Single Technology Appraisal

Iptacopan for treating paroxysmal nocturnal haemoglobinuria [ID6176]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Iptacopan for treating paroxysmal nocturnal haemoglobinuria [ID6176]

Contents:

The following documents are made available to stakeholders:

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

1. **Company submission** from Novartis

2. **Company summary of information for patients (SIP)** from Novartis

3. **Clarification questions and company responses:**
   a. Main response
   b. Follow up response
   c. Supplementary analyses (48 weeks)
   d. Submission addendum

4. **Patient group, professional group and NHS organisation submissions** from:
   a. PNH Support:
      i. Main submission
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   b. Royal College of Pathologists & National PNH Service
   c. NHS England

5. **External Assessment Report** prepared by Centre for Reviews and Dissemination and Centre for Health Economics - York

6. **External Assessment Report – factual accuracy check**

7. **Expert personal perspectives**:
   a. Joint statement from **Dr Morag Griffin**, Joint service lead PNH Leeds – clinical expert, nominated by National PNH Service, Royal College of Pathologists, and Novartis (company) & **Dr Austin Kulasekararaj**, Consultant Haematologist and Lead for Kings National PNH service – clinical expert, nominated by PNH Support and Novartis (company).
   b. Louise Peacock – patient expert, nominated by PNH Support
   c. Alex Naylor - patient expert, nominated by PNH Support

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Iptacopan for treating paroxysmal nocturnal haemoglobinuria [ID6176]

Document B

Company evidence submission

October 2023

File name	Version	Contains confidential information	Date
ID6176_Iptacopan_PNH_NICE_Doc B_ [REDACTED]	1	Redacted	26th Oct 2023

Contents

Tables and figures

Abbreviations

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
AIC	Akaike information criterion
AIPW	Augmented inverse probability weighted
BD	Twice daily
BIC	Bayesian information criterion
BMF	Bone marrow failure
BMI	Body mass index
BNF	British National Formulary
BTH	Breakthrough haemolysis
C3	Complement component 3
C5	Complement component 5
CAC	Complement-amplifying condition
CASP	Critical Appraisal Skills Programme
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CEP	Cost-effectiveness plane
CFB	Change from baseline
CI	Confidence interval
CSR	Clinical study report
DSU	Decision Support Unit
EORTC QLQ-C30	European Organization for the Research and Treatment of Cancer Core Quality of Life questionnaire
ERG	Evidence Review Group
ESS	Effective sample size
EVH	Extravascular haemolysis
FACIT	Functional Assessment of Chronic Illness Therapy
FB	Factor B
GB	Great Britain
GPI	Glycosylphosphatidylinositol
Hb	Haemoglobin
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
IRT	Interactive Response Technology
ITC	Indirect treatment comparison
IV	Intravenous
IVH	Intravascular haemolysis
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward

Abbreviation	Definition
LYG	Life years gained
mAB	Monoclonal antibody
MAC	Membrane attack complex
MAVE	Major adverse vascular event
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NO	Nitric oxide
OS	Overall survival
PAS	Patient Access Scheme
PASLU	Patient Access Schemes Liaison Unit
PNH	Paroxysmal nocturnal haemoglobinuria
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
PSSRU	Personal Social Services Research Unit
Q2W	Every 2 weeks
Q8W	Every 8 weeks
QALY	Quality adjusted life year
QoL	Quality of life
RBC	Red blood cell
RCT	Randomised controlled trial
RWE	Real world evidence
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SMD	Standardised mean difference
SmPC	Summary of product characteristics
SoC	Standard of care
TSD	Technical Support Document
UK	United Kingdom
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WPAI	Work Productivity and Activity Impairment
WTP	Willingness-to-pay

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

Paroxysmal nocturnal haemoglobinuria (PNH) is an ultra-rare chronic blood disorder characterised by intravascular haemolysis (IVH), thrombosis, and bone marrow failure (1, 2)

- The incidence of PNH in Great Britain (GB) has been estimated at 1 in 770,000 per year, with a predicted prevalence of 1 in 62,500 (3). There are an estimated 926 people in England living with PNH (4)
- The clinical presentation of PNH is often heterogenous; key manifestations include haemoglobinuria, anaemia, smooth muscle dystonia, thrombosis, hypertension, and chronic kidney disease (5-13)
- Debilitating fatigue is a common symptom, affecting approximately 80% of patients with PNH (6)
- The symptom burden typically results in patients with PNH having lower quality of life (QoL) compared with the general population (14)
- Before the approval of eculizumab in 2007, PNH was associated with poor overall survival (OS; 10-year OS: 50–65%) (15, 16), largely as a result of thrombotic complications (2, 17).

Despite current treatments, patients can experience residual anaemia and may require blood transfusions. The administration of current infusion treatments is also a burden to patients

- In the United Kingdom (UK), complement inhibitor treatment is the standard of care (SoC) for treating patients with PNH and haemolysis
- Current treatment options in the UK are the terminal C5 inhibitors eculizumab (18) and ravulizumab (19), and the proximal C3 inhibitor pegcetacoplan (20, 21)
- The unmet needs in PNH are associated with remaining clinical burden (e.g. residual anaemia on C5 inhibitors due to extravascular haemolysis [EVH], breakthrough haemolysis [BTH]) and the administration limitations of the treatment options currently available via infusion.

Iptacopan is a novel proximal complement inhibitor for treatment of PNH that is administered orally

- Iptacopan is a novel proximal complement inhibitor, targeting Factor B (FB), and is expected to be the first oral therapy available for PNH
- The proposed position of iptacopan in the treatment pathway is in complement inhibitor-naïve patients and in complement inhibitor-experienced patients with residual anaemia.

B.1.1 Decision problem

The submission covers the technology's full expected marketing authorisation for this indication. The decision problem addressed in this submission is provided in Table 1, which outlines any differences from the National Institute for Health and Care Excellence (NICE) final scope (22).

Table 1: The decision problem

	Final scope issued by NICE (22)	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with PNH	Adults with PNH: • Complement inhibitor-naïve patients who have haemolysis with clinical symptom(s) • Complement inhibitor-experienced patients with anaemia despite treatment with a complement inhibitor	The submission covers two subpopulations of adult patients with PNH, in line with the evidence available from iptacopan Phase 3 clinical trials (APPOINT-PNH and APPLY-PNH) and the expected licence wording. This also allows consideration of differences in relevant comparators for the two subpopulations.
Intervention	Iptacopan	Iptacopan	–
Comparator(s)	• Eculizumab • Ravulizumab • Pegcetacoplan • Danicopan with a C5 inhibitor (subject to NICE ongoing appraisal)	Complement inhibitor-naïve patients: • Eculizumab • Ravulizumab Complement inhibitor-experienced patients with anaemia: • Eculizumab • Ravulizumab • Pegcetacoplan	Pegcetacoplan is not a relevant comparator for the naïve population since its licence and NICE recommendation are restricted to patients who have anaemia after ≥3 months of treatment with a C5 inhibitor (20, 23). Danicopan with a C5 inhibitor has not been considered since it does not currently have a licence and is not expected to become established NHS clinical practice prior to the appraisal of iptacopan by committee.

	Final scope issued by NICE (22)	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Outcomes	The outcome measures to be considered include: • overall survival • intravascular haemolysis • extravascular haemolysis • breakthrough haemolysis • transfusion avoidance • haemoglobin • thrombotic events • adverse effects of treatment • health-related quality of life.	The outcome measures assessed in the submission include: • overall survival • intravascular haemolysis (as measured by lactate dehydrogenase) • extravascular haemolysis (as measured by reticulocyte count) • breakthrough haemolysis • transfusion avoidance • haemoglobin • thrombotic events • adverse effects of treatment • health-related quality of life.	Consistent with final scope
Subgroups to be considered	If the evidence allows the subgroups based on previous treatment with complement inhibitors will be considered: • treatment naïve • treatment experienced • treatment experienced with anaemia despite previous treatment	• Complement inhibitor-naïve patients • Complement inhibitor-experienced patients with anaemia despite treatment with a complement inhibitor	The submission covers all patient populations for whom evidence from iptacopan Phase 3 trials is available. The APPOINT-PNH study included complement inhibitor-naïve patients, while the APPLY-PNH study included complement inhibitor-experienced patients with anaemia. No evidence is available for treatment-experienced patients without anaemia, and the licence is not expected to cover this patient subgroup.

	Final scope issued by NICE (22)	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Special considerations including issues related to equity or equality	The NICE equality impact assessment – Scoping (24), preliminary view noted that: All protected characteristics will be considered by committee when making its recommendations. However, the committee can only make recommendations within a technology's marketing authorisation. The committee will consider the potential implications of pegcetacoplan being a self-administered subcutaneous injection† and iptacopan offering a potentially easier route of administration for people who find it difficult, or might not be able to self-administer pegcetacoplan.	The submission highlights the limitations of pegcetacoplan as a subcutaneous infusion† for patients with dexterity, visual or cognitive disabilities. These groups may find difficulty or not be able to self-administer the treatment. Iptacopan – as an oral treatment – would offer an advantage to these patients.	–

†Note, the NICE equality impact assessment document (24) refers to pegcetacoplan as an injection, however it is administered via SC infusion.
Abbreviations: C5, complement component 5; NHS, National Health Service; NICE, National Institute for Health and Social Care Excellence; PNH, paroxysmal nocturnal haemoglobinuria; SC, subcutaneous.

B.1.2 Description of the technology being evaluated

Table 2 summarises the technology (iptacopan) being evaluated in this submission.

The draft summary of product characteristics (SmPC) is presented in Appendix C.

Table 2: Technology being evaluated

UK approved name and brand name	Iptacopan (brand name pending regulatory approval)
Mechanism of action	Iptacopan is a proximal complement inhibitor that targets Factor B (FB) to selectively inhibit the alternative pathway while leaving the direct signalling from the lectin and classical pathways intact (25-27). Inhibition of FB prevents the activity of alternative pathway-related C3 convertase and the subsequent formation of C5 convertase (25-27). In PNH, intravascular haemolysis (IVH) is mediated by the downstream membrane attack complex (MAC), while extravascular haemolysis (EVH) is facilitated by C3b opsonisation (25-27). Iptacopan acts proximally in the alternative pathway of the complement cascade to control both C3b-mediated EVH and terminal complement-mediated IVH (25-27).
Marketing authorisation/ CE mark status	GB marketing authorisation is anticipated in [redacted]

Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated indication of iptacopan is as follows:
	• Iptacopan is indicated for the treatment of adult patients with PNH:
	  ○ who have haemolysis with clinical symptom(s), or
	  ○ who are anaemic after treatment with a complement inhibitor.
	Based on the draft SmPC, iptacopan is expected to be contraindicated in the following cases:
	• Hypersensitivity to the active substance or to any of the excipients.
	• In patients who are not currently vaccinated against *Neisseria meningitidis* (*N. meningitidis)* and *Streptococcus pneumoniae* (*S. pneumoniae)* unless the risk of delaying iptacopan treatment outweighs the risk of developing an infection from these encapsulated bacteria.

	• For initiation in patients with unresolved serious infection caused by encapsulated bacteria, including *N. meningitidis, S. pneumoniae* or *Haemophilus influenzae* (*H. influenzae)* type B.
Method of administration and dosage	Iptacopan 200 mg capsules are administered as an oral treatment twice daily (BD). (Note: While iptacopan was stored in a refrigerator in the clinical trials, the SmPC which will apply to commercial stock has no special storage conditions.) For patients switching from C5 inhibitors, iptacopan should be initiated no later than 1 week after the last dose of eculizumab, or no later than 6 weeks after the last dose of ravulizumab. PNH is a disease that requires chronic treatment and discontinuation of iptacopan is not recommended unless clinically indicated.
Additional tests or investigations	The use of complement inhibitors may predispose patients to serious infections with encapsulated bacteria. Patients treated with iptacopan must be vaccinated against *N. meningitidis* and *S. pneumoniae*, while vaccination against *H. influenzae* type B is recommended. Patients should be vaccinated ≥2 weeks before starting treatment or receive antibacterial prophylaxis until 2 weeks after vaccination. Patients may be revaccinated in accordance with local guidelines.
List price and average cost of a course of treatment	Proposed list price: £[redacted] for iptacopan 200 mg 56 capsules (annual treatment cost £[redacted]†)
Patient access scheme (if applicable)	A simple PAS has been offered to the NHS, and submitted to PASLU. PAS price: £[redacted] ([redacted]% discount) for iptacopan 200 mg 56 capsules (annual treatment cost £[redacted]†)

†Annual treatment cost based on 365.25 days.
Abbreviations: BD, twice daily; C3b, complement component 3b; C5, complement component 5; EU, European Union; EVH, extravascular haemolysis; FB, Factor B; GB, Great Britain; *H. influenzae, Haemophilus influenzae*; IVH, intravascular haemolysis; MAC, membrane attack complex; MHRA, Medicines and Healthcare products Regulatory Agency; *N. meningitidis, Neisseria meningitidis;* NHS, National Health Service; PAS, patient access scheme; PASLU, Patient Access Schemes Liaison Unit; PNH, paroxysmal nocturnal haemoglobinuria; *S. pneumoniae, Streptococcus pneumoniae*; SmPC, summary of product characteristics; SmPC, summary of product characteristics.

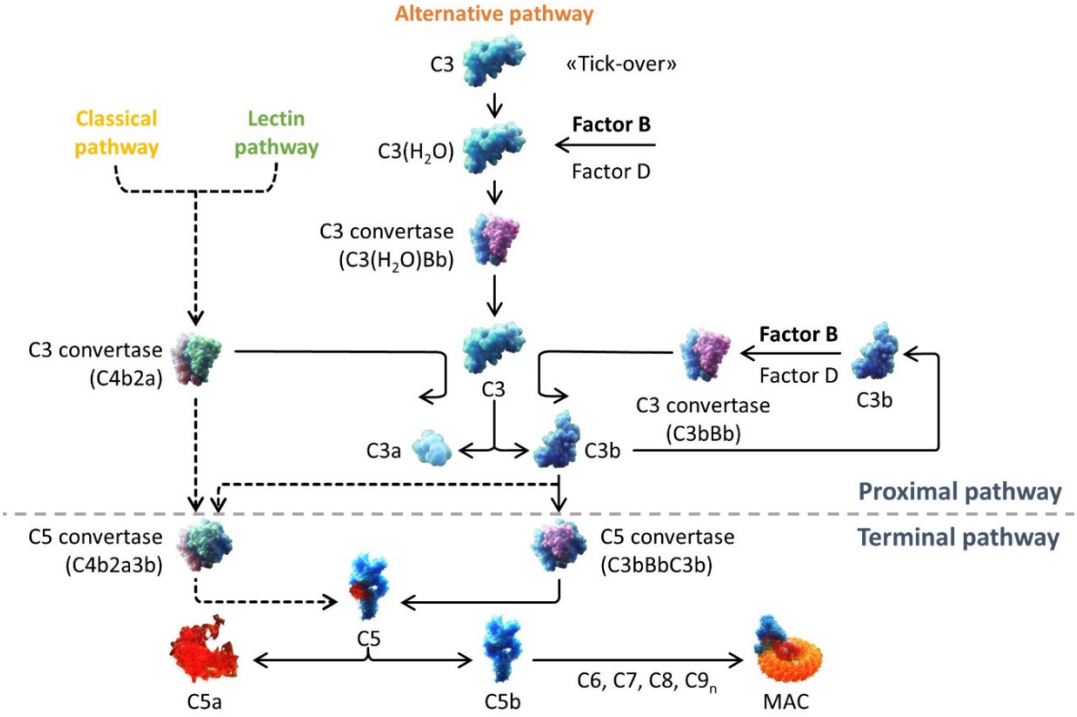
B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview and epidemiology

Paroxysmal nocturnal haemoglobinuria (PNH) is a chronic, life-threatening blood disorder characterised by damage to red blood cells (RBC) by the innate immune system (5, 28). PNH is an ultra-rare disease, with an estimated incidence in Great Britain (GB) of 1 in 770,000 per year, and a predicted prevalence of 1 in 62,500 (3). An estimated 926 people in England are living with PNH (4), which can occur at any age but is typically diagnosed between 30 and 40 years old (3, 29).

