22	ICER remains dominant
Inclusion of parameters into OSWA and PSA Weight for age Cohort proportions Utility regression coefficients Bayesian priors in response to question B5	Analysis parameters: K17:K123, N17:N123, K206:K217 K206,K212 – text change to Yes Analysis parameters:N175:N185 – text change to No Updated in response to question B 24	No change (not included in base-case analysis)
Inclusion of option to model joint variance	PSA:K8 PSA_Jointvar_include Updated to include option to test joint variance in the PSA (applies to utility covariates and Ara and Brazier general population utility variance)	No change (not included in base-case analysis)
Source: Table 10 in clarification letter response.[19]		

7.1.2 Explanation of the ERG adjustments

The changes made by the ERG (to the model received with the response to the clarification letter) were subdivided into the following three categories, according to Kaltenthaler et al. 2016:[59]

- Fixing errors (correcting the model where the company's electronic model was unequivocally wrong).
- Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice has not been adhered to).

- Matters of judgement (amending the model where the ERG considered that reasonable alternative assumptions are preferred).

After these changes were implemented in the company's model, additional scenario analyses were explored by the ERG in order to assess the impact of alternative assumptions on the cost effectiveness results.

Fixing errors

1. Error in the model "Output" sheet in the ca1culation of the proportion of time spent in the model health states. This has no impact on the model cost effectiveness results, but it is important for clinical validation.

Fixing violations

2. No violations to the NICE reference case, scope or best practice were identified by the ERG.

Matters of judgement

3. Eculizumab up-dose: based completely on the clinical trials ALXN1210-PNH-301 and ALXN1210-PNH-302. Thus, without modelling eculizumab up-dose.
4. Utilities: ravulizumab utility benefit derived from a mixed-effects regression model with treatment as covariate.
5. Utilities: additional utility benefit for treatment frequency set to 0 (instead of 0.057, as derived from the DCE).
6. Ravulizumab currently licensed 10mg/ml formulation (instead of 100mg/ml).

The overview of the changes and the bookmarks for the justification of the ERG changes are presented in Table 7.2.

Table 7.2: Company and ERG base-case preferred assumptions

Base-case preferred assumptions	Company	ERG	Justification for change
Eculizumab up-dose	Eculizumab up-dose per UK clinical practice (without continuous up-dose from the start). Continuous up-dose from start in the "equal effectiveness" scenario.	No eculizumab up-dose. Based completely on ALXN1210-PNH-301 and ALXN1210-PNH-302.	The ERG is concerned that, in the company's base-case, the proportion of time spent in the continuous up-dose health states largely overestimates what is expected in clinical practice (Section 5.2.3). The ERG is concerned that the patients requiring eculizumab up-dose were underrepresented in the trials. Trial data suggests that approximately 5% of patients in the trial population would need an eculizumab up-dose, which is approximately [redacted] lower than what is expected in UK clinical practice. The ERG wonders whether the conclusions from the trials would be the same if there were approximately [redacted]% of patients who would need an up-dose (Section 5.2.3).
Utilities – assumption 1	Ravulizumab utility derived from a mixed-effects regression model without treatment as covariate.	Ravulizumab utility benefit derived from a mixed-effects regression model with treatment as covariate.	The ERG prefers a non-significant utility benefit of 0.0103 and 0.0197 estimated from trials ALXN1210-PNH-301 and ALXN1210-PNH-302 respectively for ravulizumab, derived from a mixed-effects regression model, as the source of HRQoL benefit in the cost effectiveness model. The ERG prefers not to use the utility benefit for treatment frequency of 0.057 as derived from the DCE. The ERG is concerned that the benefit derived from the DCE overestimates ravulizumab benefit (Section 5.2.8).
Utilities – assumption 2	Ravulizumab utility benefit for treatment frequency (0.057) derived from DCE.	Additional utility benefit for treatment frequency set to 0.	
Ravulizumab formulation	Ravulizumab 100mg/ml	Ravulizumab currently licensed	Ravulizumab 10mg/ml is the currently

Base-case preferred assumptions	Company	ERG	Justification for change
	formulation	10mg/ml formulation (instead of 100mg/ml)	licensed formulation (Section 5.2.9)
Abbreviations: DCE = discrete choice experiment; ERG = Evidence Review Group			

7.1.3 Additional scenarios conducted by the ERG

The ERG conducted a series of additional scenario analyses in order to explore important areas of uncertainty in the model. These key uncertainties were related to the number of patients requiring eculizumab up-dose, the utilities and BTH excess mortality. A list of scenario analyses conducted by the ERG is given below.

Scenario analysis 1: Alternative distribution of patients in Cohort 3 in the "equal effectiveness" scenario

Cohort 3 is assumed to reflect UK clinical practice, where a continuous increased dose of eculizumab is used to manage BTH events. The reported range of PNH patients requiring this up-dose is between 5% and 29%, with an estimated mean value of [redacted]%.[12-15] In this scenario, the impact of assuming a smaller population (5%) in Cohort 3 was explored by the ERG. The rationale for this scenario is to consider a lower percentage of patients requiring continuous up-dose to align with the proportion of these patients that is suspected to be in the trials (see Section 5.2.3) and that is still within the limits provided by the company. Therefore, the ERG feels that this "equal effectiveness" scenario would be more reflective of what might occur in the trials, should eculizumab up-dose be allowed.

Scenario analysis 2: Alternative utilities and ravulizumab formulation in the company's "equal effectiveness" scenario

The assumptions on utilities and costs used in the ERG base-case as explained in Section 7.1.2, were explored in the company's "equal effectiveness scenario". Thus, in this scenario, the ERG assumed [redacted]% of patients in Cohort 3, the ravulizumab utility benefit derived from a mixed-effects regression model with treatment as covariate, the additional utility benefit for treatment frequency set to 0 and the ravulizumab formulation of 10mg/ml.

Scenario analysis 3: Alternative utilities and ravulizumab formulation in the company's base-case

The assumptions on utilities and costs used in the ERG base-case as explained in Section 7.1.2, were explored in the company's base-case. Thus, in this scenario, the ERG assumed eculizumab up-dose as in the company's base-case (continuous after second incomplete C5 inhibition-related BTH event), the ravulizumab utility benefit derived from a mixed-effects regression model with treatment as covariate, the additional utility benefit for treatment frequency set to 0 and the ravulizumab formulation of 10mg/ml.

Scenario analysis 4: ERG base-case with alternative utility values

In these scenarios, the ERG explored the impact of assuming the utility decrement of 0.057 (instead of 0) as in the company base-case, and half of this value (0.029). The remaining ERG preferred assumptions were as in ERG base-case. Thus, in this scenario, the ERG also assumed no eculizumab up-dose and the ravulizumab formulation of 10mg/ml.

Scenario analysis 5: ERG base-case with BTH excess mortality

In this scenario, the ERG base-case was run with the assumption of BTH excess mortality as reported by Jang et al. (2016).[36] A standard mortality ratio of 4.81 was thus applied for this scenario.

7.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

7.2.1 Results of the ERG preferred base-case scenario

The results of the ERG preferred base-case are provided in Table 7.3. After the implementation of the ERG's preferred assumptions, the ICER was £38,290. Ravulizumab was estimated to provide [redacted] additional QALYs at an incremental cost of £[redacted] compared to eculizumab. As can be seen in Table 7.4, the incremental QALY gains for ravulizumab stemmed from the incomplete C5 inhibition-related BTH events modelled in the eculizumab arm. Finally, in Table 7.5 it is observed that the largest differences in costs across treatment arms are due to acquisition costs in the "No BTH" health state, which resulted in £[redacted] difference for ravulizumab compared to eculizumab. Eculizumab costs associated to management of incomplete C5 inhibition-related BTH events (with no up-dose as in the trials) add up to £[redacted], which unlike the company base-case and equal effectiveness scenario, do not outweigh the higher costs of eculizumab in the "No BTH" health state. This explains why in the ERG base-case (when eculizumab up-dose is not modelled as in the clinical trials) ravulizumab is not cost saving compared to eculizumab.

Table 7.3: ERG base-case deterministic results (no eculizumab up-dose)

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
Eculizumab	[redacted]	35.08	[redacted]	[redacted]	0.00	[redacted]	£38,290
Ravulizumab	[redacted]	35.08	[redacted]				

Source: economic model.[41]
Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

Table 7.4: ERG base-case disaggregated discounted QALYs (no eculizumab up-dose)

Health state	QALY ravulizumab	QALY eculizumab	Increment	Absolute increment	% absolute increment
No BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CAC BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IncC5Inhib BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History of IncC5Inhib BTH, No BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent IncC5Inhib BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History of IncC5Inhib BTH, CAC BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History of IncC5Inhib BTH, Cont. up-dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cont. up-dose, CAC BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spontaneous remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Health state	QALY ravulizumab	QALY eculizumab	Increment	Absolute increment	% absolute increment
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	100%

Source: economic model.[41]
Abbreviations: BTH, breakthrough haemolysis; CAC, complement amplifying condition; IncC5Inhib, incomplete C5 inhibition; QALY, quality-adjusted life year.

Table 7.5: ERG base-case disaggregated costs (no eculizumab up-dose)

Health state	Cost ravulizumab	Cost eculizumab	Increment	Absolute increment	% absolute increment
No BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CAC BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IncC5Inhib BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History of IncC5Inhib BTH, No BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent IncC5Inhib BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History of IncC5Inhib BTH, CAC BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History of IncC5Inhib BTH, Cont. up-dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cont. up-dose, CAC BTH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spontaneous remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	100%

Source: economic model.[41]
Abbreviations: BTH, breakthrough haemolysis; CAC, complement amplifying condition; IncC5Inhib, incomplete C5 inhibition.

7.2.2 Results of the ERG preferred sensitivity analysis

The ERG also conducted a PSA using their preferred base-case assumptions. As shown in Table 7.1, the company included in the PSA additional parameters, following the ERG request in the clarification letter.[19] No further adjustments were made to the PSA by the ERG. The PSA results obtained after the ERG adjustments can be seen in Table 7.6. The probabilistic ICER was £46,976 per QALY gained (incremental costs were £[redacted] and incremental QALYs were [redacted]), thus, £8,686 larger than the ERG deterministic ICER. Even though the ERG was unable not retrieve PSA results disaggregated per health state (it is unclear whether this is possible in the company's model), the ERG considers that this relatively large difference might be explained by the inclusion of a prior distribution in the transition probabilities associated to experiencing incomplete C5 inhibition-related BTH events in the ravulizumab arm. Thus, unlike the deterministic ERG base-case, the ERG PSA

allows a proportion of patients in the ravulizumab arm to transition to the incomplete C5 inhibition-related BTH events related health states. The estimated size of this proportion of patients is unknown to the ERG but it is expected to be small. The CE-plane and CEAC resulting from the ERG PSA are shown in Figure 7.1 and 7.2, respectively. The CE-plane shows approximately [redacted]% of the simulations (according to the CEAC) in the south eastern quadrant, in which ravulizumab is dominant, with a few simulations showing large savings in costs. The remaining simulations are in the north eastern quadrant of the CE-plane, where ravulizumab is both more effective and more costly than eculizumab. The CEAC shows that the probability of ravulizumab being cost effective was [redacted]% at a threshold ICER of £30,000 per QALY gained.

Table 7.6: Mean PSA results - ERG base-case (no eculizumab up-dose)

Technologies	Mean costs	Mean QALYs	Incremental		ICER
			Mean costs	Mean QALYs	
Eculizumab	[redacted]	[redacted]	[redacted]	[redacted]	£46,976
Ravulizumab	[redacted]	[redacted]			

Source: economic model.[41]
Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life years gained; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

Figure 7.1: ERG preferred cost effectiveness plane (no eculizumab up-dose)

Source: economic model.[41]
QALY = quality-adjusted life year

Figure 7.2: ERG preferred cost effectiveness acceptability curve (no eculizumab up-dose)

Source: economic model.[41]

The adjustments made by the ERG to the company's base-case also had an impact on the univariate sensitivity analyses. As shown in Figure 7.3, in general the NMB was most sensitive to utilities and to the probability of an incomplete C5 inhibition-related events in eculizumab patients. These parameters resulted in NMB ranges including both negative and positive values.

Figure 7.3: ERG tornado diagram (no eculizumab up-dose)

Source: economic model.[41]
Abbreviations: BTH, break-through haemolysis; CH, cohort; NMB, Net Monetary Benefit; PAS, patient access scheme; Prob., probability; RBC, red blood cells.
Note: £30,000 willingness to pay threshold used

7.2.3 Results of the ERG additional exploratory scenario analyses

Scenario analysis 1: Alternative distribution of patients in Cohort 3 in the "equal effectiveness" scenario

Assuming 5% of patients in Cohort 3 in the "equal effectiveness" scenario had a substantial impact on the model results. As can be seen in Table 7.7, ravulizumab became a cost saving option compared to eculizumab under this assumption. The incremental QALYs predicted by the model in this scenario were [redacted] and the incremental costs [redacted].

Table 7.7: ERG scenario analyses on Cohort 3 patients in the equal effectiveness scenario

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Eculizumab	[redacted]	[redacted]	[redacted]	0.33	Ravulizumab dominates
Ravulizumab	[redacted]	[redacted]			

Source: economic model.[41]
Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

Scenario analysis 2: Alternative utilities and ravulizumab formulation in the company's "equal effectiveness" scenario

Assuming the ravulizumab utility benefit derived from a mixed-effects regression model with treatment as covariate, with the additional utility benefit for treatment frequency set to 0 and the ravulizumab formulation of 10mg/ml, while keeping the proportion of patients in Cohort 3 as in the company's "equal effectiveness" scenario ([redacted]%), did not change the conclusions drawn from the "equal effectiveness" scenario as run by the company. As can be seen in Table 7.8, in this scenario ravulizumab is associated with incremental cost savings of [redacted] and [redacted] incremental QALYs. Incremental cost savings were nearly identical to those in the company's "equal effectiveness" scenario ([redacted]) where the incremental QALYs were larger ([redacted]), as can be seen in Table 6.6. This shows the impact of assuming a different approach to utilities but overall ravulizumab remained a dominant option over eculizumab in both scenarios.

Table 7.8: ERG scenario analyses on alternative utilities and costs in the equal effectiveness scenario

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Eculizumab	[redacted]	[redacted]	[redacted]	[redacted]	Ravulizumab dominates
Ravulizumab	[redacted]	[redacted]			

Source: economic model.[41]
Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

Scenario analysis 3: Alternative utilities and ravulizumab formulation in the company's base-case

Assuming the ravulizumab utility benefit derived from a mixed-effects regression model with treatment as covariate, with the additional utility benefit for treatment frequency set to 0 and the ravulizumab formulation of 10mg/ml, under the assumptions of the company's base-case (continuous after second incomplete C5 inhibition-related BTH event), did not change the conclusions drawn from the company's base-case. As can be seen in Table 7.9, in this scenario ravulizumab is associated with incremental cost savings of [redacted] and [redacted] incremental QALYs. Incremental cost savings were nearly identical to those in the company's base-case ([redacted]) where the incremental QALYs were larger ([redacted]), as can be seen in Table 6.1. This shows the impact of assuming a different approach to utilities but overall ravulizumab remained a dominant option over eculizumab in both scenarios.

Table 7.9: ERG scenario analyses on alternative utilities and costs in the company's base-case

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Eculizumab	[redacted]	[redacted]	[redacted]	[redacted]	Ravulizumab dominates
Ravulizumab	[redacted]	[redacted]			

Source: economic model.[41]
Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

Scenario analysis 4: ERG base-case with alternative utility values

The impact of assuming the utility decrement of 0.057 (instead of 0) as in the company base-case, and half of this value (0.029) can be seen in Table 7.10 and 7.11, respectively. In both scenarios, the difference with respect to the ERG base-case was on the incremental QALYs only, since the costs were unchanged, as can be seen in Table 7.3. The two scenarios explored in this section resulted in larger QALY gains for ravulizumab because an additional utility benefit for treatment frequency was assumed. The larger the assumed benefit, the larger the incremental QALYs, which were [redacted] and [redacted], respectively; both larger than the [redacted] incremental QALYs in the ERG base-case. The ICERs were £11,790 and £17,688, respectively; both below the common threshold ICER of £30,000 per QALY gained.

Table 7.10: ERG scenario analyses with alternative utilities – decrement 0.057

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Eculizumab	[redacted]	[redacted]	[redacted]	[redacted]	£11,790
Ravulizumab	[redacted]	[redacted]			

Source: economic model.[41]
Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

Table 7.11: ERG scenario analyses with alternative utilities – decrement 0.029

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Eculizumab	[redacted]	[redacted]	[redacted]	0.92	£17,688
Ravulizumab	[redacted]	[redacted]			

Source: economic model.[41]
Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

Scenario analysis 5: ERG base-case with BTH excess mortality

The impact of assuming BTH excess mortality by applying the standard mortality ratio of 4.81 by Jang et al. (2016),[36] can be seen in Table 7.12. The ICER in this scenario was £124,433, more than three times larger than the ERG base-case. Despite resulting in more incremental QALYs than the ERG base-case ([redacted] vs. [redacted]), the increased incremental costs was the main cause for this large ICER.

This can be explained by the life years gained in the eculizumab arm. In the company base-case, eculizumab resulted in 35.08 life years, whereas in the scenario with BTH excess mortality eculizumab resulted in 34.42 life years, which in turn, had a great impact on eculizumab total costs compared to ravulizumab where the difference in life years with respect to the ERG base-case was only 0.01.

Table 7.12: ERG scenario analyses with BTH excess mortality

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Eculizumab	[redacted]	34.32	[redacted]		0.75	[redacted]	£124,433
Ravulizumab	[redacted]	35.07	[redacted]	[redacted]			

Source: economic model.[41]
Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

7.3 ERG's preferred assumptions

The ERG preferred changes to the updated company base-case were described in Section 7.1.2 of this report. The cost effectiveness results of the ERG preferred base-case are presented in Table 7.13 in four steps. In each step, the cumulative impact on the model results is shown. Additionally, in Table 7.14, the individual impact of each change on the model results is shown.

Table 7.13: ERG's preferred model assumptions – cumulative impact on results

Preferred assumption	Section in ERG report	Ravulizumab		Eculizumab		Inc. Costs (£)	Inc. QALYs	Cumulative ICER (£/QALY)
		Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
Company base-case (after clarification)	6.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ravulizumab dominates
ERG change 1: no eculizumab up-dose	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,798
ERG change 2: utilities (treatment arm as covariate)	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,538
ERG change 3: utilities (no additional utility benefit for treatment frequency)	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£37,474
ERG change 4: ravulizumab 10mg vial	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,290

Based on the CS and the electronic model of the CS.[1, 41]
Abbreviations: ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; Inc. = incremental; QALY = quality adjusted life year

Table 7.14: ERG's preferred model assumptions – individual impact on results

Preferred assumption	Section in ERG report	Ravulizumab		Eculizumab		Inc. Costs (£)	Inc. QALYs	Cumulative ICER (£/QALY)
		Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
Company base-case	6.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ravulizumab dominates
ERG change 1: no eculizumab up-dose	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,798
ERG change 2: utilities (treatment arm as covariate)	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ravulizumab dominates
ERG change 3: utilities (no additional utility benefit for treatment frequency)	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ravulizumab dominates
ERG change 4: ravulizumab 10mg vial	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ravulizumab dominates

Based on the CS and the electronic model of the CS.[1, 41]
Abbreviations: ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; Inc. = incremental; QALY = quality adjusted life year

7.4 Conclusions of the cost effectiveness section

The company developed a state transition model in Excel with eight BTH-related health states, one mortality-related health state, and a spontaneous-remission health state. Two main types of BTH events were considered in ALXN1210-PNH-301 and ALXN1210-PNH-302 and included in the model: incomplete C5 inhibitor-related BTH and CAC-related BTH. Additionally, undetermined BTH events, defined as those deemed to have neither incomplete C5 inhibition nor concomitant infection, were considered as CAC-related BTH events in the analyses. In UK clinical practice, an increased dose of eculizumab is used to manage BTH events. However, eculizumab dosing changes were not allowed in ALXN1210-PNH-301 and ALXN1210-PNH-302. In order to include eculizumab up-dosing in the economic model, the company assumed in their base-case analysis that CAC-related BTH events were managed with one single up-dose in both treatment arms. Incomplete C5 inhibition-related BTH events were only modelled in the eculizumab arm. A single eculizumab up-dose was assumed for the first two incomplete C5 inhibition-related BTH events. A continuous up-dose was assumed for the rest of the model time horizon after a second incomplete C5 inhibition-related BTH event.

