NICE National Institute for Health and Care Excellence

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Ravulizumab for treating paroxysmal nocturnal haemoglobinuria [ID1457]

Lead team presentation

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ERG: Kleijnen Systematic Reviews

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Company: Alexion

Committee meeting: 10 March 2021

Disease overview – Paroxysmal nocturnal haemoglobinuria

- Rare disease; about 725 people in England are diagnosed
- Caused by acquired mutation in the phosphatidylinositol glycan class A (PIG-A) gene in haematopoietic stem cells
  - Leading to loss of proteins linked to the cell membrane
  - Making attacks of complement system on these cells more likely
  - Resulting in haemolysis (rupture of red blood cells)
- Median age of onset is 40 years; but can occur at any age
- Progressive disease that can be life threatening if untreated
- Significant reduction in life expectancy if untreated
- Available treatment has restored life expectancy

Signs and symptoms

- Severity and frequency of symptoms vary from person to person
- Include haemoglobinuria, anaemia, breathlessness, difficulty swallowing, abdominal pain, erectile dysfunction, jaundice, fatigue, kidney damage and blood clots

Patient and carer perspectives 1

With thanks to Aplastic Anaemia Trust (ATT) and PNH Support who shared results from a survey of 54 people with PNH and 20 carers

Living with the condition

- Heavy symptom and complications burden if untreated
- Eculizumab transformed mortality and associated morbidities: needs a shared understanding of when the advantages of the burden of treatment outweigh the disruption

"We live on a 'knife edge' never knowing when the next crisis will come"
"We often feel that we know more about the illness and how it should be treated than the local health professionals we meet"
"Relentless fatigue"; "Brain fog"

Unmet need

- Patients would welcome more treatment options

"I'm not in a position to work more than a handful of hours per week in order to manage my nurse visits…frequent hospital visits and maintain a steady state of health and energy that is required with a young family."
"The frequent IVs and necessary blood tests that have left me with scarring in multiple places in my veins"

Patient and carer perspectives 2

Advantages of ravulizumab

- Improved treatment frequency; ravulizumab is given every 8 weeks
- Positive impact on quality of life
- Improved independence due to increase in an individuals ability to work
- Psychological benefit to individuals (and their families) of being able to forget their incurable chronic disease for 8 weeks at a time
- Improved symptom control

"I can actually forget I have PNH."; "The household has become a ***happier place****.";*
"… treatment is every ***2 months.*** *This means* ***fewer cannulations*** *and therefore* ***less anxiety.*** *Less disruption to my work schedule. Being able to go on holiday more easily. I don't have to tell my employer when my treatment is …"*
"… 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."

Clinical perspective

Thanks to 2 national PNH Service specialist centres for their input

Clinical effectiveness

- Likely to be similar to eculizumab
- Appropriate for most patients who are currently treated with eculizumab