PNH is an acquired blood disorder in which stem cells acquire a gene mutation resulting in the production of abnormal blood cells (30, 31). The abnormal RBCs, white blood cells (WBC), and platelets lack the anchor (glycosylphosphatidylinositol [GPI]) for two surface proteins (CD55 and CD59) that regulate complement activity (5, 10, 32, 33). The lack of CD55 and CD59 means that the RBCs are susceptible to haemolysis (destruction of RBCs) mediated by the complement system (Figure 1).

Figure 1: PNH complement cascade



Source: adapted from Brodsky (2014) (5) and Merle (2015) (33).
Abbreviations: MAC, membrane attack complex; PNH, paroxysmal nocturnal haemoglobinuria.

In PNH, this lack of CD55 and CD59 results in the destruction of RBCs within the bloodstream, known as intravascular haemolysis (IVH) (5, 10).

Furthermore, patients with PNH treated with C5 inhibitors can have extravascular haemolysis (EVH) caused by ongoing C3 deposition on surviving yet defective RBCs (2, 34, 35). This leaves the RBCs susceptible to phagocytosis outside the blood circulation in the liver or spleen as they are no longer destroyed by IVH (5, 10).

B.1.3.2 Diagnosis and classification

Patients presenting with unexplained/unusual thrombosis, haemolysis, or bone marrow failure (BMF) syndromes should be screened for PNH (36-38).

The initial evaluation of a patient with suspected PNH should include flow cytometry of peripheral RBCs and other blood cell lineages, complete blood and reticulocyte counts, biochemical markers of haemolysis (lactate dehydrogenase [LDH], bilirubin, and haptoglobin), determination of iron stores, bone marrow aspirate, biopsy, and cytogenetics (8). Blood cells that are affected by PNH are known as PNH clone cells, and PNH clone size refers to the proportion of PNH-affected cells vs normal cells within the total cell population (39). These diagnostics allow classification of patients into three subtypes based on the recommendation of the International PNH Interest Group; classic PNH, PNH in the setting of another BMF syndrome such as aplastic anaemia, and subclinical PNH (8).

To assess the severity of PNH, IVH measured by blood LDH levels is considered the most reliable indicator (40). High LDH levels (>1.5 times the upper limit of normal [ULN]) indicate increased disease activity and raise the risk of thrombosis, kidney problems, pulmonary hypertension, and death (40).

Patients with classic PNH have a large (usually >50%) clone size (8). Blood LDH is always markedly elevated in classic PNH, and as such, PNH symptoms are present and the risk of thrombosis is high (8).

When PNH is associated with another BMF syndrome, patients have a moderate clone size (8, 28). Typically there is evidence of minimal abnormalities of biochemical markers of haemolysis (such as LDH) (8, 28). PNH symptoms may be present and there is an intermediate risk of thrombosis.

Subclinical PNH is diagnosed when the PNH clone size is small (1–10%), with no evidence of clinical haemolysis (8, 28). PNH symptoms are absent and there is a low risk of thrombosis.

B.1.3.3 Clinical pathway of care

According to guidelines by the International PNH Interest Group and other PNH organisations (8, 9), the management of PNH is dependent on subtype. Guidelines recommend that patients with classic PNH are treated with a complement inhibitor. For patients with PNH in the setting of another BMF syndrome, and patients with subclinical PNH, management is focused on the concomitant BMF syndrome and ongoing monitoring of clone size. Some patients with PNH in the setting of another BMF syndrome and a large PNH clone size may benefit from complement inhibitor therapy (8, 10).

The clinical pathway of care for patients with PNH in the UK is managed via the National PNH Service, funded by National Health Service (NHS) England as a highly specialised service (41). The National PNH Service consists of two designated centres: St James's University Hospital in Leeds, and King's College Hospital in London. There are several outreach clinics across England and one in Scotland, while for Wales and Northern Ireland, haematologists in Cardiff and Belfast manage their patients under the direction of the National PNH Service (41). On diagnosis of PNH, patients are managed on a shared care basis between the National PNH Service and referring haematologists (41).

Clinical management for PNH can include treatment with a complement inhibitor (Section B.1.3.3.1), supportive care (Section B.1.3.3.2), and allogenic bone marrow transplant (Section B.1.3.3.3).

B.1.3.3.1 *Complement inhibitors*

Three complement inhibitors are currently used to treat PNH in the UK: the terminal complement component 5 (C5) inhibitors eculizumab and ravulizumab, and the proximal complement component 3 (C3) inhibitor pegcetacoplan. According to the National PNH Service annual report, in 2022, 339 patients (36.6%) were receiving treatment with complement inhibitors for PNH in England (4).

In 2007, eculizumab was the first complement inhibitor approved in the UK to treat PNH (42). Eculizumab is commissioned by NHS England to treat PNH with haemolytic activity (18, 43). Eculizumab is a humanised monoclonal antibody (mAb) that binds to C5 and inhibits the activation of terminal complement, thereby controlling IVH, reducing thrombosis risk, and improving survival (10, 42, 44). Eculizumab is administered every 2 weeks (Q2W) as an intravenous (IV) infusion (42).

Ravulizumab is a modified eculizumab molecule that binds via the same C5 target as eculizumab but has a longer terminal half-life, allowing for a greater interval between IV infusions (every 8 weeks [Q8W]) while still demonstrating similar efficacy and safety as eculizumab (44-47). Ravulizumab was recommended by NICE in 2021, for treating PNH in adults with haemolysis with clinical symptoms suggesting high disease activity, or whose disease is clinically stable after having eculizumab for ≥6 months (19).

As terminal C5 inhibitors, eculizumab and ravulizumab inhibit membrane attack complex (MAC) formation and associated IVH (27, 34). However, some patients treated with C5 inhibitors continue to suffer from anaemia, which can be due to an underlying bone marrow dysfunction, residual (breakthrough) IVH, or EVH arising from opsonisation of surviving PNH RBCs with C3 fragments (27). For patients treated with a C5 inhibitor, elevated reticulocyte levels (>100 x 10^9/L) serve as a marker for EVH (48). Persistent EVH may result in ongoing anaemia and dependence on blood transfusions (2, 48)

Pegcetacoplan is a proximal C3 inhibitor recommended by NICE in 2022 for PNH in adult patients who have anaemia after ≥3 months of treatment with a C5 inhibitor (20). As pegcetacoplan targets the complement cascade earlier than C5 inhibitors, it addresses both IVH and EVH, leading to improvement of anaemia (49). Pegcetacoplan is an infusion administered subcutaneously (SC) twice weekly (23).

Initial treatment for patients with PNH in the UK is with either eculizumab or ravulizumab, with ravulizumab being the preferred option as it requires less frequent infusions than eculizumab, which may have benefits for patients' quality of life (QoL) (19, 21, 50). As such, most patients who started treatment on eculizumab

have been switched to ravulizumab and the role of eculizumab in PNH continues to decrease (4, 21, 50). NICE approved pegcetacoplan in 2022 for patients experiencing anaemia on eculizumab or ravulizumab (20); however, currently, use in UK clinical practice remains low (50).

B.1.3.3.2 *Supportive care*

Patients with PNH often receive supportive care alongside complement inhibitors to manage their symptoms and anaemia:

- Blood transfusions: Transfusions temporarily raise blood haemoglobin (Hb) levels. However, transfusion dependence also has a negative impact on patients' health related quality of life (HRQoL) (51, 52).

- Iron overload treatment: Chronic transfusions can lead to iron overload, which is associated with an increased risk of morbidity and mortality (51). Iron overload can be treated with iron chelation therapy, which prevents the build-up of excess iron and associated complications, including hepatic, endocrinological, and cardiac dysfunction (53), but adds an additional burden for patients (51). For patients switched to a proximal inhibitor, residual iron overload accumulated during previous C5 inhibitor treatment can instead be removed with venesection (20, 50).

- Anticoagulants: Anticoagulant therapy helps to reduce the risk of thrombosis, as well as manage thrombosis if an event occurs (52, 54).

- Supplements: Iron, folic acid, and vitamin B12 supplements can support increased RBC formation in the bone marrow but cannot treat the underlying disease (52, 55).

B.1.3.3.3 *Allogeneic bone marrow transplant*

The only curative therapy for PNH is an allogeneic bone marrow transplant (10, 56). However, a bone marrow transplant is associated with considerable challenges (such as donor matching) and risks (including transplant-related morbidity and mortality), and so is not a therapeutic option for most patients (10, 52, 56).

B.1.3.4 Disease burden and unmet need

B.1.3.4.1 *Clinical burden*

PNH is characterised by a clinical triad of IVH, thrombosis, and BMF (1, 2). In addition to causing anaemia, IVH results in symptoms of smooth-muscle dystonia (e.g. abdominal pain, dysphagia, and erectile dysfunction), and a high risk of thrombosis (1, 5). Before the approval of eculizumab in 2007, PNH was associated with poor overall survival (OS; 10-year OS: 50–65%), mainly as a result of thrombotic complications (2, 15-17).

The clinical presentation of PNH is often heterogenous, however the most common symptom is debilitating fatigue, affecting approximately 80% of patients with PNH (6). Other key manifestations include haemoglobinuria, anaemia, symptoms of smooth muscle dystonia such as pain, thrombosis, hypertension, and chronic kidney disease (5-13).

B.1.3.4.1.1 Thrombosis

Before the introduction of complement inhibitors, thrombosis was the leading cause of mortality in patients with PNH (10). However, since eculizumab became available, the incidence of thromboembolic events in patients with PNH has decreased substantially (57), and life expectancy for patients with PNH is now similar to the general population (58).

B.1.3.4.1.2 Anaemia

Patients with PNH often present with anaemia (driven by IVH and BMF) and have elevated levels of LDH and haemoglobinuria (44). In patients who have not received treatment, anaemia is primarily due to IVH, while in patients who have been treated with C5 inhibitors, residual anaemia occurs mainly due to EVH (2, 34, 35). Chronic anaemia decreases the oxygen-carrying capacity of the blood. In the short term, increased heart and respiratory rates are able to counteract anaemia (59). However, if untreated, anaemia can cause multi-organ failure and be life threatening (59).

B.1.3.4.1.3 Breakthrough haemolysis

IVH is largely prevented by C5 inhibitors, and therefore, these drugs have resulted in relief from anaemia, reduction of thrombotic risk, improved QoL, and prolonged survival (1, 27, 34). However, IVH can still occur in the form of breakthrough

haemolysis (BTH), recognised by the sudden reappearance of signs and symptoms of IVH (including haemoglobinuria) associated with an increase in LDH level and a decrease in Hb (1, 27). BTH can occur as a result of suboptimal C5 inhibition, or in the context of a complement-amplifying condition such as an infection or pregnancy (1, 60). Patients experiencing BTH have an increased risk of potentially fatal thromboembolic events and other debilitating PNH-related symptoms (35).

An estimated 11–27% of patients experience BTH while on eculizumab (61-63). Although pegcetacoplan offers improvements in Hb levels vs eculizumab, BTH still occurred in 10% of patients in the pivotal trial (49).

B.1.3.4.1.4 Smooth muscle dystonia and associated symptoms

Patients with PNH may experience chronic IVH. Haemolysis releases free Hb causing the depletion of nitric oxide (NO), which is important for smooth muscle cell regulation. Reduced levels of NO can subsequently cause abdominal pain, gastrointestinal spasms, difficulty swallowing, vasoconstriction, pulmonary and systemic hypertension, renal failure, and erectile dysfunction (28, 64). Abdominal pain is one of the main causes of discomfort and impairment in PNH and is present in approximately one-third of patients at diagnosis (65). Depletion of NO can also lead to thrombosis as it can activate platelets (64).

B.1.3.4.1.5 Fatigue

Fatigue is the most common symptom among patients with PNH (reported by ≥80% of patients) (6, 10, 66), and patients view fatigue as the most important symptom they suffer from (67). Although fatigue is most pronounced during a haemolytic episode it is usually always present (6, 10, 66). Furthermore, the degree of fatigue experienced by patients is also often disproportionately higher than suggested by their levels of anaemia (68). Fatigue significantly impairs overall well-being and interferes with daily activity and work productivity, manifesting as a loss of independence, decreased physical activity, and decreased HRQoL (51). Notably, >75% of C5 inhibitor-treated patients report unresolved fatigue, with many reporting lower overall QoL, decreased productivity, and reduced activity (69).

B.1.3.4.2 *Humanistic burden*

While patients with PNH are concerned about risks of organ damage and mortality, it is the non-fatal manifestations of PNH, in particular, severe fatigue and transfusion requirements, that often have a substantial negative effect on patients' daily QoL, restricting their ability to perform everyday activities (10). As such, patients with PNH typically report having lower QoL compared with the general population (14, 66), with key influences including fatigue, pain, shortness of breath, dysphagia, and erectile dysfunction (14, 70).

A recent cross-sectional survey (conducted in 2021) of 71 patients with PNH treated with eculizumab or ravulizumab in Germany, UK, and France reported that fatigue was the most common symptom at both diagnosis (73.2%) and at the time of survey (63.4%) (66). Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scores of patients with PNH treated with eculizumab or ravulizumab were 8–10 points lower (demonstrating worse fatigue) at the time of survey than the general population average (43.5); the difference was significant and greater than the upper range of validated minimum clinically important differences (66). Similarly, mean EORTC QLQ-C30 scores were significantly lower compared with the general population across nearly all domains (66). Patients also reported cognitive problems (memory loss, confusion, brain fog, problems concentrating, difficulty focusing on tasks), which were experienced by 48% of the participants (66).

Available carer burden evidence is limited in PNH, although given the substantial symptom burden experienced by patients with PNH (14), their family and carers may need to provide additional support with daily activities and medical appointments (51).

B.1.3.4.3 *Economic burden*

The economic burden of PNH is expected to be large, due to the high direct costs associated with treatment and hospitalisation (71), and the indirect costs from absenteeism caused by symptom burden and comorbidities (71, 72).

Administration of current PNH therapies can impact patients' and carers' productivity due to the time commitments associated with treatment, such as the IV administration of eculizumab or ravulizumab, twice weekly SC infusion of

pegcetacoplan, and blood transfusions or other supportive therapies. This further increases burden on patients and could reduce QoL by impacting employment status (14, 73).

A cross-sectional survey of 71 patients with PNH treated with eculizumab or ravulizumab in Germany, UK, and France assessed work productivity using the Work Productivity and Activity Impairment (WPAI) questionnaire. In total, 57.7% of patients reported paid employment and among them, 97.6% reported overall PNH-related work impairment for a mean of 26.7% of their required weekly work time (66). Furthermore, 29.3% reported absence in the 7 days before the survey for a mean of 10.2% of required work time, and 70.3% reported affected productivity (presenteeism) for a mean of 18.7% of required work time (66). In total, 84.5% of patients surveyed reported an impairment of their normal daily activity for a mean of 37.5% of their waking time in the last week (66).

