Evidence review for a decision aid in paroxysmal nocturnal haemoglobinuria

Swift Science Writing Limited

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Abbreviations

AA	Aplastic anaemia
AGREE II	Appraisal of Guidelines, Research and Evaluation
BID	Twice a day
BTH	Breakthrough haemolysis
C5i	Complement 5 inhibitor
CDSR	Cochrane Database of Systematic Reviews
CFB	Change from baseline
CI	Confidence interval; or complement inhibitor
CNS	Central nervous system
Crov	Crovalimab
CRD	Centre for Research and Dissemination
Dani	Danicopan
DARE	Database of Abstracts of Reviews of Effects
dL	Decilitre
DVT	Deep vein thrombosis
Ecu	Eculizumab
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer – Quality of Life Questionnaire – 30-items
EVH	Extravascular haemolysis
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy – Fatigue scale
FAQ	Frequently asked question
FDA	Food and Drug Administration
g	Grams
G-BA	Gemeinsamer Bundesausschuss
GHS	Global Health Status
G-I-N	Guidelines International Network
GPI	Glycosylphosphatidylinositol
Hb	Haemoglobin
HRQoL	Health-related quality of life
HSC	Haematopoietic stem cells
HSCT	Haematopoietic stem cell transplant
HTA	Health technology agency
INAHTA	International Network of Agencies for Health Technology Assessment
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
ITC	Indirect treatment comparison
IV	Intravenous
LASA	Linear Analog Assessment scale
LDH	Lactate dehydrogenase
LS	Least square
LSM	Least square mean
MAIC	Matched adjusted indirect comparison
MAVE	Major adverse vascular event
mg	Milligrams

MI	Myocardial infarction
MINORS	Methodological Index for Non-Randomised Studies
NA	Not applicable
NED	No evidence of a difference
NICE	National Institute for Health and Care Excellence
NR	Not reported
OR	Odds ratio
OS	Overall survival
Peg	Pegcetacoplan
PF	Physical functioning
PNH	Paroxysmal nocturnal haemoglobinuria
pRBC	Packed red blood cells
PRISMA	Preferred reporting items in systematic reviews and meta-analyses
QoL	Quality of life
RaD	Rate difference
RaR	Rate ratio
Rav	Ravulizumab
RBC	Red blood cell
RCT	Randomised controlled trial
RD	Risk difference
RoB	Risk of bias
ROBIS	Risk of bias in systematic reviews
RR	Risk ratio
SD	Standard deviation
SDM	Shared decision making
SE	Standard error
SEM	Standard error of the mean
SOC	Standard-of-care
SQ	Subcutaneous
SR	Systematic review
TD	Treatment difference
TEAE	Treatment-emergent adverse event
TIA	Transient ischaemic attack
Ti, ab	Title and abstract
TID	Three times a day
ULN	Upper limit of normal
URTI	Upper respiratory tract infection
UTI	Urinary tract infection
Q2W	Every 2 weeks
Q4W	Every 4 weeks
Q8W	Every 8 weeks
ULN	Upper limit of normal

1. Introduction

SHARE TO CARE, Cologne Germany and the University Hospital RWTH Aachen are working on an on-going research project to create interactive websites to provide patients with shared-decision making (SDM) decision aids.

This project is focussed on generating the best available evidence to inform a series of research questions to support the development of a new SDM aid for adults with symptomatic paroxysmal nocturnal haemoglobinuria (PNH; haemolytic PNH).

2. Objectives and research questions

The overall aim of this project is to answer nine research questions pertaining to the treatment, effectiveness/efficacy and safety of treatments for adults with symptomatic PNH (haemolytic PNH).

The nine pre-specified research questions include:

- FAQ1: What does the treatment involve?
- FAQ2: Will the therapy affect my haemoglobin level, and transfusion avoidance?
- FAQ3: Will the treatment impact how long I live?
- FAQ4: How will the treatment impact my quality of life?
- FAQ5: What are the risks or side effects?
- FAQ6: Are there any long-term negative effects of treatment?
- FAQ7: Where can I get additional information and/or a second opinion?
- FAQ8: Is there anything I can do myself to help my disease?
- FAQ9: Living with the disease

3. Methodology

Eligibility Criteria

The inclusion and exclusion criteria applied in this review are provided in Table 1.

Table 1: Eligibility criteria for the review

Facet	Inclusion criteria	Exclusion criteria
Population	Adults ≥18 years with symptomatic paroxysmal nocturnal haemoglobinuria (haemolytic PNH)	• Children or young adults <18 years • Asymptomatic PNH patients • Patients with aplastic anaemia (AA)/PNH syndrome or AA with a low GPI clone, in whom the degree of haemolysis is too low to warrant complement inhibition

Intervention	**Terminal complement inhibitor - C5 inhibitors** ○ Crovalimab (IV/SC) ○ Eculizumab (IV) ○ Ravulizumab (IV) • Vaccination according to drug label • Symptom-orientated therapy (incl. blood transfusions)	• Any other non-licensed treatments • Transfusions of cellular products (e.g. HSCT) or transplants
Comparator	• **Proximal inhibitors** ○ anti-C3 Pegcetacoplan (SC) ○ anti-Factor B Iptacopan (oral BID) ○ anti-Factor D e.g. Danicopan (as an add-on therapy to ravulizumab or eculizumab, oral (TID)) • Vaccination according to drug label Symptom-orientated therapy (incl. blood transfusions)	• Any other non-licensed treatments • Transfusions of cellular products (e.g. HSCT) or transplants
Outcomes	**<u>Survival/mortality:</u>** • All-cause mortality • Cause-specific mortality **<u>Efficacy/effectiveness:</u>** • Transfusions (need, number & frequency) • Shortness of breath/dyspnoea **<u>Health Related Quality of life (HRQoL):</u>** • Quality of life (e.g. fatigue) **<u>Safety:</u>** • Breakthrough haemolysis • Impaired kidney function • Pulmonary hypertension • Thromboembolic events (e.g. strokes) • Any infection • Any serious infection • Meningococcal infections	
Study design	• Systematic reviews • Guidelines • HTA assessments • Primary research, including large clinical studies (primary priority) and real-world evidence (secondary priority) where evidence gaps exist that aren't addressed by SRs, guidelines or HTAs	• Literature reviews • Review/opinion pieces • Letters to the editor • Animal/*in vivo* studies • Case studies • Case series
Subgroups of interest	Pregnant women	-
Language	Any language is included	-
Geography	Any geographical location is included	-
Date limit	No date limit, although more recent evidence will be prioritised	-

Abbreviations: AA, aplastic anaemia; GPI, glycosylphosphatidylinositol; HSCT, Haematopoietic stem cell transplant; HTA, Health Technology Assessment; IV, intravenous; PNH, paroxysmal nocturnal haemoglobinuria.

Searches

Database searches were conducted on 16th or 19th July 2024 to identify systematic reviews, guidelines and health technology assessments (HTA) for PNH. Searches were conducted across multiple databases to identify relevant studies. The search strategies were developed for each database and were not limited by date, language or publication type. Searches were limited to study design to focus on systematic reviews, guidelines and HTA assessments.

Searches were conducted in:

- **Systematic reviews:**
  - Cochrane Database of Systematic Reviews (CDSR)
  - Database of Abstracts of Reviews of Effects (DARE) (www.crd.york.ac.uk)
  - Epistemonikos (Internet) (www.epistemonikos.org)
- **Guidelines**:
  - Guidelines International Network (G-I-N) (www.g-i-n.net
  - ECRI Guidelines Trust (https://guidelines.ecri.org/)
- **HTAs**:
  - HTA database (www.crd.york.ac.uk)
  - International Network of Agencies for Health Technology Assessment (INAHTA) (internet) (https://database.inahta.org/)
  - National Institute for Health and Care Excellence (NICE) guidelines (www.nice.org.uk)
  - Gemeinsamer Bundesausschuss (G-BA)/Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)
- **Other databases**:
  - Embase® (Ovid)
  - MEDLINE® (PubMed)

Search strategies and results per data source are provided in Appendix A.

Grey literature searches were conducted by searching the reference lists of priority studies for extraction to identify additional records. In addition, *ad-hoc* desktop research was performed to fill any evidence gaps. Searches were de-duplicated in EndNote™.

Screening

Screening was performed in Microsoft® Excel®. Two reviewers independently screened records in line with Cochrane guidance.[1] Any disagreements were resolved through discussion or the intervention of a third reviewer.

Data Extraction

Data extraction was conducted by a single reviewer and 20% of data were checked by a second reviewer in line with Cochrane rapid review guidance.[2] Data extraction was conducted directly into the report (i.e. a standalone data extraction workbook was not produced). The final list of included studies to extract was agreed with the SHARE TO CARE team before data extraction began.

Risk of Bias Assessment

Risk of bias (RoB) was assessed using a tool matched to the study design. Guidelines were assessed using AGREE II RoB tool. Systematic reviews were assessed using the ROBIS tool. HTA assessments were not formally assessed. Randomised controlled trials were assessed using the Cochrane RoB tool (version 1)[1] and single-arm studies were assessed using the MINORS tool.[3] A risk of bias assessment sheet was designed in Microsoft® Excel® for each tool. A single reviewer performed quality assessments.

Data Synthesis

An evidence hierarchy was used to identify the best available evidence for each research question. Where multiple relevant studies were identified, the best available evidence was defined based on:

- Date (prioritising the most recent studies)
- Risk of bias (prioritising studies rated at low risk of bias)
- Closeness of population match (prioritising studies in patients who represent the target population; however, for example, asymptomatic patients would be considered where no studies of symptomatic patients are identified)

Where data permitted, risk ratios and 95% confidence intervals were plotted using RevMan 5.4.0 for Mac to graphically represent the data.[4] Dichotomous data were plotted using the Mantel-Haenszel method with random effects. However, no formal meta-analysis or quantitative synthesis was performed. Figures were drawn in GraphPad Prism for Mac (version 10.3.0).

Protocol Amendments

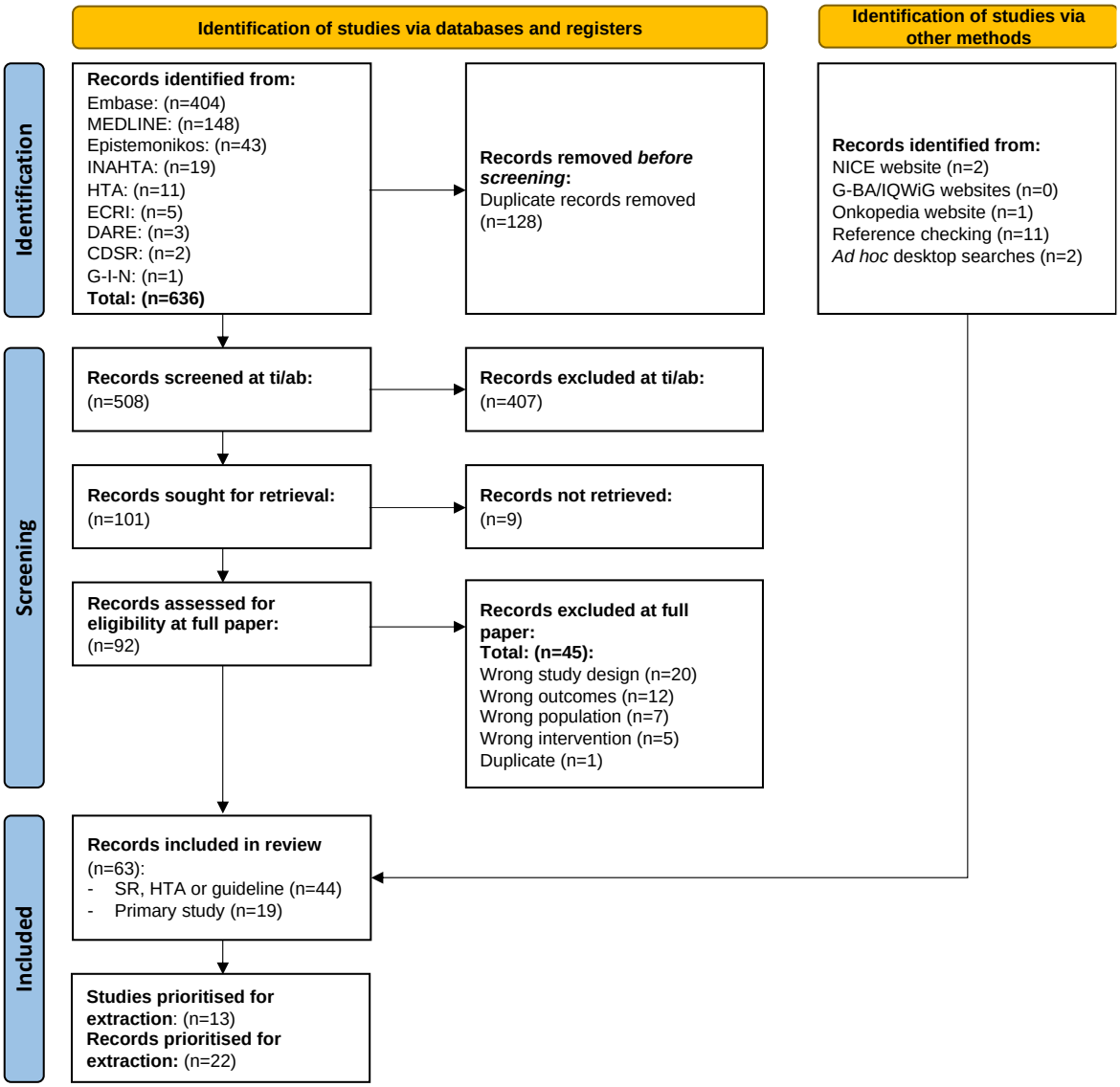
None.

4. Results

Literature searches

A total of 636 records were retrieved from database searches. After de-duplication, 508 records were screened at the title/abstract stage. 101 were identified as potentially relevant and taken through to full paper screening; full papers were not obtainable for 9 records so 92 were finally screened. At the full paper screening stage, a total of 45 records were excluded: 20 for wrong study design, 12 for wrong outcomes, 7 for wrong population, 5 for wrong intervention and 1 duplicate. The list of studies excluded during full paper screening is provided in Appendix C. Grey literature searches included an additional 16 records. Overall, a total of 13 studies (with 22 records) were included. A summary of the study flow is provided in Figure 1.

Figure 1: PRISMA flow diagram



Abbreviations: NICE, National Institute for Health and Care Excellence; PRISMA, preferred reporting items in systematic reviews and meta-analyses; ti/ab, title/abstract.

Overview of included studies

Nine frequently asked questions of key relevance to shared decision-making in PNH were compiled and eligibility criteria created to reflect consultations with the commissioner and clinical expert. A total of 13 priority studies (22 records) were identified as key sources of evidence. An overview of the 13 priority studies is provided in Table 2; the 22 data sources that trial data were extracted from, plus the FAQs that they informed, are summarised in Table 3. A list of included but deprioritised studies is provided in Appendix B.

Across the 13 priority included studies, 9 were randomised controlled trials and 4 were single-arm studies. Eight of the 13 studies reported on complement inhibitor-naïve patients and five of the 13 studies reported on complement inhibitor-experienced patients. The study sample size ranged from 27 to 246 patients (Table 2).

Ten studies were multinational and one study each was performed in the USA (SHEPHERD), UK (X03-001) and Japan (AEGIS) (Table 2).

Treatments across the trials included eculizumab (9 studies), ravulizumab (2 studies), eculizumab or ravulizumab (2 studies), pegcetacoplan (2 studies), iptacopan (2 studies), crovalimab (2 studies), danicopan plus eculizumab/ravulizumab (1 study) and standard-of-care/placebo (2 studies). An overview of the treatment evidence network is provided in Figure 2 for complement inhibitor-naïve patients, and in Figure 3 for complement inhibitor-experienced patients.

Table 2: Overview of relevant trials

Study ID	Treatments	Population	# patients	Design	Phase	Blinding	Country	RoB rating
AEGIS	Eculizumab	Complement inhibitor-naïve PNH patients	27	Single arm extension study	NR	Open-label	Japan	12/16
ALXN1210-PNH-301 (Study 301), NCT02946463	Ravulizumab Eculizumab	Complement inhibitor-naïve with clinical symptoms indicating high disease activity	125 121	Randomised	3	Open-label	Multi-national	High
ALXN1210-PNH-302 (Study 302), NCT03056040	Ravulizumab Eculizumab	Complement inhibitor-experienced with clinically stable disease	97 98	Randomised	3	Open-label	Multi-national	High
ALPHA, NCT04469465	Danicopan plus eculizumab or ravulizumab Placebo plus eculizumab or ravulizumab	Complement inhibitor-experienced PNH patients with clinically significant EVH	57 29	Randomised	3	Double-blind	Multi-national	Unclear
APPLY-PNH, NCT04558918	Iptacopan Eculizumab or ravulizumab	Complement inhibitor-experienced PNH patients with residual anaemia	62 35	Randomised	3	Open-label	Multi-national	High
APPOINT-PNH, NCT04820530	Iptacopan	Complement inhibitor-naïve PNH patients	40	Single-arm study	3	Open-label	Multi-national	12/16
COMMODORE 1, NCT04432584	Crovalimab Eculizumab	Complement inhibitor-experienced PNH patients	45 44	Randomised	3	Open-label	Multi-national	High
COMMODORE 2, NCT04434092	Crovalimab Eculizumab	Complement inhibitor-naïve PNH patients	135 69	Randomised	3	Open-label	Multi-national	High
PEGASUS, NCT03500549	Pegcetacoplan Eculizumab	Complement inhibitor-experienced PNH patients with residual	41 39	Randomised crossover	3	Open-label	Multi-national	High

Study ID	Treatments	Population	# patients	Design	Phase	Blinding	Country	RoB rating
		anaemia						
PRINCE, NCT04085601	Pegcetacoplan	Complement inhibitor-naïve PNH patients	35	Randomised	3	Open-label	Multi-national	High
	SOC, excluding complement inhibitors		18					
TRIUMPH, NCT00122330	Eculizumab	Complement inhibitor-naïve PNH patients with good bone marrow reserve	43	Randomised	3	Double-blind	Multi-national	Low
	Placebo		44					
SHEPHERD, NCT00130000	Eculizumab	Complement inhibitor-naïve PNH patients with thrombocytopenia	97	Single-arm	3	Open-label	Multi-national	13/16
X03-001	Eculizumab	Complement inhibitor-naïve PNH patients	11	Single-arm	Extension study	Open-label	UK	12/16

Abbreviations: EVH, extravascular haemolysis; PNH, paroxysmal nocturnal haemoglobinuria; SOC, standard of care; UK, United Kingdom; USA, United States of America.

Table 3: Overview of included study sources

Study ID	Record type	Key treatment comparisons	Key patient populations	Do I have to receive therapy?	FAQ1: What does treatment involve	FAQ2: Will the therapy affect my haemoglobin level, and transfusion avoidance?	FAQ3: Will the treatment impact how long I live?	FAQ4: How will the treatment impact my QoL?	FAQ5: What are the risks or side effects?	FAQ6: Are there any long-term negative effects of treatment?	FAQ7: Where can I get additional information?	FAQ8: Is there anything I can do myself to help my disease?	FAQ9: Living with the disease
Brodsky 2008[5]	Primary study	Eculizumab; placebo	CI-naïve			✓		✓	✓	✓			
Cançado 2021[6]	Consensus statement	Eculizumab; standard of care	NA	✓									
de Latour 2022[7]	Primary study	Pegcetacoplan	CI-experienced			✓	✓		✓	✓			
EMA 2024[8]	Regulatory document	Danicopan	CI-experienced		✓								
FDA 2024[9]	Regulatory document	Crovalimab	CI-naïve or CI-experienced		✓								
Goh 2024[10]	Guidelines/ expert opinion	Crovalimab; eculizumab	CI-naïve or CI-experienced	✓	✓							✓	
Hill 2005[11]	Primary study	Eculizumab	CI-naïve			✓	✓	✓	✓	✓			
Hillmen 2016[12]	Primary study	Eculizumab; placebo	CI-naïve			✓	✓	✓	✓				
Kanakura 2013[13]	Primary study	Eculizumab	CI-naïve			✓	✓		✓	✓			

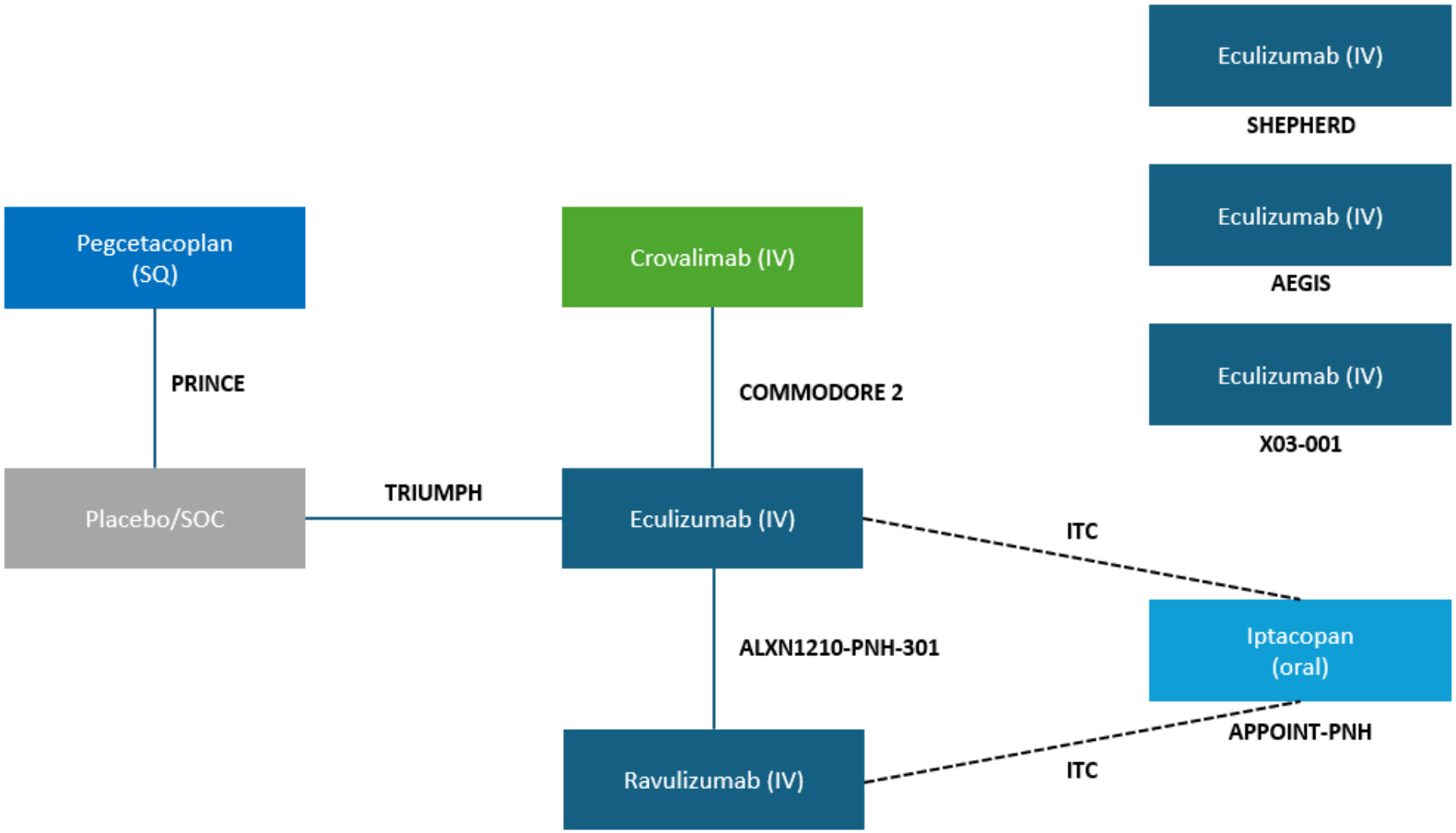
Study ID	Record type	Key treatment comparisons	Key patient populations	Do I have to receive therapy?	FAQ1: What does treatment involve	FAQ2: Will the therapy affect my haemoglobin level, and transfusion avoidance?	FAQ3: Will the treatment impact how long I live?	FAQ4: How will the treatment impact my QoL?	FAQ5: What are the risks or side effects?	FAQ6: Are there any long-term negative effects of treatment?	FAQ7: Where can I get additional information?	FAQ8: Is there anything I can do myself to help my disease?	FAQ9: Living with the disease
Kulasekararaj 2022[14]	Primary study	Ravulizumab; eculizumab	CI-naïve or CI-experienced			✓				✓			
Lee 2023[15]	SR and MA	Eculizumab; ravulizumab; pegcetacoplan	CI-naïve or CI-experienced			✓			✓	✓			
NCT04085601[16]	Registry	Pegcetacoplan; SOC (excluding CIs)	CI-naïve			✓	✓	✓	✓				
NICE 2021[17]	HTA	Ravulizumab; eculizumab	CI-naïve or CI-experienced	✓		✓	✓	✓	✓	✓			
NICE 2022[18]	HTA	Pegcetacoplan; eculizumab	CI-experienced	✓		✓	✓	✓	✓				✓
NICE 2024[19]	HTA	Iptacopan; eculizumab/ ravulizumab	CI-naïve or CI-experienced	✓	✓	✓	✓	✓	✓	✓			
NICE 2024[20]	HTA	Danicopan plus eculizumab or ravulizumab; placebo plus eculizumab or ravulizumab	CI-experienced	✓	✓	✓	✓	✓	✓				
Onkopedia 2023[21]	Guidelines	Eculizumab; ravulizumab;	CI-experienced		✓						✓	✓	

Study ID	Record type	Key treatment comparisons	Key patient populations	Do I have to receive therapy?	FAQ1: What does treatment involve	FAQ2: Will the therapy affect my haemoglobin level, and transfusion avoidance?	FAQ3: Will the treatment impact how long I live?	FAQ4: How will the treatment impact my QoL?	FAQ5: What are the risks or side effects?	FAQ6: Are there any long-term negative effects of treatment?	FAQ7: Where can I get additional information?	FAQ8: Is there anything I can do myself to help my disease?	FAQ9: Living with the disease
		pegcetacoplan											
Panse 2023[22]	Primary study	Crovalimab; eculizumab	CI-naïve or CI-experienced					✓					
Pires 2023[23]	SR	Eculizumab; ravulizumab; pegcetacoplan	CI-naïve or CI-experienced			✓	✓	✓	✓	✓			
Röth 2024[24]	Primary study	Crovalimab; eculizumab	Complement inhibitor-naïve			✓	✓	✓	✓				
Scheinberg 2024[25]	Primary study	Crovalimab; eculizumab	CI-experienced		✓	✓	✓	✓	✓				
Wong 2021[26]	Primary study	Pegcetacoplan; SOC (excluding CIs)	CI-naïve			✓	✓	✓	✓				

Abbreviations: CI, complement inhibitor; EMA, European Medicines Agency; FDA, Food and Drug Administration; HTA, health technology assessment; MA, meta-analysis; PNH, paroxysmal nocturnal haemoglobinuria; SmPC, summary of product characteristics; SOC, standard of care; SR, systematic review.