Three different patient cohorts were included in the economic analyses depending on whether patients were either complement inhibitor naïve (Cohort 1) or treatment experienced. Treatment experienced patients (and clinically stable on eculizumab) were classified as patients on the licensed dose of eculizumab (900mg – Cohort 2) and patients on a higher-than-labelled dose (1200mg – Cohort 3). Despite eculizumab dosing changes for patients who experienced BTH events not being allowed in ALXN1210-PNH-301 and ALXN1210-PNH-302, PNH National Service data suggests that an increased dose of eculizumab is used in UK clinical practice to achieve complete terminal complement inhibition in [redacted]% of the patients receiving label dose of eculizumab (900mg) treatment.[12-15, 38] Thus, Cohort 3 was included in the model to reflect the proportion of patients who receive an eculizumab dose greater than 900mg from the start of the model, which is consistent with UK clinical practice. This is the rationale for considering Cohort 3 in the "equal effectiveness" scenario, in which only CAC-related BTH events were included in the analysis. The proportion of patients in each cohort was estimated as [redacted] in Cohort 1 (treatment naïve patients) and [redacted] in Cohort 2 (treatment experienced and on eculizumab label dose). Only these two cohorts were included in the company's base-case. Additionally, in the "equal effectiveness scenario" the company assumed that a proportion of patients in Cohort 2 were allowed to start the simulation on higher-than-labelled eculizumab dose, thus in Cohort 3. Therefore, in the equal effectiveness scenario, the proportions of patients in each cohort were [redacted] in Cohort 1, [redacted] in Cohort 2 and [redacted] in Cohort 3.

The company used the data and the outcomes assessed in the two pivotal trials in the economic model for the different patient cohorts included. The base-case is aligned with the trial population and observed outcomes. Given that eculizumab was administered at its licensed dose in the pivotal trials, the efficacies of eculizumab and ravulizumab were taken directly from the respective clinical trials and treatment arms. However, up-dosing of eculizumab was included in the base-case analysis to reflect UK clinical practice.

HRQoL benefit in terms of utilities was assessed by mapping the QLQ-C30 to EQ-5D-3L. The company argued that the HRQoL benefit of ravulizumab could not be assessed in the trials and, therefore, used utility values in the cost effectiveness model that were sourced from a discrete choice experiment.

A list price of £4,533 per 300mg vial was approved for ravulizumab by the Department of Health and Social Care. A patient access scheme (PAS) price of [redacted] per 300mg for ravulizumab (representing

a discount of [redacted] on the list price) has been submitted by the company to reduce [redacted].[1]

The company's base-case results indicated that ravulizumab accrued [redacted] incremental QALYs and was cost saving compared to eculizumab. The disaggregated discounted costs by health state showed that the largest differences in costs across treatment arms were due to acquisition costs in the "No BTH" health state, which resulted in [redacted] difference for ravulizumab compared to eculizumab. However, these costs were outweighed by eculizumab due to patients requiring eculizumab up-dose. Thus, in the health state "continuous up-dose with history of incomplete C5 inhibition-related BTH event", the costs for eculizumab are [redacted], while there are no costs for ravulizumab in this health state (no incomplete C5 inhibition-related BTH events and no up-dose in the ravulizumab arm). This explains why in the company's base-case ravulizumab was cost saving compared to eculizumab. However, the proportion of time spent in the continuous up-dose health states across the complete model time horizon was [redacted]%, which is approximately twice as much as the [redacted]% reported by the company to be expected to receive an increased dose of eculizumab in UK clinical practice. As a consequence, the company's base-case results might be biased against eculizumab. The results of the additional scenarios presented by the company (including the PSA) did not change the conclusions drawn from the company's base-case.

The ERG is unclear how patients with undetermined BTH events were treated in the clinical trials. Therefore, the ERG was unable to judge the appropriateness of modelling undetermined BTH events as CAC-related BTH events. Also, the ERG feels that the rationale to assume to treat all CAC-related events with an eculizumab up-dose should have been better justified. With the evidence presented in the CS and the response to the clarification letter, the ERG preferred to assume that CAC-related BTH events would not be treated with an eculizumab up-dose, in line with what was observe in the clinical trials in which up-dose was not allowed.

As mentioned above, the ERG is concerned that the company's base-case analysis might overestimate the proportion of time spent in the continuous up-dose health states and consequently the results might be biased against eculizumab. In the "equal effectiveness" scenario, the proportion of time spent in the continuous up-dose health states *across the complete model time horizon* was assumed to be exactly [redacted]%, matching the PNH National Service estimate of the proportion of patients expected to receive an increased dose of eculizumab in UK clinical practice. This is the main reason why the ERG prefers the "equal effectiveness" scenario over the company's base-case. However, the ERG considers that it is up to the Committee to decide which scenario is clinically more plausible.

The ERG is also concerned that the sub-population of patients who would require an eculizumab up-dose might be underestimated in the trials. In response to clarification question B6,[19] the company explained that 11 out of a total of 219 patients (approximately 5%) in the trial population would need an eculizumab up-dose, which is approximately [redacted] lower than the [redacted]% estimate from the PNH National Service. This might indicate that the population in the trials was not representative of the UK population. Furthermore, the ERG wonders whether the conclusions from the trials, in which only 5% of patients would be "eligible" for an eculizumab up-dose, would be the same if there were approximately [redacted]% of patients who would need such an up-dose (as in UK clinical practice). The fact that only 5% of patients would be "eligible" for an eculizumab up-dose in the trials, as opposed to

approximately [redacted]% in UK clinical practice might indicate more severe disease in the UK treated population. Additional data may help reducing the uncertainty regarding this aspect of the analysis.

In conclusion, the ERG considers that the "equal effectiveness" scenario provides a better representation of UK clinical practice than the company's base-case scenario because it seems to overcome the main ERG concern regarding modelling eculizumab up-dose: the overestimation of the number of patients requiring an up-dose in the eculizumab arm. Nevertheless, the ERG is also concerned that the trial population might not be representative of the UK PNH population and, for that reason, the ERG prefers a base-case scenario based completely on the clinical trials, thus, with no eculizumab up-dose included in the model, even though it is acknowledged that this will not be completely representative of UK clinical practice. The ERG considers that, with the current evidence, neither the company base-case nor the equal effectiveness scenario would provide a better representation of UK clinical practice.

The ERG is also concerned about the company's assumption of a constant lifelong ravulizumab treatment effect. In response to clarification question B13,[19] the company refused to model a decline in treatment effect over time as this was not considered clinical plausible. However, it might be argued that data from over 10 years are available only for eculizumab and the long-term effects of ravulizumab are unknown. Given the time constraints associated to this project, the ERG was unable to run a scenario where a decline in treatment effect over time was included in the model. Additionally, the ERG could not validate the transition probabilities that the company derived from patient-visit-level data from the pivot trials, since the data needed for that were not provided to the ERG.

The ERG disagrees that HRQoL could not be assessed in the trial, as the administration frequency for ravulizumab was lower in the trial and substantial benefits, other than time of the patient, ought to be captured in the trial. Furthermore, the ERG argues that the methodological challenges of the discrete choice experiment outweigh its benefit as an external source for utility values. The ERG prefers a non-significant utility benefit of 0.0103 and 0.0197 from the trials ALXN1210-PNH-301 and ALXN1210-PNH-301 respectively for ravulizumab, derived from a mixed-effects regression model, as the source of HRQoL benefit in the cost effectiveness model and prefers not to use the utility benefit for treatment frequency of 0.057 as derived from the discrete choice experiment.

The company indicated that the regulatory review of two new vial sizes (3mL and 11mL) containing 100mg/mL of ravulizumab is ongoing with marketing authorisation expected to extend to these vial sizes by [redacted]: £4,533 for 3mL vial (100mg/mL), £16,621 for 11mL vial (100mg/mL). 100mg/mL formulation was used in the model base-case analysis as this formulation is expected to be approved by the time of the first appraisal committee meeting. The company also indicated that the increased drug concentration in these new vial sizes reduces the infusion times for ravulizumab. With the new vial sizes, the minimum infusion time is expected to range from 25–45 minutes for the loading dose and 30–55 minutes for maintenance doses.[26] The company assumed that the administration time for each infusion of ravulizumab 100mg/ml (infused at a 50mg/ml concentration) would be reduced to approximately the same administration time as each infusion of eculizumab. However, the ERG prefers to use the currently licensed 10mg/mL formulation in the ERG base-case analysis.

In response to the ERG clarification questions, the company made several changes to the originally submitted model. However, these changes did not have any impact on the base-case results except for the updated cost for transfusion administration. The impact was negligible. Additionally, the ERG changed various assumptions with respect to the company's base-case. The most important deviation

from the company's base-case was to assume no eculizumab up-dose to align the cost effectiveness analyses with the clinical trials. As mentioned above, the ERG acknowledged that this assumption is not completely representative of UK clinical practice. However, as the company stated in the CS, the majority (about [redacted]%) of PNH patients in UK clinical practice are managed at the standard eculizumab dose for whom an additional eculizumab up-dose is not needed. Additionally, the ERG proposed a different approach to utilities under the assumption that the ravulizumab quality of life benefit due to reduced treatment frequency might be captured by the treatment effect coefficient included in the mixed-effects regression equations used by the company to estimate utilities. This also implied that the additional ravulizumab utility for reducing treatment frequency, which was estimated from an external DCE and included in the company's base-case, was not used (set equal to 0) in the ERG preferred base-case. Finally, for the cost calculations, the ERG assumed the currently licensed 10mg/ml ravulizumab formulation, as opposed to 100mg/ml assumed by the company. The impact of this assumption was minor. These changes led to a situation where ravulizumab was not cost saving compared to eculizumab, unlike the company's base-case. The ICER from the ERG base-case was £38,290, obtained from the estimated [redacted] incremental QALYs gained by ravulizumab at an incremental cost of [redacted] compared to eculizumab. The differences with respect to the company's base-case were mostly explained by the assumption of no eculizumab up-dose. The ERG also conducted a PSA based on its preferred assumptions. The probabilistic ICER was £46,976 per QALY gained (incremental costs were [redacted] and incremental QALYs were [redacted]), thus, £8,686 larger than the ERG deterministic ICER. The ERG considers that this relatively large difference might be explained because the ERG PSA allows a (small) proportion of patients in the ravulizumab arm to transition to the incomplete C5 inhibition-related BTH events related health states. The CE-plane showed approximately [redacted]% of the simulations in the south eastern quadrant, in which ravulizumab is dominant. The remaining simulations were in the north eastern quadrant. The CEAC showed that the probability of ravulizumab being cost effective was [redacted]% (as opposed to [redacted]% in the company's PSA) at a threshold ICER of £30,000 per QALY gained. The ERG also conducted additional scenario analyses to explore important areas of uncertainty in the model. These key uncertainties were related to the so-called "equal effectiveness" scenario, utilities and BTH mortality. Other sources of uncertainty were deemed less important and were not explored in this section. The results of these analyses showed that when eculizumab up-dose was included in the analysis, ravulizumab becomes a cost saving (and more effective) option compared to eculizumab. These analyses highlight the large impact that the proportion of patients treated with eculizumab up-dose has on the overall cost effectiveness results, even though this sub-population represents a minority (approximately [redacted]%) of the total PNH patients. The other assumptions tested by the ERG had an impact on the model results only when up-dose was not included in the analyses, thus under the ERG preferred assumption. The choice of non-zero values for the additional ravulizumab utility for reducing treatment frequency, had a relatively large impact on the ERG preferred base-case ICER. When the value estimated from the DCE and used by the company in their base-case, was used (0.057), the ICER decreased to £11,790 and when this utility value was halved (0.029) the ICER was £17,688. Thus, in both cases below the £30,000 threshold ICER. Finally, when excess mortality risk of BTH events was added to the ERG preferred analysis, by applying a hazard ratio of 4.81 to patients experiencing BTH events, sourced from the Korean PNH registry by Jang et al. 2016,[36] the ICER increased to £124,433. This scenario highlights the impact of BTH excess mortality on the ERG base-case results. Additional data from the ALXN1210-PNH-301 and ALXN1210-PNH-302 trial Extension Phases reporting clinical outcomes up to 104 weeks are expected to be available in [redacted]. When the new data become available, the company will conduct an analysis of overall survival, which might be useful in reducing the uncertainty regarding BTH excess mortality.

The ERG feels it is important to emphasise that throughout the CS and the responses to the clarification letter, the company have made it clear that 'up-dosing' is only necessary in approximately [redacted]% of the population and that most patients would achieve an adequate terminal complement inhibition on the licensed eculizumab dose. However, despite being a minority, the assumptions about patients who would require an eculizumab up-dose are the main driver of the cost effectiveness results, as shown in Chapter 7 of this report.

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Appendix 1: Derivation of the transition probabilities in the cost effectiveness model

As explained in the CS,[1] trial data allowed for the identification of BTH events that occurred since the previous visit, and information on the type of event experienced. Events were 'adjudicated' to take one of the following five values: 1) 'Free C5 ≥0.5 µg/mL', 2) 'Free C5 ≥0.5 µg/mL and CAC', 3) 'CAC', 4) 'Undetermined' or 5) 'Missing value' (i.e. not 'adjudicated').

Internal clinical experts were consulted by the company to confirm the meaning of 'adjudication' values and it was concluded that BTH events were classified as missing values when a patient experienced a BTH event in the previous visit, and the event had continued. In these instances, missing values were imputed to reflect the most recent adjudicated event. Based on this, BTH events were subsequently assigned to one of the following three health states: 1) No BTH – no BTH event occurred, 2) Incomplete C5 inhibition-related BTH – a BTH event occurred and was associated with adjudication of one of: 'Free C5 ≥0.5 µg /mL' or 'Free C5 ≥0.5 µg /mL and CAC', or 3) CAC-related BTH – a BTH event occurred and was associated with adjudication of one of: 'CAC' or 'Undetermined'.

As depicted in Figure 5.1 of this report, in the model, a patient's history of incomplete C5 inhibition-related BTH impacts the likelihood of experiencing a subsequent BTH event. Consequently, separate transition probabilities were estimated conditional on whether a patient had a history of incomplete C5 inhibition-related BTH events. Persistence of incomplete C5 inhibition-related BTH events was defined as the probability of an incomplete C5 inhibition-related BTH event in the current cycle of the model, conditional on having experienced an incomplete C5 inhibition-related BTH event in the previous cycle (i.e. whether there is a history of incomplete C5 inhibition-related BTH). This was not relevant to the company's "equal effectiveness scenario" but it was modelled in the company's base-case analysis based on the persistence data observed in the clinical studies ALXN1210-PNH-301 and ALXN1210-PNH-302.

Transitions to initial CAC-related BTH events

Transition matrices were constructed based on the observed probability of experiencing CAC-related BTH events. These were calculated using patient – visit-level data from the trials. The estimation model produced a transition equation for each (initial state–follow-up state) pair that related the predictors to the probability of transitioning, through the estimated coefficients of time between visits and treatment arm. The time-between-visits covariate was held constant at a value of 14 days, to generate two-weekly transition probabilities aligning with the model cycle length. Transition probabilities were calculated for both values of the treatment covariate, a binary indicator for whether the patient received ravulizumab or eculizumab in the randomised period (i.e. first 26 weeks) and the extension period (Week 27–52) of the clinical study.

Transitions to initial incomplete C5 inhibition-related BTH events

The company's base-case analysis included incomplete C5 inhibition-related BTH events in the eculizumab arm. The steps outlined above for CAC-related BTH were also applied for determining the transitions to initial incomplete C5 inhibition-related BTH events.

In the "equal effectiveness" scenario, the company assumed that the same clinical outcomes would be experienced in both treatment arms when the permanent eculizumab up-dosing, as per UK clinical practice, was used. Therefore, no incomplete C5 inhibition-related BTH events were modelled for either eculizumab or ravulizumab.

Transitions to subsequent incomplete C5 inhibition-related BTH events

In the company's base-case analysis, transitions to subsequent incomplete C5 inhibition-related BTH events (occurring when there is a history of previous BTH events) were also modelled. These transition probabilities differed from those observed for initial BTH events. The approach used to derive them is outlined below.

Transition matrices for *subsequent* incomplete C5 inhibition-related BTH events were determined in the same manner as for the *initial* incomplete C5 inhibition-related and CAC-related BTH event transitions, with the following exceptions:

- To determine the likelihood of subsequent incomplete C5 inhibition-related BTH events, the sample was restricted to patients with a history of incomplete C5 inhibition-related BTH events.
- Only observations that occurred after the first incomplete C5 inhibition-related BTH event were included in the estimation.
- These selection criteria substantially limited the sample for the ALXN1210-PNH-302 clinical study and, thus, could only be derived for ALXN1210-PNH-301.
- Since no patient in the ravulizumab arm of either clinical study experienced an incomplete C5 inhibition-related BTH event, the estimation was only performed for patients in the eculizumab arm.

This estimation allowed for two initial states, either 'No BTH' or 'Incomplete C5 inhibition-related BTH' and observed the subsequent health states from either of these starting states

Persistence of incomplete C5 inhibition-related BTH events

'Persistence' refers to the probability of experiencing an incomplete C5 inhibition-related BTH event in the current cycle of the model, conditional on having experienced an incomplete C5 inhibition-related BTH event in the previous cycle. This was modelled based on observed persistence in the trials.[23]

Duration of BTH (incomplete C5 inhibition-related and CAC-related) symptoms

In modelling the utility impact of incomplete C5 inhibition-related and CAC-related BTH events separately, the model accounts for the duration of each event type of event within the two-week model cycle. Specifically, the company assumed, based on internal medical opinion, that symptoms and complications of CAC-related BTH events would be incurred for the full cycle (14 days), and the duration of an incomplete C5 inhibition-related BTH event may be specified as between 1–14 days. CAC-related BTH events required an additional eculizumab dose until the infection or CAC has resolved. However, incomplete C5 inhibition-related BTH events occur in patients receiving eculizumab as a result of incomplete C5 inhibition.[16] This is often observed in the last one to two days of the 14-day dosing interval; a pattern that is repeated across dosing cycles. The assumed duration of an incomplete C5 inhibition-related BTH event is two days. Since the time from a BTH event at a given visit was not reported in the trials, the company consulted published literature to estimate the duration of symptoms and complications of an incomplete C5 inhibition-related BTH event. According to Kelly et al. (2008) and Brodsky (2014), BTH symptoms due to incomplete C5 inhibition often occurred one to two days before the next dose in a 14-day dosing schedule.[60, 61] By extrapolation, it was assumed that incomplete C5 inhibition-related BTH symptoms due to incomplete

C5 inhibition would last for two days in the base-case analysis. Variation of the duration was considered in sensitivity analyses.

Appendix 2: Probabilities of transfusions and estimation of units of RBC per transfusion

Table A2.1: Transfusion requirements – observed events by trial and treatment arm

		Trial ALXN1210-PNH-301		Trial ALXN1210-PNH-302	
		Eculizumab	Ravulizumab	Eculizumab	Ravulizumab
Patients not experiencing BTH					
Visits with no BTH		[redacted]	[redacted]	[redacted]	[redacted]
Visits with transfusion and no BTH		[redacted]	[redacted]	[redacted]	[redacted]
Prob. transfusion in 2-week period	Mean	[redacted]	[redacted]	[redacted]	[redacted]
	SE	[redacted]	[redacted]	[redacted]	[redacted]
Units of RBC per transfusion	Mean	[redacted]	[redacted]	[redacted]	[redacted]
	SE	[redacted]	[redacted]	[redacted]	[redacted]
Patients experiencing BTH					
Visits with BTH		[redacted]	[redacted]	[redacted]	[redacted]
Visits with transfusion and BTH		[redacted]	[redacted]	[redacted]	[redacted]
Prob. transfusion in 2-week period	Mean	[redacted]	[redacted]	[redacted]	[redacted]
	SE	[redacted]	[redacted]	[redacted]	[redacted]
Units of RBC per transfusion	Mean	[redacted]	[redacted]	[redacted]	[redacted]
	SE	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 28, Appendix P to CS.[21]
Abbreviations: BTH, breakthrough haemolysis; RBC, red blood cell; SE, standard error.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Ravulizumab for treating paroxysmal nocturnal haemoglobinuria [ID1457]

'*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 Tuesday 24 November 2020** 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 Eculizumab dosing in UK practice

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 31-32 ERG state that "the utilised doses of eculizumab in both trials was stated not to reflect UK clinical practice, which according to the CS, recommends a permanent escalation to at least 1200mg for maintenance dosing"	Please be clear that this is only for the minority of patients for whom the standard. licensed 900mg maintenance dosing does not provide complete complement inhibition and who therefore experience breakthrough haemolysis e.g. "utilised doses of eculizumab in both trials was stated not to *fully* reflect UK clinical practice, which according to the CS, recommends a permanent escalation to at least 1200mg for maintenance dosing *in the minority of patients for whom the licensed 900mg maintenance dosing does not provide complete complement inhibition*"	The current statement is incorrect and it is important that the naïve reader understands that permanent escalation of eculizumab dosing is applied when patients on the standard, licensed dose of eculizumab are experiencing breakthrough haemolysis due to incomplete terminal complement inhibition. Such dosing escalation in the minority of patients allows all patients to achieve complete terminal complement inhibition as observed with ravulizumab weight-based dosing.	The suggested change has been made.