The effect of PNH on ability to work is further demonstrated by results of a recent international survey in patients treated with C5 inhibitors (N=143; median age 47 years) using the WPAI questionnaire (74). 15% of patients reported that they had stopped working, 21% had changed to flexible working hours, and 11% had reduced their work responsibilities due to PNH. Among employed patients (50%), mean absenteeism and presenteeism were 9% and 26%, respectively, while overall work impairment was 32%. Activity impairment for all patients was 34% (74).

Taken together, these studies demonstrate that PNH impacts patients' ability to work and perform daily activities, and this is observed despite currently available treatments.

B.1.3.4.4 *Remaining unmet need*

The unmet needs in PNH are associated with the remaining clinical burden (e.g. residual anaemia on C5 inhibitors due to EVH, BTH) and administration limitations of the currently available treatment options. Current unmet need in PNH is evidenced by [redacted].

B.1.3.4.4.1 Residual anaemia and transfusion dependence

Although treatment with C5 inhibitors has improved outcomes for patients with PNH, some patients still experience residual complement-mediated haemolysis, unresolved anaemia, and anaemia-related complications (transfusion dependence, fatigue, and impaired QoL) (69). These patients may require regular blood transfusions which further increases the treatment burden, and as discussed in Section B.1.3.3.2, may lead to iron overload. Of note, ~30% of patients with PNH receiving C5 inhibitors report ongoing transfusion requirements (27, 50, 75, 76), over 75% of patients report unresolved fatigue (69), and many report lower QoL compared with the general population (14).

B.1.3.4.4.2 Mode of administration

Currently, all available complement inhibitors are either IV or SC infusion therapies and there is no approved oral treatment for PNH.

Ravulizumab offers advantages compared with eculizumab in terms of reduced IV infusion frequency (Q8W vs Q2W), but still requires administration by a healthcare professional with a typical infusion duration of 1 hour (77). In patients receiving treatment with C5 inhibitors, the IV route of administration remains a disadvantage for patients, causing them to worry about their veins, the need for frequent cannulations, and disruptions to their family life (78).

Pegcetacoplan, as a twice weekly SC infusion (23), is the first treatment that can be self-administered, but this may be difficult for patients with visual or physical disability. Additionally, SC infusions may also be unsuitable for some obese patients due to absorption issues (79); the pegcetacoplan pivotal trial excluded patients with a body mass index (BMI) ≥35.0 kg/m^2 (80). The SC infusion of pegcetacoplan via a syringe system infusion pump is also time consuming. After removing the drug from the fridge 30 minutes before administration, the typical infusion time is approximately 30 minutes if using two infusion sites, or approximately 60 minutes if using one site (23). While the standard dosing is a twice weekly infusion, UK clinicians have reported that between 10 and 30% of their patients receiving pegcetacoplan require more frequent infusions, either every 3 days or thrice weekly (50).

Of note, the time demands associated with administration of the current therapies are likely underestimated as they do not account for the cannulation required for IV infusion or the preparation of the SC infusion device (23).

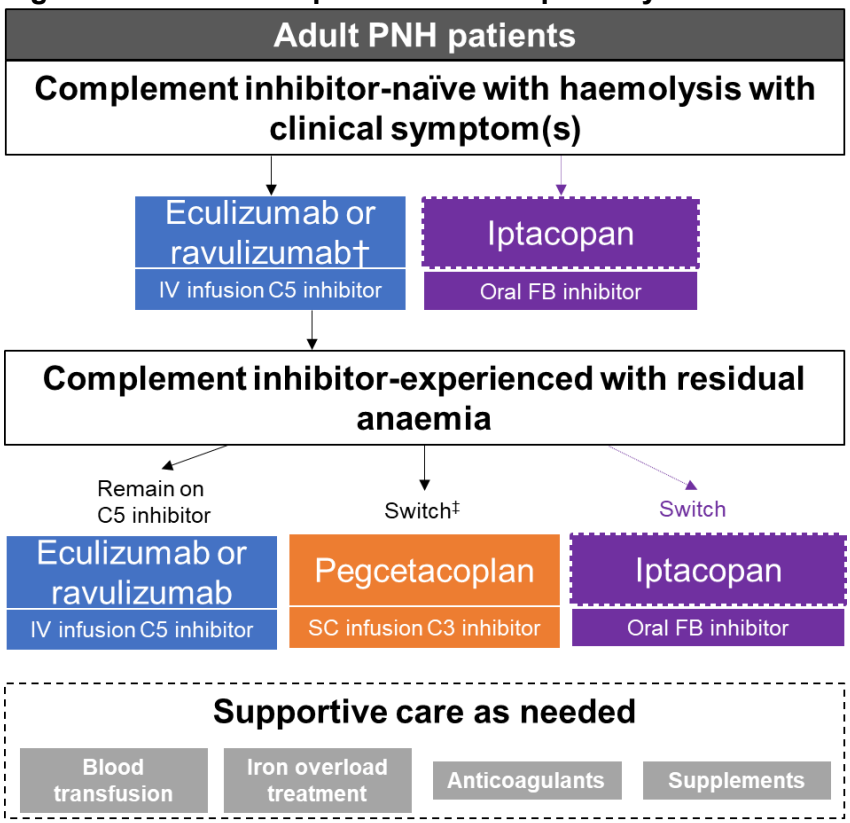
As reported by several UK clinicians, some patients who would be eligible to switch to pegcetacoplan prefer to remain on their C5 inhibitor IV infusion treatment, despite the potential of pegcetacoplan to improve their anaemia (50). Based on insights from clinicians, patients choose to not switch to pegcetacoplan for a number of reasons, including the practicality of twice weekly application (e.g. impact on ability to travel), they do not feel comfortable with self-infusion, or they perceive the nature of the SC infusion as cumbersome (50). According to clinicians, to date only 20–30% of patients have switched to pegcetacoplan (50).

B.1.3.5 Proposed positioning of iptacopan

Iptacopan is anticipated to be the first oral complement inhibitor monotherapy approved for PNH. The proposed positioning of iptacopan is in adult patients with PNH who are complement inhibitor-naïve or complement inhibitor-experienced with residual anaemia (Figure 2), in line with the patient populations included in the iptacopan Phase 3 clinical trials and the anticipated marketing authorisation. If recommended by NICE, it is expected that iptacopan can be integrated into the existing National PNH Service as a further treatment option (50).

The evidence to support the proposed positioning is presented in Section B.2.

Figure 2: Future anticipated treatment pathway for PNH with iptacopan



Source: NICE TA698 (19), NICE TA778 (20) and proposed positioning for iptacopan.
†Ravulizumab is also recommended for patients whose disease is clinically stable after having eculizumab for ≥6 months (NICE TA698) (19); ‡Pegcetacoplan is recommended for patients who have anaemia after ≥3 months of treatment with a C5 inhibitor (NICE TA778) (20).
Abbreviations: C3, complement component 3; C5, complement component 5; FB, Factor B; IV, intravenous; PNH, paroxysmal nocturnal haemoglobinuria; SC, subcutaneous.

B.1.4 Equality considerations

It is not considered that this appraisal will exclude any people protected by equality legislation, lead to a recommendation that would have a different impact on people protected by equality legislation compared with the wider population, or lead to recommendations that would have an adverse impact on people with a particular disability.

However, all currently available treatments for PNH are administered via SC or IV infusion (23, 42, 45), and therefore, may disadvantage patients with needle phobia. Some patients may find self-administering pegcetacoplan, as a SC infusion, difficult, or might not be able to self-administer pegcetacoplan at all. This may include patients with dexterity, visual or cognitive disabilities. SC infusions may also be unsuitable for some obese patients due to absorption issues (79, 80).

As iptacopan is expected to be the first oral monotherapy for PNH, any recommendation made by the committee would give these patients access to a potentially more suitable treatment option.

B.2 Clinical effectiveness

The efficacy of iptacopan 200 mg twice daily (BD) in paroxysmal nocturnal haemoglobinuria (PNH) has been demonstrated for key clinical outcomes in two Phase 3 trials

APPOINT-PNH, a single-arm trial, demonstrated efficacy of oral iptacopan in complement inhibitor-naïve patients (N=40)

- Improvements in anaemia, shown by haemoglobin (Hb) assessed between Day 126 and Day 168 in the absence of transfusions
  - 92.2% of patients (95% confidence interval [CI]: 82.5, 100.0) had a sustained Hb increase of ≥2 g/dL compared with baseline (primary endpoint)
  - 62.8% of patients (95% CI: 47.5, 77.5) achieved sustained Hb levels of ≥12 g/dL
  - Adjusted mean change from baseline (CFB) in Hb: +4.28 g/dL (95% CI: 3.87, 4.70)
- Between Day 14 and Day 168, no patient required a transfusion, and no patient experienced breakthrough haemolysis (BTH)
- Resolution of intravascular haemolysis (IVH) as shown by decrease in lactate dehydrogenase (LDH) levels assessed between Day 126 and Day 168 compared with baseline: –83.55% (95% CI: –84.90%, –82.08%)
- Improvement in patient-reported fatigue as shown by increase in the mean Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score measured between Day 126 and Day 168 compared with baseline: +10.75 points (95% CI: 8.66, 12.84).

APPLY-PNH, a randomised, active-controlled trial comparing oral iptacopan (N=62) with intravenous C5 inhibitors (N=35), demonstrated superior efficacy of iptacopan across the majority of endpoints in complement inhibitor-experienced patients with residual anaemia

- Improvements in anaemia vs C5 inhibitors, shown by Hb assessed between Day 126 and Day 168 in the absence of transfusions
  - Sustained Hb increase of ≥2 g/dL compared with baseline: treatment difference in marginal proportions iptacopan vs C5 inhibitors of 80.3% (95% CI: 71.3, 87.6; unadjusted two-sided p-value <0.0001; primary endpoint 1)
  - Achievement of sustained Hb levels ≥12 g/dL: treatment difference in marginal proportions iptacopan vs C5 inhibitors of 67.0% (95% CI: 56.3, 76.9; p<0.0001; primary endpoint 2)
  - Mean CFB in Hb: adjusted mean difference iptacopan vs C5 inhibitors of +3.63 g/dL (95% CI: 3.18, 4.08; p<0.0001)
- Between Day 14 and Day 168, 60/62 patients in the iptacopan group and 14 of 35 patients in the C5 inhibitor group did not require transfusions (treatment difference in marginal proportions of 70.3%; 95% CI: 52.6, 84.9; p<0.0001)
- Up to Day 168, two clinical BTH events were reported in 2/62 patients (3.2%) in the iptacopan group vs 11 clinical BTH events in 6/35 patients (17.1%) in the C5 inhibitor group (rate ratio 0.10; 95% CI: 0.02, 0.61; p=0.01183)
- The adjusted geometric mean ratio in LDH in the iptacopan group relative to the C5 inhibitor group was 0.99 (95% CI: 0.89, 1.10; p=0.8345), demonstrating a minimal CFB in either group
- Improvement in patient-reported fatigue as shown by increase in the mean FACIT-Fatigue score between Day 126 and Day 168 compared with baseline: adjusted mean difference iptacopan vs C5 inhibitors of +8.29 points (95% CI: 5.28, 11.29; p<0.0001).

The efficacy of iptacopan is supported by the results of indirect treatment comparisons (ITCs) in complement inhibitor-naïve and -experienced patients

- In the complement inhibitor-naïve population, ITCs were conducted between iptacopan and C5 inhibitors, comparing data from APPOINT-PNH vs Study 301, as well as APPOINT-PNH vs UK/France real-world evidence data (APPEX). Results of both ITCs consistently favoured iptacopan over C5 inhibitors, although not all results in the ITC vs Study 301 were statistically significant
- In the complement inhibitor-experienced population with residual anaemia, an ITC was conducted between iptacopan (APPLY-PNH) and pegcetacoplan (PEGASUS), with most results favourable for iptacopan.

Iptacopan 200 mg BD (oral) has a favourable safety profile and is generally well tolerated as demonstrated in the two Phase 3 trials

- APPOINT-PNH in complement inhibitor-naïve patients
  - There were no treatment discontinuations or dose interruptions due to adverse events (AE), and no deaths during the study
  - In the core 24-week treatment period, one patient (2.5%) experienced a severe AE, otherwise AEs were mild or moderate
  - Overall, including the extension period until the data cut-off, four patients (10%) experienced serious adverse events (SAE)
- APPLY-PNH in complement inhibitor-experienced patients with residual anaemia
  - There were no treatment discontinuations or dose interruptions due to AEs (1 discontinuation due to pregnancy), and no deaths during the study
  - The proportion of patients experiencing an AE was comparable between the iptacopan and C5 inhibitor treatment groups
    - Any AEs: iptacopan 82.3%; C5 inhibitor 80.0%
  - Most AEs were mild or moderate
    - Severe AEs: iptacopan: 4.8%; C5 inhibitor: 8.6%
  - The proportion of patients experiencing an SAE was comparable between the iptacopan and C5 inhibitor treatment groups
    - SAEs: iptacopan 9.7%; C5 inhibitor 14.3%.

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify all relevant evidence on the clinical effectiveness and safety of iptacopan and all potentially relevant comparators for the treatment of patients with paroxysmal nocturnal haemoglobinuria (PNH). The SLR identified 109 publications for inclusion:

- 45 publications, clinical study reports (CSRs), or clinical trial records reported on 16 unique clinical trials (Table 3)
- 63 publications and one CSR reported on the findings of observational studies; this includes the APPEX study which was used to inform an indirect treatment comparison (ITC) (Section B.2.9.2) and transition probabilities in the economic model for C5 inhibitors in the complement inhibitor-naïve population (Section B.3).

Full details of the process and methods used in the SLR, as well as a description of the included studies and results, are provided in Appendix D.

Table 3: Clinical trials identified by the clinical effectiveness SLR

Trial (key reference)	Intervention	Comparator
Trials evaluating complement inhibitor-naïve PNH patients		
Hillmen 2004 (81)	Eculizumab	—
SHEPHERD Brodsky 2008 (82)	Eculizumab	—
TRIUMPH Hillmen 2006 (83)	Eculizumab	Placebo
Eculizumab extension study (including patients from Hillmen 2004, SHEPHERD, and TRIUMPH) Hillmen 2007 (84)	Eculizumab	—
AEGIS Kanakura 2011 (85)	Eculizumab	—
Study 201 Roth 2018 (86)	Ravulizumab 1,000 mg Q4W Ravulizumab 1,600 mg Q6W Ravulizumab 2,400 mg Q8W Ravulizumab 5,400 mg Q12W	—
Study 301 Lee 2019 (47)	Ravulizumab	Eculizumab
Wong 2019 (87)	Pegcetacoplan	—
Jang 2022 (88)	Iptacopan 25 mg BD	Iptacopan 50 mg BD
APPOINT-PNH CSR (89)	Iptacopan	—
Risitano 2021 (90)	Danicopan	—
Jang 2023 (91)	SB12 (eculizumab biosimilar) to eculizumab	Eculizumab to SB12 (eculizumab biosimilar)
Trials evaluating complement inhibitor-experienced PNH patients with anaemia		
PEGASUS Hillmen 2021 (49)	Pegcetacoplan	Eculizumab
Risitano 2021 (92)	Iptacopan + eculizumab	—
APPLY-PNH CSR (93)	Iptacopan	C5 inhibitors (eculizumab, ravulizumab)
Kulasekararaj 2021 (94)	Danicopan + eculizumab	—

Abbreviations: BD, twice daily; CSR, clinical study report; QXW, every X weeks; SLR, systematic literature review.