Health-related quality of life

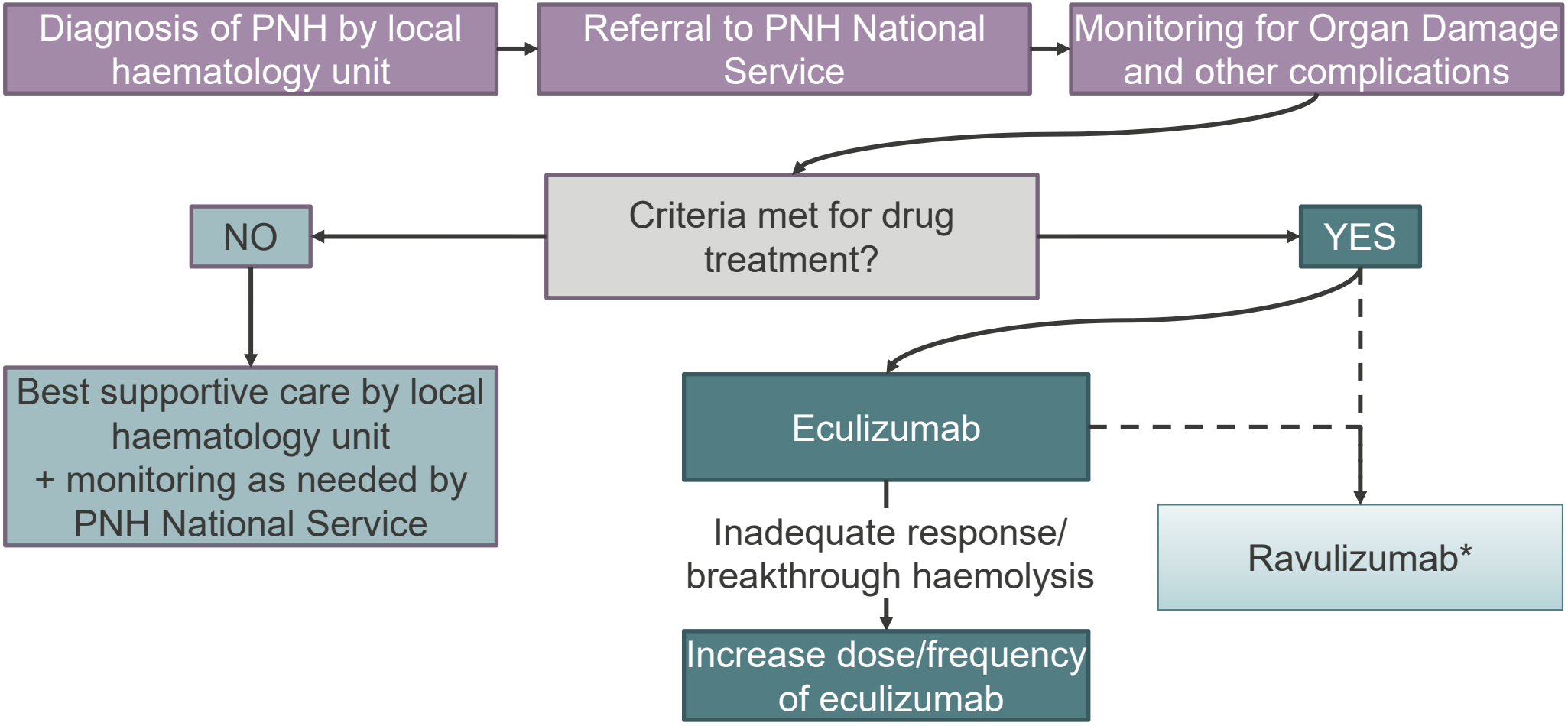
- Improved HRQoL and greater normality because of less frequent infusions and less breakthrough haemolysis compared with eculizumab
- Work-related, social, mental and emotional improvements

Clinical experts caution that health-related quality of life is not captured in health-economic model

- *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*
- *Patients have fewer episodes of breakthrough haemolysis on ravulizumab which reduces attendance and admissions to hospital, and the requirements for blood transfusions etc.*

Treatment pathway

- Treatment of PNH is managed by 2 highly specialist centres in England (Leeds and London) via a shared care agreement with local haematology units
- Infusions are given at home



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*Proposed position of ravulizumab in treatment pathway

Ravulizumab (Ultomiris, Alexion Pharma UK)

Marketing authorisation (granted July 2019)	Treatment of adults 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
Mechanism of action	• Monoclonal antibody binds to the complement protein C5 acting as complement inhibitor • Reduces haemolysis in PNH • Re-engineered eculizumab; ravulizumab is not degraded with its target and is released back into the blood stream
Administration	• Intravenous infusion every 8 weeks • Must be diluted prior to administration • Minimal time of infusion 25 to 75 minutes depending on body weight (based on 100mg/ml formulation)
Price	List price: • £15.11 per mg based on 1,100 mg vial Average cost per month: £27,217 based on body weight ≥60 kg to <100 kg Average cost per year: £326,604 Patient Access Scheme is in place and has been updated following technical engagement