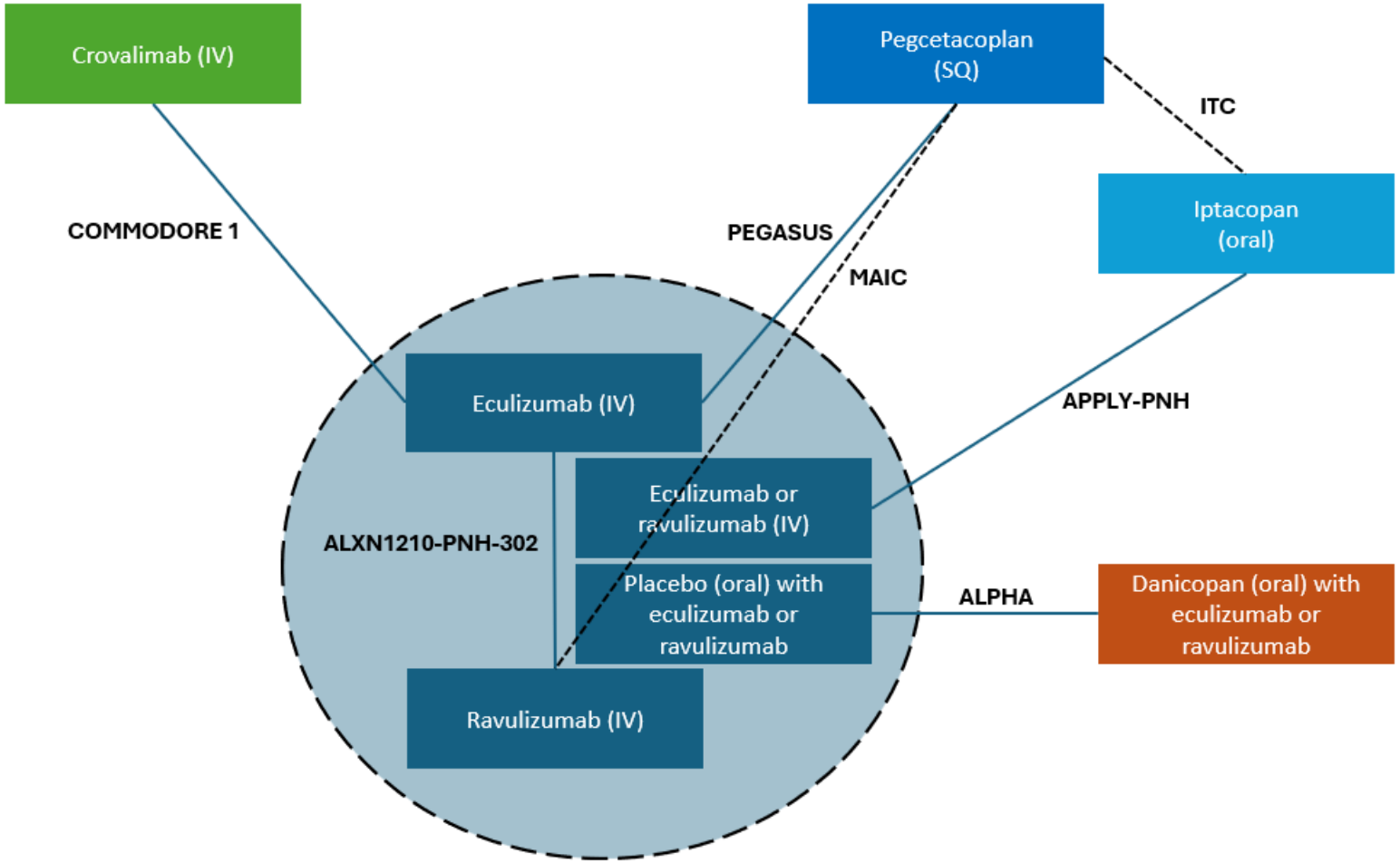
* Only AEGIS was added as a new study as the other RCTs had already provided high quality evidence for other drugs of interest.

Figure 2: Overview of treatment evidence network for complement inhibitor-naïve patients



Abbreviations: ITC, indirect treatment comparison; IV, intravenous; SOC, standard-of-care; SQ, subcutaneous.

Figure 3: Overview of treatment evidence network for complement inhibitor-experienced patients



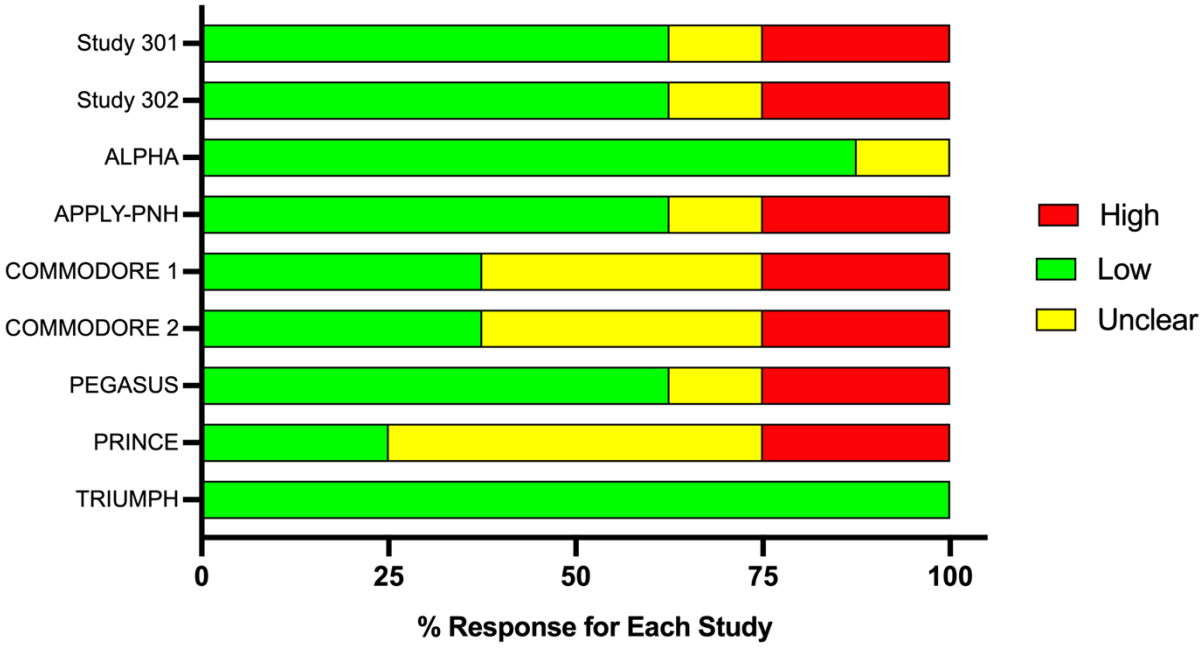
Abbreviations: ITC, indirect treatment comparison; IV, intravenous; MAIC, matched adjusted indirect comparison; SQ, subcutaneous.

Risk of bias

The risk of bias in each included study was assessed with a RoB tool matched to the study design[1]. The nine randomised controlled trials were assessed with the Cochrane RoB1 tool at the study level, and the four single-arm studies were assessed with the MINORS tool at the study level[3].

Nine randomised controlled trials (Study 301, Study 302, ALPHA, APPLY-PNH, COMMODORE 1, COMMODORE 2, PEGASUS, PRINCE, TRIUMPH) were assessed using the Cochrane RoB1 tool (Figure 4). One study (TRIUMPH) was rated at an overall low risk of bias. One study (ALPHA) was rated at an overall unclear risk of bias due to a lack of information on whether outcome assessors were blinded. Most RCTs (Study 301, Study 302, APPLY-PNH, COMMODORE 1, COMMODORE 2, PEGASUS, PRINCE) were rated at an overall high risk of bias; this rating was predominantly driven by the open-label nature of these trials meaning that neither the participants nor personnel were blinded.

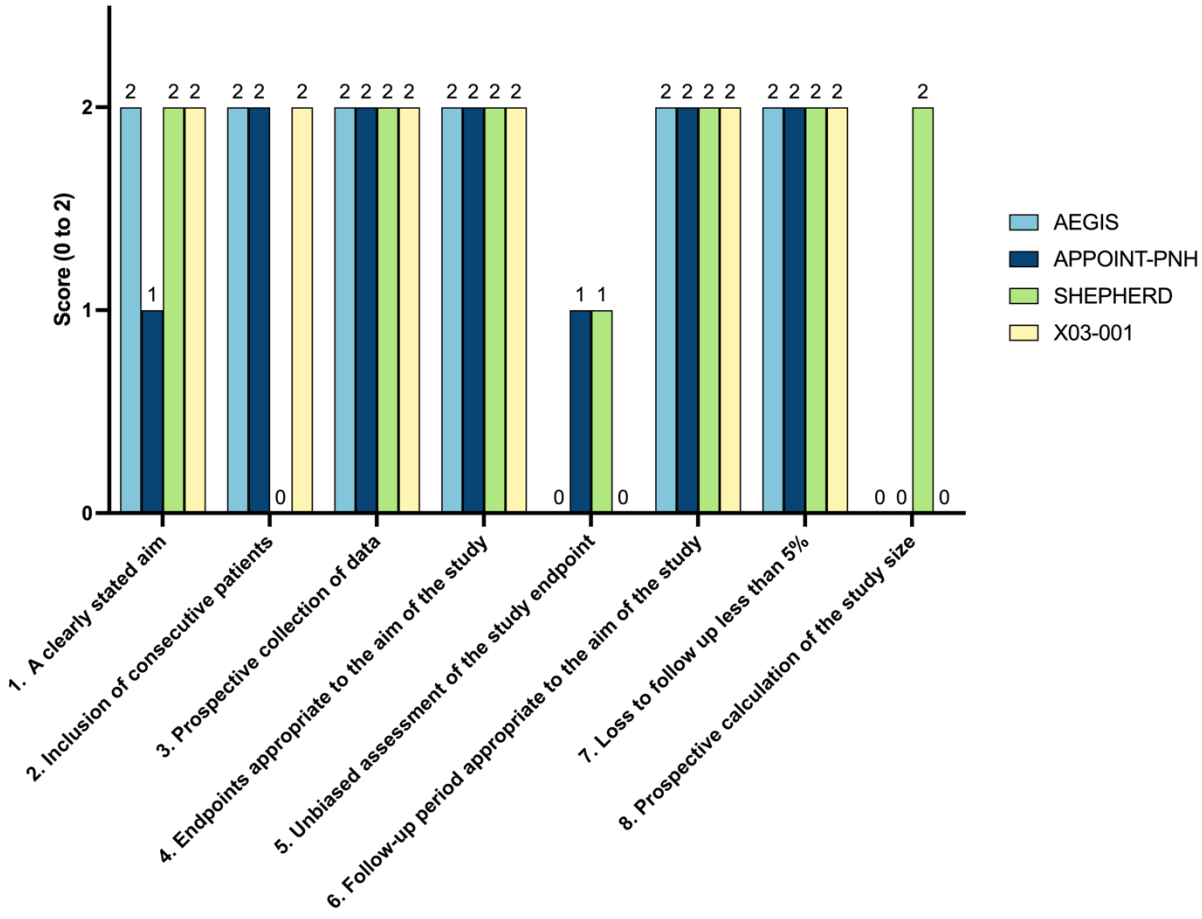
Figure 4: Risk of bias across the included randomised controlled trials



Four single arm studies (AEGIS, APPOINT-PNH, SHEPHERD, X03-001) were assessed using the MINORS tool (Figure 5). Out of 16 potential points, one study (SHEPHERD) was rated at 13 points, and three studies (AGEIS, APPOINT-PNH, X01-001) were rated at 12 points.

A full summary of the risk of bias assessments, including those for study sources (e.g. systematic reviews, guidelines), is provided in Appendix D.

Figure 5: Risk of bias across the included single arm studies



Research questions

Introduction to the disease

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare, life-threatening disease that develops when haematopoietic stem cell(s) (HSC) acquire a particular type of genetic mutation. These mutations reduce the level of protective proteins on the surface of the red blood cells that the HSC produces and leads to them being destroyed by the complement system in a process known as haemolysis. This is the classical (haemolytic) form of PNH.[6] PNH can occur at any age but typically manifests at 30-40 years of age.

The global incidence of PNH is estimated at 1 to 1.5 cases per million individuals,[27] and its prevalence is estimated at 15.9 per million in Europe,[28] although this is a potential underestimate. In Germany, it is estimated that there are approximately 63 adults with PNH.[29] Classical (haemolytic) PNH is diagnosed in approximately 30% of PNH patients. Classical PNH is a chronic, progressive disease that presents with symptoms including muscle dystonias (such as oesophageal spasm or erectile dysfunction), severe fatigue, anaemia, abdominal pain, kidney failure and thrombosis.[30]

Conventional treatments for classical PNH have typically been targeted towards the symptoms of the disease, including blood transfusions to treat haemolysis, anti-coagulants to prevent thrombosis and allogeneic haematopoietic stem cell transplant (HSCT) to replace bone marrow deficiencies. HSCT is the only potentially curative treatment option as this can potentially eradicate the affected HSC; however, only a small proportion of severely affected patients (e.g. those with bone marrow deficiency, those who are resistant to eculizumab/thromboprophylaxis or those with recurrent complications) are typically offered HSCT as it has substantial side effects and can be lethal, in addition to the lack of suitable donors.[31 32] Oral iron supplements together with folate acid and vitamin B12 supplements are also typical treatment options.

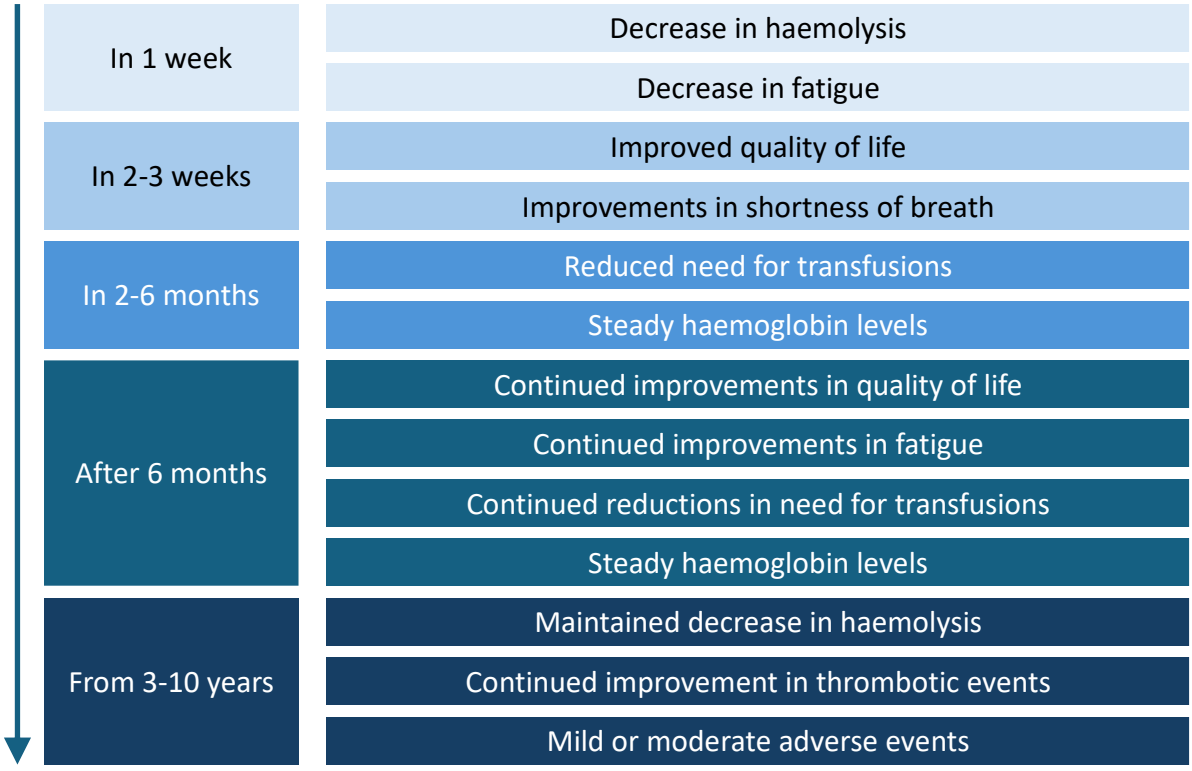
The modern standard-of-care for symptomatic patients with classical PNH now includes monoclonal antibody C5 inhibitors (C5is; eculizumab, ravulizumab, crovalimab).[33] Most people with PNH have ravulizumab. People who still have anaemia after having a C5 inhibitor usually have pegcetacoplan or ravulizumab. Additional recent treatment options include iptacopan (a proximal complement inhibitor that targets Factor B[19]) and danicopan (a Factor D inhibitor) as an add-on to eculizumab/ravulizumab.[20] These targeted approaches block different elements of the complement cascade to prevent haemolysis, and thus the appearance of symptoms.

Do I have to receive treatment? Can I delay treatment? When should I start treatment?

Patients with mild symptoms can take a watchful waiting approach that includes monitoring every 6-12 months for signs of haemolysis, bone marrow disorder, new complications or the expansion of additional immune cell clones.[10] However, once symptoms become more moderate or severe, such as disabling fatigue, thrombosis, transfusion dependence, frequent pain paroxysms, renal insufficiency or other organ complications, active treatment is recommended.[30]

PNH is typically a progressive disease that will only get worse with time, so the sooner patients start treatment the better. This will delay progression to kidney disease and the potential need for dialysis and kidney transplant. Most patients notice an improvement in their symptoms within hours or a few days of starting complement inhibitor treatment. For eculizumab treatment, a typical timeline of treatment response is provided in Figure 6.

Figure 6: Typical timeline of treatment with eculizumab



Adapted from Cançado 2021[6]

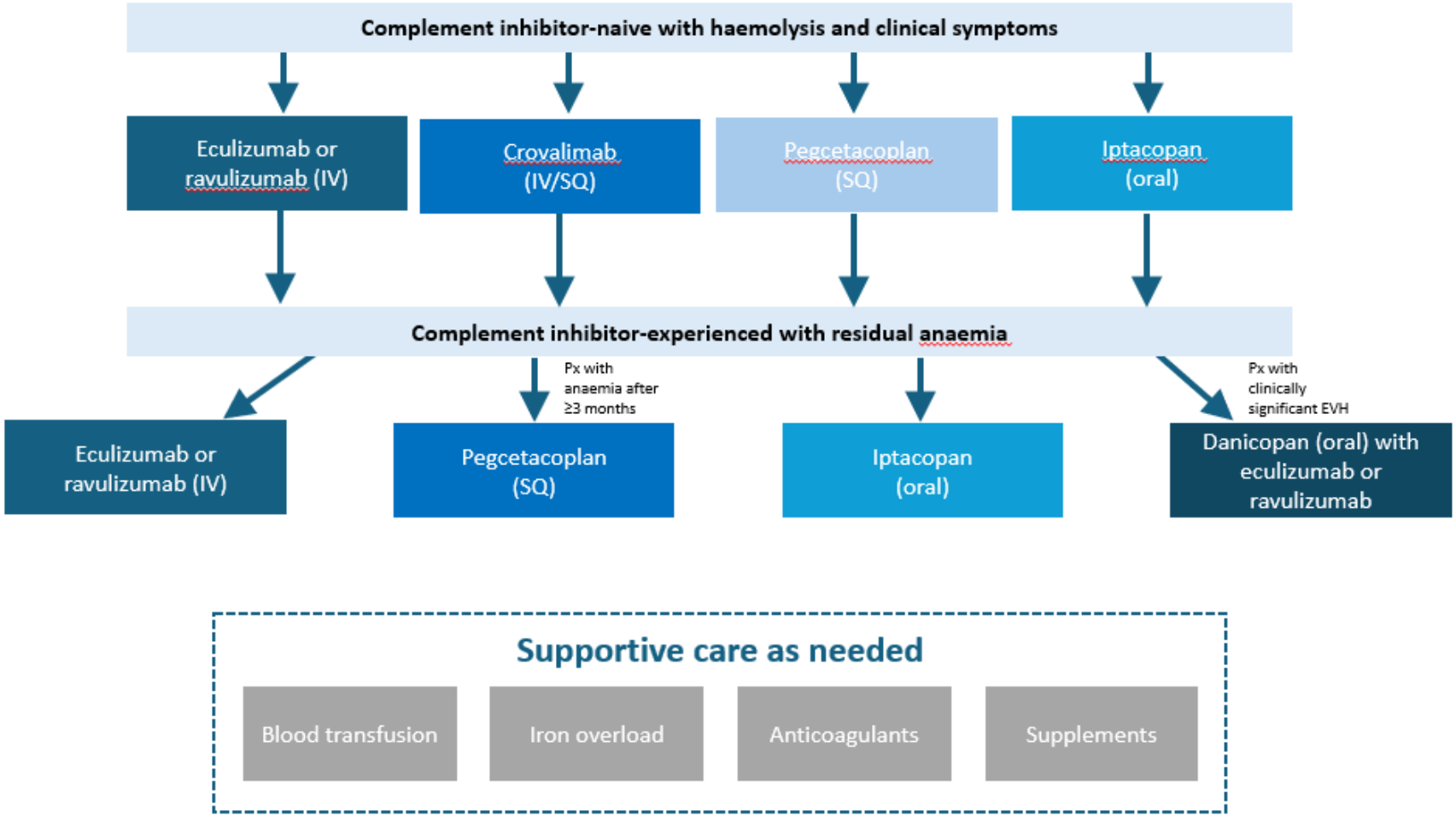
An overview of current treatment options for PNH is provided in Figure 7. Typically, complement C5 inhibitors (including ravulizumab, eculizumab or crovalimab) are given as terminal complement inhibitor treatment options. Alternatively pegcetacoplan, a C3-inhibitors can be started in therapy naïve patients as the first in class proximal complement inhibitor. Recently, iptacopan, a Factor B inhibitor, has also emerged as a potential new proximal complement inhibitory (blocking Factor B) treatment option.

If complement C5 inhibitors have an inadequate effect (such as on-going or emerging transfusion dependency or regular breakthrough haemolysis), due to pharmacokinetic reasons, the dose can be increased, the interval between dosing can be shortened or patients can switch to a different C5 inhibitor.

If patients on a complement C5 inhibitor experience clinically relevant extravascular haemolysis, leading to severe fatigue or impaired quality of life or continued or emerging transfusion dependency, patients can switch to pegcetacoplan or iptacopan. Alternatively, danicopan can be considered as an add-on to existing treatment with eculizumab or ravulizumab.

Supportive care, which includes blood transfusions, iron overload therapy, anticoagulants and iron supplements, may also be necessary.

Figure 7: Current treatment pathway options for PNH



Abbreviations: EVH, extravascular haemolysis; IV, intravenous; SQ, subcutaneous.
Adapted from NICE TA698,[17] NICE TA778,[18] NICE TA11132[19] and NICE TA10980[20]

FAQ1: What does the treatment involve?

Eculizumab is a C5 inhibitor that is currently approved for PNH patients who have already received transfusions.[21] It is administered intravenously (IV) by a healthcare professional. The injection is initially administered once a week for 4 weeks (600mg IV) over 25-45 minutes, and then administered every two weeks (900mg IV) over 25-45 minutes.[21] Treatment is usually followed by a 60-minute observation period.[21]

Ravulizumab is a C5 inhibitor that is currently approved for adult patients with PNH who either have a) haemolysis together with one or more clinical symptom suggesting high disease activity, or b) who are clinically stable after receiving eculizumab for at least 6 months.[21] Ravulizumab is a re-engineered version of eculizumab that lasts longer in the body and so can be given less frequently. Similar to eculizumab, ravulizumab is administered by IV infusion by a healthcare professional, and the dose varies based on the patient's weight. At the start of treatment, patients receive a single loading dose (between 2,400 to 3,000 mg IV) over 24-45 minutes, and 2 weeks later this is followed by maintenance dosing (3,000 to 3,600 mg IV every 8 weeks) over 30-55 minutes.[21]

Since eculizumab and ravulizumab are given intravenously, in some cases, there can be an issue with the canulation needed to administer the drugs if access to the person's veins is poor.

Crovalimab is a new C5 inhibitor similar to eculizumab and ravulizumab, and the dose varies by bodyweight. A loading dose is initially administered by a healthcare professional via IV infusion (1,000 to 1,500 mg IV) followed by four more fixed-dose loading doses that can be self-administered subcutaneously just under the skin (340mg SQ) and finally a subcutaneous maintenance dose (680 to 1,020 mg SQ) that is self-administered every 4 weeks.[25] The IV dose takes between 60 to 90 minutes to administer while the SQ dose takes a few minutes.[9] Crovalimab is positioned as an intermediate option between eculizumab and ravulizumab where the maintenance dose is less frequent than eculizumab (every 2 weeks) and more frequent than ravulizumab (every 8 weeks) but can be self-administered in the maintenance phase for extra convenience (whereas both eculizumab and ravulizumab continue to be administered IV by a healthcare professional). For patients switching from eculizumab or ravulizumab, the first loading dose of crovalimab needs to be administered whenever the next complement inhibitor is due.

Pegcetacoplan is a C3 inhibitor that is approved as a second-line treatment for adult PNH patients who have been treated with C5 inhibitors (e.g. eculizumab, ravulizumab) but remain anaemic after treatment for at least 3 months.[21] Pegcetacoplan is self-administered as a SQ injection just under the skin. This can be more convenient as a healthcare professional doesn't have to give the injection and patients can be more self-sufficient in their treatment. However, pegcetacoplan is administered more frequently than other treatments; this may be less convenient and could increase the likelihood of injection site reactions. It may also be unsuitable for those with visual or physical disabilities, or those who are obese (since this can decrease drug absorption). Pegcetacoplan is administered twice a week (on day 1 and day 4) or every three days at a dose of 1,080 mg in a 20ml infusion using a pump.[21] For the first 4 weeks of treatment, pegcetacoplan is given alongside the current dose of C5 inhibitor treatment to minimise the risk of haemolysis, after which

pegcetacoplan is given on its own (without the C5 inhibitor).[21] After removing the drug from the fridge 30 minutes before administration, the typical infusion time is approximately 30 minutes for two infusion sites or approximately 60 minutes for one infusion site.[19]

Iptacopan is a Factor B inhibitor that can be either given to patients who have not previously received complement inhibitors but are experiencing haemolysis and clinical symptoms, or patients who still have residual anaemia while receiving another complement inhibitor.[19] Ipcatopan is an oral medication, and the 200mg capsules are administered twice daily. For patients switching to iptacopan from C5 inhibitors, treatment with iptacopan should start no later than one week after the last dose of eculizumab or no later than six weeks after the last dose of ravulizumab.[19]

Danicopan is a Factor D inhibitor that is approved as an add-on for adult PNH patients who still have residual anaemia while receiving either eculizumab or ravulizumab.[20] It is administered as an oral therapy with or without food, which can be easier for patients with needle phobias or those who have problems with accessing veins.[20] The recommended starting dose is 150mg three times a day around 8 hours apart. This dose can be increased to 200 mg three times a day after 4 weeks depending on how the patient is responding to the drug.[8] Danicopan is given alongside maintenance treatment with either eculizumab or ravulizumab.

Treatment with eculizumab, ravulizumab, pegcetacoplan, iptacopan and danicopan is likely to be life-long or until a better treatment is available. Regular check-ins to monitor treatment response are needed: these are typically scheduled monthly during the initial 3 months followed by once every 3 months.[10]

Any patients receiving complement inhibitors are recommended to receive vaccinations against *Neisseria meningitidis* types A, C, W, Y and B at least two weeks prior to starting treatment together with *Streptococcus pneumoniae* vaccination;[10 30] and *Haemophilus influenzae* type B vaccination within 2 years prior to starting therapy.[30] Patients should be re-vaccinated every 3-5 years after starting treatment and should seek immediate medical attention if they experience any signs or symptoms of infection.[30] If patients aren't vaccinated at the time they would like to start complement inhibitor therapy, it is recommended to delay getting vaccinated due to the risk of haemolysis. Instead, primary antibiotic prophylaxis is administered for two weeks followed by vaccination.[21]

Patients who receive complement inhibitors may also need supportive care to help manage any on-going symptoms or anaemia. This can include blood transfusions, iron overload treatment, anticoagulants, and iron, folic acid and vitamin B12 supplementation. PNH patients with a history of thromboembolic events who are receiving complement inhibitors are recommended to continue long-term anti-coagulation therapy: in patients who are well controlled, this could be for 3-6 months; for patients with additional risk factors, this may be lifelong.[10]

Finally, allogeneic HSCT remains the only curative treatment for PNH; however, it is usually reserved for severe PNH patients who are unresponsive to other treatments. This is because of the challenges of finding a matching donor and the serious risks of side effects or death,

particularly after conventional conditioning regimens.[21 31] The choice of conditioning regimen can be driven by patients wishing to preserve their fertility etc.

FAQ2: Will the therapy affect my haemoglobin level, and transfusion avoidance?

Transfusions and transfusion avoidance

A total of 13 studies (9 RCTs, 4 single-arm) provided evidence on transfusions across all drugs of interest (

Table 4). Eight studies (4 RCTs) reported on complement inhibitor-naïve patients, and five studies (all RCTs) reported on complement inhibitor-experienced patients. Risk of bias ranged from high to low.