B.2.2 List of relevant clinical effectiveness evidence

The primary sources of clinical efficacy evidence for iptacopan in PNH are the Phase 3 trials, APPOINT-PNH (complement inhibitor-naïve patients) and APPLY-PNH (complement inhibitor-experienced patients with residual anaemia) (89, 93). An overview of these trials is provided in Table 4.

Jang et al 2022 (91) was not considered to provide relevant evidence as the iptacopan dose included in this trial (25 mg BD or 50 mg BD) differed from the expected approved iptacopan dose (200 mg BD). Risitano et al 2021 (92) was not considered relevant for this submission either as iptacopan was studied as an add-on therapy to eculizumab in this trial, while the expected licence for iptacopan is for use as a monotherapy.

Table 4: APPOINT-PNH and APPLY-PNH: Overview of clinical studies

Study	APPOINT-PNH	APPLY-PNH
Study design	Phase 3, multi-centre, single-arm, open-label trial	Phase 3, multi-centre, randomised, open-label, active comparator-controlled, parallel group trial
Population	Adult patients with PNH and haemolysis (LDH >1.5 ULN) and anaemia (Hb <10 g/dL) who were naïve to complement inhibitor therapy, including C5 inhibitor treatment	Adult patients with PNH and residual anaemia (Hb <10 g/dL) despite a stable regimen of C5 inhibitor treatment (eculizumab or ravulizumab) for ≥6 months before randomisation
Intervention(s)	Iptacopan, 200 mg BD (oral capsules)	Iptacopan, 200 mg BD (oral capsules)
Comparator(s)	NA	C5 inhibitors. Patients received either eculizumab or ravulizumab (patients continued the same treatment with the same stable regimen as prior to randomisation [IV infusion])
Indicate if the trial supports the application for marketing authorisation	Yes	Yes
Indicate if study used in the economic model	Yes	Yes

Study	APPOINT-PNH	APPLY-PNH
Rationale if study not used in model	–	–
Reported outcomes specified in the decision problem†	• Increase from baseline **Hb‡** levels ≥2 g/dL • Hb levels ≥12 g/dL • Absence of packed-RBC **transfusions‡** (transfusion avoidance) • CFB in Hb (g/dL) • % CFB in LDH levels (U/L) (marker of IVH) • **Occurrences of BTH** • CFB in reticulocyte counts (10^9/L) (marker of EVH) • CFB in FACIT-Fatigue scores • **EQ-5D-5L¶** • EORTC-QLQ C30 • Occurrences of MAVEs (thrombotic events) • **Safety assessments (including deaths)**	• Increase from baseline **Hb‡** levels ≥2 g/dL • Hb levels ≥12 g/dL • Absence of packed-RBC **transfusions‡** (transfusion avoidance) • CFB in Hb (g/dL) • % CFB in LDH levels (U/L) (marker of IVH) • **Occurrences of BTH** • CFB in reticulocyte counts (10^9/L) (marker of EVH) • CFB in FACIT-Fatigue scores • **EQ-5D-5L¶** • EORTC-QLQ C30 • Occurrences of MAVEs (thrombotic events) • **Safety assessments (including deaths**)
All other reported outcomes	• Number and units of RBC transfusions • PNH-related signs and symptoms • RBC markers • Haptoglobin • Hb stabilisation • C3 deposition on PNH type RBCs • PNH clone size	• Number and units of RBC transfusions • PNH-related signs and symptoms • RBC markers • Haptoglobin • Hb stabilisation • C3 deposition on PNH type RBCs • PNH clone size

†Outcomes in **bold** are used in the economic model; ‡Hb and transfusion data from APPOINT-PNH and APPLY-PNH are utilised in the economic model, but transition probabilities were derived from IPD rather than utilising the endpoints as defined in the studies; ¶Mapped to EQ-5D-3L for the economic modelling.
Abbreviations: BD, twice-daily; BTH, breakthrough haemolysis; C3, complement component 3; CFB, change from baseline; EORTC, European Organization for the Research and Treatment of Cancer; EVH, extravascular haemolysis; FACIT, Functional Assessment of Chronic Illness Therapy; Hb, haemoglobin; IPD, individual patient data; IV, intravenous; IVH, intravascular haemolysis; LDH, lactate dehydrogenase; MAVE, major adverse vascular event; NA, not applicable; PNH, paroxysmal nocturnal haemoglobinuria; QXW, every X weeks; RBC, red blood cell; ULN, upper limit of normal.

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

A summary of the methodology of the APPOINT-PNH and APPLY-PNH trials is provided in Table 5.

Table 5: APPOINT-PNH and APPLY-PNH: Summary of trial methodology

Trial name	APPOINT-PNH	APPLY-PNH
Trial design	A multicentre, single-arm, open-label trial	A multicentre, randomised, open-label, active comparator-controlled, parallel group trial
Key eligibility criteria for participants	• Patients ≥18 years of age with a diagnosis of PNH (RBC and WBC clone size ≥10%) • Naïve to complement inhibitor treatment, including C5 inhibitor • Hb level <10 g/dL • LDH >1.5 x ULN • Vaccination against *Neisseria meningitidis, Streptococcus pneumoniae* and *Haemophilus influenzae*	• Patients ≥18 years of age with a diagnosis of PNH (RBC and WBC clone size ≥10%) • Stable regimen of C5 inhibitor treatment (eculizumab or ravulizumab) for ≥6 months prior to randomisation • Hb level <10 g/dL • Vaccination against *Neisseria meningitidis, Streptococcus pneumoniae* and *Haemophilus influenzae*

Trial drugs	• Iptacopan (LNP023) 200 mg BD (oral capsules), N=40	• Iptacopan (LNP023) 200 mg BD (oral capsules), N=62
		• C5 inhibitors, N=35
		  ○ Eculizumab (IV infusion)[†] or
		  ○ Ravulizumab (IV infusion)[†]

Settings and locations where data were collected	China, France, Germany, Italy, Republic of Korea, Malaysia, Singapore, UK (one site: London [4 UK patients])	Brazil, Czech Republic, France, Germany, Italy, Japan, Republic of Korea, Netherlands, Spain, Taiwan, UK (two sites: Leeds, London [overall 11 UK patients]), USA
Primary endpoint(s)	• Increase from baseline Hb levels ≥2 g/dL (assessed between Day 126 and Day 168) in the absence of pRBC transfusions[‡] between Day 14 and Day 168	• Increase from baseline Hb levels ≥2 g/dL (assessed between Day 126 and Day 168) in the absence of pRBC transfusions[‡] between Day 14 and Day 168 • Hb levels ≥12 g/dL (assessed between Day 126 and Day 168) in the absence of pRBC transfusions[‡] between Day 14 and Day 168

Trial name	APPOINT-PNH	APPLY-PNH
Secondary endpoints	• Hb levels ≥12 g/dL (assessed between Day 126 and Day 168) in the absence of pRBC transfusions‡ between Day 14 and Day 168 • Absence of pRBC transfusions‡ (assessed between Day 14 and Day 168) • CFB in Hb (g/dL) (as mean of visits between Day 126 and Day 168) • % CFB in LDH levels (U/L) (as mean of visits between Day 126 and Day 168) • Occurrences of BTH (assessed between Day 1 and Day 168) • CFB in reticulocyte counts (10^9/L) (as mean of visits between Day 126 and Day 168) • CFB in FACIT-Fatigue score (as mean of visits between Day 126 and Day 168) • Occurrences of MAVEs (assessed between Day 1 and Day 168) • Safety assessments (assessed between Day 1 and Day 168)	• Absence of pRBC transfusions‡ (assessed between Day 14 and Day 168) • CFB in Hb (g/dL) (as mean of visits between Day 126 and Day 168) • CFB in FACIT-Fatigue score (as mean of visits between Day 126 and Day 168) • CFB in reticulocyte counts (10^9/L) (as mean of visits between Day 126 and Day 168) • % CFB in LDH levels (U/L) (as mean of visits between Day 126 and Day 168) • Occurrences of BTH (assessed between Day 1 and Day 168) • Occurrences of MAVEs (assessed between Day 1 and Day 168) • Safety assessments (assessed between Day 1 and Day 168)
Exploratory endpoints	• Haematological parameters, bilirubin, units of pRBC transfusions, and PNH signs and symptoms • Proportion of patients with stabilised Hb (avoidance of a ≥2 g/dL decrease from baseline) • CFB in EORTC QLQ-C30, EQ-5D-5L, and PGIS • % C3d+ RBCs • Type I, Type II & III RBCs and PNH clone size (in RBCs and WBCs) • Pharmacokinetics • Patient experience	• Haematological parameters, bilirubin, units of pRBC transfusions, and PNH signs and symptoms • CFB in EORTC QLQ-C30, EQ-5D-5L, and PGIS • % C3d+ RBCs • Type I, Type II & III RBCs and PNH clone size (in RBCs and WBCs) • Pharmacokinetics • Patient experience

Trial name	APPOINT-PNH	APPLY-PNH
Pre-planned subgroup analyses of primary endpoint(s)	• Length of time since diagnosis (<3 years, ≥3 years) • Age (<45 years, ≥45 years) • Baseline Hb (<8 g/dL, ≥8 g/dL) • History of MAVE (yes, no) • Transfusions in the last 6 months (yes, no) • Number of transfusions in the last 6 months (<2, ≥2) • China vs countries other than China	• Length of time since diagnosis (<5 years, ≥5 years) • Age (<45 years, ≥45 years) • Sex (male, female) • Baseline Hb (<9 g/dL, ≥9 g/dL) • History of MAVE (yes, no) • C5 inhibitor in the last 6 months (eculizumab, ravulizumab) • Transfusion in the last 6 months (yes, no) • Number of transfusions in the last 6 months (<2, ≥2) • LDH levels at baseline (≤1.5 x ULN, >1.5 x ULN) • Duration of C5 inhibitor treatment (<12 months, ≥12 months)

Source: Novartis, Data on file, APPOINT-PNH CSR (89); Novartis, Data on file, APPLY-PNH CSR, (93).
†Patients randomised to the C5 inhibitor arm continued with the same treatment (eculizumab or ravulizumab) and same stable regimen (dose and intervals) as that prior to randomisation; ‡Patient did not receive a transfusion nor met any of the predefined criteria for transfusion.
Abbreviations: BD, twice daily; BTH, breakthrough haemolysis; CFB, change from baseline; EORTC, European Organization for the Research and Treatment of Cancer; FACIT, Functional Assessment of Chronic Illness Therapy; Hb, haemoglobin; IV, intravenous; LDH, lactate dehydrogenase; MAVE, major adverse vascular event; PGIS, Patient Global Impression of Severity; PNH, paroxysmal nocturnal haemoglobinuria; pRBC, packed red blood cell; ULN, upper limit of normal, UK, United Kingdom; USA, United States of America; WBC, white blood cell.

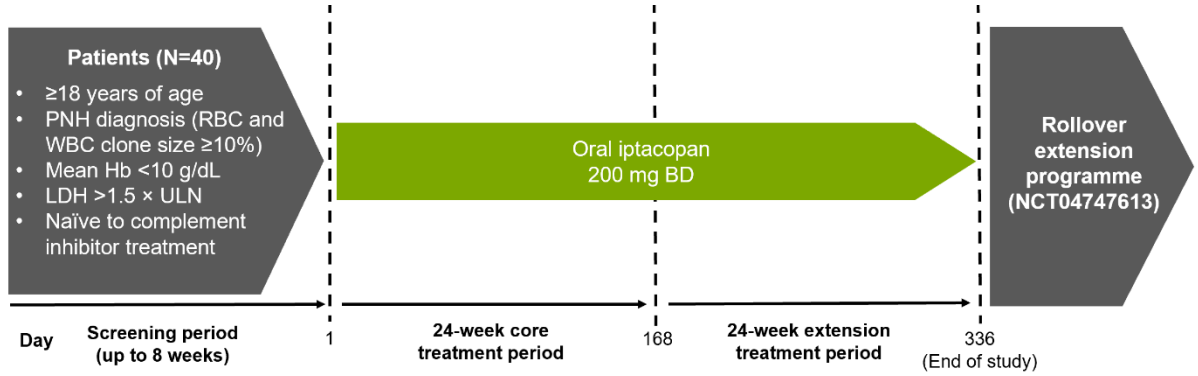
B.2.3.1 Trial design

B.2.3.1.1 *APPOINT-PNH*

The APPOINT-PNH trial was a Phase 3, multi-centre, single-arm, open-label trial, comprising three periods (Figure 3):

- A screening period lasting up to 8 weeks
- Core treatment period: A 24-week single arm, open-label period for evaluation of efficacy and safety
- Extension treatment period: A 24-week open-label, iptacopan treatment extension period.

Figure 3: APPOINT-PNH: Study design



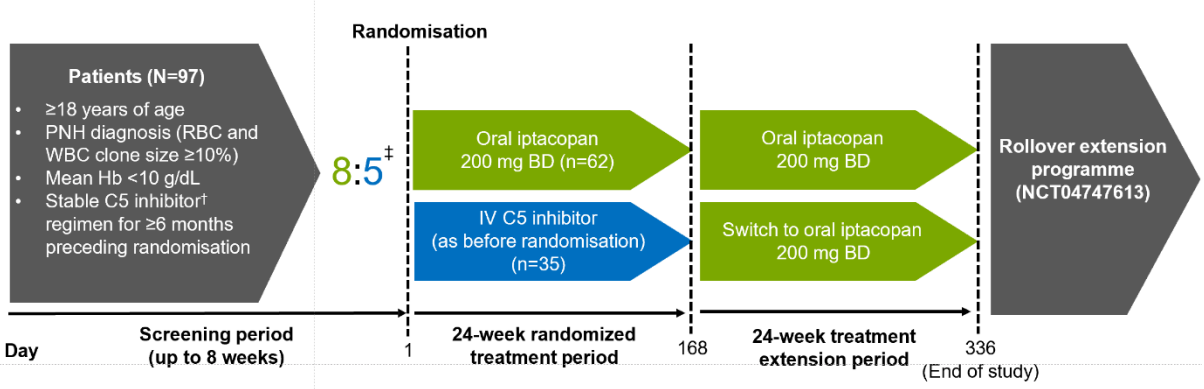
Source: NCT04820530 (95)
Abbreviations: BD, twice-daily; Hb, haemoglobin; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal haemoglobinuria; RBC, red blood cells; ULN, upper limit of normal; WBC, white blood cells.

B.2.3.1.2 *APPLY-PNH*

The APPLY-PNH trial was a Phase 3, multi-centre, randomised, open-label, active comparator-controlled, parallel group trial, comprising three periods (Figure 4):

- A screening period lasting up to 8 weeks
- Randomised treatment period: A 24-week randomised, open-label, active comparator-controlled treatment period for the primary efficacy and safety analyses
- Extension treatment period: A 24-week open-label, iptacopan treatment extension period.