Issue 2 Clarification question description

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 32 ERG state that "the ERG requested clarification regarding the justification of not administering a dose more typical of UK clinical practice"	Please delete this sentence.	This was not requested within the ERG clarification questions received. If it had been requested, our response would have been as follows: Incomplete terminal complement inhibition is treated variably in	For clarity, the text has been amended to: 'The ERG requested justification of why eculizumab administered at a dose that would be observed in UK clinical practice (i.e. allowing 'up-dosing' in patients with incomplete complement inhibition) might not be more

		different healthcare environments, based on the experience of the treatingt physicians. It always amounts to increasing the blood level of complement inhibitor to a level that would provide complete C5 inhibition for an individual patient, but there is no 'standard' approach to up-dosing. In the UK, common practice is to incrementally increase the dose until complete C5 inhibition is achieved and patients no longer experience breakthrough haemolysis events, but other options to control breakthrough haemolysis due to incomplete terminal complement inhibition include shortening of the eculizumab dosing interval. While adjusting the dose to an individual patient's needs can be done in clinical practice, the same is not true for a clinical trial, where one has to control for variables outside of the trial hypothesis.	effective than ravulizumab.'

Issue 3 Innovation description

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 26 ERG state "according to the company, ravulizumab is innovative because it represents	Please delete this statement	Suspect this has been left in from a previous report in error as this is not a statement relevant to the innovation of ravulizumab in PNH and is not something the company	We apologise for this error; the statement has been deleted.

the first opportunity to achieve an as yet unrealised objective of neoadjuvant treatment: to adapt subsequent treatment on the basis of tumour response to neoadjuvant therapy (CS, Section B.2.12)"		describe in Section B.2.12	

Issue 4 Potential inaccuracies in ERG model results presented

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 101 ERG Scenario analysis 2: Alternative utilities and ravulizumab formulation in the company's "equal effectiveness" scenario	Please check reported results. Company rerun of the model to validate results yields the same costs but different QALYs. Therefore, it is suspected that the reported ICER is incorrect	Clarification needed – suspect inaccurate result. Can you please provide us full information on what was changed if this is correct?	We thank the company for pointing this out. The QALYs shown in the ERG report correspond to Cohort 3 instead of the aggregated population. This has been corrected.
Page 17/Page 97/Page 109 Incorrect calculation. ICER and cost and QALYs presented do not match.	The written statements say: "The probabilistic ICER was [redacted] per QALY gained (incremental costs were [redacted] and incremental QALYs were [redacted]), thus, £[redacted] larger than the ERG deterministic ICER." Table 7.6, however, reports [redacted] incremental QALYs. Both calculations could not lead to the reported ICER • [redacted] = [redacted] • [redacted] = [redacted] (even thinking about	Clarification needed – at least one result is inaccurate	We thank the company for pointing this out too. The probabilistic ICER shown in the ERG report corresponds to the average across all simulated ICERs (PSA sheet column AK) instead of the ratio of average incremental costs by average incremental QALYS, as it should be. Reporting incremental QALYs as [redacted] seems like a reporting error. PSA results in Table 7.6

	rounding and using [redacted] doesn't get near the ICER reported) Please can you recheck these results and the description of outcomes on the cost effectiveness (CE)-plane.		were obtained from the economic model and they are correct, except for the ICER, which should be £46,976. We apologise for these errors which have now been corrected. The CE-plane and the CEAC figures are correct.

Issue 5 Clarifications needed

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 17/ Pag 92 Stated that "Ravulizumab currently licensed 10mg/ml formulation (instead of 100mg/ml)."	Please rephrase and remove strikethrough text "Ravulizumab currently licensed 100mg/ml formulation (~~instead of 100mg/ml).~~" Please could the ERG revise their basecase to use the 100 mg/ml formulation.	The 10mg/mL formulation will not be available in the UK where 100mg/mL vials only will be launched. The 100mg/mL vial has now been approved by the European Medicines Agency.[1]	Not a factual inaccuracy; the change in formulation was notified after submission of the ERG report. If further analyses are required by the committee/NICE technical team these can be considered during the technical engagement phase. The ERG would like to emphasise that, as shown in the ERG report (see e.g. Table 7.13), changing ravulizumab formulation has a minimal impact on the model results.
Page 31	Please include the italicized addition to the current status to clarify for the naïve reader why	Clarification needed	The requested clarifying text

The dosing of trials discussion does not acknowledge the rationale for differences in terms of comparator doses	the trials differed in terms of comparator doses: The trials differed in terms of comparator doses of eculizumab *due to the different populations enrolled*. ALXN1210-PNH-301 utilised 600mg induction doses on Days 1, 8, 15, and 22 and then increased to 900mg maintenance doses afterwards, while the ALXN1210-PNH-302 trial delivered 900mg of eculizumab all throughout *(as patients had received induction doses at least 6 months prior to enrolment)*.		has been added.
Page 40 Stated that "if the 95% CI for the mean difference also lies above zero or the 95% CI for the odds ratio also lies above one, then it also be concluded that ravulizumab is superior to eculizumab"	Please align to the CSR description of testing for superiority: "if noninferiority was established for all key secondary endpoints, then superiority was assessed using a closed-testing procedure using a 2-sided 0.05 test of significance for each parameter"	Clarification needed as the CI for the odds ratio lying above one on its own would not lead to an assessment of superiority due to the hierarchical testing procedure employed in the trials	The requested correction has been made.
Page 57 Stated that "The ERG is unclear why the company assumed that CAC-related BTH events were treated with a single eculizumab up-dose in the eculizumab arm, and with an additional dose of eculizumab in the ravulizumab arm"	Please rephrase and remove strikethrough text "The ERG is ~~un~~clear why the company assumed that CAC-related BTH events were treated with a single eculizumab up-dose in the eculizumab arm, and with an additional dose of eculizumab in the ravulizumab arm" The treatment of CAC BTH events is discussed in the CS, see Section B3.2.6. The assumption regarding treatment with a single up-dose of eculizumab was guided by discussions with clinicians in July 2018 during the model development phase and December 2018 during	Information was provided in the CS	Not a factual error. As explained on page 57 of the ERG report, with the information provided in the CS and in the response to the clarification letter, it is unclear why this assumption was made. The ERG considers that it is up to the Committee to decide upon the plausibility of this assumption. Nevertheless, the ERG would like to emphasise that, as

	the model validation discussion. In the July 2018 advisory board "*MB asked whether BTH should be separated into PK- and PD-induced. AH suggested that it should in the UK, because it is managed differently (PK would lead to indefinite up-dosing; PD would lead to a single additional dose*)." Note at this time PD events refer to CAC BTH events, PK events related to incomplete C5 related events. As the treatment of eculizumab was agreed at this advisory board it wasn't discussed in detail in December 2018, where focus was placed on ravulizumab "*Management options for BTH on ravulizumab were discussed for the cost-effectiveness model. The options considered were as follows: No action, An extra eculizumab dose, Variation of ravulizumab dose according to the SPC":* A decision was made to model a single dose of eculizumab in ravulizumab patients, as ethically no treatment is not an option when licensed treatments are available and, the SPC doesn't contain information on the safe treatment of CAC-related BTH.		shown in the ERG report (see e.g. Table 6.4 and Table 6.7), the proportion of time spent on CAC BTH related health states is almost negligible (less than [redacted]%). Therefore, the impact of this assumption on the model results is also expected to be minimal.
Page 57 Stated that "The same statement also suggests that there were other causes that triggered CAC-related BTH events, but it is not mentioned which ones and how these were treated"	Please rephrase and add text in italics "The same statement also suggests that there were other causes that triggered CAC-related BTH events, *these are described in response to clarification A6 and B11*" Full details on the triggers to CAC-related BTH	Statement regarding lack of information provision is incorrect	Not a factual error. The sentence refers to the statement on page 83 of the CS. We do agree with the company that additional information is provided in the response to the clarification letter, which is further

	are provided in response to clarification A6 and B11, please see Appendix A6 and Appendix B11, additional detail is provided in the publication Brodsky et al, 2020		discussed on page 57 of the ERG report.
Page 57 Stated that "This suggests that CAC-related events and incomplete C5 inhibition events might also occur simultaneously"	Please rephrase and remove strikethrough text ""~~This suggests that~~ CAC-related events and incomplete C5 inhibition events might also occur simultaneously" Full details on the BTH events are provided in response to clarification A6 and B11, please see Appendix A6 and Appendix B11, additional detail is provided in the publication Brodsky et al, 2020. In study ALXN1210-PNH-301, two patients, treated with eculizumab, were recorded as having concurrent CAC and incomplete C5 BTH. In study ALXN1210-PNH-302, one patient, treated with eculizumab, were recorded as having concurrent CAC and incomplete C5 BTH.	Information was provided	The requested correction has been made as follows: "Therefore, CAC-related events and incomplete C5 inhibition events might also occur simultaneously."
Page 61 Stated that: "However, the ERG is unclear why the company has reported the previous comparison "across the model time horizon of 20 years" and not across the complete model time horizon (55 years for Cohort 1 and 52 years for Cohorts 2 and 3) where the proportion of time spent in the	Supplying this information to provide clarification. The 20 years' time horizon was chosen as a reasonable approximation of available evidence. Eculizumab has been available for over 8 years now. Therefore, evidence is unavailable to estimate what proportion of time patients may be on increased dose over a lifetime horizon. A mid-point of 20 years was therefore chosen.	Clarification needed	Not a factual error. We thank the company for the additional clarification, but the suggested amendment relates to information provided after submission of the ERG report.

continuous up-dose health states is approximately two times larger”			
Page 61 Stated that “While the ERG has no reasons to disagree with this statement, the ERG is concerned that the sub-population of patients who would require an eculizumab up-dose might be underestimated in the trials and, therefore, these trial populations might not be representative for the UK”	Please rephrase and remove strikethrough text “~~While~~ the ERG has no reasons to disagree with this statement, ~~the ERG is concerned that the sub-population of patients who would require an eculizumab up-dose might be underestimated in the trials and, therefore, these trial populations might not be representative for the UK~~ There are no prognostic indicators, clinically or demographically available that can predict which patients require an eculizumab up-dose in advance of when they need it. This was discussed in the July 2018 Advisory board “*Physicians commented that there are no predictive factors for BTH and that weight and clone size are not predictive.”* Therefore, the suggestion that trial populations might not be representative on the basis of the trial protocol not allowing up-dosing is unwarranted	Inaccurate to suggest that the trial populations might not be representative in terms of the need for up-dosing on the basis of the trial protocol not allowing up-dosing	Not a factual error. We would like to clarify that our concern that that the sub-population of patients who would require an eculizumab up-dose might be underestimated in the trials is not based on the trial protocol not allowing up-dosing, but because, based on the trial data, approximately 5% of patients would need an eculizumab up-dose, instead of the [redacted]% expected in clinical practice. We do understand that there are no prognostic indicators, clinically or demographically available that can predict which patients require an eculizumab up-dose in advance. However, we consider that this does not invalid our concern, which in our opinion, might be relevant for Committee discussion.
Page 14/ Page 61/ Page 93/Page	Supplying this information to provide	Clarification needed	Not a factual error.

107 Stated that "Note that 11 out of a total of 219 patients is approximately 5% of patients in the trial population who would need an eculizumab up-dose, which is approximately [redacted] lower than the [redacted]% estimate from the PNH National Service"	clarification. Eculizumab has been available for over 8 years now. The proportion of patients continuously updosed [redacted] has taken at least 8 years to get to this point. This was discussed at both the July 2018 advisory board "*AH noted that [redacted] of patients receiving eculizumab do not have adequate blockage of compliment activity"* and the December 2018 advisory board. Therefore, evidence suggests that a comparison of the events rate observed over 6 months is not comparable to the current UK clinical practice eculizumab continuously updosed average is not appropriate.		We refer to the previous response.
Page 71 Stated that: "trial already shows no HRQoL benefit of the infusion frequency "	As noted elsewhere by the ERG there is a trend towards improved QoL as measured by the EORTC as well as the FACIT Fatigue – also the ALXN120-PNH-302 preference data show clear patient preference for reduced frequency. It is not surprising that statistical significance was not reached for HRQoL benefits given the small sample size available in the trials due to the ultra-orphan nature of the disease.	Factually inaccurate	Not a factual error. Patient preference data can reflect preferences for non-health benefits and hence do not provide evidence for HRQoL benefit. The trial data are insufficient to claim HRQoL benefit. 'Trends towards benefit' are recognized within the report but claiming HRQoL benefit (the opposite of the ERG statement) would be a false statement. However, we have amended the statement to be more specific: 'trial ~~already~~ shows no *statistically significant* HRQoL benefit of the infusion frequency'

Page 71 Stated that: “It is unclear why 0.057 was chosen.“	Supplying the information to provide clarification. The life expectancy attribute levels were chosen to be in a similar range to the typical time horizon used in time trade off research (e.g. 10 to 20 years is used in the valuation of EQ-5D). 12 years was used rather 10 because it divides up more easily for the levels. The highest level (12 years was chosen) as this is standard practice in TTO research.	Clarification needed	Not a factual error. We thank the company for their response, but the clarification does not address the issue. The clarification does not explain why the parameter estimate for the attribute of 12 years reduced life expectancy was chosen to calculate disutility rather than, for example, the parameter estimate for 8 years reduced life expectancy: TTO does not have a common practice of choosing the ’highest level’ attribute.
Page 71 Stated: “It is not clear why their life expectancy was not chosen “	Please delete this text “It is not clear why their life expectancy was not chosen “ The DCE study (report provided in response to clarification question B17), report provides detailed information related to the study design. The choice questions clearly state that depending on your choice your overall length of life will be reduced by 0, 4, 8 or 12 years. Participants were told that the disease was a life-long disease. If you take a treatment for a life long disease then it is reasonable to assume that you will need to continue taking that treatment for the rest of your life. So the choices did imply time spent with each of the attributes. If participant were told that they could expect to live for example 30 years to align with	Clarification needed	Not a factual error. We thank the company for their response, but the clarification does not address the issue. The use of a reduction in subjective life expectancy is in itself reasonable. The trouble lies in the calculation of disutilities that combines reductions in subjective life expectancy with a general population statistic. To clarify: The DCE asks respondents to trade in reductions in length of life, where length of life is not specified by based on

	reasonable life expectancy for the average trial participant then this would justifiably be considered unlikely by the majority of people (either too young to die or too old). This would set up a framing effect which would influence the results.		subjective life expectancy of the sample. It then uses a general population statistic to calculate QALYs: the national average life expectancy minus the mean age of the study. TO be consistent, the study should have asked respondents their subjective life expectancy, to make sure that the years that are traded-off can be related to subjective life expectancy. Also, the national statistic should have been age specific: life expectancy of older people is higher than life expectancy at birth. However, we have clarified the text as follows: "Secondly, the DCE calculated the disutility using the average 2015 UK life expectancy relative to the age of the sample, which may not align with the subjective life expectancy of the participants in the sample itself. It is not clear why their own subjective life expectancy was not measured and used to calculate disutilities".

Issue 6 Factual inaccuracies / minor edits

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 16 Inaccurate description. "*Also, the ERG feels that the rationale to assume to treat all CAC-related events with an eculizumab up-dose should have been better justified*"	Please rephrase to include text in italics and remove text sticked through. "Also, the ERG feels that the rationale to assume to treat all CAC-related events with *one single up-dose* ~~an~~ eculizumab ~~up-dose~~ should have been better justified"	Minor edit	The suggested edit has been applied.
Page 26/ Page 59 *"However, approximately* [redacted] *of UK PNH patients require an eculizumab dosing adjustment to achieve complete terminal complement inhibition and prevent the symptoms of their PNH and accompanying haemolysis to recur….. Therefore,"* - Key information has been omitted from this statement	Please add the following text, In some patients this was historically achieved by reducing the eculizumab dosing interval from 14 days to 12 days[1], whereas now the dose is adjusted incrementally until the optimal dose for a specific patient is reached. Terminal complement inhibition is usually controlled with 1200mg dosing, although a small proportion may require 1500mg or 1800mg per infusion	Minor edit	Not a factual inaccuracy; the suggested amendment relates to information provided after submission of the ERG report.
Table 4.3, Page 31 Transfusion units not in bold text	Please bold transfusion units text as this outcome was directly used in the economic modelling	Minor edit	The requested edit has been made.
Table 4.6, Page 37 Data presented from the International PNH registry introduced as June 2020 data in text and table title, and total	Please either reduce the table and present the June 2020 data for those characteristics that more recent data were available (as per Table 4 of the company response to clarification questions), or revise text and table labelling and total patient numbers to reflect the June 2019	Factual inaccuracy	The heading and accompanying text, for Table 4.6, have been amended to correctly describe the 2019 data presented.

patient numbers taken from these data but all characteristics presented from the June 2019 data (n=[redacted])	data currently presented.		
Page 37 Trial misspelt	Please correct the sentence: Therefore, there is a question about the generalisability of the trial populations to UK practice.	Minor edit	Typographical error corrected.
Table 4.8. Page 42 Dyspnoea data from Day 183 in the ravulizumab arm presented alongside abdominal pain data so all data below are misaligned	Please correct alignment of data presentation	Minor edit	This alignment error has been corrected.
Page 46 The number of patients who experienced an AE after switching from eculizumab to ravulizumab during the extension period reported as 119; this is the total number of patients, the correct figure is 89	Please correct the sentence to: The number of participants who had experienced an AE who had switched from eculizumab to ravulizumab during the extension period was 89 .	Factual inaccuracy	This error has been corrected.
Page 56 Stated that “Based on the information presented in the CS, the ERG is unclear how patients with undetermined BTH events were treated in the clinical trials. This was part of clarification question B11, but no clear answer	Please rephrase and remove strikethrough text and add text in italics ““Based on the information presented in the CS, the ERG is ~~un~~clear how patients with undetermined BTH events were treated in the clinical trials, *however clinical input for the company suggested that they are counted as CAC events*. ~~This was part of clarification~~	Factual inaccuracy Statement is incorrect, question B11 did not ask for this information and it was provided in the CS	Not a factual error. The ERG understands the modelling assumption regarding undetermined BTH events as CAC events. However, the sentence on page 56 of the ERG report refers to the clinical trials.

regarding undetermined BTH events was provided"	~~question B11, but no clear answer regarding undetermined BTH events was provided~~" BTH events of undetermined aetiology were identified as an uncertainty during the model development phase. The CS discusses undetermined BTH events under sections B3.2.6 (BTH classification) and B3.3.1. Additionally, undetermined BTH events were discussed in detail at the December 2018 advisory board for which full detail of the meeting minutes are provided. Based on clinical feedback received, undetermined BTH events were classed as CAC BTH events and were not associated with incomplete C5 inhibition (elevated C5 levels). Alexion only claim differentiation of BTH events due to incomplete C5 inhibition between ravulizumab and eculizumab Question B11 did not ask for this information. It asked within the context of both CAC related and undetermined BTH events taking place on the ravulizumab arm: "Please provide the time-to-event for both switchers and non-switchers and explain how the events were resolved." The response to clarification question B11 therefore didn't seek to reiterate clinical information already provided in the CS, rather to answer the question on why BTH events may still occur in patients using ravulizumab and provide the requested data.		Regarding question B11, we do realise now that its formulation might be unclear, but we were expecting that with "explain how the events were resolved" this (how undetermined events were treated in the trials) would have been covered. Again, we would like to emphasise that, as shown in the ERG report (see e.g. Table 6.4 and Table 6.7), the proportion of time spent on CAC BTH related health states is almost negligible (less than [redacted]%). Therefore, whether CAC events include also undetermined events, or whether these are modelled separately, is expected to have a minimal impact on the model results.
Page 57 Stated that "*Therefore, the ERG is*	Please remove this text. The CS states clearly that when patients with eculizumab are	Factual inaccuracy	The company is correct that the statement is inaccurate. It

*uncertain whether the approach of assuming that eculizumab was up-dosed would only capture the additional costs due to up-dosing but not the additional effects associated with up-dosed eculizuma*b"	continuously updosed they do not experience incomplete C5 BTH events, therefore, to suggest an additional cost is incurred without the consequent reduction incomplete C5 inhibition is incorrect		has been amended as follows: "Therefore, the ERG is uncertain whether the base-case approach to eculizumab up-dosing would completely capture the additional effects associated with up-dosed eculizumab, as there are no clinical data to validate the base-case results."
Page 68 Stated: "*In the ALXN1210-PNH-302 trial, global health in the ravulizumab arm was higher with a mean of 75.25 vs 57.51 in the eculizumab arm (Appendix R of CS, Table 31 and 32, page 96).[2]"*	Please rephrase and include text in italics and remove strikethrough text In the ALXN1210-PNH-302 trial, global health in the ravulizumab arm was higher with a mean of 75.25 vs *69.47* in the eculizumab arm (Appendix R of CS, Table 31 ~~and 32~~, page 96 and *Clarification question B14 Table 5 as amended).[2]"*	Factual inaccuracy	The requested edit has been made.
Page 79 "require eculizumab continuous up-dose, almost exclusively due to managing incomplete C5 inhibition-related BTH events, even though a small proportion is due to managing CAC BTH events	Please remove the strikethrough text, the text is misleading, CAC BTH is treated with a single dose of eculizumab. Note health state costs are inclusive of drug treatment costs. "require eculizumab continuous up-dose, almost exclusively due to managing incomplete C5 inhibition-related BTH events, ~~even though a small proportion is due to managing CAC BTH events~~	Factual inaccuracy	The requested edit has been made.
Page 101 ravulizumab is associated with incremental cost savings of	Please correct statement to match results ravulizumab is associated with incremental cost savings of [redacted]	Minor edit	This error has been corrected.