Summary of company submission

Comparator	Eculizumab
Clinical trials and results	**PNH-301 – RCT comparing ravulizumab with eculizumab (in treatment-naïve adults)** Clinical effectiveness: ravulizumab ≈ eculizumab HRQoL: ravulizumab ≈ eculizumab **PNH-302 – RCT comparing ravulizumab with eculizumab (in adults who are stable on eculizumab)** Clinical effectiveness: ravulizumab ≈ eculizumab HRQoL: ravulizumab ≈ eculizumab
Model	State transition model with 10 health states: 8 BTH-related health states, 1 mortality-related health state, and 1 spontaneous-remission health state
Company ICER	Ravulizumab dominant (cheaper and more QALYs than eculizumab)
Technical team preferred ICER	

BTH: breakthrough haemolysis; HRQoL: health-related quality of life

Key clinical evidence

Study Duration	
Randomised period 26 Weeks	Extension period up to 2 years
PNH-301: Ravulizumab compared with eculizumab Adults with PNH who are complement-inhibitor naïve Co-primary efficacy endpoints: • Transfusion avoidance • Haemolysis as measured by LDH-N Secondary endpoints included HRQoL	• All participants could enter extension period • All participants had ravulizumab (participants randomised to eculizumab switched to ravulizumab)
PNH-302: Ravulizumab compared with eculizumab Adults with PNH who are clinically stable following ≥6 months treatment with eculizumab Primary efficacy endpoint • Haemolysis, as measured by percentage change in LDH Secondary endpoints included HRQoL	• All participants could enter extension period • All participants had ravulizumab (participants randomised to eculizumab switched to ravulizumab)

PNH: paroxysmal nocturnal haemoglobinuria, LDH: lactate dehydrogenase, LDH-N: normalisation of lactate dehydrogenase levels, HRQoL: health related quality of life

Clinical evidence – randomized period (26 weeks)

	PNH-301			PNH-302		
	Ravulizumab (n=125)	Eculizumab (n=121)	Treatment effect (95% CI)	Ravulizumab (n=97)	Eculizumab (n=98)	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)	87.6 (81.1, 94.2)	82.7 (75.2, 90.2)	5.5 (-4.3, 15.7)
HRQoL* absolute change, mean (SD)	13.2 (21.4)	12.9 (21.8)	4.8 (-7.7, 17.1)	1.15 (16.51)	-1.93 (15.34)	4.2 (-6.6, 15.0)
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)

Results are for full analysis set (FAS) population
*European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire C30 (QLQ-C30) global health score/quality of life (GHS/QOL);
Source: company submission table 8