Figure 4: APPLY-PNH: Study design



Source: NCT04558918 (96)
†Eculizumab or ravulizumab; ‡Randomisation stratified by prior C5 inhibitor treatment and RBC transfusions in the preceding 6 months.
Abbreviations: BD, twice-daily; C5, complement component 5; Hb, haemoglobin; IV, intravenous; PNH, paroxysmal nocturnal haemoglobinuria; RBC, red blood cells; WBC, white blood cells.

B.2.3.2 Randomisation

APPOINT-PNH was a single-arm trial; therefore, no randomisation took place.

In APPLY-PNH, randomisation was stratified into four strata, defined by the combination of the two stratification factors. Patients who met the eligibility criteria at screening were stratified based on the type of prior C5 inhibitor treatment (eculizumab or ravulizumab) and based on the transfusion history as reported during the last 6 months prior to randomisation (i.e. transfusion received/not received). Patients were randomised via Interactive Response Technology (IRT) in an 8:5 ratio to either iptacopan at a dose of 200 mg orally BD or C5 inhibitor IV infusion. Patients randomised to the C5 inhibitor arm continued with the same treatment and regimen during the randomised treatment period as they had received prior to randomisation.

B.2.3.3 Blinding

Both APPOINT-PNH and APPLY-PNH were open-label trials.

B.2.3.4 Eligibility criteria

Key eligibility criteria for APPOINT-PNH and APPLY-PNH are presented in Table 5. The full inclusion/exclusion criteria are provided in Appendix M.

B.2.3.5 Concomitant medications

Concomitant medications prohibited if not on a stable regimen are provided in Appendix M.

B.2.3.6 Patient disposition and baseline characteristics

B.2.3.6.1 *Patient disposition*

In APPOINT-PNH, a total of 40 patients were enrolled in the study and completed the 24-week core treatment period. As of the data cut-off date (2nd Nov 2022), 39 patients[a] had entered the extension treatment period; 7 patients (17.5%) had completed the 24-week extension treatment period and continued to receive open-label iptacopan therapy in the roll-over extension study (NCT04747613), while

[a] One further patient's last visit was on the data cut-off day, and therefore they did not enter the extension treatment period by that date. However, the patient started the extension treatment the day after the data cut-off.

iptacopan extension treatment within APPOINT-PNH was ongoing for 32 patients (80.0%).

In APPLY-PNH, a total of 97 patients were randomised in the study, 62 in the iptacopan group and 35 in the C5 inhibitor group. A total of 96 patients completed the 24-week randomised treatment period on treatment, 61 (98.4%) in the iptacopan group and 35 (100%) in the C5 inhibitor group. One patient in the iptacopan group discontinued study treatment due to pregnancy. This patient continued study assessments until the end of the randomised treatment period.

Of the 96 patients completing the randomised treatment period on study treatment, 94 patients entered the treatment extension period during which all patients received iptacopan. Two patients, initially randomised to the C5 inhibitor group, did not enter the extension period: one patient due to the investigator's decision (patient's clinical condition) and one patient had their last visit in the randomised treatment period on the cut-off date and therefore did not enter the extension treatment period by the cut-off date. As of the data cut-off (26th Sep 2022), of the 94 patients who entered the extension treatment period, 51 (54.3%) patients had completed the 24-week extension treatment period on iptacopan, 42 (44.7%) patients were receiving treatment, and one patient (1.1%) had discontinued study treatment due to pregnancy and continued all study assessments until the end of the extension treatment period.

B.2.3.6.2 *Baseline demographics*

The APPOINT-PNH study population (Table 6) represented adult patients with PNH who were naïve to complement inhibitor therapy. The median age of the included patients was 38.5 years (range 18–81 years), 42.5% (17 patients) were female, and 30.0% (12 patients) were White.

The APPLY-PNH study population (Table 6) represented adult patients with PNH who had residual anaemia following treatment with a C5 inhibitor. The patient demographics were generally well-balanced between the iptacopan and C5 inhibitor treatment groups. The median age was 53.0 years (range 20–84 years), 69.1% (67 patients) were female, and 76.3% (74 patients) were White.

Table 6: APPOINT-PNH and APPLY-PNH: Patient baseline demographics

	APPOINT-PNH	APPLY-PNH		
	Iptacopan 200 mg BD N=40	Iptacopan 200 mg BD N=62	C5 inhibitor N=35	Overall N=97
Age (years)				
Median (min–max)	38.5 (18–81)	53.0 (22–84)	45.0 (20–82)	53.0 (20–84)
Mean (SD)	42.1 (15.85)	51.7 (16.94)	49.8 (16.69)	51.0 (16.79)
Female, n (%)	17 (42.5)	43 (69.4)	24 (68.6)	67 (69.1)
Race, n (%)				
White	12 (30.0)	48 (77.4)	26 (74.3)	74 (76.3)
Black or African American	1 (2.5)	2 (3.2)	2 (5.7)	4 (4.1)
Asian	27 (67.5)	12 (19.4)	7 (20.0)	19 (19.6)
Chinese	22 (55.0)	2 (3.2)	1 (2.9)	3 (3.1)
Indian	NR†	0	1 (2.9)	1 (1.0)
Japanese	NR†	7 (11.3)	3 (8.6)	10 (10.3)
Korean	3 (7.5)	2 (3.2)	0	2 (2.1)
Other	2 (5.0)	–	–	–
Missing	–	1 (1.6)	2 (5.7)	3 (3.1)

Source: Novartis, Data on file, APPOINT-PNH CSR, Table 10.5 (89); Novartis, Data on file, APPLY-PNH, Table 10.5 (93).
†APPOINT-PNH only classified Asian patients as Chinese, Korean, or Other.
Abbreviations: BD, twice daily; CSR, clinical study report; NR, not reported; SD, standard deviation.

B.2.3.6.3 *Baseline disease characteristics*

In APPOINT-PNH, the baseline disease characteristics (Table 7) reflected a complement inhibitor-naïve PNH patient population with anaemia and intravascular haemolysis (IVH); mean baseline haemoglobin (Hb) level was 8.16 (standard deviation [SD]: 1.087) g/dL and mean baseline lactate dehydrogenase (LDH) level was 1,698.8 U/L (SD: 683.33). 70.0% of patients had received ≥1 red blood cell (RBC) transfusion in the 6 months prior to study treatment and 52.5% had received ≥2 transfusions. Five patients (12.5%) had a history of ≥1 major adverse vascular event (MAVE).

In APPLY-PNH, the baseline disease characteristics (Table 7) were well balanced between the two treatment groups. The population consisted of patients with PNH and residual anaemia despite C5 inhibitor treatment, with overall a mean baseline Hb level of 8.90 (SD: 0.775) g/dL; 57.7% of patients had received ≥1 RBC transfusion in the 6 months prior to randomisation and 39.2% ≥2 transfusions. Mean C5 inhibitor treatment duration prior to randomisation was 3.95 years. Prior to

randomisation, 64.9% of patients had received eculizumab with a median dose of 900 mg, and 35.1% had received ravulizumab with a median dose of 3,300 mg. Mean baseline LDH level was 270.4 (SD: 75.34) U/L. As expected for a patient population receiving C5 inhibitor treatment, 91.8% of patients had LDH of ≤1.5 x ULN, while only 7.2% had LDH levels >1.5 x ULN indicating a small number of patients with significant residual IVH. In total, 21 (21.6%) patients, including 12 (19.4%) in the iptacopan group, had a history of ≥1 MAVE.

Table 7: APPOINT-PNH and APPLY-PNH: Baseline disease characteristics

	APPOINT-PNH	APPLY-PNH		
	Iptacopan 200 mg BD N=40	Iptacopan 200 mg BD N=62	C5 inhibitor N=35	Overall N=97
Disease duration, years				
Mean (SD)	4.699 (5.5379)	11.88 (9.813)	13.55 (10.937)	12.48 (10.208)
Median (min–max)	3.625 (0.01–23.20)	NR (0.7–40.2)	NR (1.5–42.0)	NR (0.7–42.0)
Length of time since diagnosis, n (%)				
<3 years	18 (45.0)	NR	NR	NR
≥3 years	22 (55.0)	NR	NR	NR
C5 inhibitor medication history – 6 months prior to randomisation -n (%)				
Eculizumab	NA	40 (64.5)	23 (65.7)	63 (64.9)
Ravulizumab	NA	22 (35.5)	12 (34.3)	34 (35.1)
Duration of C5 inhibitor treatment (years)				
Mean (SD)	NA	3.79 (3.534)	4.23 (3.868)	3.95 (3.644)
Median (min–max)	NA	2.56 (0.5–16.6)	2.74 (0.4–16.3)	2.61 (0.4–16.6)
Eculizumab dose administered (mg)				
Median (min–max)	NA	900.0 (900–1,200)	900.0 (900–1,500)	900.0 (900–1,500)
Ravulizumab dose administered (mg)				
Median (min–max)	NA	3,300.0 (3,000–3,600)	3,300.0 (3,000–3,600)	3,300.0 (3,000–3,600)
Baseline Hb, n (%)				
Mean (SD)	8.155 (1.0871)	8.933 (0.7026)	8.853 (0.8975)	8.904 (0.7749)
Baseline LDH level (U/L)				
Mean (SD)	1,698.8 (683.33)	269.1 (70.14)	272.7 (84.80)	270.4 (75.34)
≤1.5 x ULN, n (%)	NR	58 (93.5)	31 (88.6)	89 (91.8)
>1.5 x ULN, n (%)	NR	4 (6.5)	3 (8.6)	7 (7.2)

	APPOINT-PNH	APPLY-PNH		
	Iptacopan 200 mg BD N=40	Iptacopan 200 mg BD N=62	C5 inhibitor N=35	Overall N=97
Transfusion in the last 12 months prior to screening, n (%)				
Yes	27 (67.5)	37 (59.7)	22 (62.9)	59 (60.8)
Transfusion in the last 6 months prior to randomisation, n (%)				
Yes	28 (70.0)	35 (56.5)	21 (60.0)	56 (57.7)
Number of transfusions in the last 6 months prior to study treatment				
<2	19 (47.5)	38 (61.3)	21 (60.0)	59 (60.8)
≥2	21 (52.5)	24 (38.7)	14 (40.0)	38 (39.2)
Number of transfusions in the last 6 months prior to study treatment among patients who had a transfusion				
N	28	35	21	56
Mean (SD)	3.1 (2.09)	3.1 (2.62)	4.0 (4.39)	3.4 (3.38)
Median (min–max)	2.0 (1–8)	2.0 (1–13)	2.0 (1–19)	2.0 (1–19)
Platelets (10^9/L)				
Mean (SD)	159.4 (61.09)	160.2 (63.83)	147.3 (77.01)	155.6 (68.77)
Absolute reticulocyte counts (10^9/L)				
Mean (SD)	154.33 (63.666)	193.22 (83.637)	190.59 (80.922)	192.27 (82.254)
Baseline FACIT-Fatigue total score				
Mean (SD)	32.78 (10.170)	34.7 (9.82)	30.8 (11.45)	33.4 (10.52)
Median (min–max)	34.25 (13.0–50.5)	34.8 (11–52)	31.5 (10–50)	33.0 (10–52)
Total PNH RBC clone size (%)†				
Mean (SD)	42.706 (21.2276)	64.645 (27.4543)	57.391 (29.7258)	62.028 (28.3576)
History of MAVE				
Yes	5 (12.5)	12 (19.4)	9 (25.7)	21 (21.6)
History of aplastic anaemia				
Yes	16 (40.0)	9 (14.5)	5 (14.3)	14 (14.4)

Source: Novartis, Data on file, APPOINT-PNH CSR, Table 10.6, Table 14.1-3.2 (89); Novartis, Data on file, APPLY-PNH, Table 10.6, Table 14.1-3.2 (93).
†Total PNH clone size is calculated as sum of percentages of positive RBC of Type II and Type III.
Abbreviations: BD, twice daily; CSR, clinical study report; FACIT, Functional Assessment of Chronic Illness Therapy; Hb, haemoglobin; LDH, lactate dehydrogenase; NA, not applicable; NR, not reported; SD, standard deviation.

B.2.3.7 Prior and concomitant therapies

The APPOINT-PNH study enrolled patients diagnosed with PNH who had not previously been treated with complement inhibitor therapies. In APPLY-PNH, all patients had used eculizumab or ravulizumab for ≥6 months prior to randomisation.

The most common (>10%) concomitant therapies taken in APPOINT-PNH and APPLY-PNH are reported in Table 8.

Table 8: APPOINT-PNH and APPLY-PNH: Most common (>10%) concomitant medications (SAS)

	APPOINT-PNH	APPLY-PNH	
	Iptacopan 200 mg BD N=40 n (%)	Iptacopan 200 mg BD N=62 n (%)	C5 inhibitor N=35 n (%)
Number of patients with ≥1 medication in any ATC class	**39 (97.5)**	**62 (100.0)**	**34 (97.1)**
Folic acid and derivatives	13 (32.5)	40 (64.25)	23 (65.7)
Calcineurin inhibitors	12 (30.0)	2 (3.2)	2 (5.7)
Glucocorticoids	11 (27.5)	9 (14.5)	2 (5.7)
Unspecified herbal and traditional medicine	11 (27.5)	2 (3.2)	0
Proton pump inhibitors	10 (25.0)	13 (21.0)	10 (28.6)
Anilides	8 (20.0)	12 (19.4)	9 (25.7)
Beta-lactamase sensitive penicillin	7 (17.5)	8 (12.9)	4 (11.4)
Bile and liver therapy	7 (17.5)	–	–
Fluroquinolones	6 (15.0)	11 (17.7)	5 (14.3)
Other viral vaccines	6 (15.0)	21 (33.9)	7 (20.0)
Androstan derivatives	5 (12.5)	0	1 (2.9)
Dihydropyridine derivatives	5 (12.5)	6 (9.7)	4 (11.4)
Penicillins with extended spectrum	5 (12.5)	7 (11.3)	2 (5.7)
Antacids with sodium bicarbonate	4 (10.0)	–	–
Liver therapy	4 (10.0)	–	–
Other antihistamines for systemic use	4 (10.0)	1 (1.6)	1 (2.9)
Iron chelating agents	2 (5.0)	9 (14.5)	8 (22.9)
Deferasirox	1 (2.5)	9 (14.5)	6 (17.1)
Deferoxamine mesilate	1 (2.5)	0	1 (2.9)
Deferiprone	–	0	1 (2.9)
Deferoxamine	–	0	1 (2.9)
Vitamin K antagonists	–	8 (12.9)	2 (5.7)
Combinations of penicillins	1 (2.5)	7 (11.3)	2 (5.7)
Propionic acid derivatives	1 (2.5)	7 (11.3)	0
Thyroid hormones	1 (2.5)	7 (11.3)	2 (5.7)

Source: Novartis, Data on file, APPOINT-PNH CSR, Table 14.3-1.5a (89); Novartis, Data on file, APPLY-PNH, Table 14.3-1.6a (93).
Abbreviations: ATC, Anatomical Therapeutic Chemical; BD, twice daily; CSR, clinical study report; PNH, paroxysmal nocturnal haemoglobinuria; SAS, safety analysis set.

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

A summary of analysis sets and statistical analysis methods for APPOINT-PNH and APPLY-PNH is provided in Table 9.