[redacted]			

Issue 7 Incorrect marking

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG response
Page 25	the company responded: "*UK clinical practice demonstrates that the majority of PNH patients (~[redacted]%) are managed*	the company responded: "*UK clinical practice demonstrates that the majority of PNH patients (~ [redacted]%) are managed*	This marking has been added.
Page 26	However, approximately [redacted]% of UK PNH patients require an eculizumab dosing adjustment to achieve complete terminal complement inhibition	However, approximately [redacted]% of UK PNH patients require an eculizumab dosing adjustment to achieve complete terminal complement inhibition	This marking has been added.
Page 32	The company stated that the majority (about [redacted]%) of PNH patients in UK clinical practice managed at the standard eculizumab dose of 900mg every two weeks.	The company stated that the majority (about [redacted]%) of PNH patients in UK clinical practice managed at the standard eculizumab dose of 900mg every two weeks.	This marking has been added.
Table 4.5, Page 36	Weight at first infusion data for both trials and haemoglobin., haptoglobin and aplastic anaemia data not marked up	These data should be marked as AIC as per CS Table 6	This marking has been added.
Table 4.10, Page 45	Percent change in LDH, change in FACIT-Fatigue score and Haemoglobin stablisation data not marked up.	These data should be marked as AIC as per CS Table 9	This marking has been added.
Table 4.11, Page 45	LDH-normalisation and change in FACIT-Fatigue score data not marked up.	These data should be marked as AIC as per CS Table 10	This marking has been added.
Page 59	"UK clinical practice demonstrates that the majority of PNH patients (~[redacted]%) are	"UK clinical practice demonstrates that the majority of PNH patients (~ [redacted]%) are managed at the standard dose of	This marking has been added.

	managed at the standard dose of eculizumab. However, approximately [redacted]% of UK PNH patients require an eculizumab dosing adjustment to achieve complete terminal complement inhibition	eculizumab. However, approximately [redacted]% of UK PNH patients require an eculizumab dosing adjustment to achieve complete terminal complement inhibition	
Page 70	[redacted]	[redacted]	This marking has been added.

1. Alexion Pharmaceuticals. Alexion Receives Marketing Authorization from European Commission for New Formulation of ULTOMIRIS® (ravulizumab) with Significantly Reduced Infusion Time. 2020. Available at: https://ir.alexion.com/node/22936/pdf. Accessed: 20 November 2020.
2. Versteegh MM, Leunis A, Luime JJ, et al. Mapping QLQ-C30, HAQ, and MSIS-29 on EQ-5D. *Med Decis Making*. 2012; 32(4):554-68.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Ravulizumab for treating paroxysmal nocturnal haemoglobinuria [ID1457]

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 Monday 11 January 2021**

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.
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- 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.

NICE National Institute for Health and Care Excellence

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 four 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)

1. Introduction to an increased PAS discount

Alexion is pleased to confirm that an increased PAS discount has been offered to NHS England for approval. 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. In both the cost-utility analyses and the equal effectiveness scenario presented in the company submission, the incremental cost-effectiveness ratio (ICER) remains dominant. Cost savings are increased by £[redacted] and £[redacted], respectively, representing absolute per-patient cost savings of between £[redacted] and £[redacted] to NHS England. Importantly, the ICER remains dominant or within standard thresholds for cost-effectiveness applied in England (£20,000 per quality-adjusted life years [QALY]) across all company and ERG scenarios (see Section 4).

It is hoped that this increased discount alleviates any initial uncertainty around the cost-effectiveness of ravulizumab, and can enable a positive recommendation in the 10 March 2021 Appraisal Committee Meeting (ACM), avoiding any further unnecessary delay in 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 trial populations to UK patients	**NO**	Alexion maintains that the patient populations in the ALXN-PNH-301 and ALXN-PNH-302 trials are representative of the UK patient population. UK patients were enrolled across both studies in the Phase III programme, with a significant participation in the ALXN-PNH-302 study where 20% of patients were from the UK, representing the largest single country cohort in the study. Having probed during the technical engagement call, the ERG concerns on generalisability appear to stem from naïve comparison of UK patients enrolled to the International PNH Registry, with the characteristics of patients enrolled to the ravulizumab clinical trials, with particular reference to disease severity based on major adverse vascular event (MAVE) rates and history of aplastic anaemia. Appropriate caution should be applied when making such comparisons as evolutions within the management pathway over the 10+ years since these programmes were initiated are likely to have impacted the baseline characteristics

		of patients enrolled. Indeed, we heard from the clinical expert at the technical engagement call that these differences can be readily explained and do not indicate a lack of generalisability of the trial data. The clinical expert noted that a difference in MAVE rates would be expected given that in modern practice, PNH patients in the UK are treated based on symptoms, rather than waiting for a thrombotic event to occur. The clinical expert also advised that aplasia is probably present in most PNH patients but might not be diagnosed in up to two-thirds of patients; data for this characteristic is therefore unlikely to be accurate and thus not appropriate to make comparisons upon. We have acknowledged the higher rate of Asian patients enrolled to the ravulizumab trial programme than we would see in UK practice. There is no known evidence that treatment effects of complement inhibitors would be impacted by race/ethnicity and subgroup analyses of ALXN1210-PNH-301 and -302 showed no significant differences (see Appendix E of the company submission). There are known differences in the average weight of Asian patients vs UK patients but weight is not a treatment effect modifier (as confirmed by the clinical expert at the technical engagement call) and we have used UK weight data in the modelling. In conclusion, there is no reason to believe the clinical trial populations have less severe disease than UK patients and are not generalisable, and as heard in the technical engagement call, clinical experts consider the trial populations “pretty representative” of patients treated in UK practice.

Key issue 2: Dosing of eculizumab	**NO**	It is well accepted that some patients need a higher than standard dose of eculizumab to achieve complete C5 inhibition and thus prevent breakthrough haemolysis (BTH) due to incomplete C5 inhibition. As noted by the clinical expert on the technical engagement call, this is attributed to the 'flat' nature of eculizumab dosing i.e. 900mg maintenance dose for adult patients regardless of weight. We clearly see how this dose of eculizumab does not maintain serum free C5 levels below 0.5 µg/mL for all patients in the ALXN1210-PNH-301 and -302 clinical trials (see Figures 8 and 11–13 of the Company Submission, Section B.2.6.1). The National PNH Service team in England therefore have a procedure for eculizumab dose escalation in cases of incomplete C5 inhibition, whereby patients with two incomplete C5 inhibition-related BTH events are permanently 'up-dosed' to a higher-than label dose of eculizumab.[2] The practice of up-dosing is not reflected in the eculizumab label and therefore could not be incorporated into the clinical trial protocols, which regulatory agencies dictated should align to label dosing. In the ALXN1210-PNH-301 and ALXN1210-PNH-302 clinical trials, C5 BTH events were observed only in the eculizumab arm (n=11)[3], with no BTH events due to incomplete C5 inhibition seen in patients receiving ravulizumab. The BTH events observed in the eculizumab arm would have triggered a dosing review in UK clinical practice and subsequent up-dosing for those patients deemed to have incomplete C5 inhibition in order to minimise the risk of further C5 BTH events.

		It is worth noting that in the clinical trial programme, patients received eculizumab for only 26 weeks before switching to ravulizumab and relatively low numbers of C5 BTH events were observed in the eculizumab arm over this 26-week period (6% in ALXN1210-PNH-301 and 4% in ALXN1210-PNH-302[3]). As the clinical expert explained during the technical engagement call, in clinical practice, where patients are receiving longer-term eculizumab treatment, inadequate C5 inhibition-related BTH events on standard dose eculizumab emerge over a 1-2 year period [see response to Issue 5]). The ravulizumab label dosing is weight-based to ensure all patients receive an appropriate dose of complement inhibitor to achieve complete and sustained C5 inhibition across the 8-week dosing interval, and thus prevent C5-related BTH events. Data from the ravulizumab clinical trial programme, based on mean free C5 concentration data and C5-related BTH events, demonstrate that when treated with standard (weight-based) ravulizumab, patients achieve complete and sustained C5 inhibition and thus do not experience C5-related BTH events. Indeed, no C5-related BTH events were observed in the ravulizumab arm of either the ALXN1210-PNH-301 or the ALXN-PNH-302 clinical trials over the first year of treatment.[3] Further, the clinical expert attending the technical engagement call reported he had seen no C5-related BTH events with over 5 years of ravulizumab use.

		As noted by the clinical expert at the technical engagement call, eculizumab and ravulizumab are essentially the 'same' drug (they share 99% homology and the same mode of action) and the difference seen with regard to BTH is not so much driven by difference in efficacy, but reflects the extended bioavailability of ravulizumab, due to the modifications in its structure which allow for 'recycling ' of the active compound that leads to a longer half-life, as well as the weight based dosing, to provide complete and sustained inhibition of C5. The submitted cost-utility analysis and equal effectiveness scenario both model the English clinical practice of up-dosing and acknowledge these dosing differences and the impact on BTH due to incomplete C5 inhibition events. In contrast, the ERG base case ignores English clinical practice and fails to acknowledge the impact of BTH due to incomplete inhibition. The ERG base case, in which all patients receive long-term label dose eculizumab while only experiencing the same rates of C5-related BTH events seen in the short-term clinical trials (~5%), is not clinically plausible. In a scenario without up-dosing, data from real world practice shows that approximately [redacted]% of patients treated long-term with eculizumab standard dose would experience C5-related BTH events. Therefore, in the ERG base case, the impact of incomplete C5 inhibition in the eculizumab arm in terms of costs, QALYs, morbidity and mortality are underestimated. Additionally, ERG not modelling a single up-dose of eculizumab, as part of the treatment of CAC-related BTH events, in either

		treatment arm, ignores an essential part of the emergency clinical care of PNH patients, during CAC-related BTH events. It should however be acknowledged that even if the ERG base case does not change to reflect clinical practice, with the new PAS offered by Alexion (representing a [redacted]% discount on list price), ravulizumab is Dominant in comparison to eculizumab in both the equal effectiveness and cost utility analysis (i.e., more effective [providing more QALYs] and cost saving). The company's submitted cost-utility base case models the observed clinical trial outcomes while also incorporating English clinical practice dosing; this model assumes that after two incomplete C5 inhibition-related BTH events, patients would be treated with eculizumab at a continuously higher dose than the licensed dose. Health outcomes are expressed in terms of quality-adjusted life-years (QALYs), and cost components included are those associated with drug acquisition and administration, BTH event management and blood transfusions. This analysis demonstrated that ravulizumab is dominant versus eculizumab. This analysis, when modelling English clinical practice, calculates a proportion of patients up-dosed consistent with current clinical practice after a period of 20 years. It is acknowledged that the lifetime proportion of time up-dosed is uncertain, therefore we have provided a way to test this below (see Key issue 4). The company's submitted equal effectiveness scenario analysis is consistent with the non-inferiority trial designs and incorporates eculizumab dosing consistent with

		English clinical practice, with [redacted]% of eculizumab-treated patients receiving a higher than licensed dose. In this scenario, inclusion of eculizumab up-dosing means incomplete C5 inhibition-related BTH events in eculizumab-treated patients are not observed. The scenario assumes that if all patients currently treated with eculizumab, including patients on a higher-than-licensed dose, switch to ravulizumab, no patient would experience an incomplete C5 inhibition while on treatment, consistent with the observed outcomes for ravulizumab in ALXN1210-PNH-301 and ALXN1210-PNH-302. This analysis demonstrates that ravulizumab is cost saving when compared with eculizumab in English clinical practice. From the outset of our engagement with NICE, Alexion has acknowledged the evidence gap with regard to 'switching' higher-dose eculizumab patients to ravulizumab. There is a Phase IV proof-of-concept study (ALXN1210-PNH-401) approved to formally investigate this in the UK with patients stable on high-dose eculizumab planned to switch to ravulizumab and observed for 52 weeks but initiation of the trial and patient recruitment has been delayed due to the COVID-19 pandemic. While there are no published trial data yet available, anecdotal evidence supporting the safe switch of such patients has been received from markets where ravulizumab is already commercially available (US, Germany, Japan) and we are starting to see some case studies published that support the use of ravulizumab in these patients. Fureder and Valent reported in August 2020 in HemaSphere a

		case where a “standard” ravulizumab dosing-interval of 8 weeks was sufficient in a patient previously treated with a double standard 1800mg dose of eculizumab.[4] The clinical expert clearly stated at the technical engagement call that the clinical community would not want to see further delays to patient access to ravulizumab because of lack of data in the high dose cohort of patients.
Key issue 3: Short follow-up in the trials	**NO**	Data from the ALXN1210-PNH-301 and ALXN1210-PNH-302 trial Extension Phases reporting outcomes up to 52 weeks are available and included in the company submission. Longer-term safety data are provided from earlier phase clinical trials in the company submission (Appendix F). There are also reports on longer-term use shared by UK patients and clinicians involved in the ravulizumab clinical trial programme (see response to Issue 8). Further data from the ALXN1210-PNH-301 and ALXN1210-PNH-302 trial Extension Phases reporting outcomes up to 104 weeks are expected to be available in [redacted]. We do not anticipate that these data will be available in time to inform current decision making. However, if we were able to get early sight of the data, we may be able to submit a clinical addendum to these responses at a later date, prior to the ACM in March.

Key issue 4: Appropriateness of the company's base-case analysis	**YES**	Alexion maintains that the base case analysis, which reflects the UK practice of up-dosing, is appropriate for consideration of the NICE decision problem. UK clinicians have more than 15 years' experience of treating PNH patients with eculizumab, gained during the clinical development programme and subsequent to the licensing of the drug. The PNH registry has collected safety and effectiveness data for eculizumab over the past 8 years. The proportion of patients continuously up-dosed ([redacted]%) based on UK PNH registry data reflects an 8-year time horizon. However, the proportion of patients continuously up-dosed is uncertain in the long term beyond this. We heard from the clinical expert at the technical engagement call that a slight increase to [redacted]% was seen in this proportion in the latest data from the UK PNH Service. The ERG's key concerns related to a discrepancy between the calculated long-term proportion of patients up-dosed over the cost utility model time horizon of 55 years ([redacted]%) and the observed proportion of up-dosed patients as seen in UK clinical practice ([redacted]%), which was used in the equal effectiveness scenario. The ERG noted that due to this discrepancy, the equal effectiveness scenario was preferred over the cost utility analysis. Acknowledging the uncertainty here, we have adjusted the submitted cost-effectiveness model to reflect a scenario where the proportion of patients continuously up-dosed approximates [redacted]% across the model time horizon of 55 years. Additional scenarios were modelled where the proportion of patients

		continuously up-dosed was set to either 5.0% or 29.0%, corresponding to the upper and lower estimates of up-dosed patients available from the literature.[5-8] The probability of a first incomplete C5 inhibition-related BTH event was adjusted, via separate multipliers applied to the transition probabilities for cohort 1 (treatment naïve) and cohort 2 (treatment-experienced) patients. The multipliers were estimated as follows: 1. The aggregate population estimate of [redacted]%, was divided into the proportional contributions from cohort 1 ([redacted]%) and cohort 2 ([redacted]%) a. The proportional contribution is based on the proportion of patients in Cohort 1 ([redacted]%) and Cohort 2 ([redacted]%) multiplied by the aggregate population estimate. 2. A Goal seek function was used to estimate a multiplier such that the proportion contribution of cohort 1 equalled [redacted]%- = [redacted] 3. A Goal seek function was used to estimate a multiplier such that the proportion contribution of cohort 2 equalled [redacted]%- = [redacted] 4. The multipliers were separately applied to the first incomplete C5 inhibition BTH event transitions for eculizumab for cohort 1 and cohort 2 to calculate an aggregate population estimate of [redacted]%