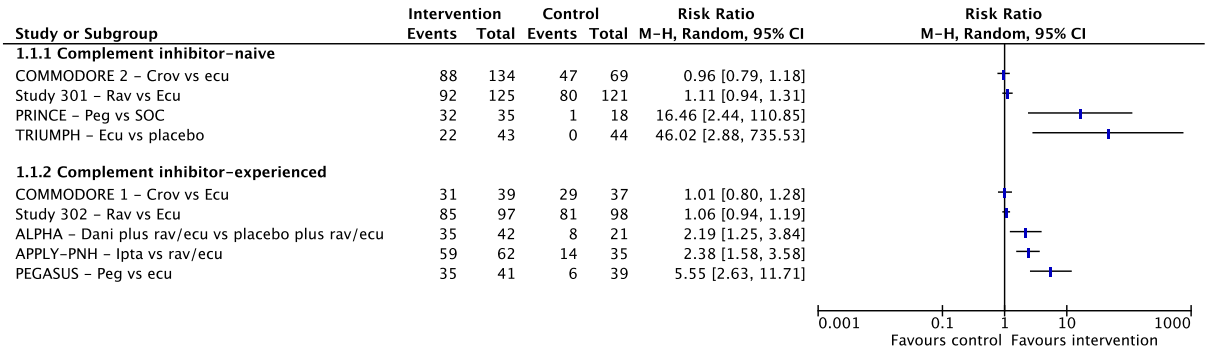
In complement inhibitor-naïve patients, RCT evidence indicated similar rates of transfusion avoidance for eculizumab, ravulizumab and crovalimab; and both pegcetacoplan and eculizumab were significantly better than conventional standard of care/placebo at avoiding transfusions (Figure 8).

In complement inhibitor-experienced patients, RCT evidence indicated similar rates of transfusion avoidance for eculizumab, ravulizumab and crovalimab. Danicopan as an add-on to eculizumab/ravulizumab significantly improved rates of transfusion avoidance compared to eculizumab/ravulizumab alone. Iptacopan was significantly better than eculizumab/ ravulizumab; and pegcetacoplan was significantly better than eculizumab for transfusion avoidance (Figure 8).

Single-arm study evidence also reported significant improvements from baseline in transfusion avoidance (

Table 4).

Figure 8: Forest plot of transfusion avoidance



Abbreviations: Crov, crovalimab; dani, danicopan; ecu, eculizumab; ipta, iptacopan; peg, pegcetacoplan; rav, ravulizumab; SOC, standard-of-care. Note that the drug named first in the study name is the experimental arm; the drug named second in the study name is the control.

Long term transfusion avoidance

Five studies reported on longer-term transfusion avoidance, three in complement inhibitor-naïve patients (AEGIS, Study 301, SHEPHERD) and two in complement inhibitor-experienced patients (Study 302, PEGASUS). In complement inhibitor-naïve patients, rates of transfusion avoidance for eculizumab at ≥48 weeks of follow-up ranged from 52.6% to 96%; and were 73.3% for ravulizumab in an >12-18 months extension period. In complement inhibitor-experienced patients, rates of transfusion avoidance for pegcetacoplan after crossover ranged from 72-73% at 48 weeks of follow-up; and were 85.3% for ravulizumab in an >12-18 months extension period (Table 18).

Conclusion for the decision Aid:

In **complement-inhibitor (CI) naïve** patients the need for transfusions occurs in approximately 94 to 100 of 100 patients in patients without CI therapy. The need for transfusions with proximal and terminal CIs is about 9 to 49 of 100 patients. Differences between proximal and terminal CIs have not yet been investigated directly. CIs can reduce the need for transfusions by approximately 51 to 86 of 100 patients compared to standard of care or placebo (2 studies; RoB high).

In **CI-experienced patients** rates of patients, who needed transfusions with ravulizumab, eculizumab or crovalimab ranged between 12 and 85 of 100 (R0B unclear/high). Only 5 of 100 patients taking iptacopan needed transfusions in one study (RoB high). With pegcetacoplan 15 of 100 patients needed transfusions in one other study (RoB high). Transfusion rates were similar for terminal CIs (crovalimab, ravulizumab, eculizumab; 9-22 of 100). In a single study danicopan as add-on to eculizumab/ravulizumab reduced the rate of patients, who need transfusions to 17 of 100 compared to 62 of 100 with eculicumab/ravulicumab alone (reduction by 45 of 100; one study; RoB unclear).

Table 4: Transfusions and transfusion avoidance

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
Complement inhibitor-naïve patients										
AEGIS	Eculizumab	Complement inhibitor-naïve PNH patients	Change from baseline in number of pRBC units transfused	66 weeks	NR	NR	Mean change (SE): -4.7 (1.20), P<0.001	Open-label single arm	NA	12/16
			Transfusion avoidance	Baseline	12/29 (40.7%)	NR	NR		NA	
				Last 6 months of extension period	25/26 (96%)					
ALXN1210-PNH-301	Ravulizumab	Complement inhibitor-naïve with clinical symptoms indicative of high disease activity	Received any pRBC transfusion	26 weeks	32/125 (25.6%)	NR	NR	Open-label RCT	Ravulizumab	High
	Eculizumab				40/121 (33.1%)					
	Ravulizumab		Number of transfusions per patient		NR	Mean (SD): 3.3 (4.2)	NR		Ravulizumab	
	Eculizumab					Mean (SD): 3.6 (3.1)				
	Ravulizumab		Transfusion avoidance		92/125 (73.6%)	NR	TD (95% CI): 6.8 (-4.66, 18.14)		Ravulizumab	
	Eculizumab				80/121 (66.1%)					
	Ravulizumab			>12-18 months extension	178/243 (73.3%)	NR	NR		NA	

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
APPOINT-PNH	Iptacopan	Complement inhibitor-naïve PNH patients	Met the criteria for transfusion	Between Day 1 and Day 168	6/40 (15.0%)	NR	NR	Single-arm study	NA	12/16
			Received ≥1 transfusion		5/40 (12.5%)	NR				
			Number of transfusions		NR	Mean (SD): 1.0 (0.0)				
			Didn't need a RBC transfusion	Between Day 14 and Day 168	40/40 (100%)	NR				
			Marginal % of patients avoiding transfusion		97.6% (95% CI: 92.5 to 100.0)	NR				
APPOINT-PNH / Study 301	Iptacopan		Transfusion avoidance	NR	24/31 (78.6%)	NR	I vs R: OR (95% CI): 1.32 (0.46, 3.73), P=0.6011 I vs E: OR (95% CI): 1.88 (0.67, 5.28), P=0.2281	ITC	Iptacopan	12/16 & High
	Eculizumab				92/125 (73.5%)					
	Ravulizumab				80/121 (66.1%)					
COMMODORE 2	Crovalimab	Complement inhibitor-naïve PNH patients	Transfusion avoidance	Week 25	88/134 (65.7%)	NR	Adjusted mean change (95% CI): -2.8 (-15.7, 11.1)	Open-label RCT	Eculizumab	High
	Eculizumab				47/69 (68.1%)					

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
PRINCE	Pegcetacoplan	Complement inhibitor-naïve PNH patients	Units of pRBCs transfused	Week 26	NR	Median (range): 0.0 (0, 19)	Median difference (95% CI): 3 (2, 4), P<0.0001	Open-label RCT	Pegcetacoplan	High
	SOC, excluding complement inhibitors					Median (range): 3.0 (0, 13)				
	Pegcetacoplan		Transfusion avoidance		32/35 (91.4%)	NR	Difference (95% CI): 0.7241 (0.5583, 0.8899), P<0.0001		Pegcetacoplan	
	SOC, excluding complement inhibitors				1/18 (5.6%)					
SHEPHERD	Eculizumab	Complement inhibitor-naïve PNH patients with thrombocytopenia	Units of pRBCs transfused	52 weeks	NR	Mean (SE): 5.9 (1.06)	Change from baseline: <0.001	Single arm	NA	13/16
			Transfusion independence		51/97 (52.6%)	NR	NR			
TRIUMPH	Eculizumab	Complement inhibitor-naïve PNH patients with good bone marrow reserve	Number of units of pRBC transfused	Week 26	NR	Mean (SD): 3.0 (0.7)	NR	Double-blind RCT	Eculizumab	Low
	Placebo					Mean (SD): 11.0 (0.8)				
	Eculizumab		Transfusion independence		22/43 (51%)	NR	P<0.0001		Eculizumab	
	Placebo				0/44 (0%)					

X03-001	Eculizumab	Complement inhibitor-naïve PNH patients	Transfusion rate	Baseline	NR	Mean 2.1	P=0.001	Open-label extension study	NA	12/16
				64 weeks		Mean 0.5				
Complement inhibitor-experienced patients										
ALXN1210-PNH-302	Ravulizumab	Complement inhibitor-experienced with clinically stable disease	Received any pRBC transfusion	26 weeks	10/97 (10.3%)	NR	NR	Open-label RCT	Ravulizumab	High
	Eculizumab				14/98 (14.3%)					
	Ravulizumab		Number of transfusions per patient		NR	Mean (SD): 2.7 (2.8)	NR		Eculizumab	
	Eculizumab					Mean (SD): 2.0 (1.3)				
	Ravulizumab		Transfusion avoidance		85/97 (87.6%)	NR	TD (95% CI): 5.5 (-4.3, 15.7)		Ravulizumab	
	Eculizumab				81/98 (82.7%)					
	Ravulizumab			>12-18 month extension	163/191 (85.3%)	NR	NR		NA	
ALPHA	Danicopan plus eculizumab or ravulizumab	Complement inhibitor-experienced PNH patients with clinically significant EVH	Transfusion avoidance (remained transfusion-free and didn't need a transfusion per guidelines)	Baseline to week 12	35/42 (83.3%)	NR	Adjusted TD (95% CI): 41.7% (22.7, 60.8), P=0.0004	Double-blind RCT	Danicopan plus eculizumab or ravulizumab	Unclear
	Placebo plus eculizumab or ravulizumab				8/21 (38.1%)					
	Danicopan plus eculizumab or ravulizumab			Week 24	38/55 (69.1%)		NR		NA	

APPLY-PNH	Iptacopan	Complement inhibitor-experienced PNH patients with residual anaemia	Met the criteria for transfusion	Between Day 1 and Day 168	8/62 (12.9%)	NR	NR	Open-label RCT	Iptacopan	High
	Eculizumab or ravulizumab				21/35 (60.0%)					
	Iptacopan		Received ≥1 transfusion		5/62 (8.1%)	NR	NR			
	Eculizumab or ravulizumab				19/35 (54.3%)					
	Iptacopan		Number of transfusions		NR	Mean (SD): 1.4 (0.89)	NR			
	Eculizumab or ravulizumab					Mean (SD): 4.9 (3.97)				
	Iptacopan		Didn't need a transfusion	Between Day 14 and Day 168	59/62 (94.8%)	NR	TD (95% CI): 68.9% (51.4, 83.9), P<0.0001			
	Eculizumab or ravulizumab				14/35 (40%)					
COMMODORE 1	Crovalimab	Complement inhibitor-experienced PNH patients	Transfusion avoidance	24 weeks and extension periods (NR)	31/39 (79.5%)	NR	Weighted difference (95% CI): 1.8 (-16.7, 19.9)	Open-label RCT	Crovalimab	High
	Eculizumab				29/37 (78.4%)					
	Crovalimab		Number of pRBC units transfused		NR	Mean (95% CI): 4.75 (2.53, 6.97)	NR		Crovalimab	
	Eculizumab					Mean (95% CI): 10.00 (7.80, 12.20)				

PEGASUS	Pegcetacoplan	Adults with PNH who continue to have anaemia despite treatment with eculizumab	Didn't avoid a transfusion	16 weeks (3 months)	6/41 (14.6%)	NR	NR	Open-label RCT	Pegcetacoplan	High
	Eculizumab				33/39 (84.6%)					
	Pegcetacoplan		Avoided a transfusion		35/41 (85.4%)	RD (95% CI): 0.6253 (0.4830 to 0.7677), P<0.0001	NR			
	Eculizumab				6/39 (15.4%)					
	Pegcetacoplan to pegcetacoplan			48 weeks	30/41 (73%)	NR	NR		NA	
	Eculizumab to pegcetacoplan				28/39 (72%)					
APPLY-PNH vs. PEGASUS	Iptacopan	Complement inhibitor-experienced	Avoided a transfusion	NR	14/15 (98.7%)	NR	I vs P: OR (95% CI): 12.71 (1.87, 86.22), P=0.009	Unanchored ITC	Iptacopan	High
	Pegcetacoplan				35/41 (85.4%)					
	Eculizumab				6/39 (15.4%)					
	Eculizumab/ ravulizumab				NR/7 (NR%)					

PEGASUS vs. Study 302	Pegcetacoplan	Complement inhibitor-experienced	% more transfusion avoidance	NR	NR	NR	% change (95% CI): 71.4% (53.5, 89.3), P<0.0001	MAIC	Pegcetacoplan	High
	Ravulizumab									
	Eculizumab (anchor)						NA		NA	

Abbreviations: CI, confidence interval; dL, decilitre; g, grams; EVH, extravascular haemolysis; Hb, haemoglobin; ITC, indirect treatment comparison; MAIC, matched adjusted indirect comparison; NA, not applicable; OR, odds ratio; PNH, paroxysmal nocturnal haemoglobinuria; RBC, red blood cell; RCT, randomised controlled trial; RD, risk difference; TD, treatment difference.

* Defined as did not receive transfusions nor meet protocol-defined criteria for transfusion between Day 14 and Day 168.

FAQ3: Will the treatment impact how long I live?

Before the approval of eculizumab in 2007, PNH had poor overall survival (OS) (10-year OS: 50-65%),[34] largely as a result of thrombosis. However, since thrombosis is now generally well managed by complement inhibitors, most PNH patients receiving treatment have an overall survival and rate of death that is the same as the general population.[18]

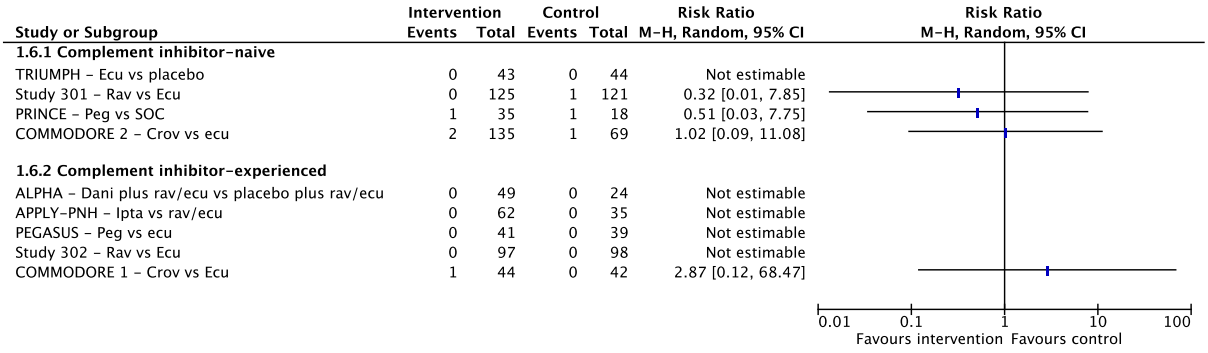
A total of 12 studies (9 RCTs, 3 single-arm) provided evidence on mortality across all drugs of interest (Table 5). Seven studies (4 RCTs) reported on complement inhibitor-naïve patients, and five studies (all RCTs) reported on complement inhibitor-experienced patients. Risk of bias ranged from high to low.

In complement inhibitor-naïve patients, RCT evidence indicated low rates of mortality throughout, with 0-2 deaths per study arm. No deaths were coded as related to treatment (Figure 9).

In complement inhibitor-experienced patients, RCT evidence indicated very low rates of mortality throughout, with 0-1 deaths per study arm. No deaths were coded as related to treatment (Figure 9).

Single-arm study evidence also indicated no deaths on study (Table 5).

Figure 9: Forest plot of deaths



Long term mortality

Four studies reported on longer-term mortality, three in complement inhibitor-naïve patients (AEGIS, APPOINT-PNH, X03-001) and one in complement inhibitor-experienced patients (PEGASUS). In complement inhibitor-naïve patients, rates of mortality were zero for eculizumab at 52 or 66 weeks (2 studies) and zero for iptacopan at 24-48 weeks. In complement inhibitor-experienced patients, the rate of mortality was 1.3% for pegcetacoplan at 48 weeks (the patient died from COVID19) (Table 18).

Conclusion for the decision aid:

Before the approval of eculizumab in 2007, PNH had poor overall survival (OS) (10-year OS: 50-65 of 100 patients) largely as a result of thrombosis. However, since thrombosis is now generally well managed by complement inhibitors, most PNH patients receiving treatment have an overall survival and rate of death that is the same as the general population. No differences between terminal and proximal CIs can be found in clinical studies.

Table 5: Deaths

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change / effect estimate	Study type	Favours?	RoB rating
Complement inhibitor-naïve patients										
AEGIS	Eculizumab	Complement inhibitor-naïve PNH patients	Death during study	66 weeks	0/27 (0%)	NR	NR	Open-label single arm	NA	12/16
ALXN1210-PNH-301	Ravulizumab Eculizumab	Complement inhibitor-naïve with clinical symptoms indicative of high disease activity	Death	26 weeks	0/125 (0%) 1/121 (0.8%)	NR	NR	Open-label RCT	Ravulizumab	High
APPOINT-PNH	Iptacopan	Complement-naïve PNH patients	Death	1-24 weeks (randomised period) and 24-48 weeks (extension period)	0/40 (0%)	NR	NR	Single-arm study	NA	12/16
COMMODORE 2	Crovalimab Eculizumab	Complement inhibitor-naïve PNH patients	AEs leading to death	Week 25	2/135 (1.5%) 1/69 (1.4%)	NR	NR	Open-label RCT	Eculizumab	High
PRINCE	Pegcetacoplan SOC, excluding complement inhibitors	Complement inhibitor-naïve PNH patients	Death	Week 26	1/35 (2.9%) 1/18 (5.6%)	NR	NR	Open-label RCT	Pegcetacoplan	High
TRIUMPH	Eculizumab Placebo	Complement inhibitor-naïve PNH patients with good bone marrow reserve	Death	During study	0/43 (0%) 0/44 (0%)	NR	NR	Double-blind RCT	NED	Low
X03-001	Eculizumab	Complement inhibitor-naïve PNH patients	Death	52 weeks	0/11 (0%)	NR	NR	Open-label extension study	NA	12/16

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change / effect estimate	Study type	Favours?	RoB rating
Complement inhibitor-experienced patients										
ALXN1210-PNH-302	Ravulizumab	Complement inhibitor-experienced with clinically stable disease	Death	26 weeks	0/97 (0%)	NR	NR	Open-label RCT	NED	High
	Eculizumab				0/98 (0%)					
ALPHA	Danicopan plus eculizumab or ravulizumab	Complement inhibitor-experienced PNH patients with clinically significant EVH	Deaths	NR	0/49 (0%)	NR	NR	Double-blind RCT	NED	Unclear
	Placebo plus eculizumab or ravulizumab				0/24 (0%)					
APPLY-PNH	Iptacopan	Complement inhibitor-experienced PNH patients with residual anaemia	Death	During study	0/62 (0%)	NR	NR	Open-label RCT	NED	High
	Eculizumab or ravulizumab				0/35 (0%)					
COMMODORE 1	Crovalimab	Complement inhibitor-experienced PNH patients	Death	24 weeks and extension periods (NR)	1/44 (2.3%)	NR	NR	Open-label RCT	Eculizumab	High
	Eculizumab				0/42 (0%)					
PEGASUS	Pegcetacoplan	Adults with PNH who continue to have anaemia despite treatment with eculizumab	Death	16 weeks (3 months)	0/41 (0%)	NR	NR	Open-label RCT	NED	High
	Eculizumab				0/39 (0%)					
	Pegcetacoplan			48 weeks	1/77 (1.3%) (death due to COVID19)	NR	NR	Open-label extension	NA	

Abbreviations: CI, confidence interval; dL, decilitre; g, grams; Hb, haemoglobin; NED, no evidence of a difference; PNH, paroxysmal nocturnal haemoglobinuria; RCT, randomised controlled trial; RD, risk difference.

FAQ4: How will the treatment impact my quality of life?

Fatigue

A total of 12 studies (9 RCTs, 3 single-arm) provided evidence on fatigue across all drugs of interest (**Fehler! Verweisquelle konnte nicht gefunden werden.**). Seven studies (4 RCTs) reported on complement inhibitor-naïve patients, and five studies (all RCTs) reported on complement inhibitor-experienced patients. Risk of bias ranged from high to low.

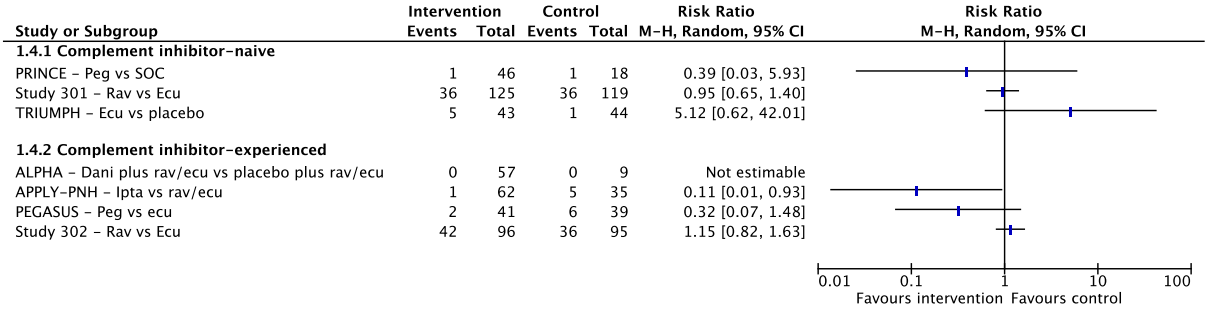
Evidence was captured for three tools to measure fatigue: EORTC QLQ-C30 fatigue, FACIT-Fatigue and fatigue as an adverse event.

In complement inhibitor-naïve patients, RCT evidence indicated numerically lower rates of fatigue for pegcetacoplan vs SOC (PRINCE); similar rates of fatigue for ravulizumab vs eculizumab (Study 301); and numerically higher rates of fatigue for eculizumab vs placebo. However, none of these were statistically significant differences (**Fehler! Verweisquelle konnte nicht gefunden werden.**).

In complement inhibitor-experienced patients, RCT evidence indicated significantly lower rates of fatigue for iptacopan vs ravulizumab/eculizumab (APPLY-PNH); numerically lower rates of fatigue for pegcetacoplan vs eculizumab (PEGASUS); and similar rates of fatigue for ravulizumab vs eculizumab (Study 302). No fatigue was evident in either arm of one trial (ALPHA) comparing danicopan plus eculizumab/ravulizumab vs eculizumab/ravulizumab (**Fehler! Verweisquelle konnte nicht gefunden werden.**). Additional positive changes in FACIT-Fatigue subscales over time for pegcetacoplan vs eculizumab (PEGASUS) are provided in **Fehler! Verweisquelle konnte nicht gefunden werden.**.

Single-arm study evidence also reported significant improvements from baseline in fatigue (**Fehler! Verweisquelle konnte nicht gefunden werden.**).

Figure 10: Forest plot of fatigue



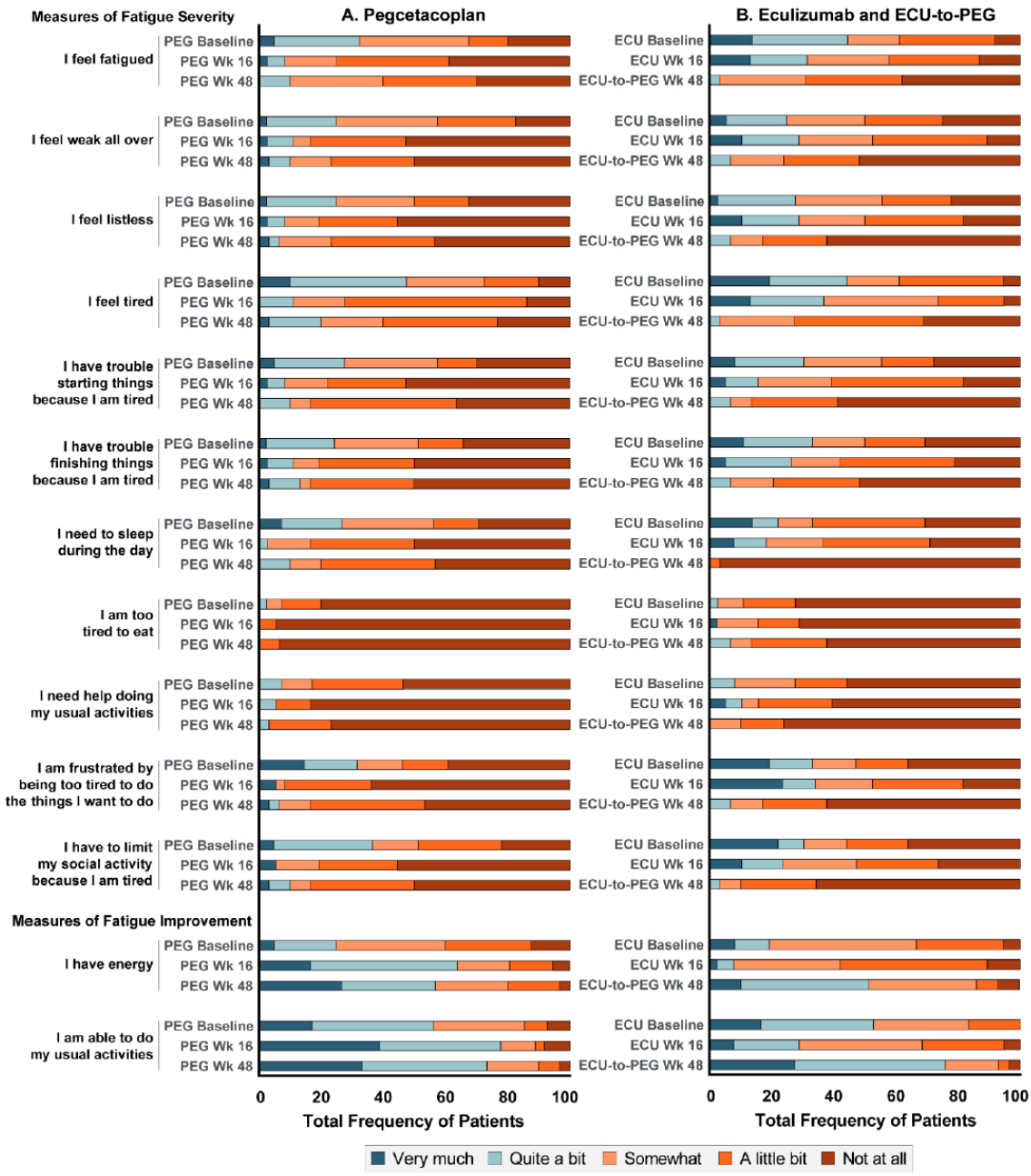
Conclusion for the decision aid:

In **complement inhibitor-naïve patients**, rates of fatigue ranged between 0 and 30 of 100 patients (3 studies; RoB high). In one study (PRINCE) fatigue appeared in 2 of 100 patients with pegcetacoplan (proximal CI) and in 6 of 100 with standard of care (without CIs; RoB high). In the same study the level of fatigue was improved by 7.78 points on a scale from 0 (high fatigue) to 52 (low fatigue) compared to only 3.26 points with standard of care (no comparative treatment; high RoB; not significant).

One study showed similar rates of fatigue for ravulizumab vs eculizumab (terminal CI; RoB high); and numerically higher rates of fatigue for eculizumab vs placebo (terminal CI; one study; RoB high). However, none of these were statistically significant differences and the comparison between terminal and proximal CIs is only indirect. We did not identify a direct comparison of terminal and proximal CIs.