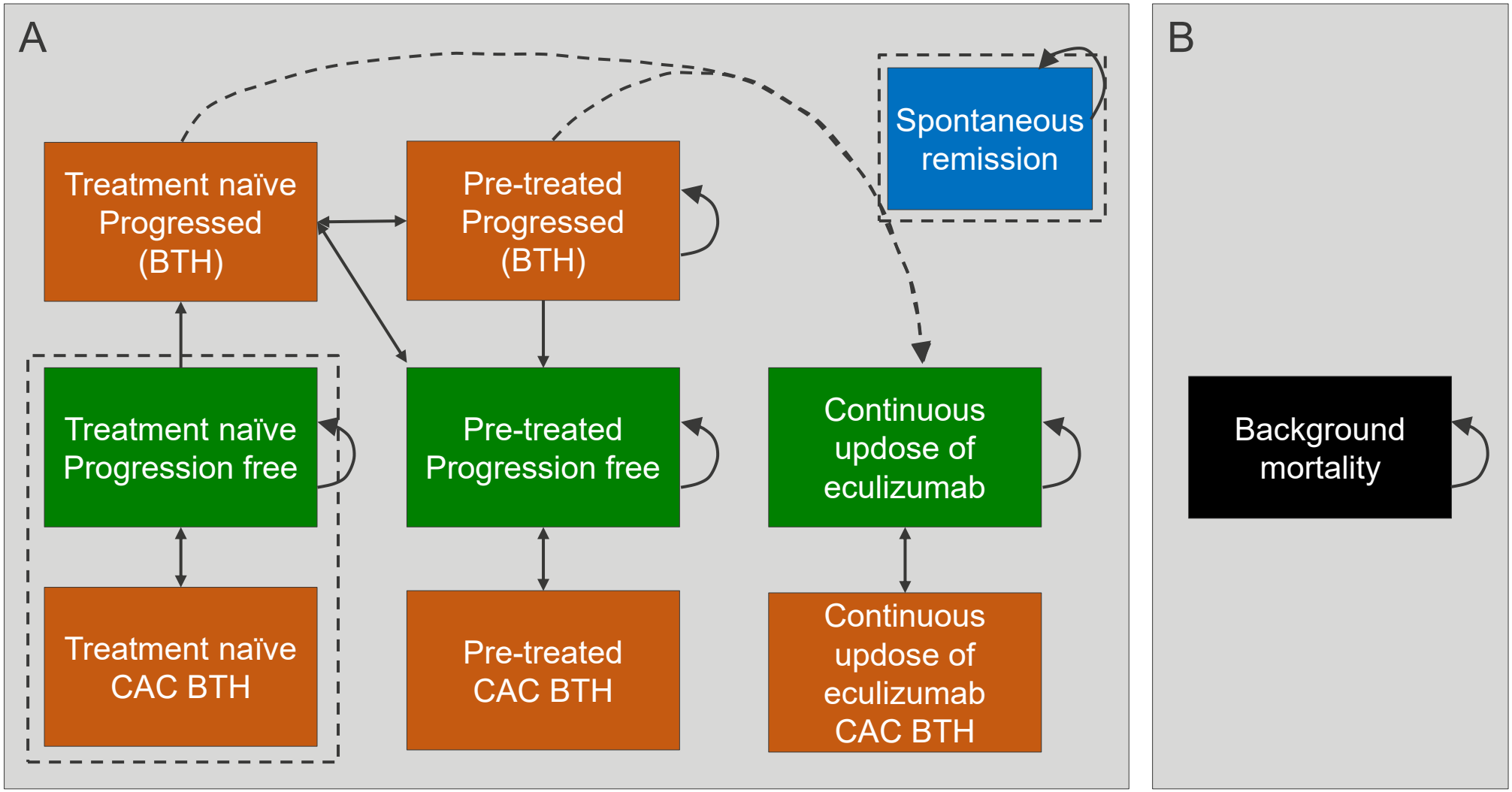
Clinical evidence – Extension period (>12 to 18 months); ravulizumab long-term effectiveness

- All participants got ravulizumab in the extension periods

	PNH-301	PNH-302
	Ravulizumab arm	Ravulizumab arm
Transfusion avoidance, n (%)	** (**)	** (**)
Change in FACIT-Fatigue score from baseline, n Mean (SD)*	*** ** (**)	** ** (**)
Breakthrough haemolysis, n (%)	** (**)	** (**)

Results are for intention to treat (ITT) population
FACIT: Functional Assessment of Chronic Illness Therapy;
*EORTC QLQ-C30 data not provided for extension period;
Source: company technical engagement response addendum table 1

Company's economic model



BTH: breakthrough haemolysis; CAC: complement amplifying condition.
Adopted from figure 14 from company submission

Key issues identified in the ERG report

Generalisability of trials

Are trials generalisable to people seen in UK clinical practice?

- **TE issue 1.** Generalisability
- **TE issue 2.** Dosing of comparator

Long-term effect of ravulizumab

What is the long-term effectiveness of ravulizumab?

- **TE Issue 3.** Short follow-up in the trials
- **TE Issue 8.** Ravulizumab treatment effect duration

Up-dosing of eculizumab in model

What proportion of up-dosing should be used in the model?

- **TE Issue 4.** Appropriateness of the company's base-case analysis
- **TE Issue 5.** Appropriateness of the company's "equal effectiveness" scenario
- **TE Issue 6.** Generalisability of the ERG base-case to UK clinical practice
- **TE Issue 9.** Treating undetermined and CAC-related BTH events

Utility values

Which approach should be used to estimate utility values?