		A similar method was used to calculate multipliers such that the aggregate population estimate equals either 5.0% or 29.0%, which corresponds to the upper and lower estimates of updosed patients available from the literature. [5-8] The multiplier adjustment is controlled via a switch on the 'Inputs' sheet ('Inputs'!H140). The adjustment to the probability of a first incomplete C5 inhibition BTH event is implemented on the 'BTH & Transfusion probs' sheet. ('BTH & Transfusion probs'!$AY5:BM28). The adjustment assumes that there will be no change in the ([redacted]%) proportion of patients up-dosed in the future. With this adjustment, and based on the revised PAS, the cost-utility analysis remains dominant, with an incremental cost saving of £[redacted]. These cost savings are similar to the reported savings in the equal effectiveness scenario but are slightly lower due to slow accrual of up-dosed patients over time and discounting. When the adjustment models the upper (29%) or lower (5%) proportion of patients who experience BTH and hence are up-dosed on eculizumab, as detailed in the literature, the ICER remains dominant with cost savings ranging from £[redacted] - £[redacted].
Key issue 5: Appropriateness of the company's "equal effectiveness" scenario	**NO**	As noted above, the ERG has acknowledged they consider the equal effectiveness scenario is the more plausible clinical scenario presented; Alexion welcomes this. The equal effectiveness scenario is also designed to reflect the UK clinical practice of up-dosing, in which approximately [redacted]% of patients require a higher than label

		dose of eculizumab. These data are considerably more robust in terms of real-world dosing of eculizumab in the UK compared with the trial data. At the technical engagement call, we heard the clinical expert describe how the current proportion of patients needing up-dosing would have emerged over a 1-2 year time period; this explains why the proportion of patients with BTH due to incomplete C5 inhibition in the 26-week period of the trial is lower than that seen in clinical practice. In their report, the ERG wonders whether the "conclusions from the trials in which only 5% of patients would be eligible for an eculizumab up-dose would be the same if there were approximately [redacted]% of patients who would need such an up-dose." As detailed in our response to Issue 2, the ERG conclusions in this analysis are not clinically plausible. The clinical outcomes and conclusions of the equal effectiveness analysis should only be considered for a patient population receiving eculizumab long-term. Irrespective of clinical plausibility, with the revised PAS discount, ravulizumab remains a Dominant and cost-saving treatment option compared with eculizumab in both the ERG and the company equal effectiveness analysis (see Section 4).
Key issue 6: Generalisability of the ERG base-case to UK clinical practice	**NO**	The ERG notes a preference for a base case scenario based completely on the clinical trials, thus, with no eculizumab up-dosing included in the model and incomplete C5 inhibition BTH events modelled as per observations in the 26 week controlled trial periods. The ERG acknowledges, however, that such a base case

		scenario is not reflective of clinical practice. We heard from the clinical expert at the technical engagement call that patients receiving a higher dose of eculizumab should certainly not be excluded from the modelling or from consideration by the Committee. As detailed in our response to Issue 2, the ERG base case ignores English clinical practice and fails to acknowledge the impact of BTH due to incomplete inhibition and in doing so underestimates the impact on costs, QALYs, morbidity and mortality in the eculizumab arm of the model. The ERG base-case also does not account for the UK approach to managing other BTH events (undetermined or CAC-related [see response to Issue 9]). Moreover, it does not acknowledge the benefits of ravulizumab dosing to patients and carers, which are directly related to their time and therefore not captured in the treatment effect utility estimates from clinical trial HRQoL data (see response to Issue 7). Additionally, as discussed at technical engagement the ERG base-case includes the ravulizumab 10 mg/ml formulation, which will not be launched commercially in the UK, over the ravulizumab 100 mg/ml formulation. This decision was due to the 10mg/mL being the only formulation with regulatory approval at the time of the ERG review; the 100mg/mL formulation, however, was approved by the EMA in November 2020 and therefore should be included in the base case. While this does not have a large impact on the economic case, it is an issue of importance to

		patients as the infusion times with the 100mg/mL formulation is much lower than with the 10mg/mL formulation. For example, infusion time for a maintenance dose (3300 mg) for a patient weighing between 60 – 100 kg. is approximately 40 minutes with the ravulizumab 100 mg/ml formulation, compared with 120 minutes using the ravulizumab 10 mg/ml formulation.[9] The maintenance dose infusion time with the 100mg/mL formulation of ravulizumab approximates the infusion time for a maintenance dose of eculizumab (35 minutes ±10 minutes).[10] Infusion times for the 100mg/mL formulations are detailed in the ravulizumab SmPC.[9] In light of the above issues, Alexion believes that the ERG base case is not reflective of UK clinical practice and does not capture the full HRQoL benefit offered by ravulizumab, and therefore requests that it is adjusted to reflect a more appropriate analysis. If, however, the suggested changes to the ERG base case are not accepted, with the revised PAS offered by Alexion ([redacted]% discount), in the current ERG base case analysis, ravulizumab in comparison with eculizumab is Dominant.
Key issue 7: Health-related quality of life	**NO**	The substantial benefits of the reduced infusion frequency described in the patient submissions and by the clinical expert at the technical engagement call were directly related to the significantly reduced level of engagement required between the patient and their carers and the health care system. Due to the clinical trial design, which required patients in both eculizumab and ravulizumab arms to attend

		appointments on the same schedules, the full extent of this benefit could not be captured in the trial-reported HRQoL analyses. This was acknowledged by the ERG who nonetheless excluded any additional benefit from their base case analysis. Some examples of the burden described by patients/carers, relating to the 2-week infusion need of eculizumab, were: restrictions on making plans, travelling, work (including the ability to work); negative impact on social and family life; and the constant reminder of illness. Such burden would not have been reduced in the clinical trials due to protocol-denoted assessment needs outside of the infusion but will be reduced in clinical practice. The impact on patients of reduced frequency of regular infusions is considered in the company submitted model based on outputs from a discrete choice experiment (DCE), whereby the general public was asked about their willingness to trade various treatment attributes. Alexion believes the DCE was a well-conducted study and has already published an abstract and will follow up with further publications. In addition, Alexion provided the full details of the study as requested by the ERG. Despite our confidence in the DCE study, we do recognise the inherent uncertainty in the approach and as such had included scenario analyses in our submission, applying a utility increment of 0.025, 0.05 and no utility increment; the utility increment presented in the company's submitted economic base case was 0.057.

		Given the uncertainty, Alexion accepts that the true utility impact of ravulizumab over eculizumab likely falls somewhere between the Alexion base case estimate and the ERG's assumption of zero additional utility benefit beyond that observed in the clinical trial. During the technical engagement call, the ERG appeared to agree that this is likely, but indicated they had wanted to take a conservative approach in their base-case given the uncertainty.
Key issue 8: Ravulizumab treatment effect duration	**NO**	In the patient submissions we note a comment from a patient that they have had really good symptom control with no infections or BTH in 3 years with ravulizumab treatment. We also heard from the clinical expert at the technical engagement call that there are ravulizumab data for up to 5 years available for some UK trial patients with no signs of antidrug antibodies or a waning treatment effect and that he was comfortable that ravulizumab is safe and effective over the longer term based on the data available. In the absence of extensive data beyond 52 weeks for ravulizumab at this time (see response to Issue 3), eculizumab data are used to inform longer-term assumptions of treatment effect (efficacy and safety); these data give no indication of any waning of treatment effect over time, showing the rate of events such as BTH and transfusions remain reasonably constant over time.[5, 11, 12] The clinical expert concurred that they had observed no treatment waning with eculizumab over his 15+ years of experience across the clinical development programme and in clinical practice.

		This approach is considered appropriate as ravulizumab was derived from eculizumab: the technologies share over 99% homology, the same mode of action and have proven non-inferiority across the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials. There are, therefore, no biological or clinical rationale as to why the long-term effects of these two complement inhibitor treatments would differ. At the technical engagement call, we heard from the clinical expert that they are comfortable that ravulizumab is safe and effective over the longer term based on the data available, and from the NICE technical team that the described approach to modelling ravulizumab treatment effect duration over the longer-term seemed reasonable and biologically plausible.
Key issue 9: Treating undetermined and CAC-related BTH events	**NO**	BTH, characterized by the return of intravascular haemolysis and reappearance of classical PNH symptoms may occur due to suboptimal C5 inhibition, and/or due to complement-amplifying conditions (CACs) such as infection, surgery, or pregnancy that may lead to increased complement activation resulting from higher C3b density. In the ALXN-PNH-301 and ALXN-PNH-302 studies, BTH events were categorized as the following: (1) temporal association that is free C5–related, defined as BTH associated with time-matched occurrence of free C5 ≥0.5 µg/mL; 2) complement amplifying condition–related, defined as BTH due to an inciting event (e.g. infection, trauma, or surgery); or (3) BTH unrelated to elevated C5 and without a reported time-matched complement-amplifying condition.

		In UK clinical practice, CAC-related BTH events or undetermined BTH events are typically treated with an additional single dose of eculizumab or by shortening the dosing interval. In the case of a CAC-related BTH, the underlying infection is also treated.[13, 14] At the technical engagement call, we heard from the clinical expert that it is reasonable to expect that these BTH events are treated differently to incomplete C5 inhibition-related BTH events given their temporal nature. Also, it is reasonable to expect them to be treated the same way irrespective of whether a patient is on ravulizumab or eculizumab. In the cost-utility analysis, significant clinical consultation was completed to understand the aetiology of BTH events observed in the clinical trials and classify them and their treatment correctly. Classification of incomplete C5 inhibition events and CAC-related BTH events was consistent with the clinical trial protocols. Classification of the undetermined BTH events was also discussed with clinicians. After further internal clinical consultation, it was decided that these events should be treated as CAC-related BTH events in the cost-utility analysis, based on the absence of incomplete C5 inhibition. These conclusions and assumptions were further discussed and validated at two advisory boards, one during model development, in July 2018[13], and one in preparation for UK reimbursement discussions in December 2018.[14]

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: Scenario analysis 5: ERG base-case with BTH excess mortality	**Section 1.7.2 ERG scenarios (pg. 16), Section 1.7.3 Conclusion (pg. 17)** Section 7.1.3 Additional scenarios conducted by the ERG (pg. 93) **Section 7.2.3 Results of the ERG additional exploratory scenario analyses (pg. 100/101)**	NO	At the technical engagement call, the clinical expert highlighted that in the UK, BTH due to incomplete C5 inhibition does not have any mortality impact, though this may result from current UK clinical practice. The ERG scenario was presented based on a scenario initially provided in the company submission only to illustrate model sensitivity to assumptions around mortality and provide a worst-case estimate. Inclusion of this excess BTH mortality scenario was not intended as a clinically reliable scenario, however, as there are multiple issues with the data source that make it non-generalisable to the UK PNH patient population. There is limited evidence to accurately model any minimal excess mortality risk of BTH events and no published evidence is available for an eculizumab-treated UK PNH population. The

	Section 7.4 Conclusions of the cost effectiveness section (pg. 107)		scenario was therefore based on data from a study by Jang et al, (2016), which was the only published analysis identified.[15] The Jang study was a retrospective analysis of 301 Korean PNH patients with active PNH disease who had not received eculizumab. The latter point makes the data non-generalisable to the UK, where the use of eculizumab has considerably reduced BTH frequency and therefore associated mortality. Therefore, the inclusion of this scenario alongside the ERG base case, which, in itself, is not a clinically reliable scenario, cannot be considered a reliable cost effectiveness estimate.

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 ICER
Key Issue 4	Patients treated with eculizumab moved to continuous up-dosing of eculizumab following two incomplete C5 BTH events, based on the events rates calculated from the ALXN-PNH-301 and ALXN-PNH-302 clinical trials and following UK clinical practice guidance.	The probability of an incomplete C5 inhibition-related BTH event was reduced such that the lifetime proportion of patients up-dosed approximated [redacted]%	Dominant The ICER remains Dominant.

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 table below.

	Original PAS discount			Increased PAS discount			Impact
	Incremental QALYs	**Incremental costs**	**Submitted ICER**	**Incremental QALYs**	**Incremental costs**	**Revised ICER**	
Cost - utility analysis	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	Dominant The ICER remains Dominant. Cost savings have increased by £[redacted]
Company's preferred base case following technical engagement. Equal effectiveness.	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	Dominant The ICER remains Dominant, incremental QALYs are

(At the clinically stable dose of eculizumab, patients do not experience BTH due to incomplete C5 inhibition, the proportion up-dosed is [redacted]% corresponding to UK clinical practice).							decreased by [redacted] and incremental costs have decreased by £[redacted] compared to submitted base case
ERG change 1: no eculizumab up-dose (key issue 6) (ERG report Table 1.11/Table 7.13)	[redacted]	[redacted]	£14,798	[redacted]	[redacted]	Dominant	Dominant The ICER is now Dominant. Cost savings have increased by £[redacted]

ERG change 2: utilities treatment arm as covariate (key issue 7) (ERG report Table 1.11/Table 7.13)	[redacted]	[redacted]	£11,538	[redacted]	[redacted]	Dominant	Dominant The ICER is now Dominant. Cost savings have increased by £[redacted]
ERG change 3: utilities no additional utility benefit for treatment frequency (key issue 7) (ERG report Table 1.11/Table 7.13)	[redacted]	[redacted]	£37,474	[redacted]	[redacted]	Dominant	Dominant The ICER is now Dominant. Cost savings have increased by £[redacted]
ERG preferred base case analysis (ERG report Table 1.11/Table 7.3/Table 7.13)	[redacted]	[redacted]	£38,290	[redacted]	[redacted]	Dominant	Dominant The ICER is now Dominant.

							Cost savings have increased by £[redacted]
ERG Scenario analysis (ERG report Table 7.7: ERG scenario analyses on Cohort 3 [5%] patients in the equal effectiveness scenario)	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	Dominant The ICER remains Dominant. Cost savings have increased by £[redacted]
ERG Scenario analysis (ERG report Table 7.8: ERG scenario analyses on alternative utilities and costs in the equal effectiveness scenario)	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	Dominant The ICER remains Dominant. Cost savings have increased by £[redacted]

ERG Scenario analysis (ERG report Table 7.9: ERG scenario analyses on alternative utilities and costs in the company's base-case)	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	Dominant The ICER remains Dominant. Cost savings have increased by £[redacted]
ERG Scenario analysis (ERG report Table 7.10: ERG scenario analyses with alternative utilities – decrement 0.057)	[redacted]	[redacted]	£11,790	[redacted]	[redacted]	Dominant	Dominant The ICER is now Dominant. Cost savings have increased by £[redacted]
ERG Scenario analysis (ERG report Table 7.11: ERG scenario analyses with	[redacted]	[redacted]	£17,688	[redacted]	[redacted]	Dominant	Dominant The ICER is now Dominant.

alternative utilities – decrement 0.029)							Cost savings have increased by £[redacted]
ERG Scenario analysis (ERG report Table 7.12 ERG scenario analyses with BTH excess mortality)	[redacted]	[redacted]	£124,433	[redacted]	[redacted]	£12,404	£12,404 per QALY. The ICER is now cost-effective at £20,000 per QALY. Cost savings have increased by £[redacted]
ERG's preferred model assumptions – individual impact on results ERG change 1: no eculizumab up-dose	[redacted]	[redacted]	£14,798	[redacted]	[redacted]	Dominant	Dominant The ICER is now Dominant.

(ERG report Table 7.14)							Cost savings have increased by £[redacted]
ERG's preferred model assumptions – individual impact on results ERG change 2: utilities (treatment arm as covariate) (ERG report Table 7.14)	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	Dominant The ICER remains Dominant. Cost savings have increased by £[redacted]
ERG's preferred model assumptions – individual impact on results ERG change 3: utilities (no additional utility benefit for treatment frequency) (ERG report Table 7.14)	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	Dominant The ICER remains Dominant. Cost savings have increased by £[redacted]

ERG's preferred model assumptions – individual impact on results ERG change 4: ravulizumab 10mg vial (ERG report Table 7.14)	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	Dominant The ICER remains Dominant. Cost savings have increased by £[redacted]

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NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Ravulizumab for treating paroxysmal nocturnal haemoglobinuria [ID1457]

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 **Monday 11 January 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 paroxysmal nocturnal haemoglobinuria (PNH) and current treatment options

NICE National Institute for Health and Care Excellence

About you	
1.Your name	Alex Naylor
2. Are you (please tick all that apply):	**X** a patient with PNH? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with PNH? **X** a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	PNH Support
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) **X** 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 **X** I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	**X** 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:

	X 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 PNH? If you are a carer (for someone with PNH) please share your experience of caring for them.	I was diagnosed in 2017, after a routine blood test flagged further investigation. It took six months of tests before being diagnosed. Within days of meeting the PNH Team at King's College Hospital I started on eculizumab at the standard dose (900mg IV). After three or four months I was still suffering from anaemia, fatigue and tests showed that the dose wasn't high enough to have a suitable effect on my disease. My prescription was increased to 1200mg and shortly afterwards I became pregnant. Early into my pregnancy I decided that I was too fatigued to work. My pregnancy was closely managed as it is considered high risk due to the heightened risk of thrombosis in a PNH patient; during this time my eculizumab dose was increased twice more (1500mg in second trimester and 1800mg in third trimester). I had one blood transfusion and a case of suspected meningitis during my pregnancy. After the birth of my child (July 2018) my eculizumab dose was brought down to 900mg but was again increased to 1200mg after a number of infections which brought about breakthrough haemolysis. During these infections I would be treated with additional eculizumab and antibiotics. The chronic symptoms of anaemia, fatigue, cognitive issues (language processing, memory loss), insomnia and breathlessness were always present. Having a small infant and these symptoms have meant that I wasn't in a position to return to work. In autumn of 2019 I noticed that I had worsening abdominal bloating and pain, and issues with my digestion; along with further regular infections that were treated with

	additional eculizumab and antibiotics. In spring 2020 my regular dose of eculizumab was increased to 1500mg in an effort to boost my energy levels and alleviate the symptoms mentioned above and to help stave off further infections. This was then amended to 1200mg on a 12 day cycle, instead of the standard 14 day cycle, in an effort to 'tweak' the dose to my benefit. The management of my condition and physical health mean that I regularly suffer from anxiety and at times can become depressed. Investigative hospital visits can leave me mentally and physically exhausted and I often need a day of rest to recoup. The frequent IVs and necessary blood tests that are needed have left me with scarring in multiple places in my veins. I regularly have to have 3-4 pricks before a suitable vein is found and this happens every 12 days. I have chronic fatigue, anaemia and cognitive issues, insomnia and joint pain as well as abdominal issues which are thought to be linked to low nitric oxide levels and smooth muscle dystonia. I'm not in a position to work more than a handful of hours per week in order to manage my nurse visits (to administer eculizumab at home), frequent hospital visits and maintain a steady state of health and energy that is required with a young family. I sorely miss my ability to work as it gave me a sense of worth and independence and would allow me to provide for my family as well as educating my son in the importance of work, self development and ambition.
Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for PNH 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. Personally, eculizumab has been life changing and the care I have received from the PNH specialists has always been excellent. However, from my experience, having only one treatment pathway isn't suitable for all patients and therefore an unmet need. Having to advocate for oneself when dealing with other healthcare professionals who don't know of PNH, especially when ill, is very very hard. 7b. My views and experience are in line with the majority of patients I have met.

8. If there are disadvantages for patients of **current NHS treatments** for PNH (for example how the treatment is given or taken, side effects of treatment etc) please describe these	The psychological burden of managing the fortnightly IVs is a huge disadvantage, closely followed by the physical effects of scarred veins, and the energy peaks and troughs before and after an IV. All the aspects of coordinating one's nurse visits at home are a disadvantage: when will the medication be delivered, when will the nurse arrive, arranging parking permits for nurses, cleaning an area for the nurse to work in, disposing of the packaging and waste after the appointment, managing work commitments and meetings around the nurse's visit.
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? 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.	9a. The advantages seem limitless. Having spent 3+ years planning my life in fortnightly, and more recently 12 day cycles, the possibility of having an 8-weekly IV is mindblowing. I could potentially forget that I have an incurable disease if my health stayed positive. I would be able to work full time, study, change career and care for my family without always thinking about planning my next IV or managing the related fatigue. As a family we could plan for a holiday that would be longer than 10 days (as is our current preference, as it allows for possible breakthrough haemolysis following travel). I currently limit myself to UK-based and occasionally short haul flights due to this concern as well. 9b. Self-care and care of my family. This is the most important advantage to me because when I am ill and suffer from my PNH all of my family (immediate and extended) is impacted in a ripple effect (childcare, hospital visits, time off work, stress of the entire situation). When I am well, the pressure on the rest of my family diminishes; my husband doesn't need to take time off, neither of us needs to rely on family and friends to help with childcare, housework, navigating and advocating during hospital visits. Time and energy isn't spent on communicating my needs or recuperating and focusing on getting well again. 9c. Ravulizumab can overcome the issues mentioned in question 8 by simply being required less often - having an IV every eight weeks (56 days) rather than 12-14 days. The disadvantages listed won't directly improve but having to

	encounter these disadvantages less often (4-4.5 times less) would immediately make me feel less stressed, anxious and ill, and this would have a positive impact on my state of health.
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.	None that I am aware of.
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. 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	N/A
Equality	

12. Are there any potential equality issues that should be taken into account when considering PNH and treatment? Please explain if you think any groups of people with PNH 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 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.	N/A
Other issues	

13. Are there any other issues that you would like the committee to consider?	N/A

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 ravulizumab for patients? If there are several benefits please list them in order of importance. Are there any benefits of this treatment that have not been captured? b. What are the benefits of this treatment for carers?	I refer to a survey conducted by PNH Support of PNH patients and carers and submitted as part of this appraisal on 8 September 2020 (from pages 253 to 296 of the TE papers) which noted the following: 14a. Main benefits to patients who have received ravulizumab: i. Improved symptom control (anaemia, fatigue, breakthrough haemolysis, cognitive issues) ii. Positive impact of 8 weekly IV against fortnightly IV iii. Psychological benefits and improved mental health 14b. Benefits for carers where patients have received ravulizumab: i. Positive impact of 8 weekly infusions: positive impact on family life due to improved energy levels of the patient, ability to plan and less disruption as a result of 8 weekly infusions; positive psychological impact

	as a result of the 8 weekly infusions and less anxiety for the carer caused by fortnightly infusions; independence provided by 8 weekly infusions due to being less intrusive and having the ability to plan more freely, travel and take holidays and give the patient independence; and positive impact of 8 weekly infusions on patient's employment which made work easier to manage ii. symptom control: improved or stayed the same when compared to eculizumab
15. Are there any important issues that have been missed in ERG report?	The impact and potential benefits on the wider economy and society when patients are well enough to work. A patient receiving eculizumab on a fortnightly IV cycle and who isn't working could potentially have a very different level of engagement with employers, business and society more widely compared to a patient receiving ravulizumab on an eight weekly IV cycle. There would be less visits needed to administer the drug (cost of homecare nurse, cost of courier to deliver drugs, etc.). If the patient were in good health and had improved symptom control there could potentially be less hospital visits required.