In **complement inhibitor-experienced patients**, one RCT (APPLY-PNH) indicated significantly higher reduction of fatigue for iptacopan (proximal CI; 8.59 points improvement on a scale between 0 and 52) vs. ravulizumab/ eculizumab (terminal CI; 0; 31 point improvement; one study, RoB high). Another RCT (ALPHA) indicated an improvement in fatigue for danicopan as add on to eculicumab/ ravulicumab (proximal and terminal CI; 7.97 points improvement, one study; RoB unclear) compared to eculicumab/ ravulicumab alone (terminal CI; 1.85 points improvement, one study; RoB unclear). Another RCT (PEGASUS) indicates lower rates of fatigue for pegcetacoplan (proximal CI; 9.22 points improvement, one study; RoB high) vs eculizumab (terminal CI; 2.65 points improvement; RoB high).

Figure 11: FACIT-Fatigue changes over time for pegcetacoplan vs eculizumab – PEGASUS study



Abbreviations: ECU=eculizumab. PEG=pegcetacoplan. Proportions of categorical results for the FACIT-Fatigue scale items for (**A**) pegcetacoplan-treated patients at baseline, Week 16 (randomised period) and Week 48 (open-label extension), and (**B**) patients treated with eculizumab at baseline through Week 16 who were then switched from eculizumab to pegcetacoplan through Week 48. The FACIT-Fatigue scale measures fatigue using thirteen separate 5-point Likert-like scales (0=very much; 4=not at all). Eleven questions measure fatigue severity, and two questions measure fatigue improvement for which scores are recoded so that higher scores indicate lower levels of fatigue.

Reproduced from de Latour 2022[7]

Table 6: Fatigue

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
Complement inhibitor-naïve patients										
AEGIS	Eculizumab	Complement inhibitor-naïve PNH patients	Change from baseline in FACIT-Fatigue*	66 weeks	NR	NR	Mean change (SE): 5.0 (1.93), P=0.02	Open-label single arm	NA	12/16
ALXN1210-PNH-301	Ravulizumab	Complement inhibitor-naïve with clinical symptoms indicative of high disease activity	Fatigue	Baseline	80/125 (64.0%)	NR	NR	Open-label RCT	Ravulizumab	High
	Eculizumab				76/119 (63.9%)					
	Ravulizumab			Day 183	36/125 (28.8%)					
	Eculizumab				36/119 (30.3%)					
	Ravulizumab		EORTC QLQ-C30 Fatigue		≥10-point improvement: 92/125 (73.6%)	Mean absolute change (SD): -20.2 (24.5)	TD (95% CI): 9.1 (-2.5, 20.5)		Ravulizumab	
	Eculizumab				≥10-point improvement: 77/121 (63.6%)	Mean absolute change (SD): -18.6 (24.5)				
	Ravulizumab		Change in FACIT-Fatigue		NR	LSM (95% CI): 7.07 (5.55, 8.60)	TD (95% CI): 0.67 (-1.21, 2.55)		Ravulizumab	
	Eculizumab					LSM (95% CI): 6.40 (4.85, 7.96)				

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
	Ravulizumab		FACIT-Fatigue* score	2 years	NR	Mean (SD): 43.5 (8.10)	Mean % change from day 183: 1.6% (36.38)		NA	
APPOINT-PNH	Iptacopan	Complement-naïve PNH patients	Feeling weak or tired	Baseline	28/40 (70.0%)	NR	NR	Single-arm study	NA	12/16
				Day 168	8/40 (20.0%)					
			Severe or worsening of fatigue needing transfusion	NR	4/40 (10%)					
			Improvement in FACIT-Fatigue*	Baseline	NR	Mean (SD): 32.78 (10.170)				
				Day 168		Mean (SD): 43.9 (6.24)				
				Between Day 126 and Day 168 from baseline		Mean CFB (95% CI): 10.75 (8.66, 12.84)				
COMMODORE 2	Crovalimab	Complement inhibitor-naïve PNH patients	≥5-point improvement from baseline in FACIT-Fatigue	Baseline to week 25	75/128 (58.6%)	NR	NR	Open-label RCT	Crovalimab	High
	Eculizumab				36/66 (54.5%)					
	Crovalimab		Change from baseline in FACIT-Fatigue*		NR	Adjusted mean CFB (95% CI): 7.8 (6.5,	Difference (95% CI): 2.6 (0.7, 4.6)		Eculizumab	

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
						9.0)				
	Eculizumab					Adjusted mean CFB (95% CI): 5.2 (3.4, 6.9)				
PRINCE	Pegcetacoplan	Complement inhibitor-naïve PNH patients	Fatigue	Baseline to week 26	1/46 (2.17%)	NR	NR	Open-label RCT	Pegcetacoplan	High
	SOC, excluding complement inhibitors				1/18 (5.56%)					
	Pegcetacoplan		Change from baseline in FACIT-Fatigue*		NR	LSM (SE): 7.78 (1.210)	LSMD (95% CI): 4.51 (-0.21, 9.24), P=0.061		Pegcetacoplan	
	SOC, excluding complement inhibitors					LSM (SE): 3.26 (2.113)				
SHEPHERD	Eculizumab	Complement inhibitor-naïve PNH patients with thrombocytopenia	Change from baseline in EORTC-QLQ C30 - Fatigue	52 weeks	NR	Mean change (SE): -27.5 (2.32) P<0.001	NR	Single arm	NA	13/16
			Change in FACIT-Fatigue*		NR	Median: 10.0	Change from baseline (SD): 12.1 (1.1), P<0.001			
TRIUMPH	Eculizumab	Complement inhibitor-naïve PNH	Fatigue	Baseline to week 26	5/43 (12%)	NR	NR	Double-blind RCT	Placebo	Low
	Placebo				1/44 (2%)					
	Eculizumab		Change in EORTC		NR	Mean	NR		Eculizumab	

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
		patients with good bone marrow reserve	QLQ-C30 Fatigue			change: 10.0				
	Placebo					Mean change: -16.9				
	Eculizumab		Improvement in FACIT-Fatigue*		NR	Mean (SE): 6.4 (1.2)	P<0.001		Eculizumab	
	Placebo					Mean (SE): 4.0 (1.7)				
Complement inhibitor-experienced patients										
ALXN1210-PNH-302	Ravulizumab	Complement inhibitor-experienced with clinically stable disease	Fatigue	Baseline	29/96 (30.2%)	NR	NR	Open-label RCT	Eculizumab	High
	Eculizumab				38/95 (40.0%)					
	Ravulizumab			Day 183	42/96 (43.8%)					
	Eculizumab				36/95 (37.9%)					
	Ravulizumab		Fatigue as TEAE in ≥5% of patients	26 weeks	6/97 (6.2%)	NR	NR		Eculizumab	
	Eculizumab				6/98 (6.1%)					
	Ravulizumab		EORTC QLQ-C30 Fatigue	26 weeks	≥10-point improvement: 41/97 (42.3%)	Mean absolute change (SD): -4.97 (17.26)	TD (95% CI): 9.6 (-4.1, 22.9)		Ravulizumab	
	Eculizumab				≥10-point improvement: 31/98 (31.6%)	Mean absolute change (SD): -0.71 (15.27)				

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
	Ravulizumab		Change in FACIT-Fatigue		NR	LSM (95% CI): 2.0 (0.6, 3.4)	TD (95% CI): 1.5 (-0.2, 3.2)		Ravulizumab	
	Eculizumab					LSM (95% CI): 0.54 (-0.8, 1.9)				
	Ravulizumab		FACIT-Fatigue* score	2 years	NR	Mean (SD): 41.2 (10.70)	Mean % change from day 183: -1.2% (25.62)		NA	
ALPHA	Danicopan plus eculizumab or ravulizumab	PNH patients with clinically significant EVH	Fatigue as a TEAE reported by ≥5% of patients	12 weeks	0/57 (0%)	NR	NR	Double-blind RCT	NED	Unclear
	Placebo plus eculizumab or ravulizumab				0/9 (0%)					
	Danicopan plus eculizumab or ravulizumab		Improvement in FACIT-Fatigue*	Baseline to week 12	NR	LSM (SEM): 7.97 (1.13)	TD (95% CI): 6.12 (2.33, 9.91), P=0.0021		Danicopan plus eculizumab or ravulizumab	
	Placebo plus eculizumab or ravulizumab					LSM (SEM): 1.85 (1.58)				
	Danicopan plus			Baseline to week	NR	Mean CFB (95% CI):	NR		NA	

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
	eculizumab or ravulizumab			24		6.19 (4.10, 8.29)				
APPLY-PNH	Iptacopan	Complement inhibitor-experienced PNH patients with residual anaemia	Feeling weak or tired	Baseline	32/62 (51.6%)	NR	NR	Open-label RCT	Iptacopan	High
	Eculizumab or ravulizumab				23/35 (65.7%)					
	Iptacopan			Day 168	12/62 (19.4%)	NR	NR			
	Eculizumab or ravulizumab				19/35 (54.2%)					
	Iptacopan		Fatigue	Up to Day 168	1/62 (1.6%)	NR	NR			
	Eculizumab or ravulizumab				5/35 (14.3%)					
	Iptacopan		Improvement in FACIT-Fatigue*		NR	Mean CFB (95% CI): 8.59 (6.72, 10.47)	Adjusted MD (95% CI) 8.29 (5.28, 11.29), P<0.0001			
	Eculizumab or ravulizumab					Mean CFB (95% CI): 0.31 (-2.20, 2.81)				

COMMODORE 1	Crovalimab	Complement inhibitor-experienced PNH patients	Adjusted mean change in FACIT-Fatigue*	24 weeks and extension periods (NR)	NR	Mean change (95% CI): 1.1 (-1.5, 3.7)	Difference in mean change (95% CI): 3.7 (0.1, 7.4)	Open-label RCT	Crovalimab	High
	Eculizumab					Mean change (95% CI): -2.6 (-5.4, 0.1)				
PEGASUS	Pegcetacoplan	Adults with PNH who continue to have anaemia despite treatment with eculizumab	Improvement in FACIT-Fatigue*	16 weeks (3 months) from baseline	NR	LSM (SE): 9.22 (1.607)	LS mean difference (95% CI): 11.87 (5.49, 18.25), P=0.0005	Open-label RCT	Pegcetacoplan	High
	Eculizumab					LSM (SE): -2.65 (2.821)				
	Pegcetacoplan to pegcetacoplan		FACIT-Fatigue score		NR	Mean (SD): 41.81 (9.61)	NR		NA	
	Eculizumab to pegcetacoplan					Mean (SD): 42.52 (8.67)				
	Pegcetacoplan to pegcetacoplan			48 weeks	NR	Mean (SD): 40.60 (10.12)	Mean CFB (SD): 10.14 (9.06)		NA	
	Eculizumab to pegcetacoplan					Mean (SD): 30.62 (11.77)	Mean CFB (SD): 9.62 (10.34)			
	Pegcetacoplan		% patients with fatigue	NR	2/41 (4.9%)	NR	NR		Pegcetacoplan	

	Eculizumab				6/39 (15.4%)					
	Pegcetacoplan		Fatigue as a TEAE affecting ≥10% of patients	48 weeks	8/77 (10%)	NR	NR		NA	

Abbreviations: CFB, change from baseline; CI, confidence interval; dL, decilitre; EVH, extravascular haemolysis; g, grams; Hb, haemoglobin; HRQoL, health-related quality of life; LS, least square; LSM, least square mean; MD, mean difference; NED, no evidence of a difference; NR, not reported; PNH, paroxysmal nocturnal haemoglobinuria; RCT, randomised controlled trial; RD, risk difference; SD, standard deviation; SE, standard error; TEAE, treatment-emergent adverse event.

* The FACIT-Fatigue scale can generate a score between 0 and 52, where a higher score indicates better HRQoL. A 5-point increase in FACIT-Fatigue score is generally accepted as clinically meaningful.

Dyspnea

A total of 10 studies (8 RCTs, 2 single-arm) provided evidence on dyspnea across all drugs of interest except danicopan (**Fehler! Verweisquelle konnte nicht gefunden werden.**). Six studies (4 RCTs) reported on complement inhibitor-naïve patients, and four studies (all RCTs) reported on complement inhibitor-experienced patients. Risk of bias ranged from high to low.

Evidence was captured for three tools to measure dyspnea: EORTC IL-40 dyspnea, EORTC QLQ-C30 – dyspnea, and dyspnea as an outcome/adverse event.

In complement inhibitor-naïve patients, RCT evidence indicated similar rates of dyspnea for ravulizumab vs eculizumab (Study 301) and numerically lower rates of dyspnea for pegcetacoplan vs SOC (PRINCE). Changes in dyspnea scores were significantly improved for eculizumab vs placebo (TRIUMPH). Dyspnea scores were similar (worsened) for crovalimab vs eculizumab (COMMODORE 2) (**Fehler! Verweisquelle konnte nicht gefunden werden.**).

In complement inhibitor-experienced patients, RCT evidence indicated lower rates of dyspnea for ravulizumab vs eculizumab (Study 302); iptacopan vs eculizumab/ravulizumab (APPLY-PNH); and pegcetacoplan vs eculizumab (PEGASUS). Dyspnea scores were improved for crovalimab vs eculizumab (COMMODORE 1) (**Fehler! Verweisquelle konnte nicht gefunden werden.**).

Single-arm study evidence also reported improvements from baseline in dyspnea for iptacopan (APPOINT-PNH) and eculizumab (SHEPHERD) (**Fehler! Verweisquelle konnte nicht gefunden werden.**).

Conclusion for the decision aid:

In **complement inhibitor-naïve patients**, changes in dyspnea scores were significantly improved for eculizumab vs placebo: difference in EORTC-QLQ C30 of 16,8 points (one study; RoB low). RCT evidence indicated similar rates of dyspnea for ravulizumab vs eculizumab: 2-6 of 100 patients (2 studies; RoB high). Dyspnea scores were similar (worsened) for crovalimab vs eculizumab (one study; RoB high). We did not identify studies on proximal CIs for this question.

In **complement inhibitor-experienced patients**, all studies showed reductions in dyspnea compared to baseline. The remaining rates of dyspnea varied between 0 and 28 of 100 patients. Proximal CIs seemed to have lower rates of dyspnea but differences were not statistically significant.

Table 7: Dyspnea/shortness of breath

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change / effect estimate	Study type	Favours ?	RoB rating
Complement inhibitor-naïve patients										
ALXN1210-PNH-301	Ravulizumab	Complement inhibitor-naïve with clinical symptoms indicative of high disease activity	Dyspnea	Baseline	42/125 (33.6%)	NR	NR	Open-label RCT	NED	High
	Eculizumab				39/121 (31.9%)					
	Ravulizumab			Day 183	18/125 (14.4%)					
	Eculizumab				17/121 (14.3%)					
APPOINT-PNH	Iptacopan	Complement-naïve PNH patients	Shortness of breath	Baseline	12/40 (30.0%)	NR	NR	Single-arm study	NA	12/16
				Day 168	4/40 (10.0%)					
COMMODORE 2	Crovalimab	Complement inhibitor-naive PNH patients	EORTC IL-40 - dyspnea	Baseline to week 25	NR	Mean absolute change (95% CI): -13.4 (-16.9, -9.9)	NR	Open-label RCT	Crovalimab	High
	Eculizumab					Mean absolute change (95% CI): -14.8 (-19.9, -9.7)				
PRINCE	Pegcetacoplan	Complement inhibitor-naïve PNH patients	Dyspnea	Week 26	1/46 (2.17%)	NR	NR	Open-label RCT	Pegcetacoplan	High
	SOC, excluding complement inhibitors				1/18 (5.56%)					

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change / effect estimate	Study type	Favours ?	RoB rating
SHEPHERD	Eculizumab	Complement inhibitor-naïve PNH patients with thrombocytopenia	Change from baseline in EORTC-QLQ C30 - dyspnea	52 weeks	NR	Mean change (SE): -20.7 (2.96) P<0.001	NR	Single arm	NA	13/16
TRIUMPH	Eculizumab	Complement inhibitor-naïve PNH patients with good bone marrow reserve	Change from baseline in EORTC-QLQ C30 - dyspnea	Baseline to week 26	NR	Mean change: 8.9	Absolute difference: 16.8, P<0.001	Double-blind RCT	NED	Low
	Placebo					Mean change: -7.9				
Complement inhibitor-experienced patients										
ALXN1210-PNH-302	Ravulizumab	Complement inhibitor-experienced with clinically stable disease	Dyspnea	Baseline	6/96 (6.3%)	NR	NR	Open-label RCT	Ravulizumab	High
	Eculizumab				10/95 (10.5%)					
	Ravulizumab			Day 183	6/96 (6.3%)					
	Eculizumab				17/95 (17.9%)					
	Ravulizumab			26 weeks	0/97 (0%)				Ravulizumab	
	Eculizumab				6/98 (6.1%)					
APPLY-PNH	Iptacopan	Complement inhibitor-experienced PNH patients with residual anaemia	Shortness of breath	Baseline	18/62 (29%)	NR	NR	Open-label RCT	Iptacopan	High
	Eculizumab or ravulizumab				12/35 (34.3%)					
	Iptacopan			Day 168	4/62 (6.5%)	NR	NR			
	Eculizumab or ravulizumab				10/35 (28.5%)					

COMMODORE 1	Crovalimab	Complement inhibitor-experienced PNH patients	EORTC IL-40 - dyspnea	Baseline to week 25	NR	Mean absolute change (95% CI): 3.2 (-3.3, 9.7)	NR	Open-label RCT	Crovalimab	High
	Eculizumab					Mean absolute change (95% CI): -0.4 (-5.4, 4.7)				
PEGASUS	Pegcetacoplan	Adults with PNH who continue to have anaemia despite treatment with eculizumab	Dyspnea	NR	1/41 (2.4%)	NR	NR	Open-label RCT	Pegcetacoplan	High
	Eculizumab				2/39 (5.1%)					

Abbreviations: CI, confidence interval; dL, decilitre; g, grams; Hb, haemoglobin; NED, no evidence of a difference; PNH, paroxysmal nocturnal haemoglobinuria; RCT, randomised controlled trial; RD, risk difference.

(Generic) Health related Quality of Life (HrQoL)

A total of 8 studies (6 RCTs, 2 single-arm) provided evidence on HRQoL across all drugs of interest apart from iptacopan or danicopan (Table 12). Six studies (4 RCTs) reported on complement inhibitor-naïve patients, and two studies (both RCTs) reported on complement inhibitor-experienced patients. Risk of bias ranged from high to low.

Evidence was captured for two HRQoL tools: EORTC QLQ-C30 and Linear Analog Assessment scale (LASA) score.

In complement inhibitor-naïve patients, RCT evidence indicated numerical improvements in HRQoL for ravulizumab vs eculizumab (Study 301), crovalimab vs eculizumab (COMMODORE 2), pegcetacoplan vs SOC (PRINCE) and eculizumab vs placebo (TRIUMPH). Additional positive changes in EORTC-QLQ C30 subscales for crovalimab vs eculizumab (COMMODORE 2), eculizumab alone (SHEPHERD) or eculizumab vs placebo (TRIUMPH) are presented in

Table 8, Table 9 and

Table 10, respectively.

In complement inhibitor-experienced patients, RCT evidence indicated numerical improvements in HRQoL for ravulizumab vs eculizumab (Study 302) and crovalimab vs eculizumab (COMMODORE 1). Additional positive changes in EORTC-QLQ C30 subscales for crovalimab vs eculizumab (COMMODORE 1) are provided in

Table 8.

Single-arm study evidence also reported significant improvements from baseline in EORTC QLQ-C30 GHS (Table 12). Additional positive changes in EORTC-QLQ C30 subscales for eculizumab are presented in Table 11.

Conclusion for the decision aid:
In **complement inhibitor-naïve** patients CIs (terminal and proximal) can improve (generic) quality of life (2 studies; RoB high/low). Ravulizumab and crovalimab might slightly improve QoL even better than eculizumab (two studies; n.s.; RoB high). We did not identify studies comparing terminal and proximal CIs in complement inhibitor-naïve patients.

In **complement inhibitor-experienced patients**, RCT evidence indicated numerical improvements in (generic) HRQoL for terminal CIs (ravulizumab vs eculizumab and crovalimab vs eculizumab; two studies; n.s.; RoB high). We did not identify studies on proximal CIs or comparisons of terminal and proximal CIs.

Table 8: Change in quality of life during treatment – COMMODORE 2 and 1 study

	COMMODORE 1[a]		COMMODORE 2[b]	
	Crova (n=38)	Ecu (n=32)	Crova (n=128)	Ecu (n=66)
Absolute change from baseline to Week 25 in EORTC QLQ-C30 scores, mean (95% CI)[c]				
Physical functioning	0.9 (−3.9, 5.7)	0.4 (−4.7, 5.6)	12.3 (9.2, 15.4)	14.2 (9.2, 19.3)
Role functioning	1.3 (−7.1, 9.7)	−3.7 (−10.9, 3.6)	12.9 (8.1, 17.7)	11.6 (6.1, 17.2)
GHS/QoL	5.7 (−2.4, 13.8)	−1.0 (−6.9, 4.9)	13.4 (10.1, 16.7)	9.9 (4.8, 14.9)
Absolute change from baseline to Week 25 in EORTC IL-40 scores, mean (95% CI)[d]				
Dyspnea	3.2 (−3.3, 9.7)	−0.4 (−5.4, 4.7)	−13.4 (−16.9, −9.9)	−14.8 (−19.9, −9.7)
Dysphagia	0.9 (−3.1, 4.9)	−4.2 (−9.2, 0.9)	−4.4 (−7.7, −1.1)	−6.1 (−12.1, 0.0)
Headaches	−1.8 (−9.4, 5.9)	−1.0 (−11.4, 9.3)	−6.8 (−11.2, −2.4)	−4.6 (−9.1, 0.0)
Abdominal pain	−0.9 (−7.9, 6.1)	−2.1 (−8.9, 4.7)	−8.9 (−12.8, −4.9)	−7.1 (−13.7, −0.4)
Chest pain	0.0 (−2.6, 2.6)	0.0 (−5.3, 5.3)	−4.7 (−7.7, −1.7)	−8.1 (−13.3, −2.9)
Erectile dysfunction[e]	6.7 (−14.5, 27.8)	7.1 (−11.6, 25.9)	−18.0 (−24.5, −11.4)	−10.0 (−19.3, −0.7)

EORTC, European Organisation for Research and Treatment of Cancer; GHS/QoL, global health status/quality of life; IL, item library; QLQ, Quality of Life Questionnaire. Clinical data cutoff: Nov 16, 2022. All data were assessed from baseline through Week 25.
[a] C5 inhibitor–experienced pts. [b] C5 inhibitor–naive pts. [c] Higher scores indicate better functioning/quality of life. [d] Higher scores indicate worse symptoms. [e] Evaluated in male pts only. For COMMODORE 1, n=15 for crova and n=14 for ecu. For COMMODORE 2, n=65 for crova and n=30 for ecu.

Reproduced from Panse 2023.[22]

Table 9: Change in quality of life during treatment – SHEPHERD study

Table 6. Change in EORTC QLQ-C30 scores following treatment with eculizumab

Scale	Mean (SE) change baseline to wk 52*	*P*†
Global health status	19.7 (2.05)	<.001
Functioning scales		
Role	20.4 (2.67)	<.001
Social	17.4 (2.84)	<.001
Cognitive	8.6 (2.26)	<.001
Physical	14.8 (1.63)	<.001
Emotional	15.6 (2.26)	<.001
Symptom scales		
Fatigue	−27.5 (2.32)	<.001
Pain	−8.1 (2.61)	<.001
Nausea and vomiting	−2.5 (1.54)	.002
Single-item measures		
Dyspnea	−20.7 (2.96)	<.001
Loss of appetite	−7.0 (2.11)	<.001
Insomnia	−11.6 (2.77)	<.001
Diarrhea	−1.8 (1.96)	<.001
Financial difficulties	−0.7 (2.78)	.768
Constipation	0.4 (2.03)	.985

*An increase in the score on the scales for global health status and functioning indicates improvement, whereas a decrease in the scores on the symptom scales and single-item measures indicates improvement.
†Mixed-model analysis based on change from baseline.

Reproduced from Brodsky 2008.[5]

Table 10: Change in quality of life during treatment – TRIUMPH study

Table 3. Change in the Quality of Life during Treatment.*

Scale	Mean Change in Score from Baseline to Week 26†		Absolute Difference	P Value‡
	Placebo Group	Eculizumab Group		
Global health status scale	−8.5	10.9	19.4	<0.001
Functioning scales				
Role	−6.9	17.9	24.8	<0.001
Social	2.0	16.7	14.7	0.003
Cognitive	−6.1	7.9	14.0	0.002
Physical	−3.5	9.4	12.9	<0.001
Emotional	−3.7	7.5	11.2	0.008
Symptom scales				
Fatigue	10.0	−16.9	26.9	<0.001
Pain	5.3	−12.3	17.6	0.002
Nausea and vomiting	2.8	−0.4	3.2	0.06
Single-item measures				
Dyspnea	8.9	−7.9	16.8	<0.001
Loss of appetite	3.3	−10.3	13.6	<0.001
Insomnia	4.9	−7.9	12.8	0.01
Financial difficulties	0.0	−10.3	10.3	0.19
Constipation	0.0	−6.3	6.3	0.20
Diarrhea	5.7	4.8	0.9	0.15

* The quality of life was assessed with the EORTC QLQ-C30 instrument.
† A positive value for a score on the scales for global health status and functioning indicates improvement, whereas a negative value for a score on the symptom scales and for a score on the single-item measures indicates improvement.
‡ P values are from a mixed model, with baseline scores as the covariate, treatment and time as fixed effects, and the patient identifier as a random effect.

Reproduced from Hillmen 2006.[12]

Table 11: Change in quality of life from baseline during treatment – X03-001 study

Domain*	Mean baseline score†	64-wk change from baseline score‡	*P*§
Global health status	56.1	13.8	.009
Physical functioning	70.9	14.3	<.001
Emotional functioning	70.5	12.5	<.001
Role functioning	66.7	14.5	.003
Cognitive functioning	77.3	10.3	.001
Fatigue	47.5	−17.8	<.001
Dyspnea	39.4	−16.6	<.001
Insomnia	30.3	−8.2	.031
Pain	21.2	−8.2	.023
Constipation	3.0	4.1	<.001

*Quality of life was assessed using the European Organization for Research and Treatment of Cancer QLQ-C30 instrument.

†Mean values of linearly transformed scores.

‡Values represent least-square means. Positive change indicates improvement on Global Health Status and Functional scales, and negative change indicates improvement on Symptom scales.

§From a mixed analysis-of-covariance model with visit as a fixed effect, patient as a random effect, and baseline as a covariate.