Table 9: APPOINT-PNH and APPLY-PNH: Analysis sets and statistical analysis methods

	APPOINT-PNH	**APPLY-PNH**
Analysis sets	• Screening set: all patients who were screened • Enrolled set: all patients enrolled in the study, equivalent to the screening set • Full analysis set: all patients with confirmed eligibility to whom study treatment was assigned. This data set was used for analysis of all efficacy endpoints • Safety set: all patients who received ≥1 dose of study treatment	• Randomised analysis set: all randomised patients • Full analysis set: all patients to whom study treatment had been assigned by randomisation (excluding patients who had been assigned in error [mis-randomised patients]). According to the intent to treat principle, patients were analysed according to the treatment they had been assigned to, considering the strata in which they were included during the randomisation procedure. This data set was used for analysis of all efficacy endpoints in the randomised treatment period • Safety set: all patients who received ≥1 dose of study treatment • Combined safety set: all patients who received ≥1 dose of iptacopan 200 mg BD either in the randomised treatment period or in the treatment extension period. This analysis set was used to describe safety results including data collected during the extension period and includes only data after the first administration of iptacopan up to the cut-off date
Statistical analysis of primary endpoint(s)	**Proportion of patients achieving Hb increase from baseline of ≥2 g/dL** The primary analysis of the primary endpoint was a logistic regression to estimate the response probability. The covariates in logistic regression included sex, age (indicator of age ≥45 years), an indicator variable of	**Proportion of patients achieving Hb increase from baseline of ≥2 g/dL** **Proportion of patients achieving Hb levels ≥12 g/dL** For each of the two primary endpoints, the test of hypothesis was initially implemented by fitting a conditional logistic regression model, which conditioned on stratum within which

	APPOINT-PNH	APPLY-PNH
	baseline Hb ≥8 g/dL and an indicator of transfusion dependence (i.e. whether the patient had any transfusion in the last 6 months prior to starting study treatment). The proportion of responders was derived from the estimated marginal probabilities derived from the model fit as the mean of the individual logistic regression model predictions. The 95% CIs were derived by the bootstrap method. If the logistic regression failed to converge in ≥1 of the imputed datasets or the bootstrap samples, then the estimates were obtained using simple proportion. The primary analysis of the primary endpoint was the assessment of the proportion of patients reaching the status of responder (increase in Hb levels ≥2 g/dL from baseline without requiring RBC transfusions). The lower bound of the 2-sided 95% CI of the response rate obtained from the primary analysis was compared to a threshold of 15%. The threshold of 15% was derived by indirectly estimating Hb response in two studies with eculizumab (35, 83).	patients were randomised, and included as covariates sex, age (indicator of age ≥45 years), and an indicator variable of baseline Hb ≥9 g/dL. Cases of non-convergence due to sparsity of events were handled with a penalised likelihood (Firth) approach. Hence, the tests of the hypotheses associated to the two primary endpoints were conducted by fitting a logistic regression model, based on Firth's penalised maximum likelihood method. The models included treatment, the randomisation stratum, sex, age (indicator of age ≥45 years), and an indicator variable of baseline Hb ≥9 g/dL as covariates. Superiority of iptacopan in achieving a larger proportion of patients who reached a sustained Hb response (without requiring RBC transfusions) compared with C5 inhibitor treatment was tested by the null hypothesis comparing the probability of response in iptacopan to the probability of response on C5 inhibitor treatment for both primary endpoints.
Statistical analysis of secondary endpoints	**Proportion of patients achieving Hb levels ≥12 g/dL** Logistic regression model was planned by considering the similar analysis approach as primary analysis. Due to convergence issue, the proportion of responders were derived using simple proportion as for primary endpoint, with the 95% CI obtained using the bootstrap method. The number and percentage of patients reaching a fixed threshold ≥ 12 g/dL on three out of four measurements were taken at the visits occurring in last six weeks (from Day 126 to Day 168).	**Transfusion avoidance** Transfusion avoidance was evaluated by comparing the proportion of patients not receiving nor meeting the criteria for administration of RBC transfusion between Day 14 and Day 168. The comparison of treatments was conducted by means of the odds ratio derived using conditional logistic regression with standardised marginal proportions derived using logistic regression. **CFB in Hb (g/dL)** The model for the estimation is a MMRM considering an unstructured covariance structure, with stratification factors and including main effect of treatment, visit and baseline, and

	Transfusion avoidance Transfusion avoidance was evaluated as the proportion of patients who did not receive and did not meet the criteria for administration of RBC transfusion between Day 14 and Day 168, and similarly to the estimation applied to the primary estimand by means of standardised marginal proportions. Logistic regression model was planned by considering the similar analysis approach as primary analysis. Due to convergence issue, the proportion of transfusion avoidance was estimated using simple proportion as for the primary endpoint, with the 95% CI obtained using the bootstrap method. **CFB in Hb (g/dL)** For this analysis, if a patient had a transfusion during the core treatment period, then the Hb values 30 days following the transfusion was considered missing and Hb data was imputed. The model for the estimation is a MMRM considering an unstructured covariance structure. The model included transfusion dependence, age (indicator of age ≥45 years), sex, visit, baseline haemoglobin, and the interactions between visits and baseline levels. The treatment estimates were computed as the mean changes from baseline corresponding to the average of Hb levels measured in the last 6 weeks of treatment (that is the visits occurring between Day 126 and Day 168). **%CFB in LDH levels (U/L)** The treatment effect on percent CFB in LDH was assessed using a MMRM of log transformed ratio to baseline based on all observations collected during follow-up. The model for the estimation was a MMRM considering an unstructured covariance structure. The	the interactions between visits and treatment and visits and baseline levels. Additional covariates were age (as binary indicator) and sex. The treatment contrasts were computed as the comparison of treatments corresponding to the average measured in the last 6 weeks of randomised treatment (that is the visits occurring between Day 126 and Day 168). **CFB in FACIT-Fatigue score** The comparison between treatments was an average of treatment estimates derived for visits occurring between Day 126 and Day 168 as obtained from a repeated measures model. The model included the main effects of stratification factors, treatment baseline covariates and interaction terms. **CFB in reticulocyte counts (10^9/L)** The estimation of the CFB in absolute reticulocyte counts was derived from a longitudinal repeated measures model. The comparison between treatments used the average of model derived estimates for each treatment obtained at visits occurring between Day 126 and Day 168 as obtained from a repeated measures model. The model included stratification factors, treatment, baseline, and interaction terms. **%CFB in LDH levels (U/L)** The treatment effect on percent CFB in LDH was assessed using a longitudinal repeated measure model of log transformed ratio to baseline based on all observations collected during the randomised period. The model is same as the model described for all continuous endpoints. Treatment comparisons were derived based on the average of the log transformed ratio in each treatment estimated between Day 126 and Day 168.

	model included transfusion dependence, age (indicator of age ≥45 years), sex, visit, log-transformed baseline LDH and the interactions between visits and log-transformed baseline levels. Estimation was derived based on the average of the log transformed ratio from baseline estimated between Day 126 and Day 168. **Occurrences of BTH** Analysis was conducted applying a negative binomial model with covariates as per the primary analysis. Due to the zero events during core treatment, the rates of clinical BTH and 95% CI were estimated using the Wilson method (97). **CFB in reticulocyte counts (10^9/L)** The estimation of the CFB in absolute reticulocyte counts was derived from a MMRM. The model for the estimation was a MMRM considering an unstructured covariance structure. The model included transfusion dependence, age (indicator of age ≥45 years), sex, visit, baseline reticulocyte counts, and the interactions between visits and baseline levels. The estimation used the average of model derived estimates obtained at visits occurring between Day 126 and Day 168. **CFB in FACIT-Fatigue score** The model for the estimation was a MMRM considering an unstructured covariance structure. The model included transfusion dependence, age (indicator of age ≥45 years), sex, visit, baseline in scores of fatigues, and the interactions between visits and baseline levels. The estimation was an average of treatment estimates derived for visits occurring between Day 126 and Day 168.	**Occurrences of BTH** Analysis was conducted applying a negative binomial model with covariates as per the primary analysis. Following the treatment policy strategy for handling treatment discontinuations, the offset variable will be defined as the time from Day 1 till minimum (end of study, end of randomised treatment period). If this model failed to converge or to give valid estimates (if all events were in one level of ≥1 of the covariates) due to low frequency of occurrences, then the model was run considering only treatment as a factor in the negative binomial model. If the model failed to converge or to give valid estimates, then a Poisson model with treatment as a factor was fitted. If there was one treatment with no observed events and rate ratio cannot be computed, then rate difference and corresponding p-value were presented. **Occurrences of MAVEs** Analysis was conducted by applying negative binomial model. Following the treatment policy strategy for handling treatment discontinuations, the offset variable was defined as the time from Day 1 till minimum (end of study, end of randomised treatment period). If the model failed to converge or to give valid estimates, then a Poisson model with treatment as a factor was fitted. If there was one treatment having no events and rate ratio could not be computed, then rate difference and corresponding p-value were presented.

	APPOINT-PNH	APPLY-PNH
	Occurrences of MAVEs Analysis was conducted by applying negative binomial model.	
Sample size and power calculation	The sample size was calculated based on the half-width (the margin of error in the estimate) of a 2-sided 95% CI for the proportion of patients reaching the status of responder (primary endpoint). The proposed sample size of 40 patients was sufficient to achieve a target absolute margin of error not larger than 0.155. For the sample size of 40 patients, assuming an observed proportion of responders of 40%, there is 96.4% probability that the lower bound of the 2-sided 95% CI will exclude a threshold of 15%.	Under an assumption that 50% of responders on iptacopan treatment would achieve an increase in Hb of ≥2 g/dL from baseline compared with 16% of responders on C5 inhibitor treatment, the sample size of 56 patients on iptacopan and 35 patients on C5 inhibitor treatment provided 83.2% power for this endpoint at a significance level of 0.0125. Power for the endpoint corresponding to the achievement of sustained levels of Hb ≥12 g/dL was calculated under the assumption that the proportions were 35% on iptacopan treatment and 5% on C5 inhibitor treatment, resulting in a power of 89.1% for a significance level of 0.0125.

Source: Novartis, Data on file, APPOINT-PNH CSR (89); Novartis, Data on file, APPLY-PNH CSR (93).
Abbreviations: BD, twice-daily; BTH, breakthrough haemolysis; CFB, change from baseline; CI, confidence interval; FACIT, Functional Assessment of Chronic Illness Therapy; Hb, haemoglobin; LDH, lactate dehydrogenase; MAVE, major adverse vascular event; MMRM, mixed methods regression model; RBC, red blood cell.

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

The APPLY-PNH trial was quality assessed using the Cochrane Risk of Bias 2 tool (98). Overall, and across all domains, the risk of bias was low. The APPOINT-PNH trial was quality assessed using a modified Critical Appraisal Skills Programme (CASP) checklist (99). The APPOINT-PNH trial satisfies the criteria of a well-conducted single-arm clinical trial.

The quality assessment of each randomised trial identified in the SLR is provided in Appendix D.

B.2.6 Clinical effectiveness results of the relevant studies

B.2.6.1 APPOINT-PNH

B.2.6.1.1 *Primary endpoint: Haematological response based on increase from baseline Hb levels of ≥2 g/dL*

APPOINT-PNH met its primary endpoint; the marginal proportion of patients with sustained increase in Hb levels from baseline of ≥2 g/dL (assessed between Day 126 and Day 168) in the absence of RBC transfusions between Day 14 and Day 168 was 92.2% (95% confidence interval [CI]: 82.5, 100.0). The lower bound of the 2-sided 95% CI was 82.5%, which exceeded the prespecified threshold of 15% more than 5-fold. The 15% threshold was prespecified in the protocol and considered to be sufficient to demonstrate that, in patients with PNH and haemolysis and anaemia, iptacopan results in a haematological response in the absence of transfusions. The threshold of 15% was derived from historical studies with C5 inhibitor therapy (35, 83, 100).

Subgroup analyses were consistent with the primary analysis, including a subgroup analysis by country (China vs Other) (Appendix E).

B.2.6.1.1.1 Sensitivity analyses

Sensitivity analyses of the primary endpoint are presented in Table 10. In general, the consistency of the marginal proportions and the 95% CIs across the analyses

confirms the robustness of the primary efficacy analysis from changes in underlying assumptions regarding handling of missing data.

Table 10: APPOINT-PNH: Summary of primary, sensitivity and supplementary analyses for the primary endpoint – ≥2 g/dL increase in Hb from baseline between Day 126 and Day 168 in the absence of RBC transfusions between Day 14 and Day 168 (FAS)

Endpoint: ≥2 g/dL increase in Hb from baseline† in the absence of RBC transfusions‡	Iptacopan 200 mg BD N=40 n/M	Marginal proportion (95% CI)¶
Primary analysis • Only central lab data included • Missing Hb was imputed via MI and an assumption was made that patients had signs and/or symptoms at missed visits for determining transfusion avoidance	31/33	92.2 (82.5, 100.0)
Sensitivity analysis including local lab data • If central lab data missing, local laboratory data was included	35/37	94.1 (85.0, 100.0)
Additional sensitivity analysis 1 • MI Hb between >7 and ≤9 g/dL (or between >6 and ≤8 g/dL for patients in China) were considered by default as not having signs and/or symptoms and therefore not meeting the criteria for transfusion (hence, only patients with Hb ≤7 g/dL or ≤6 g/dL for patients in China were considered to meet the criteria for transfusion)	31/33	94.6 (87.5, 100.0)
Additional sensitivity analysis 2 • Determining transfusion avoidance without imputation	31/33	94.6 (87.5, 100.0)
Supplementary analysis • Patients requiring rescue therapy were considered as failures for the primary haematological response endpoint. (However, no patient received rescue therapy during the core treatment period.)	31/33	92.2 (82.5, 100.0)

Source: Novartis, Data on file, APPOINT-PNH CSR, Table 11-3 (89).
†Between Day 126 and 168 (≥3 out of 4 scheduled measurements); ‡Between Day 14 and Day 168. Requiring RBC transfusion refers to any patient receiving transfusions or meeting protocol defined criteria or imputed haemoglobin values ≤9 g/dL (≤8 g/dL for Chinese population); ¶The marginal proportion of responders was computed using simple proportion in the 100 multiply imputed datasets and then combined. There were two patients who were not responders based on observed data, 36 patients who were responders in all 100 multiply imputed datasets, two patients were responders in 3% and 83% of the datasets. The 95% CI was obtained using the bootstrap method.
Abbreviations: BD, twice daily; CI, confidence interval; CSR, clinical study report; FAS, full analysis set; Hb, haemoglobin; M, the number of patients with response variable defined based on non-missing data (evaluable patients); MI, multiple imputation; n, the number of patients who responded based on non-missing data; RBC, red blood cell.

B.2.6.1.2 *Secondary endpoints*

B.2.6.1.2.1 Haematological response based on Hb levels of ≥12 g/dL

The marginal proportion of patients achieving sustained Hb levels of ≥12 g/dL (assessed between Day 126 and Day 168) in the absence of RBC transfusions was 62.8% (95% CI: 47.5, 77.5) (Table 11).

Table 11: APPOINT-PNH: Number (%) of patients achieving sustained Hb levels of ≥12 g/dL between Day 126 and Day 168 in the absence of RBC transfusions between Day 14 and Day 168 (FAS)

Having Hb levels ≥12 g/dL† without requiring RBC transfusions‡	Iptacopan 200 mg BD N=40
n/M	**19/33**
Marginal proportion (95% CI)¶	62.8 (47.5, 77.5)

Source: Novartis, Data on file, APPOINT-PNH CSR, Table 11-4 (89).
†Between Day 126 and 168 (≥3 out of 4 scheduled measurements); ‡Between Day 14 and Day 168. Requiring RBC transfusion refers to any patient receiving transfusions or meeting protocol defined criteria or imputed Hb values ≤9 g/dL (≤8 g/dL for Chinese population); ¶The marginal proportion of responders was computed using simple proportion in the 100 multiply imputed datasets and then combined. The 95% CI was obtained using the bootstrap method.
Abbreviations: BD, twice daily; CI, confidence interval; CSR, clinical study report; FAS, full analysis set; Hb, haemoglobin; M, the number of patients with response variable defined based on non-missing data (evaluable patients); RBC, red blood cell.