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- I was diagnosed with PNH in 2017 and have been treated with eculizumab on a 12-14 day cycle since then. I have had varying doses of 900mg, 1200mg and 1500mg.
- The duration and frequency of administering eculizumab brings a heavy psychological burden on patients and carers.
- Many patients consider the treatment and care provided by the PNH National Service to be excellent. Treatment with eculizumab has many advantages however some have unmet needs including breakthrough haemolysis, fatigue and other symptoms that require additional management.

- The two main advantages of receiving treatment with ravulizumab is that it offers better symptom control and the longer period between doses (8 weekly cycle) means a positive impact on the burden of treatment that many patients feel.
- The above mentioned advantages impact on patients and carers, bringing a positive change to quality of life. Impacting on their interaction with and contribution to society, especially a sense of independence and ability to work.

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.

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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.

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NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Ravulizumab for treating paroxysmal nocturnal haemoglobinuria [ID1457]

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.

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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.
-

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NICE National Institute for Health and Care Excellence

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- Your response should not be longer than 15 pages.

PART 1 – Living with or caring for a patient with paroxysmal nocturnal haemoglobinuria (PNH) and current treatment options	
About you	
1.Your name	Maria Piggin
2. Are you (please tick all that apply):	**x**☐ a patient with PNH? **x**☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with PNH? x☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	PNH Support
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) x☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement x☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement x ☐ I agree with it and **will be** completing

5. How did you gather the information included in your statement? (please tick all that apply)	x☐ I am drawing from personal experience. x☐ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: I founded and have managed the PNH Support patient group (www.pnhuk.org) since 2015 and been interacting with PNH patients closely since then. I founded and am the Chair of the PNH Global Alliance – an umbrella group of international PNH patient organisations which was established in 2018 (www.pnhgobalalliance.com). x☐ 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 PNH? If you are a carer (for someone with PNH) please share your experience of caring for them.	I was diagnosed with PNH in New Zealand in 1997 after approximately 3 years of investigations. At that time there was no treatment and I never met another PNH patient until years later. I moved to the UK in 2001 and was under the care of University College Hospital London until being referred to the PNH National Service. I was assessed for suitability to be treated with eculizumab in approximately 2009. At the time, it was decided that my symptoms were not severe enough that my quality of life would be improved by the burden of a 2 weekly eculizumab infusion. In mid 2013, my haematologist recommended that I be treated with eculizumab. My PNH symptoms pre- treatment with eculizumab included breathlessness caused by all levels of physical exertion including simple things such as walking up hills or climbing stairs. When undertaking exercise such as a moderately long bike ride, short run or long walk I would often experience severe abdominal cramps and nausea. Other symptoms were tiredness and fatigue, jaundice, stomach pain, headaches, dizziness and dysphagia which woke me at night and continued until lunchtime on a bad day and would also prevent me from

	drinking and eating. My cognitive ability also deteriorated including memory loss and word finding ability. I would spend a lot of time during weekends sleeping as I worked full time during the week. I was also acutely aware of the ever present risk of thrombosis. By 2013, I was receiving blood transfusions approximately every 3 to 6 months through haematology day clinics and whenever I got an infection such as food poisoning or a chest infection, I would also usually be admitted to hospital. I am lucky to have never experienced thrombosis or to have any collateral organ damage as a result of my PNH. PNH is a very individual disease and even though I have previously had a PNH clone of approximately 90%, many patients are affected much more severely than me. After commencing treatment with eculizumab in 2013, all my symptoms ceased except for variable levels of fatigue which continue today. The improvement to my quality of life was significant, however I am aware not all patients treated with eculizumab experience the same benefits. Even after commencing treatment with eculizumab, I was always anxious about acquiring an infection which could result in my symptoms reoccurring or breakthrough haemolysis. In 2015, I founded the charitable incorporated organisation, PNH Support (no. 1161518) as there was no independent patient group covering England and Wales and I was aware that an independent group was needed to order to engage appropriately with stakeholders. Scotland had established a group in approximately 2007. I am the chair of PNH Support and there are currently two other trustees (also PNH patient and family members). We have approximately 120 PNH patients and family members as official members and 250 who utilise our closed Facebook group. In 2017, I commenced the 302 trial with ravulizumab (randomised to the ravulizumab arm) and have been receiving it ever since. Having an infusion 8 weekly instead of 2 weekly has been life changing for me, not only because of the convenience of less infusions but also psychologically as I can essentially forget I have PNH for 8 weeks at a time. I also no longer have the anxiety of hoping that the 2 weekly infusion will happen in a timely fashion including: that it has been scheduled by the homecare company correctly; if the drug is

	being delivered separately, that it is delivered on time; that the nurse won't be stuck in traffic and will arrive on time; and that the nurse will be able to access a vein and not require a second nurse to attend prolonging the appointment by a number of hours. I don't have to juggle the 2 weekly infusion around my work or only work part time in order to accommodate it. I am also able to go on holiday for longer than 13 days at a time which has been especially valuable to me as my immediate family live in New Zealand. I find that my symptom control is essentially the same as when I was treated with eculizumab and I have had no breakthrough haemolysis when experiencing an infection whilst on ravulizumab which did happen on eculizumab. I still experience variable fatigue and also have some continuing cognitive issues like memory loss.
Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for PNH 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. <u>Excellent access to care and advice</u> I consider the care provided by the PNH National Service to be excellent. They are extremely accessible and available which has been especially relevant and appreciated during the pandemic as so many patients are anxious and in need of bespoke advice e..g whether they should have the COVID 19 vaccine. Even before the pandemic, the service was always accessible by phone or email to provide advice. This is especially valuable when many healthcare professionals don't know about PNH and need to consult with the Service when treating patients for other conditions they may have which may impact their PNH. <u>Advantage of home infusions</u> Being able to receive infusions at home is very valuable (and has mitigated risks posed by attending hospital during the pandemic). The PNH National Service liaise between the homecare companies which deliver the eculizumab and ravulizumab infusions to patients in their homes to ensure continuity of care and oversight over this process. <u>Excellent access to clinical trials and the benefit of research</u> PNH patients have excellent access to clinical trials of innovative therapies and also benefit from research being conducted by the Service. As a result, I was able to take part in the ravulizumab trial and I was also offered the choice of another trial at the same time.

	Burden of 2 weekly infusion with eculizumab When I was treated with eculizumab the 2 week treatment burden was high as I referred to at question 6 above. 7b. I am aware (from a recent survey of PNH patients and carers referred to in PNH Support's submission to this appraisal dated 8 September 2020 – from pages 253 to 296 of the TE papers) as follows: Treatment with eculizumab A number of patients noted the positive impact of being treated with eculizumab on their symptom control and their quality of life more generally. Value of home infusions Patients and carers surveyed also valued being able to receive infusions at home or work especially during the pandemic. Unmet need whilst being treated with eculizumab Surveyed patients commented on the limitations of treatment with eculizumab including the lack of, or diminishing, symptom control over the 2 week period. Surveyed patients and carers noted that the 2 weekly eculizumab infusion is a significant burden: in terms of psychological impact (of anticipating the smooth occurrence of the infusion; constant reminder of the disease); the logistics of the homecare visit (arrival of nurse, delivery of drug, ability to access a vein to administer the drug, impact on the veins of repeated cannulation); juggling the infusion around employment; childcare; the ability to make plans; participate fully in social and family life; and go on holiday for longer than 2 weeks. As a result, many would like different treatment options.
8. If there are disadvantages for patients of **current NHS treatments** for PNH (for example how the	Burden of 2 weekly infusion with eculizumab

treatment is given or taken, side effects of treatment etc) please describe these	Surveyed patients treated with eculizumab find the burden of the 2 weekly infusion significant. This burden includes organising their life (and their family's) around the 2 weekly infusion as well as their employment arrangements. Some patients don't tell their employers they have PNH and need a 2 weekly infusion for fear of discrimination which makes arranging the infusion more stressful. Some are unable to work full time as a result of the 2 weekly treatment burden. Other related issues experienced by patients with 2 weekly infusions are: the psychological impact (of anticipating the smooth running of the infusion; constant reminder of the disease); the logistics of the homecare visit (childcare; timely arrival of nurse, timely delivery of drug (if applicable), ability to access a vein to administer the drug (if this does not happen another nurse needs to attend which prolongs the visit); the ability to be free to make plans, and go on holiday for longer than 2 weeks. Unmet need whilst being with treatment with eculizumab Some surveyed patients treatment with eculizumab continue to experience fatigue and other symptoms which impact their quality of life including their ability to socialise, participate in family life and work full time or at all. Some patients need increased doses of eculizumab or more frequent infusions than 14 days. Some patients treated with eculizumab still require blood transfusions due to anaemia and extra vascular haemolysis. Impact of repeated cannulation on veins Some patients are affected by the negative impact of repeated cannulation on their veins.
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?	9a. Improved symptom control with ravulizumab Most surveyed patients who were being treated with ravulizumab reported improved symptom control and the remainder reported the same symptom control compared to treatment with eculizumab. I consider my symptom control on ravulizumab to be approximately the same as when I was being treated with eculizumab. I am aware from the ravulizumab trial data that less breakthrough haemolysis was experienced by patients, to which I can attest.

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.	<u>8 weekly infusion period</u> The ability to have an infusion every 8 weeks rather than 2 weeks has had a significant impact on my quality of life i.e. not having to fit these infusions into my life and not having the stress and anxiety of anticipating and organising these. I can now work full time and I essentially forget I have PNH for 8 weeks at a time. I can also go on holiday for longer than 14 days for which I am grateful as my immediate family live in New Zealand. These sentiments were also reflected in the surveyed patients being treated with ravulizumab. Patients noted their ability to work, their improved quality of life more generally, positive impact on family life and relationships, the positive psychological impact of the 8 weekly infusion and being able to forget about PNH for 8 weeks at a time. 9b. As my symptom control is the same with eculizumab and ravulizumab, I would say that the 8 weekly infusion is the most important advantage to me personally. However, for those patients surveyed, the most important advantage of ravulizumab is the improved symptom control compared to eculizumab because it increases their quality of life, permits them to participate more fully as contributing members of society through employment and enjoy a social and family life. 9c. Ravulizumab overcomes the burden of the 2 weekly eculizumab infusion as it is an 8 weekly infusion. Most patients on ravulizumab who were surveyed reported improved symptom control and the others experienced the same as treatment with eculizumab. Therefore ravulizumab may address the unmet needs of those patients who still experience symptoms whilst being treated with eculizumab. Ravulizumab reduces the number of times patients' need to be cannulated as this is an 8 weekly instead of 2 weekly infusion and will therefore reduce the negative impact on repeated cannulation.
Disadvantages of this treatment	
10. If there are disadvantages of ravulizumab over current treatments on the NHS please describe	N/A

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.	
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. 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	No.
Equality	
12. Are there any potential equality issues that should be taken into account when considering PNH and	N/A

treatment? Please explain if you think any groups of people with PNH 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 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 ravulizumab for patients? If there are several benefits please list them in order of importance. Are there any benefits of this treatment that have not been captured? b. What are the benefits of this treatment for carers?	I refer to a survey conducted by PNH Support of PNH patients and carers and submitted as part of this appraisal on 8 September 2020 (from pages 253 to 296 of the TE papers) which noted the following: 14a. <u>Patients being treated with ravulizumab</u> stated that the main benefits of ravulizumab are (in order of importance): 1. Improved symptom control: most surveyed patients reported they experienced fewer symptoms than when treated with eculizumab (e.g. improved blood counts; no infections or breakthrough haemolysis; less fatigue, consistent energy levels; no blood transfusions) and the remainder said their symptom control was the same as treatment with eculizumab 2. The positive impact of the 8 weekly infusion including: positive psychological impact (including working and contributing to society, reduction of stress associated with the 2 weekly eculizumab infusions and ability to forget about having the disease for period of time); improved quality of life generally as a result of the 8 weekly infusions (ability to exercise; be independent); positive impact on employment including being able to work full time, treatment being less disruptive of work and not requiring them to take sick days; and positive impact on social and family life including planning, being able to take holidays, less disruption and stress to partners and relationships.

	14b. Carers of patients being treated with ravulizumab stated that the main benefits of ravulizumab are (in order of importance): 1. Positive impact of 8 weekly infusions including: positive impact on family life due to improved energy levels of the patient, ability to plan and less disruption as a result of 8 weekly infusions; positive psychological impact as a result of the 8 weekly infusions and less anxiety for the carer caused by fortnightly infusions; independence provided by 8 weekly infusions due to being less intrusive and having the ability to plan more freely, travel and take holidays and give the patient independence; and positive impact of 8 weekly infusions on patient's employment which made work easier to manage 2. Improved symptom control than when treated with eculizumab (e.g. feels a lot better, more energy) or the same as with eculizumab
15. Are there any important issues that have been missed in ERG report?	The impact to the economy, and to society more generally, of a patient being treated with ravulizumab should be taken into account. Patients being treated with ravulizumab who experience improved symptom control will be able to return to work, or work full time, or otherwise contribute more fully to society e.g. caregiving or volunteering. Those patients who were prevented from working full time ,or at all, due to the restrictions of a 2 weekly infusion schedule will now be able to do so as a result of an 8 weekly infusion schedule. The ravulizumab 8 weekly infusion also allows family members of patients to contribute more fully to the economy and to society more generally through employment (which may have been limited or prevented by needing to care for a patient or take over a patient's caring responsibilities whilst they are having a 2 weekly infusion). Patients treated with ravulizumab have less contact with homecare nurses and may need to attend less hospital visits due to less breakthrough haemolysis and blood transfusions than those treated with eculizumab. This means their risk of being infected with coronavirus is reduced avoiding putting extra strain on the NHS and potentially negatively affecting their PNH resulting in a hospital admission.

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- I was diagnosed with PNH in 1997 and I founded PNH Support in 2015 which I continue to chair and run. I have been treated with ravulizumab for 3 years since 2017 and was treated with eculizumab for 4 years before that from 2013.
- Most PNH patients and carers recently surveyed by PNH Support considered the current treatment and care provided by the PNH National Service to be excellent. Treatment with eculizumab has impacted patients positively although some have unmet needs in terms of fatigue and other symptoms and extravascular haemolysis which requires treatment with regular blood transfusions.
- Surveyed patients and carers welcomed more treatment options as the burden of the eculizumab two weekly infusions on patients (and their families) was wide ranging and negatively impacted many facets of their lives including their employment, psychological health, family and social life, ability to plan and take holidays as well as caused damage to veins from repeated cannulation.
- The major advantage of ravulizumab to surveyed patients was the improved symptom control closely followed by the frequency of ravulizumab infusions (i.e. 8 weekly) which provide relief to the burden of the 2 weekly eculizumab infusions outlined above.
- The improved symptom control provided by ravulizumab and its infusion schedule permits patients and their families an improved overall quality of life and the ability to contribute to society more fully, especially in terms of employment.

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.

……

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The information that you provide on this form will be used to contact you about the topic above.

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☐ **Please tick this box** if you would like to receive information about other NICE topics.

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NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Ravulizumab for treating paroxysmal nocturnal haemoglobinuria [ID1457]

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 **Monday 11 January 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 paroxysmal nocturnal haemoglobinuria (PNH) and current treatment options	
About you	
1. Your name	**Austin Kulasekararaj**
2. Name of organisation	**King's College Hospital NHS Foundation Trust**
3. Job title or position	**Consultant Haematologist and Lead for King's National PNH service**
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 PNH? ☒ a specialist in the clinical evidence base for PNH 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 PNH	
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.)	- to avoid mortality and morbidity due to PNH - to stop end organ damage - prevent thrombosis and its complications - avoid and stop blood transfusions
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm,	- improvement in survival and QoL - reduction/stop thrombosis -reduce and abolish the need for blood transfusions

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 this condition?	• Patients- convenience of treatment (current treatment is fortnightly) and a stability/improvement in QoL • Physicians- better, complete and sustained complement inhibition, improvement in QoL and reduction in breakthrough haemolysis (BTH)
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	- PNH patients with eculizumab, if they have clinically significant haemolysis manifesting as thrombosis, transfusion dependency, anaemia and or end organ damage. -PNH patients who are pregnant are also treated during pregnancy and 3-6 months postpartum, despite not meeting all the above criteria - exceptional cases after discussion in multi disciplinary meeting
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	PNH national service guidelines
• 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.)	As PNH is a rare and ultra orphan disease, patients are predominantly managed in two NHSE commissioned PNH centres in England (London and Leeds). The approach to treatment is similar and coordinated between the two centres. All new patients starting on treatment are discussed in the national MDT between the centres,

• What impact would the technology have on the current pathway of care?	This would be a major change to the pathway of PNH patients, both currently on eculizumab and treatment naïve, as they would be treated with/changed to Ravulizumab. This would be of great benefit for patients in view of the reduced frequency of infusions, less BTH and better QoL/convenience of treatment.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
• How does healthcare resource use differ between the technology and current care?	• Markedly reduced use of healthcare resource, especially less visits by patients to health care settings due to less BTH and complications of the treatment • Reduced need for indwelling intravenous catheters • Less visits to patients' home by home care nurses for delivery of infusions (6 versus 26) (more pertinent in the current global climate due to COVID19 pandemic)
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics-PNH centres in England (London and Leeds)
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None, as all the existing systems will be used including home care nursing

13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, although the clinical data and trial data shows non-inferiority from the efficacy perspective, the less chance of BTH and the convenience of treatment for the patients due to less frequent infusions is the major advantage.
• Do you expect the technology to increase length of life more than current care?	Not known, although unlikely to be dissimilar to eculizumab. Please note complement inhibition with eculizumab has already improved the survival of PNH patients and survival of PNH patients on eculizumab is similar to age/sex matched controls
• Do you expect the technology to increase health-related quality of life more than current care?	Yes, in view of less frequent infusions compared to the SOC ie eculizumab Less BTH and hence likely to improve HRQoL
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Not tested in pregnancy and paediatric population Not trailed in patients on a higher dose of eculizumab, which constitutes approximately 20% of the patients in England
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	More easier to use - Less frequent cannulations

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.)	- No additional concomitant medications needed - Less need for frequent prescriptions ie every 8 weeks rather than 2 weekly (less administrative and nursing work regards scheduling), additionally less need to rearrange treatment due to failed cannulations, patient cancellations and unavailability of patients at the scheduled visits/time - -less exposure to health care professions both at home (less infusions) and in hospital (due to less BTH) All of this extremely important in the context of this prolonged global COVID19 pandemic
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	This is will be not specific to Ravulizumab and applies to any complement inhibition. If patients are having PNH clonal regression ie decline in PNH clone and achieves a clone of <10% with no evidence of haemolysis, the treatment would be stopped
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 the quality-adjusted life year (QALY) calculation?	As indicated the convenience of less frequent infusions for patients will translate into a number of benefits for patients – less days off work, less mental stress as two weeks comes around too often!, concern about failed cannulation at every visit, more productivity, ability to plan activities and life for patients, ability to plan travel and holidays, etc

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?	The current clinical need is met with eculizumab by improving both the survival and QoL, but Ravulizumab will sustain this improvement in survival, but will also improve QOL (due to less frequent infusions) and also less chance of BTH, and a sustained control of dysregulated complement compared to eculizumab.
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes, less chance of BTH compared to eculizumab and more convenience for patients
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?	No side-effects or adverse events (AE) are different between eculizumab and ravulizumab. Ie the new technology doesn't increase the risk of getting more AE. The risk of meningococcal meningitis is likely to be alos similar between the technologies
Sources of evidence	

20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	The main outcomes from the trial was adequate complement inhibition which was sustained and complete, which translated into control of haemolysi, less BTH and also improvement in QoL for PNH patients The trials were very large and compared with the existing standard of care ie eculizumab
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes
• 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	Ongoing data which are published regularly on the long term efficacy and safety of Ravulizumab in the trials (1 year data, as below), as currently patients have been on Ravulizumab for more than 3.5 years (real world data)

by a systematic review of the trial evidence?	Kulasekararaj AG, Hill A, Langemeijer S, Wells R, González Fernández FA, Gaya A, Ojeda Gutierrez E, Piatek CI, Mitchell L, Usuki K, Bosi A, Brodsky RA, Ogawa M, Yu J, Ortiz S, Röth A, Lee JW, Peffault de Latour R. One-year outcomes from a phase 3 randomized trial of ravulizumab in adults with paroxysmal nocturnal hemoglobinuria who received prior eculizumab. Eur J Haematol. 2020 Dec 10. doi: 10.1111/ejh.13564. Epub ahead of print. PMID: 33301613.
22. How do data on real-world experience compare with the trial data?	As above
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
23b. Consider whether these issues are different from issues with current care and why.	None
Topic-specific questions	
None	

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.	
Key issue 1: Generalisability of the trial populations to UK patients	- I disagree with this statement, as PNH is a very rare disease and the trials (301/302) are the largest trials in PNH conducted to date. The patient population across the globe is not dissimilar as was shown in the data published from the international PNH registry. - Additionally, 44/195 (23%) patients in the PNH302 came from UK, whilst the trial was open in many countries globally - Regards the PNH 301, 5/245 patients were from England and this is due to the rarity of the condition ie on an average the two PNH centres treat around 15-20 new complement inhibitor naïve PNH patients per year and to enrol 25% of them into a clinical trial is very reasonable Overall, as the inclusion criteria for the trials were uniform and there is no published evidence suggestive of geographical variability in manifestations of PNH across the globe, I would feel the trial population represents UK PNH population
Key issue 2: Dosing of eculizumab	Yes, agree that up dosing of eculizumab was not permitted in the clinical trials and approximately 20% of patients on eculizumab need a dose higher than the standard dose of 900mg.