Reproduced from Hill 2005.[11]

Table 12: HRQoL

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
Complement inhibitor-naïve patients										
ALXN1210-PNH-301	Ravulizumab	Complement inhibitor-naïve with clinical symptoms indicative of high disease activity	EORTC QLQ-C30 GHS/QOL	26 weeks	≥10-point improvement: 64/124 (51.2%)	Mean absolute change (SD): 13.2 (21.4)	TD (95% CI): 4.8 (-7.7, 17.1)	Open-label RCT	Ravulizumab	High
	Eculizumab				≥10-point improvement: 55/118 (45.5%)	Mean absolute change (SD): 12.9 (21.8)				
	Ravulizumab		EORTC QLQ-C30 PF		≥10-point improvement: 60/124 (48.0%)	Mean absolute change (SD): 13.2 (15.7)	TD (95% CI): 3.7 (-8.7, 16.0)		Ravulizumab	
	Eculizumab				≥10-point improvement: 53/118 (43.8%)	Mean absolute change (SD): 11.5 (17.6)				
	Ravulizumab		EORTC QLQ-C30 GHS/QOL	2 years	NR	Mean (SD): 70.4 (20.57)	NR		NA	

COMMODORE 2	Crovalimab	Complement inhibitor-naive PNH patients	EORTC QLQ-C30 GHS/QOL	Baseline to week 25	NR	Mean absolute change (95% CI): 13.4 (10.1, 16.7)	NR	Open-label RCT	Crovalimab	High
	Eculizumab					Mean absolute change (95% CI): 9.9 (4.8, 14.9)				
PRINCE	Pegcetacoplan	Complement inhibitor-naïve PNH patients	Change from baseline in EORTC-QLQ C30 score	Baseline to week 26	NR	LSM (SE): 18.90 (2.909)	LSMD (95% CI): 21.75 (9.35, 34.16), P=0.0006	Open-label RCT	Pegcetacoplan	High
	SOC, excluding complement inhibitors					LSM (SE): -2.85 (5.703)				
	Pegcetacoplan		Change from baseline in LASA* score		NR	LSM (SE): 50.39 (9.062)	LSMD (95% CI): 55.79 (16.83, 94.74), P=0.005		Pegcetacoplan	
	SOC, excluding complement inhibitors					LSM (SE): -5.39 (17.689)				
SHEPHERD	Eculizumab	Complement inhibitor-naïve PNH patients with thrombocytopenia	Change from baseline in EORTC-QLQ C30 GHS	52 weeks	NR	Mean change (SE): 19.7 (2.05), P<0.001		Single arm	NA	13/16
TRIUMPH	Eculizumab	Complement inhibitor-naïve PNH patients with good bone marrow reserve	Change from baseline in EORTC-QLQ C30 GHS	Baseline to week 26	NR	Mean change: 10.9	Absolute difference: 19.4, P<0.001	Double-blind RCT	NED	Low
	Placebo					Mean change: -8.5				

X03-001	Eculizumab	Complement inhibitor-naïve PNH patients	EORTC-QLQ C30 GHS	Baseline 64 weeks	NR	Mean 56.1 Mean 13.8	P=0.009	Open-label extension study	NA	12/16
Complement inhibitor-experienced patients										
ALXN1210-PNH-302	Ravulizumab	Complement inhibitor-experienced with clinically stable disease	EORTC QLQ-C30 GHS/QOL	26 weeks	≥10-point improvement: 18/97 (18.6%)	Mean absolute change (SD): 1.15 (16.51)	TD (95% CI): 4.2 (-6.6, 15.0)	Open-label RCT	Ravulizumab	High
	Eculizumab				≥10-point improvement: 14/98 (14.3%)	Mean absolute change (SD): -1.93 (15.34)				
	Ravulizumab		EORTC QLQ-C30 PF		≥10-point improvement: 21/97 (21.6%)	Mean absolute change (SD): 3.26 (8.71)	TD (95% CI): 9.1 (-1.9, 19.7)		Ravulizumab	
	Eculizumab				≥10-point improvement: 12/98 (12.2%)	Mean absolute change (SD): 1.20 (8.89)				
	Ravulizumab		EORTC QLQ-C30 GHS/QOL	2 years	NR	Mean (SD): 71.6 (20.07)	NR		NA	

COMMODORE 1	Crovalimab	Complement inhibitor-experienced PNH patients	EORTC QLQ-C30 GHS/QOL	Baseline to week 25	NR	Mean absolute change (95% CI): 5.7 (-2.4, 13.8)	NR	Open-label RCT	Crovalimab	High
	Eculizumab					Mean absolute change (95% CI): -1.0 (-6.9, 4.9)				

Abbreviations: CI, confidence interval; dL, decilitre; g, grams; GHS, global health status; Hb, haemoglobin; HRQoL, health-related quality of life; LASA, Linear Analog Assessment scale; LS, least squared; NA, not applicable; NED, no evidence of a difference; PF, physical functioning; PNH, paroxysmal nocturnal haemoglobinuria; QoL, quality of life; RCT, randomised controlled trial; RD, risk difference; SE, standard error.

*The LASA consists of 3 items asking respondents to rate their perceived level of functioning. Specific domains include activity level, ability to carry out daily activities, and an item for overall QOL. Their level of functioning was reported on a 0-100 scale with 0 representing "As low as could be" and 100 representing "As high as could be".

FAQ5: What are the risks or side effects?

Evidence was sought for the following side effects: fatigue, thromboembolic events, pulmonary hypertension, shortness of breath/dyspnoea, any infections, any serious infections, meningococcal infections, and impaired kidney function.

Breakthrough haemolysis

A total of nine studies (7 RCTs, 2 single-arm) provided evidence on breakthrough haemolysis (BTH) across all drugs of interest (**Fehler! Verweisquelle konnte nicht gefunden werden.**). Four studies (2 RCTs) reported on complement inhibitor-naïve patients, and five studies (all RCTs) reported on complement inhibitor-experienced patients. Risk of bias ranged from high to unclear.

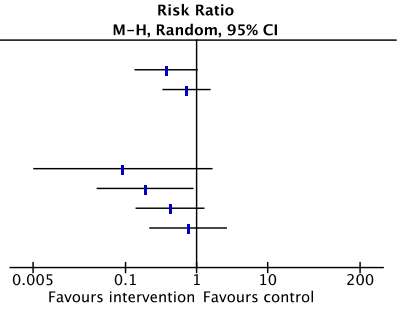
In complement inhibitor-naïve patients, RCT evidence indicated a numerical reduction in BTH rates for crovalimab or ravulizumab compared to eculizumab; however, these were not statistically significant changes (**Fehler! Verweisquelle konnte nicht gefunden werden.**).

In complement inhibitor-experienced patients, RCT evidence indicated a numerical reduction in BTH rates for crovalimab, ravulizumab or pegcetacoplan compared to eculizumab; however, these were not statistically significant changes. Danicopan as an add-on to eculizumab/ravulizumab had the same rates of BTH as eculizumab/ravulizumab alone (zero events in both treatment arms). Iptacopan was significantly better than eculizumab/ravulizumab for BTH (**Fehler! Verweisquelle konnte nicht gefunden werden.**).

Single-arm study evidence did not provide any pre- vs post- comparisons for BTH (**Fehler! Verweisquelle konnte nicht gefunden werden.**).

Figure 12: Forest plot of breakthrough haemolysis

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Risk Ratio M-H, Random, 95% CI
1.2.1 Complement inhibitor-naive					
Study 301 - Rav vs Ecu	5	125	13	121	0.37 [0.14, 1.01]
COMMODORE 2 - Crov vs ecu	14	134	10	69	0.72 [0.34, 1.54]
1.2.2 Complement inhibitor-experienced					
ALPHA - Dani plus rav/ecu vs placebo plus rav/ecu	0	57	0	29	Not estimable
Study 302 - Rav vs Ecu	0	97	5	98	0.09 [0.01, 1.64]
APPLY-PNH - Ipta vs rav/ecu	2	62	6	35	0.19 [0.04, 0.88]
PEGASUS - Peg vs ecu	4	41	9	39	0.42 [0.14, 1.26]
COMMODORE 1 - Crov vs Ecu	4	39	5	37	0.76 [0.22, 2.61]



Conclusion for the decision aid:

In **CI naïve patients** rates of breakthrough haemolysis ranged between 4 and 14 of 100 patients for all terminal CIs. Differences between terminal CIs could not be detected (2 studies; RoB high). A comparison between proximal and terminal CIs for breakthrough haemolysis could not be found.

In **CI-experienced patients** rates of breakthrough haemolysis occurred in 0 to 23 of 100 patients. No differences could be found between terminal CIs or two of the proximal CIs (pegcetacoplan or danicopan; 4 studies; RoB unclear/high). Only the proximal CI iptacopan might reduce breakthrough haemolysis in approximately 14 of 100 patients: 3 of 100 with iptacopan, 17 of 100 with ravulizumab / eculizumab (1 study; RoB high).

Table 13: Breakthrough haemolysis

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change / effect estimate	Study type	Favours?	RoB rating
Complement inhibitor-naïve patients										
ALXN1210-PNH-301	Ravulizumab	Complement inhibitor-naïve with clinical symptoms indicative of high disease activity	Breakthrough haemolysis	26 weeks	5/125 (4.0%)	NR	TD (95% CI): 6.7 (-0.18, 14.21)	Open-label RCT	Ravulizumab	High
	Eculizumab				13/121 (10.7%)					
	Ravulizumab			Extension period up to 2 years	15/243 (6.2%)	NR	NR		NA	
APPOINT-PNH	Iptacopan	Complement-naïve PNH patients	Experienced clinical* breakthrough haemolysis	Between Day 14 and Day 168	0/40 (0%)	Adjusted annualised rate: 0.00 (95% CI: 0.00 to 0.17)	NR	Single-arm study	NA	12/16
				24-48 week extension period	1/40 (2.5%)	Adjusted annualised rate: 0.06 (95% CI: 0.00 to 0.68)				
COMMODORE 2	Crovalimab	Complement inhibitor-naïve PNH patients	Breakthrough haemolysis	Week 25	14/134 (10.4%)	NR	Adjusted mean change (95% CI): -3.9% (-14.8, 5.3)	Open-label RCT	Crovalimab	High
	Eculizumab				10/69 (14.5%)					
X03-001	Eculizumab	Complement inhibitor-naïve PNH patients	Breakthrough haemolysis	52 weeks	2/11 (18%)	NR	NR	Open-label extension study	NA	12/16

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change / effect estimate	Study type	Favours?	RoB rating
Complement inhibitor-experienced patients										
ALXN1210 -PNH-302	Ravulizumab	Complement inhibitor-experienced with clinically stable disease	Breakthrough haemolysis	26 weeks	0/97 (0%)	NR	TD (95% CI): 5.1 (1.7, 11.5)	Open-label RCT	Ravulizumab	High
	Eculizumab				5/98 (5.1%)					
	Ravulizumab			Extension period up to 2 years	11/191 (5.8%)	NR	NR		NA	
ALPHA	Danicopan plus eculizumab or ravulizumab	Complement inhibitor-experienced PNH patients with clinically significant EVH	Breakthrough haemolysis of ≥ grade 3	Baseline to week 12 (IA1)	0/57 (0%)	NR	Adjusted TD (95% CI): 41.7% (22.7, 60.8), P=0.0004	Double-blind RCT	Danicopan plus eculizumab or ravulizumab	Unclear
	Placebo plus eculizumab or ravulizumab				0/29 (0%)					
APPLY-PNH	Iptacopan	Complement inhibitor-experienced PNH patients with residual anaemia	Experienced clinical* breakthrough haemolysis (≥5% of patients)	Up to Day 168	2/62 (3.2%)	Adjusted annualised rate (95% CI): 0.07 (0.02, 0.31)	RaD (95% CI): -0.60 (-1.24, 0.04) RaR (95% CI): 0.10 (0.02, 0.61), P=0.01183 RD (95% CI): -13.92 (-27.15, -0.68)	Open-label RCT	Iptacopan	High
	Eculizumab or ravulizumab				6/35 (17.1%)	Adjusted annualised rate (95% CI): 0.67 (0.26, 1.72)				

COMMODORE 1	Crovalimab Eculizumab	Complement inhibitor-experienced PNH patients	Breakthrough haemolysis	24 weeks and extension periods (NR)	4/39 (10.3%) 5/37 (13.5%)	NR	NR	Open-label RCT	Crovalimab	High
PEGASUS	Pegcetacoplan	Adults with PNH who continue to have anaemia despite treatment with eculizumab	Exposure-adjusted rate of an adverse event of haemolysis	16 weeks	NR	5 patients (40.6 events per 100 patient-years)	NR	Open-label RCT	NR	High
	Eculizumab					NR				
	Pegcetacoplan Eculizumab		% patients who experienced breakthrough haemolysis	NR – post-hoc analysis	4/41 (9.8%) 9/39 (23.1%)	NR	NR		Pegcetacoplan	
	Pegcetacoplan		Acute haemolytic event (including haemolysis, haemolytic anaemia and intravascular haemolysis)	48 weeks	18/77 (23%)	NR	NR		NA	
			Acute haemolytic event (haemolysis only)		15/77 (19.5%)	NR	NR		NA	
			Exposure-adjusted rate of an adverse event of haemolysis		NR	15 patients (33.5 events per 100 patient-years)	NR		NA	

Abbreviations: CI, confidence interval; dL, decilitre; g, grams; Hb, haemoglobin; NR, not reported; PNH, paroxysmal nocturnal haemoglobinuria; RaD, rate difference; RaR, rate ratio; RCT, randomised controlled trial; RD, risk difference; ULN, upper limit of normal.

* Defined as a decrease in Hb of ≥2 g/dL (compared to the latest assessment, or within 15 days) and/or presence of signs or symptoms (gross haemoglobinuria, painful crisis, dysphagia or any other significant clinical PNH-related signs & symptoms) *and* LDH level >1.5 x ULN and increased as compared to the last 2 assessments.

Thromboembolic events

A total of 11 studies (7 RCTs, 4 single-arm) provided evidence on thromboembolic events across all drugs of interest apart from danicopan (Table 14). Seven studies (3 RCTs) reported on complement inhibitor-naïve patients, and four studies (all RCTs) reported on complement inhibitor-experienced patients. Risk of bias was high.

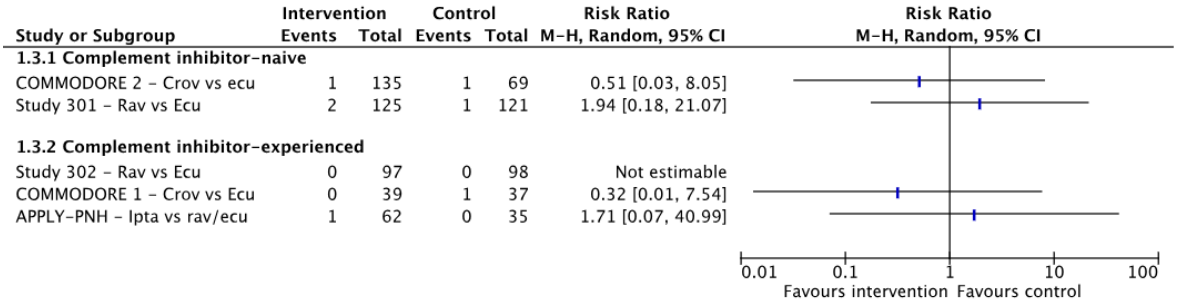
Evidence was captured for several thromboembolic outcomes, including: major adverse vascular event (MAVE), serious left ventricular failure, serious myocardial ischaemia, myocardial infarction (MI), cardiac failure, ischaemic stroke, thrombosis, transient ischaemic attack (TIA) and deep vein thrombosis (DVT). Most evidence was identified for MAVE.

In complement inhibitor-naïve patients, RCT evidence indicated numerically lower rates of MAVE for crovalimab vs eculizumab (COMMODORE 2) and numerically higher rates of MAVE for ravulizumab vs eculizumab (Study 301); however, these were not statistically significant changes (Figure 13).

In complement inhibitor-experienced patients, RCT evidence indicated that rates of MAVE were generally very low ranging from 0-1 patients per treatment arm. No events were seen in either treatment arm for crovalimab vs eculizumab (COMMODORE 1) or ravulizumab vs eculizumab (Study 302). One event was seen in the iptacopan arm compared with no events in the ravulizumab/eculizumab arm for one trial (APPLY-PNH) (Figure 13).

Single-arm study evidence also reported low levels of MAVE, with no events for two out of three eculizumab studies; and one iptacopan study (Table 14).

Figure 13: Forest plot of MAVE



Abbreviations: MAVE, major vascular adverse event.

Conclusion for the decision aid:

In **complement inhibitor-naïve patients,** thromboembolic major adverse vascular events (MAVE) occurred in 1 or 2 of 100 patients. The differences between these events in crovalimab, eculizumab or ravulizumab were not statistically significant (2 studies; RoB high). We did not find any comparisons between terminal and proximal CIs.

In **complement inhibitor-experienced patients**, rates of MAVE were generally very low ranging from 0-2 of 100 patients. No events were seen in crovalimab and one for eculizumab. This difference is not statistically significant (two studies; RoB high). One event was seen in the iptacopan arm (proximal CI) compared with no events in the ravauizumab/eculizumab (terminal CI) arm for one trial (RoB high). Due to small sample size this effect was not statistically significant.

Table 14: Thromboembolic events

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change / effect estimate	Study type	Favours?	RoB rating
Complement inhibitor-naïve patients										
AEGIS	Eculizumab	Complement inhibitor-naïve PNH patients	MAVE	66 weeks	0/27 (0%)	NR	NR	Open-label single arm	NA	
ALXN1210-PNH-301	Ravulizumab	Complement inhibitor-naïve with clinical symptoms indicative of high disease activity	MAVE	26 weeks	2/125 (1.6%)	NR	NR	Open-label RCT	Eculizumab	High
	Eculizumab				1/121 (0.8%)					
	Ravulizumab		Serious left ventricular failure		1/125 (0.8%)	NR	NR		Eculizumab	
	Eculizumab				0/121 (0%)					
	Ravulizumab		Serious myocardial ischaemia		1/125 (0.8%)	NR	NR		Eculizumab	
	Eculizumab				0/121 (0%)					
APPOINT-PNH	Iptacopan	Complement-naïve PNH patients	MAVE	1-24 weeks (randomised period) and 24-48 weeks (extension period)	0/40 (0%)	NR	NR	Single-arm study	NA	12/16
COMMODORE 2	Crovalimab	Complement inhibitor-naïve PNH patients	MAVE	Baseline to week 25	1/135 (0.7%)	NR	NR	Open-label RCT	Crovalimab	High
	Eculizumab				1/69 (1.5%)					
	Crovalimab		Myocardial infarction		1/135 (0.7%)	NR	NR		Eculizumab	
	Eculizumab				0/69 (0%)					
	Crovalimab		Cardiac		0/135 (0%)	NR	NR		Crovalimab	

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change / effect estimate	Study type	Favours?	RoB rating
	Eculizumab		failure		1/69 (1.4%)					
	Crovalimab		Ischaemic stroke		0/135 (0%)	NR	NR		Crovalimab	
	Eculizumab				1/69 (1.4%)					
PRINCE	Pegcetacoplan	Complement inhibitor-naïve PNH patients	Thrombosis	Week 26	0/35 (0%)	NR	NR	Open-label RCT	NED	High
	SOC, excluding complement inhibitors				0/18 (0%)					
SHEPHERD	Eculizumab	Complement inhibitor-naïve PNH patients with thrombocytopenia	Thrombotic event	52 weeks	2/97 (2.1%)	NR	NR	Single arm	NA	13/16
X03-001	Eculizumab	Complement inhibitor-naïve PNH patients	Thromboses	52 weeks	0/11 (0%)	NR	NR	Open-label extension study	NA	12/16
Complement inhibitor-experienced patients										
ALXN1210-PNH-302	Ravulizumab	Complement inhibitor-naïve with clinical symptoms indicative of high disease activity	MAVE	26 weeks	0/97 (0%)	NR	NR	Open-label RCT	Eculizumab	High
	Eculizumab				0/98 (0%)					
	Ravulizumab		Serious left ventricular failure		0/97 (0%)	NR	NR		NED	
	Eculizumab				0/98 (0%)					
	Ravulizumab		Serious myocardial ischaemia		0/97 (0%)	NR	NR		NED	
	Eculizumab				0/98 (0%)					

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change / effect estimate	Study type	Favours?	RoB rating
APPLY-PNH	Iptacopan	Complement inhibitor-experienced PNH patients with residual anaemia	MAVE	Between Day 1 and Day 168	1/62 (1.6%)	Adjusted annualised rate (95% CI): 0.03% (0.00, 0.25)	RaD (95% CI): 0.03 (-0.03, 0.10), P=0.31731	Open-label RCT	Iptacopan	High
	Eculizumab or ravulizumab				0/35 (0%)	NR				
	Iptacopan		TIA		1/62 (1.6%)	NR	RD (95% CI): 1.61 (-1.52, 4.75		Eculizumab or ravulizumab	
	Eculizumab or ravulizumab				0/35 (0%)					
COMMODORE 1	Crovalimab	Complement inhibitor-experienced PNH patients	MAVE	24 weeks and extension periods (NR)	0/39 (0%)	NR	NR	Open-label RCT	NED	High
	Eculizumab				1*/37 (0%)					
	Crovalimab		TIA		0/39 (0%)	NR	NR		Crovalimab	
	Eculizumab				1/37 (2.7%)					
PEGASUS	Pegcetacoplan	Adults with PNH who continue to have anaemia despite treatment with eculizumab	Thrombo embolic events	16 weeks (3 months)	0/41 (0%)	NR	NR	Open-label RCT	NED	High
	Eculizumab				0/39 (0%)					
	Pegcetacoplan		DVT	48 weeks	1/77 (1.3%)	NR	NR		NA	
			Jugular vein thrombosis		1/77 (1.3%)					
			Thrombosis (any)		2/77 (2.6%)					

Abbreviations: CI, confidence interval; dL, decilitre; DVT, deep vein thrombosis; g, grams; Hb, haemoglobin; MAVE, major adverse vascular event; NED, no evidence of a difference; PNH, paroxysmal nocturnal haemoglobinuria; RaD, rate difference; RCT, randomised controlled trial; RD, risk difference; TIA, transient ischaemic attack.
*As TIA was counted as MAVE in this report, an event was added here to the original data from the study publication.

Hypertension

A total of 2 studies (both RCTs) provided evidence on hypertension for danicopan, pegcetacoplan, eculizumab/ravulizumab and eculizumab alone (Table 15). No studies reported on hypertension in complement inhibitor-naïve patients; two studies (both RCTs) reported on complement inhibitor-experienced patients. Risk of bias ranged from high to unclear.

In complement inhibitor-experienced patients, RCT evidence indicated numerically higher rates of hypertension for danicopan plus eculizumab/ravulizumab vs eculizumab/ ravulizumab alone; and numerically higher rates for pegcetacoplan vs eculizumab. However, there were not statistically significant changes (Table 15).

Conclusion for the decision aid:

No studies reported on hypertension in **complement inhibitor-naïve** patients.

A total of 2 studies (both RCTs) provided evidence on hypertension for **complement inhibitor-experienced patients** treated with danicopan (proximal CI), pegcetacoplan, eculizumab/ravulizumab and eculizumab alone. The rates of hypertension ranged from 3 to 7 of 100 patients. No differences could be identified between the different CIs.

Table 15: Hypertension

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
Complement inhibitor-naïve patients										
No evidence identified										
Complement inhibitor-experienced patients										
ALPHA	Danicopan plus eculizumab or ravulizumab	Complement inhibitor-experienced PNH patients with clinically significant EVH	Hypertension as a TEAE reported by ≥5% of patients	12 weeks	3/59 (5.3%)	NR	NR	Double-blind RCT	Placebo plus eculizumab or ravulizumab	Unclear
	Placebo plus eculizumab or ravulizumab				1/9 (3.4%)					
PEGASUS	Pegcetacoplan	Adults with PNH who continue to have anaemia despite treatment with eculizumab	% patients with hypertension	NR	3/41 (7.3%)	NR	NR	Open-label RCT	Eculizumab	High
	Eculizumab				1/39 (2.6%)					

Abbreviations: CI, confidence interval; dL, decilitre; EVH, extravascular haemolysis; g, grams; Hb, haemoglobin; HRQoL, health-related quality of life; PNH, paroxysmal nocturnal haemoglobinuria; RCT, randomised controlled trial; TEAE, treatment-emergent adverse event.

Infections

A total of 13 studies (9 RCTs, 4 single-arm) provided evidence on infections across all drugs of interest (Table 16). Eight studies (4 RCTs) reported on complement inhibitor-naïve patients, and five studies (all RCTs) reported on complement inhibitor-experienced patients. Risk of bias was high.

Evidence was captured for several infection outcomes, including: any infection, any serious infection, any severe infection, any pneumonia, serious pneumonia, serious alpha-haemolytic *Streptococcal* bacteraemia, biliary sepsis, serious bronchitis, capsular bacteria infection, serious cellulitis, serious central nervous system (CNS) infection, COVID19 infection, serious COVID19 infection, ear infection, oral herpes, serious herpes virus infection, influenza, serious influenza, serious leptospirosis, serious lower respiratory tract infection, meningitis, serious pulmonary tuberculosis, sepsis, serious sepsis, serious septic shock, serious systemic infection, urinary tract infection (UTI), serious UTI, upper respiratory tract infection (URTI), serious URTI, any viral infection, serious viral infection, serious viral gastroenteritis, *Aspergillus* infection, *Staphylococcal* infection, serious *Pneymocystis jirovecii* infection and meningococcal infection. Most evidence was identified for upper respiratory tract infections (11 studies; 6 RCTs), serious infections (seven studies; five RCTs) and meningococcal infections (seven studies; 6 RCTs).

In complement inhibitor-naïve patients, RCT evidence indicated numerically lower rates of URTI for pegcetacoplan vs SOC (PRINCE), eculizumab vs placebo (TRIUMPH) and crovalimab vs eculizumab (COMMODORE 2) but numerically higher rates of URTI for ravulizumab vs eculizumab (Study 301); however, these were not statistically significant differences (Figure 14). In the same population, RCT evidence indicated numerically lower rates of serious infections for crovalimab vs eculizumab (COMMODORE 2) and for ravulizumab vs eculizumab (Study 301); however, these were not statistically significant differences (Figure 15).

In complement inhibitor-experienced patients, RCT evidence indicated numerically lower rates of URTI for iptacopan vs ravulizumab/eculizumab (APPLY-PNH) but numerically higher rates of URTI for ravulizumab vs eculizumab (COMMODORE 1); however, these were not statistically significant differences (Figure 14). In the same population, RCT evidence indicated that rates of serious infections were numerically lower for iptacopan vs ravulizumab/eculizumab (APPLY-PNH) but numerically higher for ravulizumab vs eculizumab (Study 302) and crovalimab vs eculizumab (COMMODORE 1). However, these were not statistically significant differences (Figure 15).

No meningococcal infections were reported in any studies (Table 16).

Figure 14: Forest plot of upper respiratory tract infection

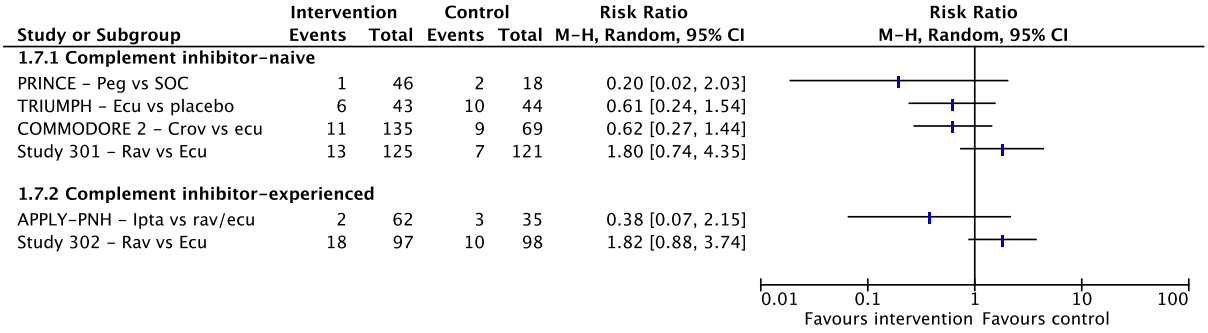
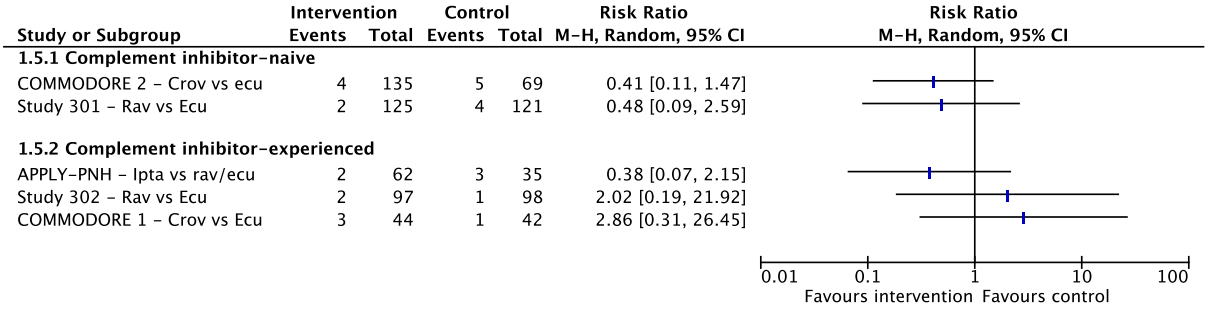


Figure 15: Forest plot of serious infection



Conclusion for the decision aid:

Upper respiratory tract infections

For **complement inhibitor-naïve patients** rates of upper respiratory infections (URTI) varied between 6 and 14 of 100 patients for terminal CIs. Rates of URTIs were 2 of 100 for pegcetacoplan (proximal CI) and 15 of 100 for iptacopan. No direct comparisons between proximal or terminal CIs could be identified (no studies for proximal CIs identified). However, URTIs seemed to be slightly rarer with proximal CIs.