B.2.6.1.2.2 Transfusion avoidance

The marginal proportion of patients avoiding transfusion (defined as did not receive transfusions nor meet protocol defined criteria for transfusion[b] between Day 14 and Day 168) was 97.6% (95% CI: 92.5, 100.0). Overall, based on observed data, no patients required RBC transfusions between Day 14 and Day 168.

B.2.6.1.2.3 Change from baseline in Hb levels (g/dL)

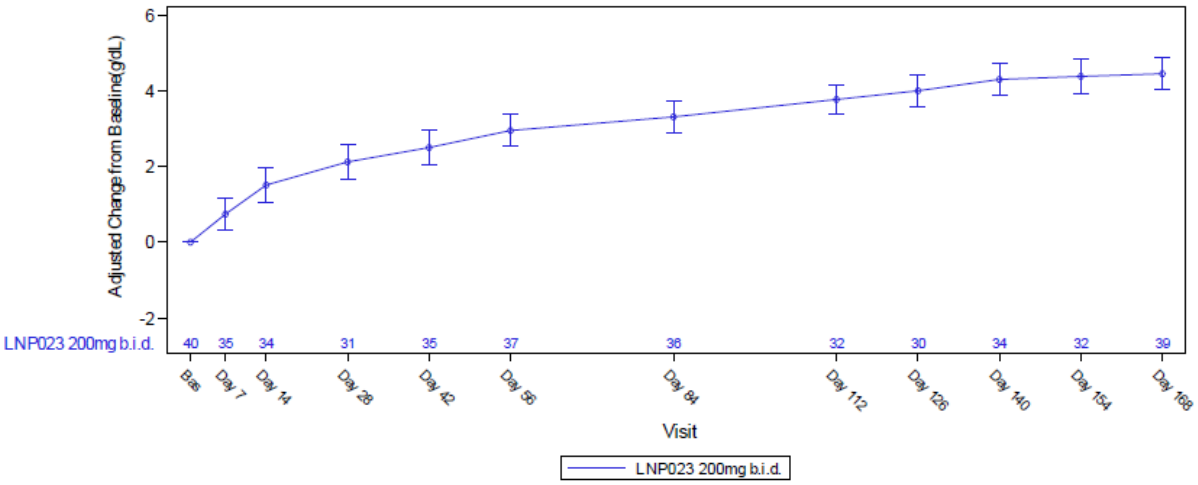
Mean (SD) Hb at baseline was 8.16 (1.09) g/dL. The adjusted mean change from baseline (CFB) in Hb as mean of visits between Day 126 and Day 168 was +4.28 g/dL (95% CI: 3.87, 4.70).

Increases in Hb levels were seen early with an adjusted mean CFB in Hb (95% CI) of 0.74 g/dL (0.31, 1.17) at Day 7 and 1.51 g/dL (1.06, 1.96) at Day 14 of iptacopan treatment (Figure 5). At each visit from Day 28 up to Day 168, the adjusted mean CFB in Hb was >2 g/dL.

[b]Hb ≤9 g/dL (≤8 g/dL for Chinese patients) with signs and/or symptoms of sufficient severity to warrant a transfusion, or, Hb ≤7 g/dL (≤6 g/dL for Chinese patients).

In order to factor out the effect of transfusions on Hb in this analysis, if a patient had a transfusion during the core treatment period, the Hb values for 30 days following the transfusion were excluded and Hb data were imputed.

Figure 5: APPOINT-PNH: Least squares means of CFB in Hb between baseline and Day 168 (FAS)



Source: Novartis, Data on file, APPOINT-PNH CSR, Figure 11.3 (89).
Intercurrent events were handled with treatment policy strategy, except for RBC transfusions which were handled as hypothetical strategy. In addition, Hb values at visits in 30 days following transfusions were considered as missing and were imputed. Treatment discontinuation for any reason was handled with a treatment policy strategy. CFB was analysed using a MMRM which included age (indicator variable of age ≥45 years), sex, history of transfusion (yes/no) prior to study treatment, visit, baseline Hb as fixed effects and the interaction between visit and baseline Hb levels. Error bars represent 95% CIs.
Abbreviations: b.i.d twice daily; Bas, Baseline; CFB, change from baseline; CI, confidence interval; CSR, clinical study report; FAS, full analysis set; Hb, haemoglobin; LNP023, iptacopan; MMRM, mixed model of repeated measures; RBC, red blood cell.

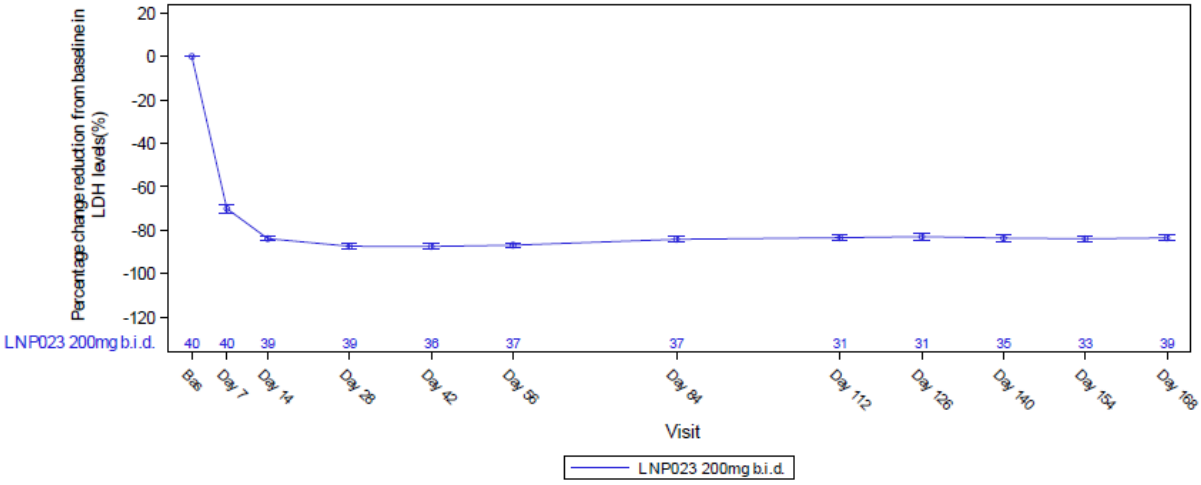
B.2.6.1.2.4 Change from baseline in LDH (U/L) levels

At baseline, mean (SD) LDH (a biomarker of IVH) was 1,698.8 (683.33) U/L.

Treatment with iptacopan resulted in an adjusted mean percent CFB in LDH levels, assessed as mean of visits between Day 126 and Day 168, of –83.55% (95% CI: –84.90%, –82.08%).

LDH decreased early, with the adjusted mean percent CFB in LDH –70.11% (95% CI: –72.11, –67.97) at Day 7, and greater than –83% (95% CI: –84.55, –86.37) at any visit after Day 7 in the core treatment period (Figure 6).

Figure 6: APPOINT-PNH: Least squares geometric means of percentage CFB in LDH levels (U/L) between baseline and Day 168 (FAS)



Source: Novartis, Data on file, APPOINT-PNH CSR, Figure 11.4 (89).
Intercurrent events are handled with treatment policy strategy. Baseline LDH was defined as the value on Day 1 (prior to starting treatment). If Day 1 value was not available, the mean of two screening/ LDH confirmatory values was used. If screening value was not available, the baseline LDH was defined as single confirmatory LDH value. Percentage CFB was analysed using a MMRM which included age (indicator variable of age ≥45 years), sex, history of transfusion (yes/no) prior to study treatment, visit, baseline LDH as fixed effects and visit*baseline LDH as interaction. The log transformation used refers to the natural log (base of e). Results were back-transformed and expressed as geometric means. Error bars represent 95% CI.
Abbreviations: b.i.d, twice daily; Bas, Baseline; CI, confidence interval; CFB, change from baseline; CSR, clinical study report; FAS, full analysis set; LDH, lactate dehydrogenase; LNP023, iptacopan; MMRM, mixed model of repeated measures.

B.2.6.1.2.5 Rates of clinical breakthrough haemolysis

In the core treatment period, none of the patients experienced clinical breakthrough haemolysis (BTH)[c]. The adjusted annualised rate of clinical BTH in patients treated with iptacopan was 0.00 (95% CI: 0.00, 0.17).

Including data from the extension treatment period up to the data cut-off (2nd Nov 2022; 7 patients had completed the extension period and 32 patients were receiving ongoing treatment in the extension period), the adjusted annualised BTH rate was 0.06 (95% CI: 0.00, 0.68) based on one patient experiencing clinical BTH in the extension period following a mild COVID-19 infection that was not suspected to be related to iptacopan.

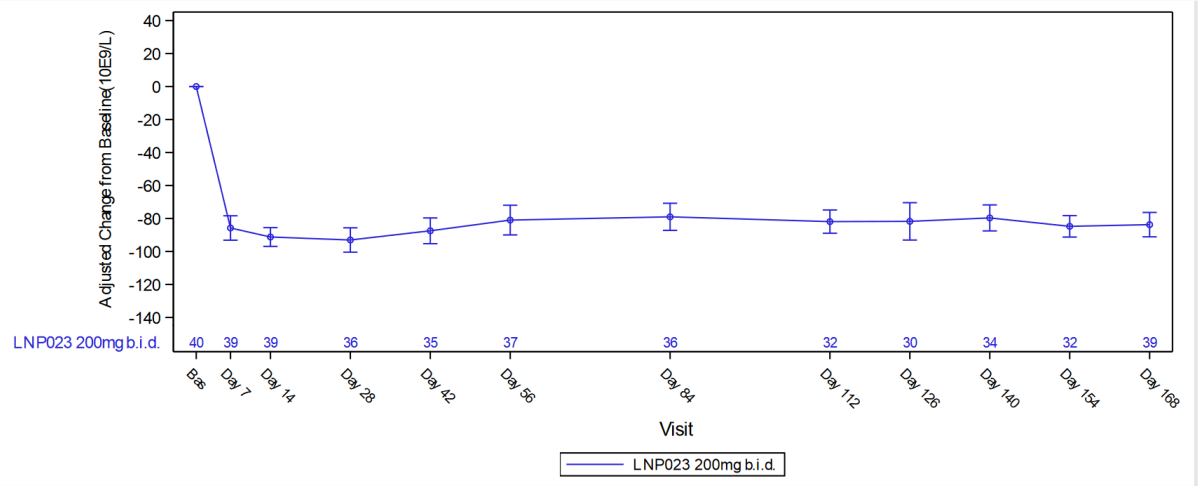
[c]Clinical BTH was defined as a decrease in Hb of ≥2 g/dL (compared to the latest assessment, or within 15 days) *and/or* presence of signs or symptoms (gross haemoglobinuria, painful crisis, dysphagia, or any other significant clinical PNH-related signs & symptoms), *and* LDH level >1.5 x ULN and increased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

B.2.6.1.2.6 Change from baseline in absolute reticulocyte counts (10^9/L)

Baseline mean (SD) absolute reticulocyte counts (a biomarker of extravascular haemolysis [EVH]) was 154.33 (63.666) x 10^9/L. The adjusted mean (95% CI) change from baseline in absolute reticulocyte counts as mean of visits between Day 126 and Day 168 was –82.48 x 10^9/L (–89.33, –75.62).

As illustrated in Figure 7, the reduction in absolute reticulocyte counts from baseline was rapid (Day 7) and sustained thereafter up to Day 168.

Figure 7: APPOINT-PNH: Least squares means of change from baseline in absolute reticulocyte counts (10^9/L) between baseline and Day 168 (FAS)



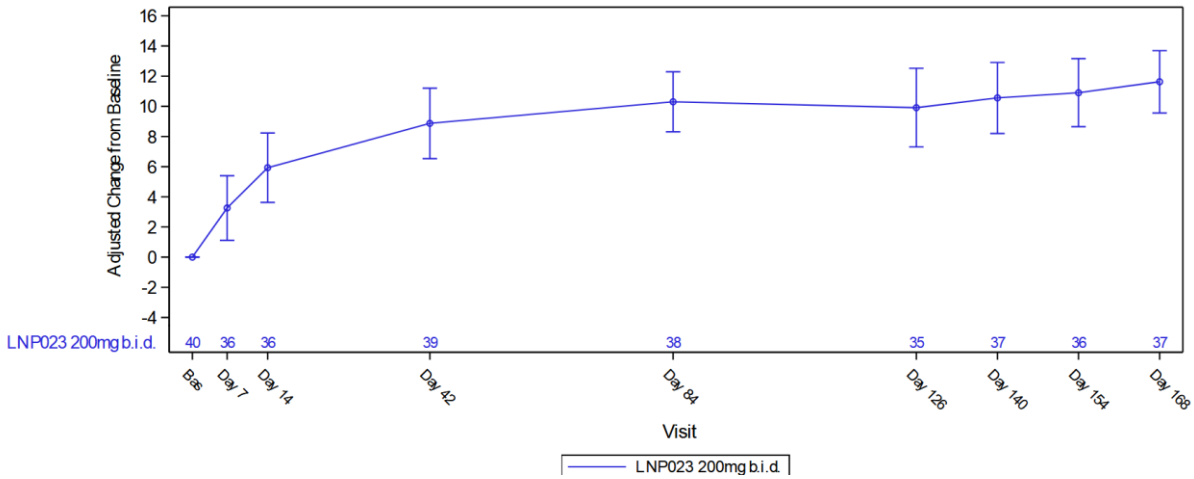
Source: Novartis, Data on file, APPOINT-PNH CSR, Figure 11.5 (89).
Intercurrent events were handled with treatment policy strategy. The baseline value of reticulocyte counts is defined to be the last result obtained at or prior to start of study treatment (Day 1).Change from baseline was analysed using a mixed model of repeated measures which includes age (indicator variable of age ≥ 45 years), sex, history of transfusion (yes/no) prior to study treatment, visit, baseline reticulocyte counts as fixed effects and visit*baseline reticulocyte counts as interaction.
Abbreviations: b.i.d, twice daily; CSR, clinical study report; FAS, full analysis set; LNP023, iptacopan.

B.2.6.1.2.7 Change from baseline in FACIT-Fatigue scores

All Functional Assessment of Chronic Illness Therapy (FACIT) scales are scored so that a high score is better. The mean FACIT-Fatigue score at baseline was 32.78 points (SD: 10.170). The adjusted mean CFB between Day 126 and Day 168 was +10.75 points (95% CI: 8.66, 12.84). At Day 168 the mean FACIT-Fatigue score reached 43.9 (SD: 6.24) points.

CFB in FACIT-Fatigue score was above +5 points at Day 14 of iptacopan treatment, above +10 points at Day 84 and thereafter remained largely stable up to Day 168 (Figure 8).