	The PNH 302 study population only included patients on a stable dose of eculizumab for atleast 6 months and nearly 25% patients were from UK. The likelihood and need for increased dose (up dosing) of eculizumab in this group (as opposed to PNH301 study population) is very low or negligible. Could the analysis of cost effectiveness done just on the PNH 302 study population to nullify the overestimation of the benefits of ravulizumab as indicated by the ERG?
Key issue 3: Short follow-up in the trials	1) The 1-year efficacy data for the both the trials has been recently published and this shows the sustained response and confirmation of the 6 month data (ie primary end point) Schrezenmeier H, Kulasekararaj A, Mitchell L, Sicre de Fontbrune F, Devos T, Okamoto S, Wells R, Rottinghaus ST, Liu P, Ortiz S, Lee JW, Socié G. One-year efficacy and safety of ravulizumab in adults with paroxysmal nocturnal hemoglobinuria naïve to complement inhibitor therapy: open-label extension of a randomized study. Ther Adv Hematol. 2020 Oct 24;11:2040620720966137. doi: 10.1177/2040620720966137. PMID: 33178408; PMCID: PMC7592174. Kulasekararaj AG, Hill A, Langemeijer S, Wells R, González Fernández FA, Gaya A, Ojeda Gutierrez E, Piatek CI, Mitchell L, Usuki K, Bosi A, Brodsky RA, Ogawa M, Yu J, Ortiz S, Röth A, Lee JW, Peffault de Latour R. One-year outcomes from a phase 3 randomized trial of ravulizumab in adults with paroxysmal nocturnal hemoglobinuria who received prior eculizumab. Eur J Haematol. 2020 Dec 10. doi: 10.1111/ejh.13564. Epub ahead of print. PMID: 33301613. 2) I can also confirm (personal experience) that all the 33 patients treated in clinical trials in King's PNH centre with Ravulizumab are continuing the treatment and these patients have been on treatment for 4.5 years (longest follow up) and 3.5 years (shortest follow-up). No additional complications have been noted and there has been no decline in treatment effect.

Key issue 4: Appropriateness of the company's base-case analysis	Although updosing of eculizumab was not allowed in trial and it is a common UK clinical practice is to increase the dose in PNH patients with incomplete C5 inhibition BTH, it is also important to analyse and do the base case analysis on the available clinical trial data ie which did not allow updose. It is also possible, a variable proportion of patients on higher dose of eculizumab (ie the 20% UK population) could have had a dose increase due to other reasons ie the rigor of monitoring for incomplete C5 inhibition in clinical practice might be less compared to clinical trials. The 5% cases (11/219) of incomplete C5 inhibition with eculizumab in both the trials is lower, compared to UK data (20%), due to various reasons- short period (6 months) and also only enrolling stable patients in PNH302 trials
Key issue 5: Appropriateness of the company's "equal effectiveness" scenario	Difficult to comment on the two models, as a clinician!
Key issue 6: Generalisability of the ERG base-case to UK clinical practice	The data for Ravulizumab in the rare population (20%) who need a higher dose of eculizumab will hopefully be addressed in a planned upcoming trial PNH401 and anticipated to start in Q2 of 2021. It is likely patients who needed a higher dose of eculizumab due to suboptimal C5 inhibition is likely to be overcome by standard dose (weight based) Ravulizumab given every 8 weekly.
Key issue 7: Health-related quality of life	Unable to comment Need perspective from PNH patients
Key issue 8: Ravulizumab treatment effect duration	As indicated above, I would not assume a decline in the treatment effect over time with Ravulizumab similar to eculizumab. The patients on Ravulizumab in our centre have reached 4.5 years (longest) and 3.5 years (shortest) of follow-up and have not noticed any decline in treatment. Obviously, this is personal experience and unpublished data

	The important events during the disease course have been accounted spontaneous remission and baseline mortality related to age and unrelated conditions. The progression in the underlying bone marrow failure (BMF)- Aplastic anaemia and MDS, can require either additional treatment to Ravulizumab for their BMF or stopping of Ravulizumab if patients progress to require a stem cell transplant or PNH remission
Key issue 9: Treating undetermined and CAC-related BTH events	None of the BTH events in the trials was allowed to be managed with up dosing, single extra dose or shortening of the infusion intervals. The BTH events were allowed to remit naturally and follow the course, and infection/trigger related BTH were treated for the underlying infection. This is not practised in real world with eculizumab, as patients will have a additional dose given and/or dose interval shortened. If the BTH is recurrent, patients will go on a permanent increase in the dose of eculizumab. The incidence of undetermined BTH events in the trials and real world is uncommon and rare events. The clinical trials are always restrictive in any extra allowance to treat BTH I personally would agree to lump the undetermined BTH events along with CAC related BTH and would have also treated with a single extra dose of eculizumab
Are there any important issues that have been missed in ERG report?	Not specifically by ERG, but how would the panel consider the impact of COVID19 pandemic in this TA, as the advantage of less hospital attendance (due to less BTH) and less home care nurse attendance (due to 6-7 infusions versus 26) is extremely important in 2021 and beyond.

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- The trial population is representative of UK PNH patients
- The ongoing follow-up (upto 4.5 years) in clinical practice of Ravulizumab is reassuring and no treatment decline is noted
- The 20% UK population who need higher dose of eculizumab due to incomplete C5 inhibition would be included in the upcoming trial of Ravulizumab and other novel complement inhibitors in clinical trials. This population was not included in the PNH301/302 trials and no updosing of eculizumab was allowed in trials for 5% who experienced incomplete C5 blockage, and this might not have changed the efficacy but would have increased the dose/cost of eculizumab
- The substantial benefit from the patient perspective ie convenience and less frequent infusions of Ravulizumab is not reflected and highlighted in the ERG analysis. This is very crucial and one that the patients and physicians will give significant weightage, in view of the non-inferiority data

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 paroxysmal nocturnal haemoglobinuria [ID1457]

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 Monday 11 January 2021**

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)	PNH Support
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

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 trial populations to UK patients	N/A	No comment
Key issue 2: Dosing of eculizumab	N/A	No comment
Key issue 3: Short follow-up in the trials	NO	We understand that there will be data available from patients on the 301 and 302 trials from the end of the trials until now.
Key issue 4: Appropriateness of the company's base-case analysis	N/A	No comment
Key issue 5: Appropriateness of the company's "equal effectiveness" scenario	N/A	No comment
Key issue 6: Generalisability of the ERG base-case to UK clinical practice	N/A	No comment

Key issue 7: Health-related quality of life	NO	In relation to the frequency of administration point, the survey undertaken by PNH Support (and submitted as part of this appraisal process – see pages 258/259 of the TE papers) shows that one of the unmet needs of patients is the 2 weekly treatment burden of eculizumab infusions and that the patients who were receiving ravulizumab stated that one of the main advantages of the treatment was the 8 weekly treatment period.
Key issue 8: Ravulizumab treatment effect duration	NO	We would expect Alexion to be able to obtain data from their PNH Registry regarding spontaneous remission of patients on eculizumab which may be useful here.
Key issue 9: Treating undetermined and CAC-related BTH events	N/A	No comment

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: Base-case analysis miscellaneous costs and resource use	5 – see table 5.21	Yes	We note that many PNH patients pay for their own prophylactic antibiotics (when not taking part in a trial) rather than the NHS, however it is doubtful this will affect the model in a significant way. We also note that emergency antibiotics which patients are recommended to keep at home for use in case of suspected meningitis and which are paid for by the NHS are not included in this model, however it is doubtful this will affect the model in a significant way.

Additional issue 2: Measuring and valuing health effects.	3, see table 3.1, 5.2.2	Yes	We don't consider that the EORTC QLQ- 330 or the EQ -5D capture the impact of ravulizumab on a patient's employment status which we consider to be relevant. Patients surveyed by PNH Support who were being treated with ravulizumab noted a positive impact on their employment status i.e. being able to work full time, take less days off sick and work being less disrupted (see pages 259/260 of the TE papers). Although both quality of life tools refer to "usual activities" in their questions and the EQ- 5D states that this includes "work", it is not considered that this will capture someone who hadn't been able to work, either at all, or full time, previously and with the benefit of the therapy, now can. We also do not consider that the question in the EORTC QLQ – 330 which states "were you limited in doing either your work or other daily activities?" would capture this scenario either as this question infers work that patients are already doing rather than a new employment status following improvement of their symptoms or reduction of their treatment burden.

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Technical engagement response form

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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)	**PNH service Leeds**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**No**

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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 trial populations to UK patients	**No**	The UK population with PNH is well represented within the clinical trials, 2% of the patients in the 301 study (previously untreated) and 20% of the patients in the 302 study were from England. In clinical practice we do not see a difference in our patient population diagnosed with PNH compared to our European colleagues.
Key issue 2: Dosing of eculizumab	**No**	80% of patients on eculizumab for PNH are stable on the standard treatment dose, dose increase is extremely uncommon in the first 6 months (duration of control arm in 301 previously untreated study). Those in the 302 study required patients to be well controlled on the standard dose eculizumab prior to entry into the clinical trial. Patients in the UK are managed optimally, thus if they experience ongoing episodes of breakthrough haemolysis supported by laboratory evidence, the dose of eculizumab is increased. The planned ALXN 401 clinical trial is for patients on higher than standard doses of eculizumab. Thus the 20% of patients on higher than standard eculizumab doses would not be considered for change of treatment to ravulizumab if NICE approves ravulizumab. This however should not preclude this assessment of ravulizumab though

		NICE as 80% of patients within our service will benefit from ravulizumab if it is approved
Key issue 3: Short follow-up in the trials	**No**	52 weeks of clinical trial data has shown effectiveness of treatment. In clinical practice all patients on ravulizumab in the clinical trials, entered the extension study and subsequently are treated on a Global access to medicines scheme and remain well controlled. The clinical team thus has in excess of three years' experience of Ravulizumab Ravulizumab has a similar mechanism of action in terms of C5 binding to that of Eculizumab. As expected current safety data demonstrated in the clinical trials to date has been similar. The main risk is that of meningitis due to binding of C5, which remains irrespective of Eculizumab or Ravulizumab
Key issue 4: Appropriateness of the company's base-case analysis	**YES**	ERG assessment is thorough, and some assumptions have been made by CS that may or not be conclusive. In particular the assumptions are around the standard dosing arm in the clinical studies and breakthrough haemolysis events. It cannot be assumed that patients in the standard arm of the clinical trials would have a dose increase (up dose) of eculizumab outside of a clinical trial in certain clinical scenarios. We agree that complement-amplifying conditions (CAC-related) Break through haemolysis (BTH) may not result in an 'up dosing' certainly if it was a one off event caused by infection, the infection would be treated, a single early or additional dose may be required and the patients would continue on their standard dose (Page 55 of ERG document). Dose increases, in our experience, are required if patients have persistent PNH symptoms or complications, despite being on eculizumab. Laboratory evidence is sought to determine whether patients have adequate complement inhibition, prior to increasing the dose of eculizumab.

		A Base case scenario based on the clinical trial data alone seems more appropriate
Key issue 5: Appropriateness of the company's "equal effectiveness" scenario	Yes	Similar to the above comments, a base-case scenario on clinical trial data is more appropriate. The patients on higher doses of eculizumab should be entered into the planned ALXN 401 study to determine efficacy
Key issue 6: Generalisability of the ERG base-case to UK clinical practice	**Yes**	As above
Key issue 7: Health-related quality of life	**No**	From the patient data collected by the support groups it is clear that ravulizumab offers quality of life improvements.
Key issue 8: Ravulizumab treatment effect duration	**No**	Whilst long term data is not available for Ravulizumab, drug mechanism of action and experience with eculizumab would not anticipate a decline in efficacy over several years. It is probable over time, as experienced with eculizumab, that some patients will experience extravascular haemolysis on ravulizumab. Extravascular haemolysis occurs due to C3 loading on red cells and early removal of opsonised red cells by the spleen. This occurs in some patients treated with C5 inhibition and is not unique to the treatment drug
Key issue 9: Treating undetermined and CAC-related BTH events	**No**	CAC-related BTH would be assessed and underlying cause treated. An early or single additional dose of eculizumab would be provided on occasion. BTH events on ravulizumab were observed less frequently in the clinical trials. If the patient was nearing their dose of ravulizumab and experienced breakthrough a dose would be provided early. As a service this has not as yet been our experience but it is likely patients with a CAC-related breakthrough will occur in due course

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Ravulizumab for paroxysmal nocturnal haemoglobinuria

ADDENDUM: Critique of the company's response to Technical Engagement

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Date completed 22/01/2021

1. [redacted]Company's response to technical engagement

The purpose of this addendum is to provide a critique of the new evidence submitted by the company as part of their response to the technical engagement key issues.[1]

1.1 In their response to technical engagement, the company submitted responses to the key issues raised in the ERG Report, and some additional evidence relevant to these issues.[1] The company has also offered a new patient access scheme (PAS) price to NHS England which has been used to update the cost effectiveness model results. [redacted]Generalisability of the trial populations to UK patients

The company argues that "*there is no reason to believe the clinical trial populations have less severe disease than UK patients and are not generalisable, and as heard in the technical engagement call, clinical experts consider the trial populations "pretty representative" of patients treated in UK practice*".[1]

ERG comment: As no new evidence has been presented, the ERG stands by the original conclusion in the ERG report:[2]

"*Both trials were international trials with most patients included from countries other than the UK. Therefore, there is a question about the generalisability of the trial populations to UK clinical practice. In the ALXN1210-PNH-301 trial, 246 patients were included with [redacted] patients treated in England. In the ALXN1210-PNH-302 trial, 195 patients were included with [redacted] patients treated in England and [redacted] patients treated in Scotland*".

It is possible that patients included in the two trials have less severe disease than UK patients and it is unclear how this difference in population characteristics influences results.

1.2 Dosing of eculizumab

In their response, the company acknowledge the evidence gap with regard to 'switching' higher-dose eculizumab patients to ravulizumab.

ERG comment: As no new evidence has been presented, the ERG stands by the original conclusion in the ERG report:

"*In UK clinical practice, an increased dose of eculizumab is used to manage breakthrough haemolysis (BTH) due to incomplete C5 inhibition. Data from the Paroxysmal nocturnal haemoglobinuria (PNH) national service indicate this is necessary for [redacted]% of the population (see CS, Section B.3.2.1), with the majority of patients remaining stable on the licensed eculizumab dose (900 mg). However, in the two ravulizumab trials included in the company submission, dose-escalation/up-dosing of eculizumab was not permitted*" (CS, page 89).[3]

This may have resulted in worse clinical outcomes for patients in the eculizumab arms of the two trials. Therefore, the effectiveness of ravulizumab may have been overestimated.

1.3 Short follow-up in the trials

In response to this issue the company states that "*Data from the ALXN1210-PNH-301 and ALXN1210-PNH-302 trial Extension Phases reporting outcomes up to 52 weeks are available and included in the company submission. Longer-term safety data are provided from earlier phase clinical trials in the company submission (Appendix F).4 There are also reports on longer-term use shared by UK patients and clinicians involved in the ravulizumab clinical trial programme (see response to*

Issue 8). Further data from the ALXN1210-PNH-301 and ALXN1210-PNH-302 trial Extension Phases reporting outcomes up to 104 weeks are expected to be available in [redacted]".[1]

ERG comment: As no new evidence has been presented, the ERG stands by the original conclusion in the ERG report:[2]

"*Data are relatively immature in that they currently provide data for up to 52 weeks for a chronic condition requiring lifelong treatment. There is uncertainty about the long-term effectiveness of ravulizumab*".[2]

On Monday 1 February, the ERG received additional trial data submitted by the company, containing 104-week data from the ALXN1210-PNH-301 and ALXN1210-PNH-302 trial Extension Phases. As stated by the company, "ravulizumab treatment effect was maintained throughout the 104 week Extension Phases of both trials with respect to transfusion avoidance, lactate dehydrogenase (LDH) normalization, fatigue improvements from baseline and haemoglobin stabilization". However, it should be noted that all patients received ravulizumab during the extension period. Therefore, comparative data of ravulizumab versus eculizumab are only available for the randomised period in both trials, which was 26 weeks.

1.4 Appropriateness of the company's base-case analysis

The ERG was concerned about the discrepancy between the calculated long-term proportion of patients up-dosed over the time horizon of 55 years in the company's base-case analysis ([redacted]%) and the estimated proportion of up-dosed patients observed in UK clinical practice. Based on data collected from the PNH registry on safety and effectiveness for eculizumab over the past 8 years, the proportion of patients continuously up-dosed was [redacted]%. However, PNH registry data reflects an 8-year time horizon and the proportion of patients continuously up-dosed in the long term (beyond 8 years) remains uncertain. Clinical experts at the technical engagement meeting confirmed that a slight increase, to approximately [redacted]%, was observed in the latest data from the PNH registry. The company has acknowledged the uncertainty regarding this issue and, consequently, has adjusted the original model to reflect a scenario where the proportion of patients continuously up-dosed approximates [redacted]% across the model time horizon of 55 years. The model adjustments are described in Section 2.1.

ERG comment: The ERG considers the updated company's base-case more appropriate than the company's base-case in the original submission. However, it is unclear to what extent this scenario differs now from the equal effectiveness scenario. In terms of cost effectiveness, the impact of this is irrelevant since ravulizumab will be clearly dominant in both scenarios. The updated company's base-case is still limited by the lack of clinical data on up-dosed patients since in ALXN1210-PNH-301 and ALXN1210-PNH-302, eculizumab up-dosing was not allowed. It is, therefore, up to the Committee to decide whether this scenario is a proper representation of UK clinical practice or not.

1.5 Appropriateness of the company's "equal effectiveness" scenario

The ERG was concerned whether the "*conclusions from the trials in which only 5% of patients would be eligible for an eculizumab up-dose would be the same if there were approximately* [redacted]*% of patients who would need such an up-dose*".[2] At the technical engagement meeting, clinical experts indicated that the current proportion of patients needing up-dosing would have emerged over a 1-2 year time period. This could explain why the proportion of patients with BTH due to incomplete C5 inhibition in the 26-week period of the trial was lower than that seen in clinical practice. The company

concluded that the "*clinical outcomes and conclusions of the equal effectiveness analysis should only be considered for a patient population receiving eculizumab long-term*".[1]

ERG comment: The ERG considers the explanation given by the experts at the technical engagement meeting plausible and agrees with the conclusion of the company that conclusions from the equal effectiveness scenario should be considered for a population receiving long-term eculizumab. However, such data were not available, as discussed in Section 1.2 above.