For **CI experienced patients** the rates of URTIs varied between 9 and 19 of 100 patients for terminal CIs. In one study the rate of URTI for Iptacopan was 3 of 100. No direct comparisons between the CIs could be identified. However, URTIs seemed to be slightly rarer with proximal CIs.

Serious infections

For **complement inhibitor-naïve patients** rates of serious infections varied between 2 and 7 of 100 patients (only terminal CIs). No differences between proximal or terminal CIs could be identified as no study on proximal CIs was identified for this outcome.

For **CI experienced patients** the rates serious infections varied between 1 and 9 of 100 patients. No differences between proximal or terminal CIs could be identified (1 study; RoB high).

Meningococcal infections

No meningococcal infections were reported in any of the studies

Table 16: Infections

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
Complement inhibitor-naïve patients										
AEGIS	Eculizumab	Complement inhibitor-naïve PNH patients	Upper respiratory tract infection as a TEAE reported in >10% of patients	First and last 12 weeks of treatment	7/27 (25.9%)	NR	NR	Open-label single arm	NA	12/16
			Pneumonia as a TEAE reported in >10% of patients		4/27 (14.8%)					
			Treatment-emergent infections	66 weeks	25/27 (92.6%)					
			Serious treatment-emergent infections		7/27 (25.9%)					
			Serious pneumonia		4/27 (14.8%)					
			Serious bronchitis		1/27 (3.7%)					
			Serious cellulitis		1/27 (3.7%)					
			Serious herpes infection		1/27 (3.7%)					
			Serious sepsis		1/27 (3.7%)					
			Serious upper respiratory tract infection		1/27 (3.7%)					
			Serious viral gastroenteritis		1/27 (3.7%)					
			Staphylococcal infection		0/27 (0%)					
			Meningococcal infection		0/27 (0%)					

ALXN1210-PNH-301	Ravulizumab	Complement inhibitor-naïve with clinical symptoms indicative of high disease activity	Upper respiratory tract infection as TEAE in ≥5% of patients	26 weeks	13/125 (10.4%)	NR	NR	Open-label RCT	Eculizumab	High
	Eculizumab				7/121 (5.8%)					
	Ravulizumab		Viral (serious viral) upper respiratory tract infection as TEAE in ≥5% of patients		9/125 (7.2%) (0/125 (0%))	NR	NR		Ravulizumab	
	Eculizumab				10/121 (8.3%) (1/121 (0.8%))					
	Ravulizumab		Any serious infection		2/125 (1.6%)	NR	NR		Ravulizumab	
	Eculizumab				4/121 (3.3%)					
	Ravulizumab		Serious leptospirosis		1/125 (0.8%)	NR	NR		Eculizumab	
	Eculizumab				0/121 (0%)					
	Ravulizumab		Serious systemic infection		1/125 (0.8%)	NR	NR		Eculizumab	
	Eculizumab				0/121 (0%)					
	Ravulizumab		Serious infection		0/125 (0%)	NR	NR		Ravulizumab	
	Eculizumab				1/121 (0.8%)					
	Ravulizumab		Serious influenza		0/125 (0%)	NR	NR		NED	
	Eculizumab				0/121 (0%)					
	Ravulizumab		Serious lower respiratory tract infection		0/125 (0%)	NR	NR		NED	
	Eculizumab				0/121 (0%)					
	Ravulizumab		Aspergillus infection		0/125 (0%)	NR	NR		NED	
	Eculizumab				0/121 (0%)					
	Ravulizumab		Sepsis		0/125 (0%)	NR	NR		NED	
	Eculizumab				0/121 (0%)					
	Ravulizumab		Meningococcal infection		0/125 (0%)	NR	NR		NED	
	Eculizumab				0/121 (0%)					
	Ravulizumab			Extension period up to 2 years	0/243 (0%)	NR	NR		NA	

APPOINT-PNH	Iptacopan	Complement inhibitor-naïve PNH patients	Upper respiratory tract infection as TEAE in ≥5% of patients	1-24 weeks (randomised period) and 24-48 weeks (extension period)	6/40 (15.0%)	NR	NR	Single arm	NA	12/16
			Severe or serious infections		4/40 (10.0%)					
			Capsular bacteria infections		2/40 (5.0%)					
			COVID19 as TEAE in ≥5% of patients		7/40 (17.5%)					
COMMODORE 2	Crovalimab	Complement inhibitor-naïve PNH patients	Infections	Week 25	23.7%)	NR	NR	Open-label RCT	Crovalimab	High
	Eculizumab				(36.2%)					
	Crovalimab		Serious infections		4/135 (3.0%)	Rate per 100 person-years (95% CI): 6.5 (1.8, 16.5)	NR		Crovalimab	
	Eculizumab				5/69 (7.2%)	Rate per 100 person-years (95% CI): 15.8 (5.1, 36.9)				
	Crovalimab		Upper respiratory tract infection		11/135 (8.1%)	NR	NR		Crovalimab	
	Eculizumab				9/69 (13.0%)					
	Crovalimab		Serious pneumonia		2/135 (1.5%)	NR	NR		Eculizumab	
	Eculizumab				0/69 (0%)					
	Crovalimab		Serious CNS infection		0/135 (0%)	NR	NR		Crovalimab	
	Eculizumab				1/69 (1.4%)					

	Crovalimab		Serious sepsis		0/135 (0%)	NR	NR		Crovalimab	
	Eculizumab				1/69 (1.4%)					
	Crovalimab		Serious UTI		0/135 (0%)	NR	NR		Crovalimab	
	Eculizumab				1/69 (1.4%)					
	Crovalimab		Serious COVID19		1/135 (0.7%)	NR	NR		Crovalimab	
	Eculizumab				1/69 (1.4%)					
	Crovalimab		Meningococcal infection		0/135 (0%)	NR	NR		NED	
	Eculizumab				0/69 (0%)					
PRINCE	Pegcetacoplan	Complement inhibitor-naïve PNH patients	Viral infection	Week 26	3/46 (6.52%)	NR	NR	Open-label RCT	SOC, excluding complement inhibitors	High
	SOC, excluding complement inhibitors				0/18 (0%)					
	Pegcetacoplan		Upper respiratory tract infection		1/46 (2.17%)	NR	NR		Pegcetacoplan	
	SOC, excluding complement inhibitors				2/18 (11.11%)					
	Pegcetacoplan		Influenza		0/46 (0%)	NR	NR		Pegcetacoplan	
	SOC, excluding complement inhibitors				1/18 (5.56 %)					
	Pegcetacoplan		UTI		0/46 (0%)	NR	NR		Pegcetacoplan	
	SOC, excluding complement inhibitors				1/18 (5.56 %)					
	Pegcetacoplan		Serious Pneumocystis jirovecii pneumonia		0/46 (0%)	NR	NR		Pegcetacoplan	
	SOC, excluding complement inhibitors				1/18 (5.56%)					
	Pegcetacoplan		Serious septic shock		1/46 (2.17%)	NR	NR		NED	
	SOC, excluding complement inhibitors				1/18 (5.56%)					

	Pegcetacoplan		Serious herpes virus infection		0/46 (0%)	NR	NR		Pegcetacoplan	
	SOC, excluding complement inhibitors				1/18 (5.56%)					
	Pegcetacoplan		Serious pulmonary tuberculosis		0/46 (0%)	NR	NR		Pegcetacoplan	
	SOC, excluding complement inhibitors				1/18 (5.56%)					
	Pegcetacoplan		Serious UTI		0/46 (0%)	NR	NR		Pegcetacoplan	
	SOC, excluding complement inhibitors				1/18 (5.56%)					
	Pegcetacoplan		Meningitis		0/35 (0%)	NR	NR		NED	
	SOC, excluding complement inhibitors				0/18 (0%)					
SHEPHERD	Eculizumab	Complement inhibitor-naïve PNH patients with thrombocytopenia	Any infection	52 weeks	89/97 (91.8%)	NR	NR	Single arm	NA	13/16
			Any serious infection		6/97 (6.2%)	NR	NR			
			Severe infection		3/97 (3.1%)	NR	NR			
			Upper respiratory tract infection in ≥10% of patients		29/97 (29.9%)	NR	NR			
			Severe upper respiratory tract infection		0/97 (0%)	NR	NR			
			Serious viral infection		1/97 (1.0%)	NR	NR			
			UTI		13/97 (13.4%)	NR	NR			

TRIUMPH	Eculizumab	Complement inhibitor-naïve PNH patients with good bone marrow reserve	Serious alpha-haemolytic streptococcal bacteraemia	Baseline to week 26	1/43 (2%)	NR	NR	Double-blind RCT	Placebo	Low
	Placebo				0/44 (0%)					
	Eculizumab		Serious central-line and UTI		0/43 (0%)	NR	NR		Eculizumab	
	Placebo				1/44 (2%)					
	Eculizumab		Serious upper respiratory tract infection		0/43 (0%)	NR	NR		Eculizumab	
	Placebo				1/44 (2%)					
	Eculizumab		Upper respiratory tract infection		6/43 (14%)	NR	NR		Eculizumab	
	Placebo				10/44 (23%)					
	Eculizumab		Viral infection		1/43 (2%)	NR	NR		Eculizumab	
	Placebo				5/44 (11%)					
X03-001	Eculizumab	Complement inhibitor-naïve PNH patients	Upper respiratory tract infection	52 weeks	3/11 (27.3%)	NR	NR	Open-label extension study	NA	12/16
Complement inhibitor-experienced patients										
ALXN1210-PNH-302	Ravulizumab	Complement inhibitor-experienced with clinically stable disease	Upper respiratory tract infection as TEAE in ≥5% of patients	26 weeks	18/97 (18.6%)	NR	NR	Open-label RCT	Eculizumab	High
	Eculizumab				10/98 (10.2%)					
	Ravulizumab		Serious viral upper respiratory tract infection		0/97 (0%)	NR	NR		NED	
	Eculizumab				0/98 (0%)					
	Ravulizumab		Any serious infection		2/97 (2.1%)	NR	NR		Eculizumab	
	Eculizumab				1/98 (1.0%)					
	Ravulizumab		Serious leptospirosis		0/97 (0%)	NR	NR		NED	
	Eculizumab				0/98 (0%)					
	Ravulizumab		Serious systemic infection		0/97 (0%)	NR	NR		NED	
	Eculizumab				0/98 (0%)					
	Ravulizumab		Serious infection		0/97 (0%)	NR	NR		NED	

	Eculizumab				0/98 (0%)					
	Ravulizumab		Serious influenza		1/97 (1.0%)	NR	NR		Eculizumab	
	Eculizumab				0/98 (0%)					
	Ravulizumab		Serious lower respiratory tract infection		1/97 (1.0%)	NR	NR		Eculizumab	
	Eculizumab				0/98 (0%)					
	Ravulizumab		Aspergillus infection		0/97 (0%)	NR	NR		NED	
	Eculizumab				0/98 (0%)					
	Ravulizumab		Sepsis		0/97 (0%)	NR	NR		NED	
	Eculizumab				0/98 (0%)					
	Ravulizumab		Meningococcal infection		0/97 (0%)	NR	NR		NED	
	Eculizumab				0/98 (0%)					
	Ravulizumab			Extension period up to 2 years	0/119 (0%)	NR	NR		NA	
ALPHA	Danicopan plus eculizumab or ravulizumab	Complement inhibitor-experienced PNH patients with clinically significant EVH	COVID19 or COVID19 pneumonia at grade ≥3	12 weeks	1/57 (1.8%)	NR	NR	Double-blind RCT	Placebo plus eculizumab or ravaulizumab	Unclear
	Placebo plus eculizumab or ravulizumab				0/29 (0%)					
	Danicopan plus eculizumab or ravulizumab		Ear infection as a TEAE reported by ≥5% of patients		0/57 (0%)	NR	NR		Danicopan plus eculizumab or ravulizumab	
	Placebo plus eculizumab or ravulizumab				2/9 (6.9%)					
	Danicopan plus		Meningococcal infections	NR	0/49 (0%)	NR	NR		NED	

	eculizumab or ravulizumab									
	Placebo plus eculizumab or ravulizumab				0/24 (0%)					
APPLY-PNH	Iptacopan	Complement inhibitor-experienced PNH patients with residual anaemia	Upper respiratory tract infection (≥5% of patients)	Baseline to day 168	2/62 (3.2%)	NR	RD (95% CI): -5.35 (-15.61, 4.92)	Open-label RCT	Iptacopan	High
	Eculizumab or ravulizumab				3/35 (8.6%)					
	Iptacopan		Urinary tract infection (≥5% of patients)		5/62 (8.1%)	NR	RD (95% CI): 5.21 (-3.53, 13.95)		Eculizumab or ravulizumab	
	Eculizumab or ravulizumab				1/35 (2.9%)					
	Iptacopan		Serious or severe infections and infestations		2/62 (3.2%)	NR	RD (95% CI): -5.35 (-15.61, 4.92)		Iptacopan	
	Eculizumab or ravulizumab				3/35 (8.6%)					
	Iptacopan		Infections caused by encapsulated bacteria		1/62 (1.6%)	NR	RD (95% CI): 1.61 (-1.52, 4.75)		Eculizumab or ravulizumab	
	Eculizumab or ravulizumab				0/35 (0%)					
	Iptacopan		Serious COVID19		1/62 (1.6%)	NR	RD (95% CI): -4.10 (-12.41, 4.20)		Iptacopan	
	Eculizumab or ravulizumab				2/35 (5.7%)					
	Iptacopan		Serious urinary tract infection		1/62 (1.6%)	NR	RD (95% CI): 1.61 (-1.52, 4.75)		Eculizumab or ravulizumab	
	Eculizumab or ravulizumab				0/35 (0%)					
COMMODORE 1	Crovalimab	Complement inhibitor-experienced PNH	Any infection	24 weeks and extensio	18/44 (41%)	135.9 (95% CI: 88.75, 199.06)	NR	Open-label RCT	Eculizumab	High

		patients		n periods (NR)		infections per 100 patient years				
	Eculizumab				15/42 (36%)	115.7 (95% CI: 71.60, 176.82) infections per 100 patient years				
	Crovalimab		Any serious infection		3/44 (7%)	15.7 (95% CI: 3.23, 45.81) serious infections per 100 patient years	NR		Eculizumab	
	Eculizumab				1/42 (2%)	11.0 (95% CI:1.33, 39.80) serious infections per 100 patient years				
	Crovalimab		UTI as TEAE in ≥5% of patients		2/44 (5%)	NR	NR		Crovalimab	
	Eculizumab				3/42 (7%)					
	Crovalimab		Serious UTI as TEAE in ≥5% of patients		1/44 (2.3%)	NR	NR		Eculizumab	
	Eculizumab				0/42 (0%)					
	Crovalimab		COVID19 infection		6/44 (14%)	NR	NR		Crovalimab	

	Eculizumab		as TEAE in ≥5% of patients		7/42 (17%)					
	Crovalimab		Influenza as TEAE in ≥5% of patients		2/44 (5%)	NR	NR		Crovalimab	
	Eculizumab				3/42 (7%)					
	Crovalimab		Meningococcal infection		0/44 (0%)	NR	NR		NED	
	Eculizumab				0/42 (0%)					
PEGASUS	Pegcetacoplan	Adults with PNH who continue to have anaemia despite treatment with eculizumab	Viral respiratory tract infection	NR	2/41 (4.9%)	NR	NR	Open-label RCT	NED	High
	Eculizumab				2/39 (5.1%)					
	Pegcetacoplan		Serious treatment-emergent infections	48 weeks	5/77 (6.5%)	NR	NR		NA	
			Upper respiratory tract infection		8/77 (10%)					
			Urinary tract infection		7/77 (9%)					
			Oral herpes		5/77 (7%)					
			Sepsis		3/77 (3.9%)					
			Biliary sepsis		1/77 (1.3%)					
			Any infection		42/77 (55%)					
			Meningococcal infection		0/77 (0%)					

Abbreviations: CI, confidence interval; CNS, central nervous system; dL, decilitre; g, grams; Hb, haemoglobin; HRQoL, health-related quality of life; LS, least squared; NA, not applicable; NED, no evidence of a difference; PNH, paroxysmal nocturnal haemoglobinuria; RCT, randomised controlled trial; RD, risk difference; SE, standard error; TEAE, treatment-emergent adverse event; UTI, urinary tract infection.

Kidney impairment

A total of 3 studies (2 RCTs, 1 single-arm) provided evidence on kidney impairment for iptacopan, pegcetacoplan, eculizumab/ravulizumab and SOC (Table 17). Two studies (1 RCT) reported on complement inhibitor-naïve patients, and one study (a RCT) reported on complement inhibitor-experienced patients. Risk of bias was high.

In complement inhibitor-naïve patients, RCT evidence indicated numerically lower rates of kidney impairment for pegcetacoplan vs SOC (PRINCE) (Table 17).

In complement inhibitor-experienced patients, RCT evidence indicated that rates of kidney impairment were numerically lower for iptacopan vs eculizumab/ravulizumab (0% vs 2.9%) (APPLY-PNH) (Table 17).

Single-arm study evidence also reported low levels of renal impairment affecting 5.0% of patients receiving iptacopan (Table 17).

Conclusion for the decision aid:

In **complement inhibitor-naïve** patients, RCT evidence indicated rates of kidney impairment lower than 5 of 100 with iptacoplan and pegcetacoplan. Differences between terminal and proximal CIs were not reported (2 studies; RoB high).

In **complement inhibitor-experienced** patients rates of kidney impairment ranged between 0 und 3 of 100. Rates of patients treated with iptacopan (proximal CI) were numerically lower than those, treated with eculizumab/ravulizumab (terminal CIs) but this difference was not statistically significant (one study; RoB high).

Table 17: Kidney impairment

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
Complement inhibitor-naïve patients										
APPOINT-PNH	Iptacopan	Complement inhibitor-naïve PNH patients	Renal impairment as TEAE in ≥5% of patients	1-24 weeks (randomised period) and 24-48 weeks (extension period)	2/40 (5.0%)	NR	NR	Single arm	NA	12/16
PRINCE	Pegcetacoplan SOC, excluding complement inhibitors	Complement inhibitor-naïve PNH patients	Acute kidney injury	Week 26	0/46 (0%) 1/18 (5.56%)	NR	NR	Open-label RCT	Pegcetacoplan	High
Complement inhibitor-experienced patients										
APPLY-PNH	Iptacopan Eculizumab or ravulizumab	Complement inhibitor-experienced PNH patients with residual anaemia	Serious renal and urinary disorders	Baseline to day 168	0/62 (0%) 1/35 (2.9%)	NR	NR	Open-label RCT	Iptacopan	High

Abbreviations: NA, not applicable; PNH, paroxysmal nocturnal haemoglobinuria; RCT, randomised controlled trial; TEAE, treatment-emergent adverse event.

FAQ6: Are there any long-term negative effects of treatment?

Several trials that contributed data for this report only followed up patients for a limited period. For example, the COMMODORE 1 and 2 trials only reported data up to week 25; and the PEGASUS trial comparing pegcetacoplan vs eculizumab followed the pegcetacoplan arm for 48 weeks but the eculizumab arm only for 16 weeks. This means that long-term data are lacking, a limitation that was highlighted in recent HTA assessments.[18]

For all drugs and outcomes of interest, any data from 48 weeks or longer was compiled to assess longer-term evidence (Table 18). This provided information from seven studies (3 RCT extension periods), including:

- Eculizumab (AEGIS (66 weeks or 2 years); SHEPHERD (52 weeks); X03-001 (52 weeks))
- Ravulizumab (Study 301 (up to 2 years); Study 302 (up to 2 years))
- Pegcetacoplan (PEGASUS (48 weeks))
- Iptacopan (APPOINT-PNH (24-48 weeks))

Four studies reported on longer-term breakthrough haemolysis, three in complement inhibitor-naïve patients (Study 301, APPOINT-PNH, X03-001) and one in complement inhibitor-experienced patients (Study 302). In complement inhibitor-naïve patients, rates of BTH were 18% for eculizumab at 52 weeks, 6.2% for ravulizumab at up to 2 years and 2.5% for iptacopan at 24-48 weeks. In complement inhibitor-experienced patients, the rate of BTH was 5.8% in ravulizumab at up to 2 years (Table 18).

Two studies reported on longer-term MAVE, both in complement inhibitor-naïve patients (AEGIS, APPOINT-PNH). Rates of MAVE were zero for eculizumab or iptacopan at 66 weeks or 24-48 weeks, respectively (Table 18).

Four studies reported on longer-term meningococcal infections, two in complement inhibitor-naïve patients (AEGIS, Study 301) and two in complement inhibitor-experienced patients (PEGASUS, Study 302). In complement inhibitor-naïve patients, no meningococcal infections were reported for eculizumab treatment up to 66 weeks or ravulizumab treatment up to 2 years. In complement inhibitor-experienced patients, no meningococcal infections were reported in ravulizumab up to 2 years or pegcetacoplan up to 48 weeks (Table 18).

Five studies reported on longer-term serious infections, three in complement inhibitor-naïve patients (AEGIS, APPOINT-PNH, SHEPHERD) and one in complement inhibitor-experienced patients (PEGASUS). In complement inhibitor-naïve patients, rates of serious infections were reported to range from 6.2% to 25.9% at ≥48 weeks for eculizumab treatment and reported at a rate of 10.0% for iptacopan at 24-48 weeks. In complement inhibitor-experienced patients, the rate of serious infections was reported as 6.5% for pegcetacoplan at 48 weeks (Table 18).

Three studies reported on longer-term infections, two in complement inhibitor-naïve patients (AEGIS, SHEPHERD) and one in complement inhibitor-experienced patients (PEGASUS). In complement inhibitor-naïve patients, rates of any infections were reported to

range from 91.8% to 92.6% at ≥48 weeks for eculizumab. In complement inhibitor-experienced patients, the rate of any infections was reported as 55% for pegcetacoplan at 48 weeks (Table 18).

Three studies reported on longer-term URTI rates, three in complement inhibitor-naïve patients (APPOINT-PNH, SHEPHERD, X03-001) and one in complement inhibitor-experienced patients (PEGASUS). In complement inhibitor-naïve patients, rates of URTI were reported to range from 27.3% to 29.9% at 52 weeks for eculizumab and reported at a rate of 15.0% for iptacopan at 24-48 weeks. In complement inhibitor-experienced patients, the rate of URTI was reported as 10% for pegcetacoplan at 48 weeks (Table 18).

Conclusion for the decision aid:
For longer term adverse events direct comparisons are scarce, patient numbers and certainty of evidence are low. Therefore, only cautious trend statements are possible:

Effect	**CI naive**	**CI experienced**
longer-term breakthrough haemolysis	6-18 of 100 in terminal CIs vs. 3 of 100 in proximal CIs	No comparison
longer-term MAVE	No difference	No comparison
longer-term meningococcal infections	No comparison	No difference
longer-term serious infections	6-26 of 100 in terminal CIs vs. 10 of 100 in proximal CIs	No comparison (but also low in proximal CIs; 7 of 100)
longer-term infections	No comparison	No comparison
longer-term URTI	27-30 of 100 in terminal CIs vs. 10 of 100 in proximal CIs	No comparison

Table 18: All long-term outcomes – ≥48 weeks

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
Complement inhibitor-naïve patients										
AEGIS	Eculizumab	Complement inhibitor-naïve PNH patients	Transfusion avoidance / transfusion independence	Last 6 months of extension period	25/26 (96%)	NR	NR	Open-label single arm	NA	12/16
ALXN1210-PNH-301	Ravulizumab	Complement inhibitor-naïve with clinical symptoms indicative of high disease activity		>12-18 months extension	178/243 (73.3%)	NR	NR	Open-label RCT	NA	High
SHEPHERD	Eculizumab	Complement inhibitor-naïve PNH patients with thrombocytopenia		52 weeks	51/97 (52.6%)	NR	NR	Single arm	NA	13/16
AEGIS	Eculizumab	Complement inhibitor-naïve PNH patients	Number of pRBC units transfused	66 weeks	NR	NR	Mean CFB (SE): -4.7 (1.20), P<0.001	Open-label single arm	NA	12/16
SHEPHERD	Eculizumab	Complement inhibitor-naïve PNH		52 weeks	NR	Mean (SE): 5.9 (1.06)	Change from baseline:	Single arm	NA	13/16

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
		patients with thrombocytopenia					<0.001			
X03-001	Eculizumab	Complement inhibitor-naïve PNH patients	Transfusion rate	Baseline 64 weeks	NR	Mean 2.1 Mean 0.5	P=0.001	Open-label extension study	NA	12/16
ALXN1210-PNH-301	Ravulizumab	Complement inhibitor-naïve with clinical symptoms indicative of high disease activity	Breakthrough haemolysis	Extension period up to 2 years	15/243 (6.2%)	NR	NR	Open-label RCT	NA	High
APPOINT-PNH	Iptacopan	Complement-naïve PNH patients		24-48 week extension period	1/40 (2.5%)	Adjusted annualised rate 0.06 (95% CI: 0.00 to 0.68)		Single-arm study	NA	12/16
X03-001	Eculizumab	Complement inhibitor-naïve PNH patients		52 weeks	2/11 (18%)	NR	NR	Open-label extension study	NA	12/16
AEGIS	Eculizumab	Complement inhibitor-naïve PNH	Death	66 weeks	0/27 (0%)	NR	NR	Open-label single	NA	12/16

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
		patients						arm		
APPOINT-PNH	Iptacopan	Complement-naïve PNH patients		1-24 weeks (randomised period) and 24-48 weeks (extension period)	0/40 (0%)	NR	NR	Single-arm study	NA	12/16
X03-001	Eculizumab	Complement inhibitor-naïve PNH patients		52 weeks	0/11 (0%)	NR	NR	Open-label extension study	NA	12/16
ALXN1210-PNH-301	Ravulizumab	Complement inhibitor-naïve with clinical symptoms indicative of high disease activity	EORTC QLQ-C30 GHS/QOL	2 years	NR	Mean (SD): 70.4 (20.57)	NR	Open-label RCT	NA	High
SHEPHERD	Eculizumab	Complement inhibitor-naïve PNH patients with thrombocytopenia		52 weeks	NR	Mean CFB (SE): 19.7 (2.05), P<0.001	NR	Single arm	NA	13/16

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
X03-001	Eculizumab	Complement inhibitor-naïve PNH patients		Baseline	NR	Mean 56.1	P=0.009	Open-label extension study	NA	12/16
				64 weeks		Mean 13.8				
AEGIS	Eculizumab	Complement inhibitor-naïve PNH patients	FACIT-Fatigue* score	66 weeks	NR	NR	Mean CFB (SE): 5.0 (1.93), P=0.02	Open-label single arm	NA	12/16
ALXN1210-PNH-301	Ravulizumab	Complement inhibitor-naïve with clinical symptoms indicative of high disease activity		2 years	NR	Mean (SD): 43.5 (8.10)	Mean % change from day 183: 1.6% (36.38)	Open-label RCT	NA	High
SHEPHERD	Eculizumab	Complement inhibitor-naïve PNH patients with thrombocytopenia		52 weeks	NR	Median: 10.0	CFB (SD): 12.1 (1.1), P<0.001	Single arm	NA	13/16
SHEPHERD	Eculizumab	Complement inhibitor-naïve PNH patients with thrombocyt	Change from baseline in EORTC-QLQ C30 - Fatigue	52 weeks	NR	Mean change (SE): -27.5 (2.32) P<0.001	NR	Single arm	NA	13/16

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
		openia								
AEGIS	Eculizumab	Complement inhibitor-naïve PNH patients	MAVE	66 weeks	0/27 (0%)	NR	NR	Open-label single arm	NA	12/16
APPOINT-PNH	Iptacopan	Complement-naïve PNH patients		24-48 weeks (extension period)	0/40 (0%)	NR	NR	Single-arm study	NA	12/16
SHEPHERD	Eculizumab	Complement inhibitor-naïve PNH patients with thrombocytopenia	Thrombotic event	52 weeks	2/97 (2.1%)	NR	NR	Single arm	NA	13/16
X03-001	Eculizumab	Complement inhibitor-naïve PNH patients	Thromboses	52 weeks	0/11 (0%)	NR	NR	Open-label extension study	NA	12/16
SHEPHERD	Eculizumab	Complement inhibitor-naïve PNH patients with thrombocytopenia	Change from baseline in EORTC-QLQ C30 - dyspnea	52 weeks	NR	Mean change (SE): -20.7 (2.96) P<0.001	NR	Single arm	NA	13/16
AEGIS	Eculizumab	Complement inhibitor-naïve PNH	Meningococcal infection	66 weeks	0/27 (0%)	NR	NR	Open-label single	NA	12/16