- **TE Issue 7.** Health-related quality of life

Issues resolved after technical engagement

	Summary	Stakeholder responses	Technical team consideration	Included in updated base case?
Generalisibility - population				
1	Trials included few people from the UK (~**% overall) People in trials might have less severe disease than people in clinical practice	Trial population ≈ people in UK clinical practice ~**% participants in PNH302 from UK No evidence to suggest geographical variability in manifestations of PNH	Trial population is generalisable	Not applicable
Long-term effectiveness of eculizumab				
3 & 8	PNH is a chronic condition Short-term trial data (up to 52 weeks) but treatment would be for life	Company submitted 2-year follow up data Ravulizumab and eculizumab have same mechanism of action so efficacy and safety likely to be similar UK clinical experience (up to 4.5 years) shows sustained response	Treatment is life long Effectiveness maintained as long as treatment is given Comparative long-term effectiveness still uncertain	Company ✓ ERG ✓

Unresolved issues after technical engagement

Outstanding issues unresolved post technical engagement	Status	Impact on ICERs	Slide
Issues 2: Generalisability • Up-dosing	Not resolved		15
Issues 4, 5, 6 & 9: Up-dosing of eculizumab in model	Not resolved		16
Issue 7: Utility values	Not resolved		17

 **Model driver**

 **Unknown impact**

 **Small/Moderate impact**

Issue 2: Generalisability of trials – up-dosing

Background

- About **% of people in clinical practice need up-dosing of eculizumab because of inadequate response and breakthrough haemolysis
- Up-dosing was not permitted in PNH-301 and PNH-302

Stakeholder comments

- Trial PNH-301 included only treatment naïve people
  - some of these people might need up-dosing of eculizumab if there were treated in the NHS
- Trial PNH-302 included only people who were on stable dose of eculizumab for at least 6 months
  - need of up-dosing might be unlikely

Does up-dosing affect effectiveness in control arm?

Issues 4, 5, 6 & 9: Up-dosing of eculizumab in the model

Background

Setting	Up-dosing
Clinical practice	About **%
Trials	Not permitted
Original company's base case	About **% + single dose for BTH event
Updated company's base case	About **%
ERG base case	None; to align with trial results

Stakeholder comments

- Company
  - About **% up-dosing observed in clinical practice (PNH registry)
  - Model should reflect clinical practice
  - Updated base case ≈ equal effectiveness scenario in original submission
- Clinical expert
  - Model should reflect clinical trial; no up-dosing included

What proportion of up-dosing should be used in the model?

Are complement amplifying condition (CAC) related breakthrough haemolysis (BTH) events treated with an eculizumab up-dose in clinical practice?

Issues 7: Utility values

Background

- EORTC-QLQ-C-30 data from trials mapped to EQ-5D
- HRQoL was better for people treated with ravulizumab but not statistically significantly different
- Utility increments ranged from 0.0098 to 0.0178 (PNH-301) and 0.0037 to 0.022 (PNH-302)
- Company used discrete choice experiment (DCE) to estimate utility increment (0.057) for reduced frequency of treatment

Stakeholder comments

- Company
  - Patient preference for less frequent treatment
  - DCE well conducted
  - Utility estimates might be optimistic
  - Most plausible values might be between company's approach which includes disutilities and ERG's approach based solely on EQ-5D
- Patient and clinical experts
  - Ravulizumab improves quality of life because it is given less frequently (every 8 weeks versus every 2 weeks)

ERG and technical team

- Acknowledge that people prefer treatments with longer breaks between sessions
- Prefer use of EQ-5D data only

Which approach should be used to estimate utility values?

Cost effectiveness results including the PAS

Deterministic results

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company's updated base case	********	***	Dominant†
Company's updated base case no up-dosing	*******	***	Dominant†
Company's updated base case EQ-5D no DCE*	********	***	Dominant†
ERG's/technical team's preferred assumptions	*******	***	Dominant†

*results provided by ERG, †cheaper and more QALYs than eculizumab

Deterministic and probabilistic analyses provided similar results in the original company submission

Probabilistic analysis not included in company's updated analysis

ERG's probabilistic analysis shows similar results to deterministic analysis

Key issues identified in the ERG report

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Utility values

Which approach should be used to estimate utility values?

- **TE Issue 7.** Health-related quality of life