1.6 Generalisability of the ERG base-case to UK clinical practice

The company has mentioned the following limitations regarding the ERG base-case analysis:

- It is based completely on the clinical trials, thus, with no eculizumab up-dosing included in the model and incomplete C5 inhibition BTH events modelled as per observations in the 26 week controlled trial periods. Therefore, this scenario is not reflective of clinical practice.
- It fails to acknowledge the impact of BTH due to incomplete inhibition and underestimates the impact on costs, QALYs, morbidity and mortality in the eculizumab arm of the model.
- It does not account for the UK approach to managing other BTH events (undetermined or CAC-related).
- It does not acknowledge the benefits of ravulizumab dosing to patients and carers, which are directly related to their time and, therefore, not captured in the treatment effect utility estimates from clinical trial HRQoL data.
- It is based on ravulizumab 10 mg/ml formulation, which will not be launched commercially in the UK, over the ravulizumab 100 mg/ml formulation. The company indicated that this is important because, for example, infusion time for a maintenance dose (3300 mg) for a patient weighing between 60 – 100 kg. is approximately 40 minutes with the ravulizumab 100 mg/ml, whereas it is approximately 120 minutes using the 10 mg/ml formulation.[5] The maintenance dose infusion time with the 100 mg/ml formulation of ravulizumab approximates the infusion time for a maintenance dose of eculizumab (35 minutes ±10 minutes).[6]

ERG comment: In the ERG report it is acknowledged that the ERG base-case scenario is not fully reflective of UK clinical practice. The ERG would like to emphasise that the preference for its base-case scenario was due to the lack of data on eculizumab up-dosing in ALXN1210-PNH-301 and ALXN1210-PNH-302. While the company's base-case might be in theory a better representation of UK clinical practice, it is also true that modelling eculizumab up-dosed patients was based on assumptions instead of evidence from the clinical trials. Therefore, the ERG considers that both approaches have advantages and disadvantages.

The ERG agrees with the company and the clinical experts at the technical engagement meeting that patients receiving a higher dose of eculizumab should not be excluded from the modelling or from consideration by the Committee. For that reason, different scenarios including eculizumab up-dosing were also explored by the ERG. However, the ERG considers that it is the company's task to provide the evidence that would allow including in the analyses eculizumab up-dosing in a more reliable way. Moreover, the ERG considers that the preference of one base-case over the other is a matter of judgement. As an example, in response to the technical engagement key issues, M. Griffin from PNH Service Leeds indicated that a "*base-case scenario based on clinical trial data alone seems more appropriate*".[7] Therefore, it is up to the Committee to decide which scenario, if any, is the most appropriate for decision making purposes.

Finally, the 10 mg/ml formulation was the only formulation with regulatory approval at the time of the ERG review. Therefore, selecting it was the only logical choice. Selecting the 100 mg/ml formulation has a negligible impact on the cost effectiveness results. The company indicated that it is "*an issue of importance to patients as the infusion times with the 100 mg/ml formulation is much lower than with the 10 mg/ml formulation*".[1] However, this is not supported by any new evidence that could be included in the cost effectiveness model.

1.7 Health-related quality of life

The company has accepted that the true utility impact of ravulizumab over eculizumab is likely to fall somewhere between the company's base-case estimate and the ERG's assumption of no additional utility benefit beyond that observed in the clinical trial.

ERG comment: The ERG agrees with this approach and as explained during the technical engagement meeting, the ERG preferred to take a conservative approach.

1.8 Ravulizumab treatment effect duration

In the absence of data beyond 52 weeks for ravulizumab, eculizumab data were used to inform longer-term assumptions of treatment effect (efficacy and safety). These data show no indication of any waning of treatment effect over time, showing the rate of events such as BTH and transfusions remain reasonably constant over time.[8-10]

The company considers this approach appropriate as ravulizumab and eculizumab share over 99% homology, the same mode of action and ravulizumab has proven non-inferiority across ALXN1210-PNH-301 and ALXN1210-PNH-302. According to the company, there are no biological or clinical rationale as to why the long-term effects of ravulizumab and eculizumab would differ.

At the technical engagement meeting, clinical experts agreed that that ravulizumab is safe and effective over the longer term based on the data available. The NICE technical considered the approach to modelling ravulizumab treatment effect duration over the longer-term reasonable and biologically plausible.

ERG comment: The ERG feels it should be emphasised that ravulizumab treatment effect duration must be modelled relative to eculizumab. The evidence provided by the company suggests no indication of a treatment effect waning for eculizumab relative to no treatment. When it is mentioned that there is no biological or clinical rationale as to why the long-term effects of ravulizumab and eculizumab would differ, it is unclear whether that refers to ravulizumab compared to no treatment or to ravulizumab compared to eculizumab. If it refers to the former, the ERG agrees. However, if it refers to the latter, the ERG considers that there is no evidence to support that, and that is the relevant comparison for this appraisal. Therefore, despite the company's and the clinical experts at the technical engagement meeting expectations, in the absence of ravulizumab long-term data, the ERG still considers it useful to conduct scenario analyses to test the robustness of the model results. Given the time constraints associated to this project, the ERG was unable to run a scenario where a decline in ravulizumab treatment effect over time, relative to eculizumab, was included in the model.

1.9 Treating undetermined and CAC-related BTH events

The company classified incomplete C5 inhibition events and CAC-related BTH events consistent with the clinical trial protocols. Undetermined BTH events were discussed with clinical experts and it was decided that these events should be treated as CAC-related BTH events in the cost-utility analysis, based on the absence of incomplete C5 inhibition.

ERG comment: The ERG concern regarding this issue was the lack of clarity in the explanations provided by the company in different sections of the company submission and the response to the clarification letter. This was clarified during the technical engagement meeting. Other than that, it was acknowledged by the ERG, that this has a minimal impact on the model results.

1.10 Additional issues

The ERG conducted an scenario analysis where additional excess BTH mortality was assumed (scenario analysis 5 in the ERG report - ERG base-case with BTH excess mortality).[2] This scenario was based on a scenario initially provided in the company submission to illustrate model sensitivity to assumptions around mortality and to provide a worst-case estimate.[3] However, at the technical engagement meeting, the company and clinical experts explained that in the UK, BTH due to incomplete C5 inhibition does not have any impact on mortality.

ERG comment: Based on the feedback received at the technical engagement call, the ERG agrees with this approach and suggests that the results of all scenarios based on BTH excess mortality should be interpreted with caution.

2. Changes made by the company to the electronic model

2.1 Changes to company's base-case assumptions

As explained in Section 1.4 of this addendum document, the company adjusted the original model to reflect a scenario where the proportion of patients continuously up-dosed approximates [redacted]% across the model time horizon of 55 years. The model was adjusted as follows:

- The probability of a first incomplete C5 inhibition-related BTH event was adjusted using multipliers that were applied to the transition probabilities for patients in cohort 1 (treatment naïve) and cohort 2 (treatment-experienced) patients.
- The population estimate of [redacted]%, was divided into proportional contributions from cohort 1 ([redacted]%) and cohort 2 ([redacted]%).
- Proportional contributions were based on the proportion of patients in cohort 1 ([redacted]%) and cohort 2 ([redacted]%) multiplied by the aggregate population estimate.
- A "Goal seek" function was then used to estimate a multiplier such that the proportion contribution of cohort 1 and cohort 2 equalled [redacted]% and [redacted]%, resulting in the multipliers [redacted] and [redacted] for cohort 1 and cohort 2, respectively.
- These multipliers were applied to the first incomplete C5 inhibition BTH event transitions for eculizumab to calculate an aggregate estimate of [redacted]%.

The multiplier adjustment can be controlled with a switch on the 'Inputs' sheet ('Inputs'!H140) of the model. The adjustment to the probability of a first incomplete C5 inhibition BTH event is implemented on the 'BTH & Transfusion probs' sheet ('BTH & Transfusion probs'!$AY5:BM28) of the model. This adjustment assumes that the ([redacted]%) proportion of patients up-dosed does not change in the future.

2.2 Increased PAS discount

A list price of £4,533 per 300mg vial was approved for ravulizumab by the Department of Health and Social Care. The company has offered a new patient access scheme (PAS) price 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. The new discount on the list price has increased by [redacted]% compared to the discount used in the original company submission. [redacted]. The impact of this new PAS price on the cost effectiveness results is described in the next sections of this addendum document.

3. Company's updated cost effectiveness results

The company's updated base-case and scenario analyses cost effectiveness results are shown in Table 3.1. These results indicate that ravulizumab was both, less costly and more effective, thus dominant, than eculizumab in all scenarios, except the ERG scenario with excess BTH mortality. However, as explained in Section 1.10 above, the results of this scenario should be interpreted with caution. All results were based on the new PAS price of ravulizumab. The effect of this new price on the results resulted in cost savings increased by £[redacted]. A short description of the scenarios presented in Table 3.1 is given below:

- Scenario 1: Company's original base-case with new PAS price for ravulizumab.
- Scenario 2: Company's base-case after Technical Engagement. This scenario us based on equal effectiveness. It is assumed that at the clinically stable dose of eculizumab, patients do not experience BTH due to incomplete C5 inhibition, the proportion up-dosed is [redacted]% corresponding to UK clinical practice. Additional details can be found in sections 1.4 and 2.1 above.
- Scenario 3: ERG change 1: no eculizumab up-dose (as described in key issue 6 - see e.g. ERG report Table 1.11/Table 7.13).[2]
- Scenario 4: ERG change 2: utilities treatment arm as covariate (as described in key issue 7 see e.g. ERG report Table 1.11/Table 7.13).[2]
- Scenario 5: ERG change 3: no additional utility benefit for treatment frequency (as described in key issue 7 - see e.g. ERG report Table 1.11/Table 7.13).[2]
- Scenario 6: ERG preferred base case analysis (see ERG report Table 1.11/Table 7.3/Table 7.13).[2]
- Scenario 7: ERG scenario analyses on Cohort 3 [5%] patients in the equal effectiveness scenario (see ERG report Table 7.7).[2]
- Scenario 8: ERG scenario analyses on alternative utilities and costs in the company's equal effectiveness scenario (see ERG report Table 7.8).[2]
- Scenario 9: ERG scenario analyses on alternative utilities and costs in the company's base-case (see ERG report Table 7.9).[2]
- Scenario 10: ERG scenario analyses with alternative utilities – decrement 0.057 (see ERG report Table 7.10).[2]
- Scenario 11: ERG scenario analyses with alternative utilities – decrement 0.029 (see ERG report Table 7.11).[2]
- Scenario 12: ERG scenario analyses with BTH excess mortality (see ERG report Table 7.12).[2]
- Scenario 13: Individual impact on results of ERG change 1: no eculizumab up-dose (see ERG report Table 7.14).[2]
- Scenario 14: Individual impact on results of ERG change 2: utilities with treatment arm as covariate (see ERG report Table 7.14).[2]
- Scenario 15: Individual impact on results of ERG change 3: no additional utility benefit for treatment frequency (see ERG report Table 7.14).[2]
- Scenario 16: Individual impact on results of ERG change 4: ravulizumab 10mg vial (see ERG report Table 7.14).[2]

Table 3.1: Updated base-case and scenario analyses results (new PAS price, discounted)

Scenario	Incremental QALYs	Incremental costs	Submitted ICER	Incremental QALYs	Incremental costs	Revised ICER	Impact on results
	Original PAS price			New PAS price			
Scenario 1 - company's base-case	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	Cost savings increased by £[redacted]
Scenario 2 - company's base-case after TE	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	Incremental QALYs decreased by [redacted]. Incremental costs decreased by £[redacted]
Scenario 3 - ERG change 1: no eculizumab up-dose	[redacted]	[redacted]	£14,798	[redacted]	[redacted]	Dominant	ICER is now Dominant. Cost savings increased by £[redacted]
Scenario 4- ERG change 2: utilities treatment arm as covariate	[redacted]	[redacted]	£11,538	[redacted]	[redacted]	Dominant	ICER is now Dominant. Cost savings increased by £[redacted]
Scenario 5- ERG change 3: no additional utility benefit for treatment frequency	[redacted]	[redacted]	£37,474	[redacted]	[redacted]	Dominant	ICER is now Dominant. Cost savings increased by £[redacted]
Scenario 6- ERG preferred base-case	[redacted]	[redacted]	£38,290	[redacted]	[redacted]	Dominant	ICER is now Dominant. Cost savings increased by

Scenario	Incremental QALYs	Incremental costs	Submitted ICER	Incremental QALYs	Incremental costs	Revised ICER	Impact on results
	Original PAS price			New PAS price			
							£[redacted]
Scenario 7 - Cohort 3 [5%] patients in equal effectiveness scenario	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	Cost savings increased by £[redacted]
Scenario 8 - Alternative utilities and costs in equal effectiveness scenario	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	Cost savings increased by £[redacted]
Scenario 9 - Alternative utilities/costs in company's base-case	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	Cost savings increased by £[redacted]
Scenario 10 - Alternative utility decrement 0.057	[redacted]	[redacted]	£11,790	[redacted]	[redacted]	Dominant	Cost savings increased by £[redacted]
Scenario 11 - Alternative utility decrement 0.029	[redacted]	[redacted]	£17,688	[redacted]	[redacted]	Dominant	Cost savings increased by £[redacted]
Scenario 12 - BTH excess mortality	[redacted]	[redacted]	£124,433	[redacted]	[redacted]	£12,404	ICER below £20,000 per QALY. Cost savings increased by £[redacted]

Scenario	Incremental QALYs	Incremental costs	Submitted ICER	Incremental QALYs	Incremental costs	Revised ICER	Impact on results
	Original PAS price			New PAS price			
Scenario 13 - Individual impact of ERG change 1: no eculizumab up-dose	[redacted]	[redacted]	£14,798	[redacted]	[redacted]	Dominant	ICER is now Dominant. Cost savings increased by £[redacted]
Scenario 14 - Individual impact of ERG change 2: utilities (treatment arm as covariate)	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	Cost savings increased by £[redacted]
Scenario 15 - Individual impact of ERG change 3: no additional utility benefit for treatment frequency	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	Cost savings increased by £[redacted]
Scenario 16- Individual impact of ERG change 4: ravulizumab 10mg vial	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant	Cost savings increased by £[redacted]

Based on company response to technical engagement[1]
Abbreviations: BTH = breakthrough haemolysis, ERG = evidence review group, ICER = incremental cost effectiveness ratio, PAS = patient access scheme, QALYs = quality adjusted life years, TE = Technical Engagement

ERG comment: Updated probabilistic sensitivity analyses (PSA) based on the new PAS and the new company's base-case were not presented by the company. This is not expected to differ much from those probabilistic results presented in the company submission and the ERG report, given the ravulizumab clearly dominates eculizumab (i.e. cost effectiveness acceptability curve equal to 1 for all values of the threshold ICER). The PSA for the updated ERG base-case (with new PAS) might still be relevant. Results from this scenario are presented in the next section.

4. Exploratory and scenario analyses undertaken by the ERG

As explained in the previous section, the ERG considers that the PSA for the updated ERG base-case scenario could be of interest. The results of this scenario are discussed in the remaining of this section. No further analyses were conducted by the ERG.

The PSA results for the updated ERG base-case with the new PAS can be seen in Table 4.1. When the new PAS is considered, ravulizumab was also dominant in the PSA (incremental costs were -£[redacted] and incremental QALYs were [redacted]) with similar results to those obtained in the deterministic analysis in Table 3.1. Note the probabilistic ICER before the new PAS was £54,125 per QALY gained, due to £[redacted] incremental costs.

The CE-plane and CEAC resulting from the ERG PSA are shown in Figure 4.1 and 4.2, respectively. The CE-plane shows [redacted]% of the simulations (according to the CEAC) in the south eastern quadrant, in which ravulizumab is dominant (it was [redacted]% before the new PAS). The CEAC shows that the probability of ravulizumab being cost effective was [redacted]% at a threshold ICER of £30,000 per QALY gained (it was [redacted] before the new PAS).

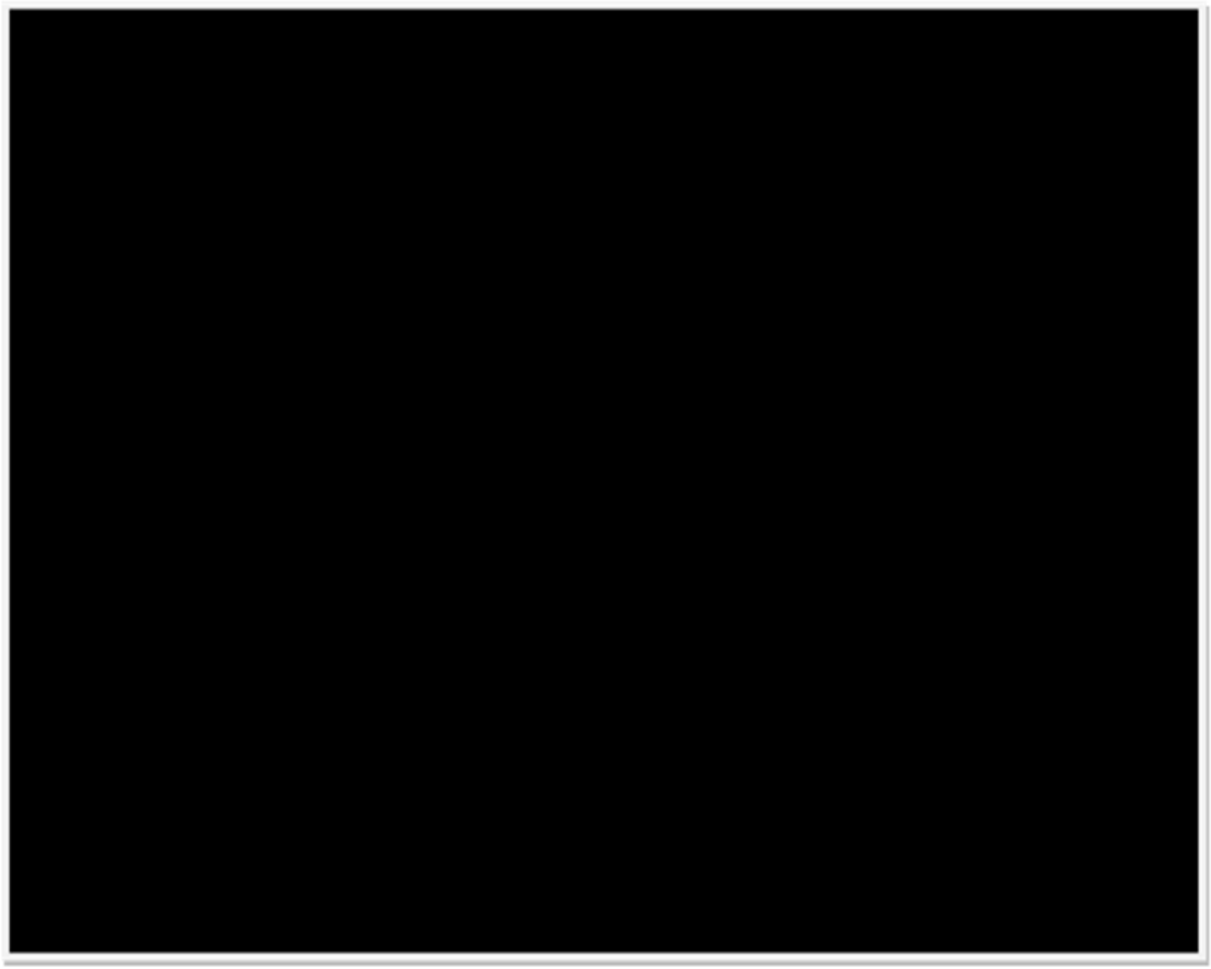
Table 4.1: Mean PSA results - ERG base-case with new PAS (no eculizumab up-dose)

Technologies	Mean costs	Mean QALYs	Incremental		ICER
			Mean costs	Mean QALYs	
Eculizumab	[redacted]	[redacted]	[redacted]	[redacted]	Ravulizumab dominates
Ravulizumab	[redacted]	[redacted]			
Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life years gained; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.					

Figure 4.1: ERG preferred cost effectiveness plane (new PAS, no eculizumab up-dose)

[redacted]

Figure 4.2: ERG preferred cost effectiveness acceptability curve (new PAS, no eculizumab up-dose)



5. ERG conclusions

As no new evidence has been presented, for most of the key issues the ERG stands by the original conclusions in the ERG report.[2]

Regarding the changes made to the economic analyses, the company adjusted the original model to reflect a scenario where the proportion of patients continuously up-dosed approximates [redacted]% across the model time horizon of 55 years. The ERG considers the updated company's base-case more appropriate than the company's base-case in the original submission. Nevertheless, the updated company's base-case is still limited by the lack of clinical data on up-dosed patients since in ALXN1210-PNH-301 and ALXN1210-PNH-302, eculizumab up-dosing was not allowed. It is acknowledged that the ERG base-case scenario is not fully reflective of UK clinical practice. The ERG considers that both approaches have advantages and disadvantages.

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. This new PAS price resulted in cost savings increased by £[redacted]. As a consequence, ravulizumab was both, less costly and more effective, thus dominant, than eculizumab also in the ERG updated base-case. The PSA for the ERG updated base-case showed [redacted] of the cost effectiveness plane.

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