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
		patients						arm		
ALXN1210-PNH-301	Ravulizumab	Complement inhibitor-naïve with clinical symptoms indicative of high disease activity		Extension period up to 2 years	0/243 (0%)	NR	NR	Open-label RCT	NA	High
AEGIS	Eculizumab	Complement inhibitor-naïve PNH patients	Any serious infection	66 weeks	7/27 (25.9%)	NR	NR	Open-label single arm	NA	12/16
APPOINT-PNH	Iptacopan	Complement inhibitor-naïve PNH patients		24-48 weeks (extension period)	4/40 (10.0%)	NR	NR	Single arm	NA	12/16
SHEPHERD	Eculizumab	Complement inhibitor-naïve PNH patients with thrombocytopenia		52 weeks	6/97 (6.2%)	NR	NR	Single arm	NA	13/16
AEGIS	Eculizumab	Complement inhibitor-naïve PNH patients	Any infection	66 weeks	25/27 (92.6%)	NR	NR	Open-label single arm	NA	12/16

SHEPHERD	Eculizumab	Complement inhibitor-naïve PNH patients with thrombocytopenia		52 weeks	89/97 (91.8%)	NR	NR	Single arm	NA	13/16
APPOINT-PNH	Iptacopan	Complement inhibitor-naïve PNH patients	Upper respiratory tract infection (general or as TEAE in ≥5% or ≥10% of patients)	24-48 weeks (extension period)	6/40 (15.0%)	NR	NR	Single arm	NA	12/16
SHEPHERD	Eculizumab	Complement inhibitor-naïve PNH patients with thrombocytopenia		52 weeks	29/97 (29.9%)	NR	NR	Single arm	NA	13/16
X03-001	Eculizumab	Complement inhibitor-naïve PNH patients		52 weeks	3/11 (27.3%)	NR	NR	Open-label extension study	NA	12/16
AEGIS	Eculizumab	Complement inhibitor-naïve PNH patients	Serious pneumonia	66 weeks	4/27 (14.8%)	NR	NR	Open-label single arm	NA	12/16
			Serious bronchitis		1/27 (3.7%)					
			Serious cellulitis		1/27 (3.7%)					
			Serious herpes infection		1/27 (3.7%)					
			Serious sepsis		1/27 (3.7%)					
			Serious upper respiratory tract infection		1/27 (3.7%)					
			Serious viral gastroenteritis		1/27 (3.7%)					
			Staphylococcal infection		0/27 (0%)					

APPOINT-PNH	Iptacopan	Complement inhibitor-naïve PNH patients	Capsular bacterial infection	24-48 weeks (extension period)	2/40 (5.0%)	NR	NR	Single arm	NA	12/16
			COVID19 as TEAE in ≥5% of patients	24-48 weeks (extension period)	7/40 (17.5%)					
SHEPHERD	Eculizumab	Complement inhibitor-naïve PNH patients with thrombocytopenia	Severe infection	52 weeks	3/97 (3.1%)	NR	NR	Single arm	NA	13/16
			Severe upper respiratory tract infection		0/97 (0%)					
			Serious viral infection		1/97 (1.0%)					
			UTI		13/97 (13.4%)					
Complement inhibitor-experienced patients										
ALXN1210-PNH-302	Ravulizumab	Complement inhibitor-experienced with clinically stable disease	Transfusion avoidance	>12-18 month extension	163/191 (85.3%)	NR	NR	Open-label RCT	NA	High
PEGASUS	Pegcetacoplan to pegcetacoplan	Adults with PNH who continue to have anaemia despite treatment with eculizumab		48 weeks	30/41 (73%)	NR	NR	Open-label RCT	NA	High
	Eculizumab to pegcetacoplan				28/39 (72%)					
ALXN1210-PNH-302	Ravulizumab	Complement inhibitor-experienced with clinically stable disease	Breakthrough haemolysis	Extension period up to 2 years	11/191 (5.8%)	NR	NR	Open-label RCT	NA	High

PEGASUS	Pegcetacoplan	Adults with PNH who continue to have anaemia despite treatment with eculizumab	Acute haemolytic event (including haemolysis, haemolytic anaemia and intravascular haemolysis)	48 weeks	18/77 (23%)	NR	NR	Open-label RCT	NA	High
			Acute haemolytic event (haemolysis only)		15/77 (19.5%)	NR	NR		NA	
			Exposure-adjusted rate of an adverse event of haemolysis		NR	15 patients (33.5 events per 100 patient-years)	NR		NA	
PEGASUS	Pegcetacoplan	Adults with PNH who continue to have anaemia despite treatment with eculizumab	Death	48 weeks	1/77 (1.3%) (death due to COVID19)	NR	NR	Open-label extension	NED	High
ALXN1210-PNH-302	Ravulizumab	Complement inhibitor-experienced with clinically stable disease	EORTC QLQ-C30 GHS/QOL	2 years	NR	Mean (SD): 71.6 (20.07)	NR	Open-label RCT	NA	High
ALXN1210-PNH-302	Ravulizumab	Complement inhibitor-experienced with clinically stable disease	FACIT-Fatigue* score	2 years	NR	Mean (SD): 41.2 (10.70)	Mean % change from day 183: -1.2% (25.62)	Open-label RCT	NA	High

PEGASUS	Pegcetacoplan to pegcetacoplan	Adults with PNH who continue to have anaemia despite treatment with eculizumab		48 weeks	NR	Mean (SD): 40.60 (10.12)	Mean CFB (SD): 10.14 (9.06)	Open-label RCT	NA	High
	Eculizumab to pegcetacoplan					Mean (SD): 30.62 (11.77)	Mean CFB (SD): 9.62 (10.34)			
	Pegcetacoplan		Fatigue as a TEAE affecting ≥10% of patients		8/77 (10%)	NR	NR		NA	
PEGASUS	Pegcetacoplan	Adults with PNH who continue to have anaemia despite treatment with eculizumab	DVT	48 weeks	1/77 (1.3%)	NR	NR	Open-label RCT	NA	High
			Jugular vein thrombosis		1/77 (1.3%)					
			Thrombosis (any)		2/77 (2.6%)					
ALXN1210-PNH-302	Ravulizumab	Complement inhibitor-experienced with clinically stable disease	Meningococcal infection	Extension period up to 2 years	0/119 (0%)	NR	NR	Open-label RCT	NA	High
PEGASUS	Pegcetacoplan	Adults with PNH who continue to have anaemia despite treatment with eculizumab		48 weeks	0/77 (0%)					High

PEGASUS	Pegcetacoplan	Adults with PNH who continue to have anaemia despite treatment with eculizumab	Serious treatment-emergent infections	48 weeks	5/77 (6.5%)	NR	NR	Open-label RCT	NA	High
			Upper respiratory tract infection		8/77 (10%)					
			Urinary tract infection		7/77 (9%)					
			Oral herpes		5/77 (7%)					
			Sepsis		3/77 (3.9%)					
			Biliary sepsis		1/77 (1.3%)					
			Any infection		42/77 (55%)					

Abbreviations: CFB, change from baseline; DVT, deep vein thrombosis; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire; FACIT, Functional Assessment of Chronic Illness Therapy; GHS, general health status; MAVE, major adverse vascular event; NA, not applicable; NR, not reported; PNH, paroxysmal nocturnal haemoglobinuria; pRBC, packed red blood cells; QoL, quality of life; RCT, randomised controlled trial; SD, standard deviation; SE, standard error; TEAE, treatment-emergent adverse event; UTI, urinary tract infection.

FAQ7: Where can I get additional information and/or a second opinion?

ORPHAnet provides additional patient-centred resources and information on PNH. This includes links to patient organisations and clinical trials. https://www.orpha.net/en/disease/detail/447?name=paroxysmal%20nocturnal%20hemoglobinuria&mode=name

In Germany, treatment guidelines are also available through the onkopedia website: https://www.onkopedia.com/de/onkopedia/guidelines/paroxysmale-naechtliche-haemoglobinurie-pnh/@@guideline/html/index.html

FAQ8: Is there anything I can do myself to help my disease?

Any patients receiving complement therapy are recommended to receive vaccinations against *Neisseria meningitidis* types A, C, W, Y and B at least two weeks prior to starting treatment with C5 inhibitor therapy[10 30] together with *Streptococcus pneumoniae*; and *Haemophilus influenzae* type B within 2 years prior to starting therapy.[30] Patients should be revaccinated every 3-5 years after starting treatment and should seek immediate medical attention if they experience any signs or symptoms of infection (such as fever, headaches with nausea or vomiting, stiff neck, rash, confusion etc.).[21 30] Staying hydrated is also important to prevent critical haemolysis.[21]

FAQ9: Living with the disease

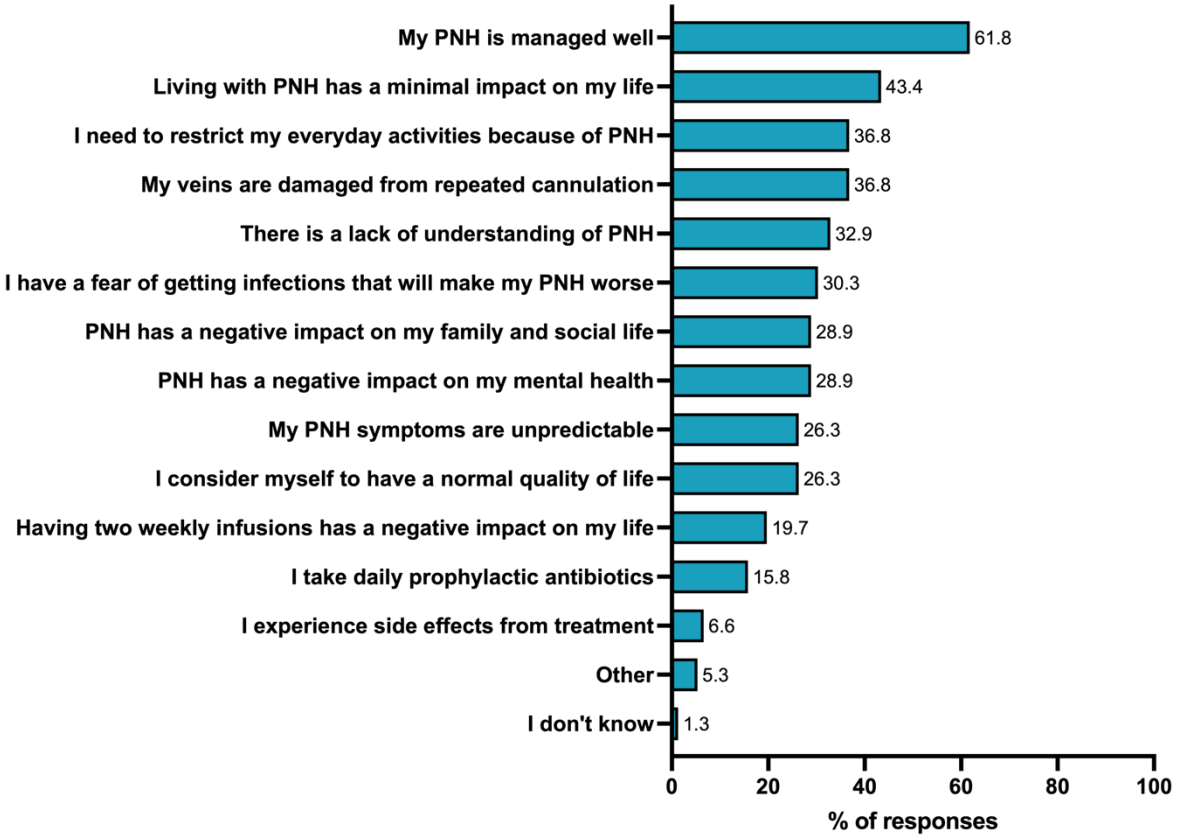
The British charity, PNH Support, conducted an online patient survey of 76 PNH patients in the UK as part of a HTA submission for pegcetacoplan to ask what life was like with PNH. Survey responses are provided in Figure 16.[18]

The majority of PNH patients (n=47; 62%) said that their PNH is managed well and 33 (43%) said living with PNH has a minimal impact on their life. Equal numbers of patients (n=28; 37%) identified that they needed to restrict daily activities because of PNH (with exercise and household chores needing to be restricted the most); and that their veins are damaged from repeated venipunture from infusions. Patients (n=25; 33%) said there is a lack of understanding of PNH and 23 (30%) had a fear of getting infections that makes their condition worse. Equal numbers of patients (n=22; 29%) said PNH has a negative impact on their mental health (with feeling anxious and fearful of their PNH progressing being the most common); and that PNH has a negative impact on family and social life (by limiting their social life, them not being able to contribute fully to family life, spend quality time with family or able to plan ahead being the main reasons). Equal numbers of patients (n=20; 26%) said they consider themselves to have a normal quality of life; and that their PNH symptoms are unpredictable.

Patients (n=15; 20%) said having two weekly infusions of complement inhibitor has a negative impact on their life (with the stress of accessing veins, the negative impact on veins of repeated venipunture and restricting full time work being the most common reasons). When patients were asked whether their employment status had been affected by having PNH, the majority (n=29; 38%) said that it wasn't affected with 19 (25%) saying that they either worked part time or were unemployed because of PNH. In addition, 9 patients (12%) had changed the type of work they do because of PNH: "Yes, I don't have as senior a position anymore. Due to PNH I don't have the energy for all the responsibility anymore",

“Yes, I can't work long hours as waitress or doing physical hard work.“ Eight patients (11%) had retired early because of PNH and three were medically retired.

Figure 16: Survey responses on living with the disease from UK PNH patients



Abbreviations: PNH, paroxysmal noctural haemoglobinuria.
Adapted from NICE TA778.[18]

Pregnant women

Pregnancies in PNH patients are associated with high maternal and foetal mortality and an increased risk of thrombosis.[21] However, there is little high quality treatment data available as the randomised trials captured in this report excluded pregnant women.

Current treatment guidelines recommend that pregnant PNH patients with mild, moderate or severe symptoms continue or initiate VTE prophylaxis with eculizumab to mitigate the risk of thrombosis.[10] This helps to reduce maternal mortality rates as well as reducing the risk of miscarriage or premature birth.[10] The dose of eculizumab can be increased in the third trimester or if breakthrough haemolysis is observed, and can be continued for at least six weeks post-partum.[10] Anti-coagulation treatment can also be started and continued for at least 6 weeks post-partum in pregnant women with risk factors for thrombosis.

Based on data from observational studies, eculizumab treatment is recommended to be continued during pregnancy as its side effect profile is well established: it is reported to be safe in pregnancy with no impact on the mother or child. Limited guidance was found for the use of drugs other than eculizumab or ravulizumab during pregnancy; however, one clinical expert providing evidence for a HTA submission recommended that pegcetacoplan

should not be used during pregnancy.[18] Since there are no data on the use of ravulizumab, pegcetacoplan, iptacopan, danicopan or crovalimab during pregnancy, current recommendations suggest that pregnant women or those trying to conceive should avoid treatment with these drugs.[8 21]

5. Discussion

Summary of main findings

This evidence review captures key drugs available to either complement inhibitor-naïve or complement inhibitor-experienced haemolytic PNH patients. Key findings from the evidence review are summarised in Table 19.

Overall, for complement inhibitor-naïve patients, ravulizumab and crovalimab generally appeared to be better than eculizumab in terms of BTH, quality of life, fatigue and serious infections; and similar to eculizumab in terms of transfusion avoidance, mortality, MAVE, dyspnea and upper respiratory tract infection. For meningococcal infections, there was no evidence of a difference between eculizumab, ravulizumab, crovalimab and pegcetacoplan (zero events in all treatment arms). No evidence was available for hypertension. In an ITC comparing iptacopan, eculizumab and ravulizumab, iptacopan was slightly better than eculizumab, and eculizumab was slightly better than ravulizumab in terms of transfusion avoidance.

Overall, for complement inhibitor-experienced patients, iptacopan generally appeared to be better than eculizumab, ravulizumab or crovalimab in terms of transfusion avoidance, BTH, fatigue, dyspnea, upper respiratory tract infection, serious infections and kidney impairment; no different to other complement inhibitors in terms of mortality; and slightly worse than eculizumab or ravulizumab in terms of MAVE. No evidence was available for iptacopan for quality of life, hypertension or meningococcal infections. For quality of life, ravulizumab and crovalimab were likely to be slightly better than eculizumab. For hypertension, limited evidence was available. For meningococcal infection, there was no evidence of a difference between eculizumab, ravulizumab, crovalimab and danicopan (zero events in all treatment arms).

In complement inhibitor-experienced patients, pegcetacoplan also appeared to be generally better than eculizumab in terms of transfusion avoidance, BTH, fatigue and dyspnea; and similar to eculizumab in terms of mortality.

In a MAIC for pegcetacoplan vs ravulizumab (with eculizumab as the anchor), pegcetacoplan significantly improved transfusion avoidance compared to ravulizumab. In an unanchored comparison between iptacopan and pegcetacoplan, iptacopan was associated with significantly higher odds of transfusion avoidance vs pegcetacoplan (OR 12.71 (95% CI 1.87, 86.22), P=0.009) in complement inhibitor-experienced patients.

Table 19: Summary of the evidence

Outcome	Source	Ecu	Rav	Crov	Peg	Ipta	Dani plus ecu/rav	RoB rating of evidence	Overview of evidence
FAQ1: What does the treatment involve?									
Do I have to receive treatment?	Goh 2024[10]	Patients with mild symptoms can take a watchful waiting approach, with monitoring every 6-12 months for signs of haemolysis, bone marrow disorder, new complications or the expansion of additional immune cell clones. However, once symptoms become more moderate or severe, such as disabling fatigue, thromboses, transfusion dependence, frequent pain paroxysms, renal insufficiency or other organ complications, active treatment is recommended						Moderate	PNH patients with even mild symptoms should begin treatment with a complement inhibitor to prevent disease progression
Can I delay treatment? When should I start treatment?	Cançado 2021[6]	PNH is typically a progressive disease that will only get worse with time, so the sooner patients start treatment the better. This will delay progression to kidney disease and the potential need for dialysis and kidney transplant. Most patients notice an improvement in their symptoms within hours or a few days of starting treatment						NA	
FAQ1: What does the treatment involve?									
Treatment schedules and doses	Onkopedia 2023,[21] NICE TA1132,[19] Scheinberg 2024,[25] FDA 2024[9]	QW for 4 weeks (600mg IV) then Q2W (900mg IV)	Loading dose (2,400 to 3,000 mg IV) then 2 weeks later, maintenance dosing Q8W (3,000 to 3,600 mg IV)	Loading dose (1,000 to 1,500 mg IV) followed by 4 more loading doses (340mg SQ) and then maintenance dosing Q4W (680 to 1,020 mg SQ)	BIW (1,080 mg SQ)	BID (200mg oral capsules)	TID (150mg oral)	High	NA

FAQ2: Will the therapy affect my haemoglobin level, and transfusion avoidance?									
Transfusion avoidance in complement inhibitor-naïve patients	NICE TA698,[17] Röth 2024,[24] Wong 2021,[26] Hillmen 2006[12]	Better than placebo	Slightly better than ecu	Slightly worse than ecu	Better than SOC	-	-	High to low	Ecu, rav, crov and peg all likely very similar and improved over SOC/placebo (i.e. symptom-oriented therapy)
Transfusion avoidance in complement inhibitor-experienced patients	NICE TA698,[17] NICE TA10980,[20] NICE TA11132,[19] Scheinberg 2024,[25] NICE TA778[18]	-	Slightly better than ecu	Slightly better than ecu	Much better than ecu	Much better than rav/ecu	Much better than rav/ecu alone	High to unclear	Ipta and peg likely much better than ecu or rav. Ecu, rav and crov all likely very similar. Dani plus ecu/rav better than ecu or rav alone but probably not better than ipta or peg alone
FAQ3: Will the treatment impact how long I live?									
Mortality in complement-naïve patients	NICE TA698,[17] Röth 2024,[24] Wong 2021,[26] Hillmen 2006[12]	No difference vs placebo	Similar to ecu	Similar to ecu	Slightly better than SOC	-	-	High to low	Ecu, rav, crov and peg likely similar to SOC (i.e. symptom-oriented therapy)
Mortality in complement-experienced patients	NICE TA698,[17] NICE TA10980,[20] NICE TA11132,[19] Scheinberg 2024,[25] NICE TA778[18]	-	No difference vs ecu	Slightly worse than ecu	No difference vs ecu	No difference vs ecu/rav	No difference vs ecu/rav alone	High to unclear	Ecu, rav, peg and ipta likely similar. Dani plus ecu/rav likely no better than ecu/rav alone. Crov may be similar to ecu, rav, peg and ipta
FAQ4: How will the treatment impact my quality of life?									
Fatigue as a TEAE in complement-naïve patients	NICE TA698,[17] Röth 2024,[24] Wong 2021,[26] Hillmen 2006[12]	Worse than placebo	Slightly better than ecu	Slightly better than ecu	Slightly better than SOC	-	-	High to low	Rav and crov likely slightly better than ecu. Peg likely slightly better than SOC. Ecu likely worse than SOC/placebo (i.e. symptom-oriented therapy)

Fatigue as a TEAE in complement-experienced patients	NICE TA698,[17] Scheinberg 2024,[25] NICE TA10980,[20] NICE TA11132,[19] NICE TA778[18]	-	Worse than ecu	Slightly better than ecu	Better than ecu	Better than ecu/rav	No difference vs ecu/rav alone	High to unclear	Ecu, rav and crov all likely similar. Peg and ipta likely better than ecu/rav. Dani plus ecu/rav likely similar to ecu/rav alone
Dyspnea in complement-naïve patients	NICE TA10980,[20] Röth 2024,[24] Wong 2021,[26] Hillmen 2006[12]	Much better than placebo	Similar to ecu	Similar to ecu	Slightly better than SOC	-	-	High to low	Ecu, rav and crov all likely similar. Peg likely slightly better than SOC, and ecu likely much better than SOC/placebo (i.e. symptom-oriented therapy)
Dyspnea in complement-experienced patients	NICE TA698,[17] NICE TA11132,[19] Scheinberg 2024,[25] NICE TA778[18]	-	Better than ecu	Better than ecu	Slightly better than ecu	Better than ecu/rav	-	High	Ipta likely better than ecu/rav. Rav and crov likely better than ecu. Peg likely better than ecu
HRQoL in complement-naïve patients	NICE TA698,[17] Röth 2024,[24] Wong 2021,[26] Hillmen 2006[12]	Much better than placebo	Better than ecu	Better than ecu	Much better than SOC	-	-	High to low	Rav and crov likely better than ecu. Ecu and peg better than SOC/placebo (i.e. symptom-oriented therapy)
HRQoL in complement-experienced patients	NICE TA698,[17] Panse 2023[22]	-	Slightly better than ecu	Better than ecu	-	-	-	High	Rav and crov likely better than ecu
FAQ5: What are the risks or side effects?									
Breakthrough haemolysis in complement-naïve patients	NICE TA698,[17] Röth 2024,[24]	-	Better than ecu	Slightly better than ecu	-	-	-	High	Rav slightly better than crov/ecu
Breakthrough haemolysis in complement-experienced patients	NICE TA698,[17] NICE TA10980,[20] NICE TA11132,[19] Scheinberg 2024[25]	-	Rav better than ecu	Slightly better than ecu	Better than ecu	Much better than ecu/rav	No difference vs ecu/rav alone	High to unclear	Rav slightly better than crov/ecu. Peg likely better than rav/ecu/crov. Ipta

									likely better than other treatments. Dani plus ecu/rav likely no better than ecu/rav alone
MAVE in complement-naïve patients	NICE TA698,[17] Röth 2024,[24]	-	Similar to ecu	Similar to ecu	-	-	-	High	Ecu, rav and crov all likely similar
MAVE in complement-experienced patients	NICE TA698,[17] NICE TA11132,[19] Scheinberg 2024[25]	-	No difference vs ecu	No difference vs ecu	-	Slightly worse than ecu/rav	-	High	Ecu, rav and crov all likely similar. Ipta possibly slightly worse than ecu/rav
Hypertension in complement-naïve patients	No evidence identified								
Hypertension in complement-experienced patients	NICE TA10980,[20] NICE TA778[18]	-	-	-	Slightly worse vs ecu	-	Slightly worse vs ecu/rav alone	High to unclear	Peg possibly slightly worse than ecu. Dani plus ecu/rav possibly slightly worse than ecu/rav alone
URTI in complement-naïve patients	NICE TA698,[17] Röth 2024,[24] Wong 2021,[26] Hillmen 2006[12]	Better than placebo	Slightly worse than ecu	Slightly better than ecu	Better than SOC	-	-	High to low	Ecu, rav and crov all likely similar. Ecu and peg better than SOC/placebo (i.e. symptom-oriented therapy)
URTI in complement-experienced patients	NICE TA698,[17] NICE TA11132[19]	-	Worse than ecu	-	-	Better than ecu/rav	-	High	Rav likely worse than ecu. Ipta likely better than ecu/rav
Serious infections in complement-naïve patients	NICE TA698,[17] Röth 2024[24]	-	Slightly better than ecu	Slightly better than ecu	-	-	-	High	Rav and crov likely slightly better than ecu
Serious infections in complement-experienced patients	NICE TA698,[17] NICE TA11132,[19] Scheinberg 2024[25]	-	Similar to ecu	Slightly worse than ecu	-	Better than ecu/rav	-	High	Ecu, rav and crov all likely similar. Ipta likely better than ecu/rav
Meningococcal infection in complement-naïve patients	NICE TA698,[17] Röth 2024,[24] Wong 2021[26]	-	No difference vs ecu	No difference vs ecu	No difference vs SOC	-	-	High	No difference between ecu, rav, crov, peg and SOC
Meningococcal infection in	NICE TA698,[17]	-	No	No	-	-	No	High to	No difference

complement-experienced patients	NICE TA10980,[20] Scheinberg 2024[25]		differenc e vs ecu	differenc e vs ecu			difference vs ecu/rav	unclear	between ecu, rav or crov; or between dani plus ecu/rav vs ecu/rav alone
Kidney impairment in complement-naïve patients	Wong 2021[26]	-	-	-	Better than SOC	-	-	High	Peg likely better than SOC (i.e. symptom-oriented therapy)
Kidney impairment in complement-experienced patients	NICE TA11132[19]	-	-	-	-	Slightly better than ecu/rav	-	High	Ipta likely slightly better than ecu/rav
FAQ6: Are there any long-term negative effects of treatment?									
Long-term transfusion avoidance in complement inhibitor-naïve patients	Kanakura 2013,[13] NICE TA698,[17] Brodsky 2008[5]	52.6% to 96% between 12-16 months	73.3% at >12-18 months	-	-	-	-	High to moderate	Ecu and rav likely similar at ≥48 weeks
Long-term transfusion avoidance in complement inhibitor-experienced patients	NICE TA698,[17] NICE TA778[18]	-	85.3% at >12-18 months	-	72-73% at 48 weeks	-	-	High	Rav likely slightly better than peg at ≥48 weeks
Long-term BTH in complement inhibitor-naïve patients	NICE TA698,[17] NICE TA11132,[19], Hill 2005[11]	18% at 52 weeks	6.2% at up to 2 years	-	-	2.5% at 24-48 weeks	-	High to moderate	Rav likely better than ecu. Ipta likely better than rav
Long-term BTH in complement inhibitor-experienced patients	NICE TA698[17]	-	5.8% at up to 20 years	-	-	-	-	High	NA
FAQ7: Where can I get additional information?									
Additional information sources	ORPHAnet provides additional patient-centred resources and information on PNH. This includes links to patient organisations and clinical trials. https://www.orpha.net/en/disease/detail/447?name=paroxysmal%20noctural%20hemoglobinuria&mode=name In Germany, patient guidelines are also available through the onkopedia website: https://www.onkopedia.com/de/onkopedia/guidelines/paroxysmale-naechtliche-haemoglobinurie-pnh/@@guideline/html/index.html								

FAQ8: Is there anything I can do myself to help my disease?		
Self-care	Goh 2024,[10] Onkopedia[21]	Any patients receiving complement therapy are recommended to receive vaccinations against Neisseria meningitidis types A, C, W, Y, and B at least two weeks prior to starting treatment with C5 inhibitor therapy together with Streptococcus pneumoniae; and Haemophilus influenzae type B within 2 years prior to starting therapy. Patients should be revaccinated every 3-5 years after starting treatment and should seek immediate medical attention if they experience any signs or symptoms of infection (such as fever, headaches with nausea or vomiting, stiff neck, rash, confusion etc.). Staying hydrated is also important to prevent critical haemolysis

Abbreviations: BID, twice daily; BIW, twice a week; Crov, crovalimab; Dani, danicopan; Ecu, eculizumab; Ipta, iptacopan; NA, not applicable; NICE, National Institute for Health and Care Excellence; Peg, pegcetacoplan; TID, three times a day; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; Rav, ravulizumab; RoB, risk of bias; SOC, standard-of-care.

The following categories were used to rate treatment differences: same rate = no difference; within 1% = similar rates; within 5% = slightly better/worse rates; more than 5% = better/worse; more than 5% and/or statistically significant = much better.

Strengths and limitations

The evidence found was based on rigorous, systematic review methods with two independent reviewers involved in screening; and two reviewers involved in data extraction (one reviewer extracted the data, and a second reviewer checked 20% of the extracted data). Searches were conducted across a wide range of databases, including Embase, MEDLINE, CDSR, DARE, Epistemonikos, G-I-N, ECRI, HTA, INAHTA, NICE and G-BA/IQWiG.

A broad range of drugs of interest were eligible for inclusion in this systematic review, which included eculizumab, ravulizumab, crovalimab, pegcetacoplan, iptacopan and danicopan together with supportive care. The use of HTA assessments as evidence sources provided an early, first-look at the evidence supporting several new drug submission that are still currently going through the HTA approval process.

Most of the evidence identified was based on data from randomised controlled trials, which were considered to represent high quality evidence. This was supported with single-arm studies, where available. However, seven of the nine included RCTs were open-label, where the assigned treatment was known; and of the two RCTs that were double-blinded, only one was rated at low risk of bias.

In some trials, the patient population was not exclusively classical haemolytic PNH patients but included patients with co-occurring pathologies (e.g) or other forms of PNH, which may have introduced heterogeneity.

Comparison with other reviews

A total of nine systematic reviews published between 2014 and 2023 were identified as part of the searching and screening process for this project.[15 23 35-41] However, none of these reviews included the broad range of drugs/studies captured here, as the trials for several eligible drugs (e.g. crovalimab, danicopan) were still on-going at their date of publication. Therefore, this appears to be the first study to bring together this level of evidence in one assessment.

Evidence gaps

In terms of outcomes, in complement inhibitor-naïve patients, limited evidence was captured for BTH, MAVE, meningococcal infections and kidney impairment; and no evidence was captured for hypertension. In complement inhibitor-experienced patients, limited evidence was captured for HRQoL, MAVE, hypertension, meningococcal infections and kidney impairment.

In terms of drugs, in complement inhibitor-naïve patients, limited evidence was captured that compared newer drugs (e.g. pegcetacoplan, danicopan, iptacopan, crovalimab) with other complement inhibitors (e.g. eculizumab, ravulizumab) as the only identified trials compared these against standard-of-care or placebo. The only data identified for iptacopan in complement inhibitor-naïve patients was based on a single arm study, not RCT evidence. No evidence was identified for danicopan in complement inhibitor-naïve patients. In complement inhibitor-experienced patients, data were captured for all drugs of interest but not across all outcomes of interest.

Recommendations for further research

In the absence of head-to-head trials comparing all the drugs of interest in haemolytic PNH patients, it will be critical to perform a network meta-analysis that provides indirect comparisons to assess which drugs are most useful for PNH treatment for outcomes beyond transfusion avoidance (the only outcome where indirect evidence was captured in this project). Future trials should consider applying double-blinding to reduce patient and sponsor bias, and ensuring that core patient-reported outcome sets are captured for PNH patients (including general quality of life, transfusion-dependency burden and the ability to work/activities of daily living).[42]

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Appendix A – Search stratagies

MEDLINE (PubMed)

Searched 16th July 2024

#	Terms	# Records
1	Hemoglobinuria, Paroxysmal[MeSH Terms]	3,922
2	paroxysmal nocturnal haemoglobinuria[Title/Abstract] OR "paroxysmal nocturnal hemoglobinuria"[Title/Abstract] OR PNH[Title/Abstract] OR "haemolytic PNH"[Title/Abstract] OR "hemolytic PNH"[Title/Abstract] OR "Marchiafava-Micheli Syndrome"[Title/Abstract] OR "Marchiafava Micheli Syndrome"[Title/Abstract]	4,105
3	#1 OR #2	5,247
4	guideline[MeSH Terms]	174,376
5	clinical practice guideline[MeSH Terms]	56,906
6	guideline*[Title/Abstract]	521,605
7	#4 OR #5 OR #6	617,277
8	Meta-Analysis[MeSH Major Topic]	6,386
9	Meta-Analysis[MeSH Terms]	30,286
10	meta analy*[Title/Abstract]	311,023
11	metaanaly*[Title/Abstract]	308,485
12	systematic review* OR "systematic overview*"[Title/Abstract]	377,883
13	review literature as topic[MeSH Terms]	25,611
14	#8 OR #9 OR #10 OR #11 OR #12 OR #13	523,021
15	health technology[MeSH Terms]	18,259
16	health technology assessment* OR HTA OR NICE[Title/Abstract]	29,240
17	#15 OR #16	47,027
18	#7 OR #14 OR #17	1,109,237
19	#3 AND #18	**148**

Embase (Ovid)

Embase <1974 to 2024 July 15> Searched 16th July 2024

#	Terms	# Records
1	exp paroxysmal hemoglobinuria/	6895
2	paroxysmal nocturnal hemoglobinuria/	6843
3	("paroxysmal nocturnal h?emoglobinuria" or PNH or "Marchiafava-Micheli Syndrome" or "Marchiafava Micheli Syndrome").ab,ti.	6296
4	(h?emolytic adj2 ("paroxysmal h?emoglobinuria" or "paroxysmal nocturnal h?emoglobinuria" or PNH)).ab,ti.	262
5	or/1-4	8122
6	practice guideline/	586896
7	guideline*.ab,ti.	801026

#	Terms	# Records
8	or/6-7	1052969
9	systematic review/	475952
10	meta analysis/	321939
11	("meta-analys*" or "meta analys*" or "systematic review*" or "systematic overview*").ab,ti.	584996
12	or/9-11	749257
13	biomedical technology assessment/	18130
14	("health technology assessment*" or HTA or NICE).ab,ti.	40694
15	or/13-14	52845
16	8 or 12 or 15	1739024
17	5 and 16	**404**

CDSR (Cochrane Library)

Searched 16th July 2024

#	Terms	# Records
#1	MeSH descriptor: [Hemoglobinuria, Paroxysmal] explode all trees	93
#2	(paroxysmal nocturnal haemoglobinuria):ti,ab,kw (Word variations have been searched)	367
#3	(paroxysmal nocturnal hemoglobinuria):ti,ab,kw (Word variations have been searched)	367
#4	PNH:ti,ab,kw	336
#5	Marchiafava Micheli Syndrome:ti,ab,kw	1
#6	#1 OR #2 OR #3 OR #4 OR #5	420
#7	Systematic review filter	**2**

DARE (CRD)

Searched 16th July 2024

	Terms	
Any field	paroxysmal nocturnal haemoglobinuria	OR
Any field	paroxysmal nocturnal hemoglobinuria	
	Total # records	**3**

Epistemonikos

Searched 16th July 2024

Terms	# Records
(title:((title:(paroxysmal nocturnal hemoglobinuria) OR abstract:(paroxysmal nocturnal hemoglobinuria)) OR (title:(paroxysmal nocturnal haemoglobinuria) OR abstract:(paroxysmal nocturnal haemoglobinuria)) OR (title:(PNH) OR abstract:(PNH)) OR (title:(Marchiafava Micheli Syndrome) OR abstract:(Marchiafava Micheli Syndrome)) OR (title:(paroxysmal hemoglobinuria) OR abstract:(paroxysmal hemoglobinuria)) OR (title:(paroxysmal haemoglobinuria) OR abstract:(paroxysmal haemoglobinuria))) OR abstract:((title:(paroxysmal nocturnal hemoglobinuria)	

Terms	# Records
OR abstract:(paroxysmal nocturnal hemoglobinuria)) OR (title:(paroxysmal nocturnal haemoglobinuria) OR abstract:(paroxysmal nocturnal haemoglobinuria)) OR (title:(PNH) OR abstract:(PNH)) OR (title:(Marchiafava Micheli Syndrome) OR abstract:(Marchiafava Micheli Syndrome)) OR (title:(paroxysmal hemoglobinuria) OR abstract:(paroxysmal hemoglobinuria)) OR (title:(paroxysmal haemoglobinuria) OR abstract:(paroxysmal haemoglobinuria))))	
Broad synthesis filter	0
Structured summary filter	7
Systematic review filter	36
Total # records	**43**

G-I-N

Searched 16th July 2024

Terms	# Records
paroxysmal nocturnal haemoglobinuria	0
paroxysmal nocturnal hemoglobinuria	0
PNH	0
paroxysmal hemoglobinuria	0
paroxysmal haemoglobinuria	0
Marchiafava-Micheli Syndrome	0
Marchiafava Micheli Syndrome	0
hemolytic	1
haemolytic	0
Total # records	**1**

ECRI

Searched 16th July 2024

Terms	# Records
paroxysmal nocturnal haemoglobinuria	0
paroxysmal nocturnal hemoglobinuria	0
PNH	0
paroxysmal hemoglobinuria	0
paroxysmal haemoglobinuria	0
Marchiafava-Micheli Syndrome	0
Marchiafava Micheli Syndrome	0
hemolytic	4
haemolytic	2
Total # records	**5***

*1 duplicate record removed

HTA

Searched 16th July 2024

	Terms	
Any field	paroxysmal nocturnal haemoglobinuria	OR
Any field	paroxysmal nocturnal hemoglobinuria	
	Selected HTA box plus HTA in progress and HTA published	**11**

INAHTA

Searched 16th July 2024

#	Terms	# records
#1	(paroxysmal nocturnal haemoglobinuria) OR (paroxysmal nocturnal hemoglobinuria) OR (PNH) OR (paroxysmal hemoglobinuria) OR (paroxysmal haemoglobinuria) OR (Marchiafava-Micheli Syndrome) OR (Marchiafava Micheli Syndrome)	**19**

NICE

Searched 16th July 2024

#	Terms	# records
#1	paroxysmal nocturnal haemoglobinuria	**11**

G-BA/IQWiG

Searched 19th July 2024

#	Terms	# records
#1	paroxysmal nocturnal haemoglobinuria	**11**

Appendix B – Deprioritised studies

Include	Citation
Included - SR, Guideline, HTA	(AWMSG), A.W.M.S.G. et al. 2009. Eculizumab (Soliris®) for the treatment of paroxysmal nocturnal haemoglobinuria. , ():
	Abdel-Kader Martín, L. et al. 2011. [Eculizumab (Soliris®) Assessment of effectivity and safety of the drug and economic analysis of use in Paroxysmal Nocturnal Haemoglobinuria therapy]. , ():
	Azevedo, P.S. et al. 2020. Eculizumab in pregnant women: A viable alternative to prevent invasive hemolysis?. Pharmacoepidemiology and Drug Safety, 29(SUPPL 3): 548
	B Sallerfors, T.F., L Jansson, N Kuric, P Olsson, P Sjögren, T Svanberg, B Widgren, H Sjövall et al. 2012. Eculizumab treatment in paroxysmal nocturnal hemoglobinuria. , ():
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	Ho, C. et al. 2008. Eculizumab for paroxysmal nocturnal hemoglobinuria: a review of clinical and cost-effectiveness. , ():
	Institut fuer Qualitaet und Wirtschaftlichkeit im, G. et al. 2019. Ravulizumab

Include	Citation
	(paroxysmale naechtliche Haemoglobinurie). , ():
	Krishnan, S. et al. 2022. Literature Review of Fatigue Scales and Association with Clinically Meaningful Improvements in Outcomes Among Patients With and Without Paroxysmal Nocturnal Hemoglobinuria. Advances in Therapy, 39(5): 1959-1975
	Manning, J.E. et al. 2022. Pregnancy in Paroxysmal Nocturnal Hemoglobinuria - a Systematic Review. Blood, 140(Supplement 1): 11438-11440
	Martí-Carvajal Arturo, J. et al. 2014. Eculizumab for treating patients with paroxysmal nocturnal hemoglobinuria. Cochrane Database of Systematic Reviews: Reviews, Issue 10():
	Nishimura, J. et al. 2012. [Bone marrow failure syndrome (idiopathic hematopoietic disorders): progress in diagnosis and treatment. Topics: III. Diagnosis and treatments; 4. Paroxysmal nocturnal hemoglobinuria]. Nihon Naika Gakkai zasshi. The Journal of the Japanese Society of Internal Medicine, 101(7): 1953-1959
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	Zullo, F. et al. 2023. Pregnancy outcome of women with Paroxysmal Nocturnal Hemoglobinuria. Italian Journal of Gynaecology and Obstetrics, 35(1): 62-70
Include – primary study	Anonymous et al. 2021. Abstracts of the 61st Annual Scientific Meeting of the British Society for Haematology. British Journal of Haematology, 193(SUPPL 1):
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	Lisukov, I. et al. 2014. Effect of eculizumab on physician-reported symptoms in the russian cohort of the paroxysmal nocturnal hemoglobinuria (PNH) international registry. Blood, 124(21):
	Roth, A. et al. 2019. Transfusion requirements in adult patients with paroxysmal nocturnal hemoglobinuria naive to complement inhibitors receiving Ravulizumab or Eculizumab: results from a phase 3 non-inferiority study. Oncology Research and Treatment, 42(Supplement 4): 97
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Appendix C – Excluded studies at full paper screening

Exclusion reason	Exclusion rationale	CITATION
Wrong population	High proportion of women with AA (64.3%)	Anonymous et al. 2017. Abstracts of the 57th Annual Scientific Meeting of the British Society for Haematology. British Journal of Haematology, 176(Supplement 1):
	Mixed population where only 70% of included patients had classical/symptomatic/haemolytic PNH - 30% had PNH/AA	DeZern, A.E. et al. 2012. Predictors of response to eculizumab therapy in paroxysmal nocturnal hemoglobinuria. Blood, 120(21):
	Paediatric patients	Institut fuer Qualitaet und Wirtschaftlichkeit im, G. et al. 2021. Ravulizumab (paroxysmale naechtliche Haemoglobinurie, paediatrische Patientinnen und Patienten). , ():
	Only 26 of 42 patients had classic PNH - others had aplastic pNH or intermediate form - mixed population with no subgroup data for classic PNH	Iori, A.P. et al. 2017. Paroxysmal nocturnal hemoglobinuria: A long-term single center experience. Bone Marrow Transplantation, 52(Supplement 1): 268
	Population includes children (age range of included patients is from 7 to 80 years)	Kulagin, A. et al. 2018. Benefits and limitations of long-term eculizumab treatment for paroxysmal nocturnal hemoglobinuria (PNH): Real-world data from large cohort study in Russia. Blood, 132(Suppl. 1):
	Mixed populations; not exclusively PNH	Malpica Castillo, L.E. et al. 2019. Adherence to Infectious Disease Screening and Immunization Guidelines When Treating Non-Malignant Immune-Mediated Hematologic Disorders. Blood, 134(Supplement 1): 792
	General review for haematological disorders, not explicitly PNH	Malpica, L. et al. 2019. Preventing infectious complications when treating non-malignant immune-mediated hematologic disorders. American Journal of Hematology, 94(12): 1396-1412
Wrong intervention	Treatment unclear	Bosch Benitez, J.M. et al. 2011. Paroxysmal nocturnal hemoglobinuria (PNH) in the Canary Islands: Description of nine cases. Haematologica, 96(SUPPL. 2): 523
	No intervention	Chou, W.C. et al. 2016. Characteristics of Taiwanese patients of PNH in the international PNH registry. Thrombosis Journal, 14(Supplement 1): 39
	Only talks about HSCT, which is not an intervention of interest	Garg, A. et al. 2020. Current status of stem cell transplantation in paroxysmal nocturnal hemoglobinuria. Journal of Applied Hematology, 11(4): 161-168
	No specific treatment	Lim, R.J. et al. 2017. Paroxysmal nocturnal

Exclusion reason	Exclusion rationale	CITATION
	given	hemoglobinuria (PNH) and thrombosis: Experience from an Asian tertiary centre. Research and Practice in Thrombosis and Haemostasis, 1(Supplement 1): 1138-1139
	Prophylactic antibiotics	Patriquin, C.J. et al. 2020. Use of prophylactic antibiotics in patients with paroxysmal nocturnal hemoglobinuria treated with eculizumab. HemaSphere, 4(Supplement 1): 390-391
Wrong outcomes	Economic outcomes only	Anderson, S. et al. 2021. Cost per responder analysis for pegcetacoplan and eculizumab in the treatment of adults with paroxysmal nocturnal hemoglobinuria. Blood, 138(SUPPL 1): 4956
	No relevant outcomes	Anonymous et al. 2012. . Onkologie, 35(SUPPL. 6):
	Only reviews screening and monitoring, not treatment per se	Anonymous et al. 2024. Expert consensus on clonal screening and monitoring of complement inhibitor therapy in paroxysmal nocturnal hemoglobinuria (2024). Zhonghua xue ye xue za zhi = Zhonghua xueyexue zazhi, 45(2): 109-114
	No overt clinical/safety outcomes, only talks about traditional treatments	Doutrelon, C. et al. 2015. [Paroxysmal nocturnal hemoglobinuria: An unknown cause of thrombosis?]. J Mal Vasc, 40(6): 384-90
	Only reports on LDH levels (not an outcome of interest)	Elrosasy, A. et al. 2023. The efficacy of complement inhibitors in the treatment of paroxysmal nocturnal hemoglobinuria: A systematic review and network meta-analysis. European Journal of Clinical Investigation, 53(Supplement 1):
	Transfusion avoidance and Hb normalisation only clinical parameters reported	Fishman, J. et al. 2023. The cost-effectiveness of pegcetacoplan in complement treatment-naive adults with paroxysmal nocturnal hemoglobinuria in the USA. Journal of Comparative Effectiveness Research, 12(10): e230055
	No extractable data	Hillmen, P. et al. 2021. MODEL STRUCTURE CONSIDERATIONS FOR COST-EFFECTIVENESS EVALUATION OF C3 INHIBITOR PEGCETACOPLAN VERSUS C5 INHIBITOR IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA. Journal of Managed Care and Specialty Pharmacy, 27(4-A SUPPL): S44
	No relevant outcomes reported (focus is on costs)	Institut fuer Qualitaet und Wirtschaftlichkeit im, G. et al. 2022. Pegcetacoplan (paroxysmale naechtliche Haemoglobinurie) - Bewertung gemäß § 35a Abs. 1 Satz 11 SGB V. , ():
	PNH section only deals with testing for PNH	Kakkos, S.K. et al. 2021. Editor's Choice - European Society for Vascular Surgery (ESVS) 2021 Clinical Practice Guidelines on the Management of Venous Thrombosis. European Journal of Vascular and Endovascular Surgery, 61(1): 30195
	Composite endpoint	Kulasekararaj, A. et al. 2022. Composite endpoint to

Exclusion reason	Exclusion rationale	CITATION
	developed and reported for study 301	evaluate complement inhibition therapy in patients with paroxysmal nocturnal hemoglobinuria. European Journal of Haematology, 108(5): 391-402
	Compliance rates (not an outcome of interest)	Mahajerin, A. et al. 2022. Pegcetacoplan Patient Compliance Rates In PEGASUS And PRINCE Phase 3 Trials Compared To Published Oral Medication Compliance Rates In Literature. British Journal of Haematology, 197(SUPPL 1): 205-206
	Cost burden	Tomazos, I. et al. 2019. PSY12 COST BURDEN OF BREAKTHROUGH HEMOLYSIS IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA ON ECULIZUMAB TREATMENT. Value in Health, 22(Supplement 2): S376
Wrong study design	Expert opinion	Cançado, R.D. et al. 2021. Consensus statement for diagnosis and treatment of paroxysmal nocturnal haemoglobinuria. Hematology, Transfusion and Cell Therapy, 43(3): 341-348
	Only reports on guidelines	de Almeida Soares, R.D. et al. 2020. Current global scenario of guidelines on the management of paroxysmal nocturnal hemoglobinuria: a systematic literature review. J. bras. econ. saúde (Impr.), 12(3):
	Case study	Del Castillo, M.T. et al. 2019. Eculizumab therapy followed by BMT in a pediatric patient with paroxismal nocturnal hemoglobinuria. Bone Marrow Transplantation, 53(): 691-692
	Case report	Dereme, J. et al. 2023. Targeted management of coexistent severe thrombophilias - A case report of a successful pregnancy despite paroxysmal nocturnal haemoglobinuria and hereditary protein C deficiency. Swiss Medical Weekly, 153(Supplement 274): 65S
	Minimal data on PNH - small section is just on px taking eculizumab, of which PNH px are one group	Dretler, A.W. et al. 2018. Progress toward the global control of Neisseria meningitidis: 21st century vaccines, current guidelines, and challenges for future vaccine development. Human Vaccines and Immunotherapeutics, 14(5): 1146-1160
	Minimal data on PNH - small section is just on px taking eculizumab, of which PNH px are one group	Engel, E.R. et al. 2020. Rituximab and eculizumab when treating nonmalignant hematologic disorders: Infection risk, immunization recommendations, and antimicrobial prophylaxis needs. Hematology (United States), 20(1): 312-318
	Letter	García-Erce, J.A. et al. 2012. [Anticoagulation, iron, erythropoietin and transfusion in nocturnal paroxysmal hemoglobinuria]. Med Clin (Barc), 139(1): 43-4
	Case report	Gong, S. et al. 2012. Miliary tuberculosis occurred after immunosuppressive drug in PNH patient with completely cured tuberculosis; a case report. Annals of Clinical Microbiology and Antimicrobials, 11(): 12
	Debvelopment of new qol	Groth, M. et al. 2017. Development of a disease-

Exclusion reason	Exclusion rationale	CITATION
	tool; no primary data reported	specific quality of life questionnaire for patients with aplastic anemia and/or paroxysmal nocturnal hemoglobinuria (QLQ-AA/PNH)-report on phases I and II. Annals of Hematology, 96(2): 171-181
	No formal data reported; commentary	Haspel, R.L. et al. 2008. Which patients with paroxysmal nocturnal hemoglobinuria (PNH) should be treated with eculizumab? ASH evidence-based review 2008. Hematology Am Soc Hematol Educ Program, (): 35
	Case report	Hsu, C.H.W. et al. 2018. Not happily ever after: Complications of chronic haemolysis in paroxysmal nocturnal haemoglobinuria patients on eculizumab. British Journal of Haematology, 181(Supplement 1): 202-203
	Px preference questionnaire	Kaiser, K. et al. 2020. Assessing preferences for rare disease treatment: Qualitative development of the paroxysmal nocturnal hemoglobinuria patient preference questionnaire (PNH-PPQ©). Patient Preference and Adherence, 14(): 705-715
	Expert opinion	Lee, J.W. et al. 2020. Ravulizumab for the treatment of paroxysmal nocturnal hemoglobinuria. Expert Opinion on Biological Therapy, 20(3): 227-237
	Letter	Malpica-Castillo, L.E. et al. 2020. Adherence to infectious disease screening and immunization guidelines when treating non-malignant immune-mediated hematologic disorders. American Journal of Hematology, 95(3): E72-E75
	Focus on diagnosis not treatment	Morado, M. et al. 2010. Paroxismal nocturnal hemoglobinuria: New treatments and general guidelines for diagnosis. Medicina Clinica, 134(8): 369-374
	Case report	Ninan, G.A. et al. 2023. Interventions in cerebrovascular emergencies among patients with Paroxysmal nocturnal haemoglobinuria - A word of caution: Cerebrovascular emergencies in Paroxysmal nocturnal haemoglobinuria. Journal of Stroke and Cerebrovascular Diseases, 32(11): 107305
	Case report with review	Nishimoto, M. et al. 2018. Acute kidney injury in a postpartum woman with paroxysmal nocturnal hemoglobinuria: A case report and literature review. Hemodialysis international. International Symposium on Home Hemodialysis, 22(1): E6-E10
	Case report (excluded study design)	Roth, A. et al. 2011. Management of pregnancy in paroxysmal nocturnal hemoglobinuria (PNH) in the era of eculizumab: A case report and updated review. Onkologie, 34(SUPPL. 6): 67
	Case report with review	Yang, C. et al. 2018. [Purpura fulminans related to paroxysmal nocturnal haemoglobinuria: a case report and literatures review]. Zhonghua xue ye xue za zhi =

Exclusion reason	Exclusion rationale	CITATION
		Zhonghua xueyexue zazhi, 39(11): 921-926
	Only includes Asian PNH patients; clinical trials were excluded	Yu, F. et al. 2016. A comparative analysis of clinical characteristics of patients with paroxysmal nocturnal hemoglobinuria between Asia and Europe/America. International Journal of Hematology, 103(6): 649-654
	Letter	Ziakas, P.D. et al. 2007. Thrombosis in paroxysmal nocturnal hemoglobinuria: sites, risks, outcome. An overview. Journal of thrombosis and haemostasis : JTH, 5(3): 642-5
Duplicate	Additional paper to #627	Institut fuer Qualitaet und Wirtschaftlichkeit im, G. et al. 2020. Ravulizumab (paroxysmale naechtliche Haemoglobinurie) - Addendum zum Auftrag A19-59. , ():
Unobtainable	Unobtainable	Gurnari, C. et al. 2024. Paroxysmal nocturnal hemoglobinuria-related thrombosis in the era of novel therapies: a 2043-patient-year analysis. Blood, 144(2): 145-155
	Unobtainable	Karaszi, E. et al. 2023. Reducing the risk of infections in hereditary and acquired complement deficiencies. Review of the literature and proposal for best practice in Hungary. Orvosi Hetilap, 164(25): 971-980
	Unobtainable	Nakakuma, H. et al. 2012. [Pathophysiology and management of paroxysmal nocturnal hemoglobinuria]. [Rinsho ketsueki] The Japanese journal of clinical hematology, 53(10): 1516-1527
	Unobtainable	NHSC et al. 2006. Eculizumab (Soliris) for paroxysmal nocturnal haemoglobinuria: horizon scanning technology briefing. , ():
	Unobtainable	Nhsc et al. 2007. Eculizumab (Soliris) for paroxysmal nocturnal haemoglobinuria: horizon scanning technology briefing. HTA Database, (): 6
	Unobtainable	Omine, M. et al. 2008. Overview of the clinical reference guides for the idiopathic hematopoietic disorders. Nippon rinsho. Japanese journal of clinical medicine, 66(3): 433-438
	Unobtainable	Pichon Riviere, A. et al. 2011. Efectividad del eculizumab para el tratamiento de la hemoglobinuria paroxistica nocturna [Effectiveness of eculizumab in the treatment of paroxysmal nocturnal hemoglobinuria]. HTA Database
	Unobtainable	Tsutsui, M. et al. 2019. [Successful pregnancy and delivery achieved with eculizumab administration initiated after a preceding missed abortion in a patient with paroxysmal nocturnal hemoglobinuria]. Rinsho Ketsueki, 60(4): 281-285
	Unobtainable	Usuki, K. et al. 2015. Management of pregnancy and delivery in patients with paroxysmal nocturnal hemoglobinuria. [Rinsho ketsueki] The Japanese journal of clinical hematology, 56(7): 785-794

Appendix D – Risk of bias assessments

Full details of the risk of bias assessments in the included primary studies are provided in the embedded file below.

Full details of the risk of bias assessments in the source studies (excluding HTA assessments, for which no appropriate tool could be found) are provided in the embedded file below.