Figure 8: APPOINT-PNH: Least squares means of change from baseline in FACIT-Fatigue scores between baseline and Day 168 (FAS)



Source: Novartis, Data on file, APPOINT-PNH CSR, Figure 11.6 (89).
Intercurrent events are handled with treatment policy strategy. The baseline score was defined as the mean of first assessment prior to Day 1 and the Day 1 value. Change from baseline was analysed using a MMRM which included age (indicator variable of age ≥ 45 years), sex, history of transfusion (yes/no) prior to study treatment, visit, baseline FACIT-Fatigue score, visit as fixed effects and visit*baseline FACIT-Fatigue score as interaction terms. Error bars represent 95% confidence intervals
Abbreviations: b.i.d, twice daily; CSR, clinical study report; FACIT, Functional Assessment of Chronic Illness Therapy; FAS, full analysis set; LNP023, iptacopan; MMRM, mixed model of repeated measures.

B.2.6.1.2.8 Occurrences of MAVEs

In the core treatment period as well as in the extension treatment period until the cut-off date, none of the patients experienced a major adverse vascular event (MAVE).

B.2.6.1.3 *Exploratory endpoints*

B.2.6.1.3.1 Number and units of RBC transfusions

The summary of patients requiring RBC transfusions in the core treatment period is presented in Table 12. During the core treatment period (Day 1 to Day 168), 6/40 patients (15.0%) required transfusions at least once. Five patients (12.5%) received ≥1 transfusion prior to Day 14. One additional patient met the transfusion criteria before Day 14 but did not receive a transfusion. None of the 40 patients either received or met the protocol specified criteria for transfusion between Day 14 and Day 168.

Among the patients who were transfused prior to Day 14, the mean number of units of RBC transfused per patient was 1.7 (SD: 0.45); the median was 2.0 (range: 1, 2). Patients who met the criteria for transfusion had mean Hb levels of 6.4 g/dL (SD: 1.33) prior to transfusion. Signs/symptoms requiring transfusion included

severe or worsening of fatigue in 4/6 patients, and severe or worsening dyspnoea or shortness of breath, and light headedness each in one patient.

Table 12: APPOINT-PNH: pRBC transfusions between Day 1 and Day 168 (FAS)

Characteristic	Iptacopan 200 mg BD N=40
Number of patients meeting criteria for transfusions at least once, n (%)	6 (15.0)
Number of patients receiving transfusions at least once, n (%)	5 (12.5)
Number of transfusions per patient, n	5
Mean (SD)	1.0 (0.0)
Number of units of pRBC transfused per patient, n	5
Mean (SD)	1.7 (0.45)
Hb level as reported prior to pRBC transfusion (g/dL), n	6
Mean (SD)	6.4 (1.33)

Source: Novartis, Data on file, APPOINT-PNH CSR, Table 14.2.3.3.3 (89).
Abbreviations: BD, twice daily; CSR, clinical study report; FAS, full analysis set; PNH, paroxysmal nocturnal haemoglobinuria; pRBC, packed red blood cell; SD, standard deviation.

B.2.6.1.3.2 PNH-related signs and symptoms

Overall, 39 (97.5%) of patients had PNH signs and symptoms at baseline. At the end of the core treatment period, this had reduced to 14 patients (35.0%).

At baseline, the most frequently reported symptom was feeling weak or tired (70.0%). At Day 168, this decreased to 20.0% of patients. In addition, at baseline, 72.5% of patients had haemoglobinuria, while at Day 168, no patients had haemoglobinuria. Shortness of breath was reported for 30.0% of patients at baseline, decreased to 10.0% at Day 168.

B.2.6.1.3.3 Other exploratory endpoints

The results of other exploratory endpoints (including haematological parameters and patient-reported outcomes [PRO]) are provided in Appendix M.

B.2.6.2 APPLY-PNH

B.2.6.2.1 *Primary endpoints: Haematological response*

APPLY-PNH met its two primary endpoints (Table 13). Iptacopan was statistically significantly superior to C5 inhibitors with a treatment difference in marginal proportions of patients of:

1. 80.3% (95% CI: 71.3, 87.6) for the haematological responder endpoint defined as achieving a sustained increase in Hb levels from baseline of ≥2 g/dL in the absence of RBC transfusions (unadjusted two-sided p-value <0.0001)

2. 67.0% (95% CI: 56.3, 76.9) for the haematological responder endpoint defined as achieving sustained Hb levels of ≥12 g/dL in the absence of RBC transfusions (unadjusted two-sided p-value <0.0001).

Both endpoints were assessed between Day 126 and Day 168, in the absence of RBC transfusions between Day 14 and Day 168. Based on evaluable, non-missing observed data, 51/60 patients in the iptacopan group vs 0/35 patients in the C5 inhibitor group achieved a sustained increase in Hb levels ≥2 g/dL from baseline in the absence of RBC transfusions. The marginal proportion of patients with sustained increase in Hb levels from baseline of ≥2 g/dL was 82.3% (95% CI: 73.4, 90.2) in the iptacopan group and 2.0% (95% CI: 1.1, 4.1) in the C5 inhibitor group, respectively.

Of the patients with evaluable, non-missing data, 42/60 patients in the iptacopan group vs 0/35 patients in the C5 inhibitor group achieved sustained Hb levels of ≥12 g/dL in the absence of RBC transfusions. The marginal proportion of patients with sustained Hb levels of ≥12 g/dL was 68.8% (95% CI: 58.3, 78.9) in the iptacopan group and 1.8% (95% CI: 0.9, 4.0) in the C5 inhibitor group, respectively.

Subgroup analyses (including a subgroup analysis by C5 inhibitor [eculizumab vs ravulizumab]) were consistent with the primary analysis (Appendix E).

Table 13: APPLY-PNH: Responder analysis of Hb between Day 126 and Day 168 in the absence of RBC transfusions between Day 14 and Day 168 (FAS)

Responder criterion	n/M	Marginal proportion (95% CI)†	Diff. in marginal proportion (95% CI)†	Ratio of marginal proportion (95% CI)†	Unadjusted for multiplicity
					Two-sided p-value‡
Increase in Hb levels ≥2g/dL¶ from baseline without requiring RBC transfusions§					
Iptacopan 200 mg BD N=62	51/60	82.3 (73.4, 90.2)	80.3 (71.3, 87.6)	40.20 (20.73, 74.80)	<0.0001
C5 inhibitor N=35	0/35	2.0 (1.1, 4.1)	–	–	–
Hb levels ≥12 g/dL¶ without requiring RBC transfusions§					
Iptacopan 200 mg BD N=62	42/60	68.8 (58.3, 78.9)	67.0 (56.3, 76.9)	38.17 (16.83, 78.81)	<0.0001
C5 inhibitor N=35	0/35	1.8 (0.9, 4.0)	–	–	–

Source: Novartis, Data on file, APPLY-PNH CSR, Table 11.2 (93).
†Logistic regression model using Firth correction with common intercept and randomization strata, sex, indicator variable of age ≥45 years, indicator variable of baseline Hb ≥9 g/dL as factors. The 95% CI is computed using bootstrap. ‡Logistic regression model using Firth correction with randomisation strata, sex, indicator variable of age ≥45 years, indicator variable of baseline Hb ≥9 g/dL as factors. ¶Between Day 126 and 168 (≥ 3 out of 4 scheduled measurements); §Between Day 14 and Day 168. Requiring RBC transfusions refers to any patient receiving transfusions or meeting protocol defined criteria for transfusion.
Abbreviations: BD, twice daily; CI, confidence interval; FAS, full analysis set; Hb, haemoglobin; M, evaluable patients; n, the number of patients who responded based on non-missing data; RBC, red blood cell.

B.2.6.2.1.1 Sensitivity analyses

The missing Hb data were intermittent in nature and there were few missing data. Several sensitivity analyses of the two primary endpoints were performed with negligible impact on results, which confirms the robustness of the primary analysis (Table 14). An additional supportive analysis was performed considering patients who required rescue therapy as failures for the primary endpoints. However, no patient received rescue medications or had rescue procedures during the randomised treatment period, and therefore the results are identical to the primary analysis.

Table 14: APPLY-PNH: Summary of primary and sensitivity analyses for the primary endpoints – analysis of Hb between Day 126 and Day 168 in the absence of RBC transfusions between Day 14 and Day 168 (FAS)

Analysis description	Iptacopan 200 mg BD vs C5 inhibitor Difference between % achieving endpoint (95% CI)	Unadjusted two-sided p-value
Increase in Hb levels ≥2g/dL† from baseline without requiring RBC transfusions‡		
Primary analysis	80.3 (71.3, 87.6)	<0.0001
Tipping point analysis • Imputed Hb values were lowered by a value delta (2 g/dL in the iptacopan group)¶	76.8 (66.8, 85.4)	<0.0001
Analysis including local lab data • If central lab data missing, local laboratory data was included	80.3 (71.3, 87.6)	<0.0001
Cochran-Mantel-Haenszel • Hypothesis testing using a CMH test	NA	<0.0001
Post-hoc sensitivity analysis • With MI Hb between >7 and ≤9 g/dL were considered by default as not having signs and/or symptoms and therefore not meeting the criteria for transfusion	80.3 (71.3, 87.6)	<0.0001
Post-hoc sensitivity analysis • Determining transfusion avoidance without imputation	80.3 (71.3, 87.6)	<0.0001
Hb levels ≥12 g/dL† without requiring RBC transfusions‡		
Primary analysis	67.0 (56.3, 76.9)	<0.0001
Tipping point analysis • Imputed Hb values were lowered by a value delta (2 g/dL in the iptacopan group)¶	64.1 (52.8, 74.1)	<0.0001
Analysis including local labs • If central lab data missing, local laboratory data was included	67.0 (56.4, 76.8)	<0.0001
Cochran-Mantel-Haenszel • Hypothesis testing using a CMH test	NA	<0.0001
Post-hoc sensitivity analysis • With MI Hb between >7 and ≤9 g/dL were considered by default as not having signs and/or symptoms and therefore not meeting the criteria for transfusion	67.0 (56.3, 76.9)	<0.0001
Post-hoc sensitivity analysis • Determining transfusion avoidance without imputation	67.0 (56.3, 76.9)	<0.0001

Source: Novartis, Data on file, APPLY-PNH CSR, Table 11.3 (93).
†Between Day 126 and 168 (≥3 out of 4 scheduled measurements); ‡Between Day 14 and Day 168. Requiring RBC transfusion refers to any patient receiving transfusions or meeting protocol defined criteria for transfusion; ¶Missing Hb values in each treatment group were imputed as for the primary analysis but an adjustment for the iptacopan group was applied to the imputed values. Missing haemoglobin values were imputed and missing values in the iptacopan arm were decreased by a value delta. Delta ranged from 0 g/dL (primary analysis) to 2 g/dL (considered clinically meaningful change).
Abbreviations: CI, confidence interval; CMH, Cochran Mantel Haenszel; CSR, clinical study report; Hb, haemoglobin; FAS, full analysis set; MI, multiple imputation; NA, not applicable; RBC, red blood cell.

B.2.6.2.2 *Secondary endpoints*

B.2.6.2.2.1 Transfusion avoidance

Iptacopan was statistically significantly superior to C5 inhibitor therapy with a treatment difference in marginal proportions of patients avoiding transfusions (defined as not receiving transfusions and not meeting protocol defined criteria for transfusion[d]) between Day 14 and Day 168 of 70.3% (95% CI: 52.6, 84.9; unadjusted two-sided p<0.0001) (Table 15). In the iptacopan group the marginal proportion of patients avoiding transfusions between Day 14 and Day 168 was 96.4% (95% CI: 90.7, 100.0) vs 26.1% (95% CI: 12.4, 42.7) in the C5 inhibitor group. Overall, 60 of 62 patients in the iptacopan group and 14 of 35 patients in the C5 inhibitor group did not require transfusions between Day 14 and Day 168.

Table 15: APPLY-PNH: Transfusion avoidance between Day 14 and Day 168 (FAS)

	Iptacopan 200 mg BD N=62	C5 inhibitor N=35
n/M	60/62	14/35
Marginal proportion (95% CI)†	96.4 (90.7, 100.0)	26.1 (12.4, 42.7)
Difference in marginal proportion (95% CI)†	70.3 (52.6, 84.9)	–
Ratio of marginal proportion (95% CI)†	3.72 (2.24, 7.83)	–
Unadjusted for multiplicity OR (95% CI)‡	133.53 (19.78, 901.44)	–
Unadjusted for multiplicity p-value‡	<0.0001	–

Source: Novartis, Data on file, APPLY-PNH CSR, Table 11.4 (93).
†Logistic regression model with common intercept and randomisation strata, sex, indicator variable of age ≥45 years, indicator variable of baseline Hb ≥9 g/dL as factors. The 95% CI is computed using bootstrap. ‡Conditional logistic regression model with randomisation strata, sex, indicator variable of age ≥45 years, indicator variable of baseline Hb ≥9 g/dL as factors.
Abbreviations: BD, twice daily; CI, confidence interval; CSR, clinical study report; FAS, full analysis set; Hb, haemoglobin; M, The number of patients in the treatment group with response variable defined based on non-missing data (evaluable patients); n, the number of patients who did not receive transfusions nor meet protocol defined criteria between Day 14 and Day 168; OR, odds ratio.

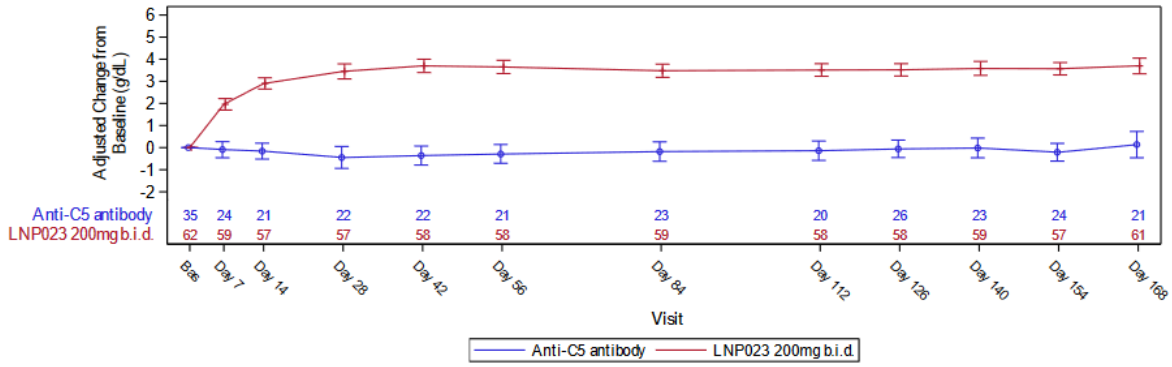
[d]Hb ≤9 g/dL with signs and/or symptoms of sufficient severity to warrant a transfusion, or Hb ≤7 g/dL, regardless of presence of clinical signs and/or symptoms.

B.2.6.2.2.2 Change from baseline in Hb levels (g/dL)

Baseline mean (SD) Hb was 8.9 (0.703) g/dL in the iptacopan group and 8.85 (0.898) g/dL in the C5 inhibitor group. Iptacopan was statistically significantly superior to C5 inhibitor therapy for CFB in Hb as mean of visits between Day 126 and Day 168, with an adjusted mean difference of +3.63 g/dL (95% CI 3.18, 4.08; unadjusted two-sided p<0.0001). In the iptacopan group the adjusted mean CFB in Hb was +3.59 g/dL (95% CI: 3.32, 3.86) vs −0.04 g/dL (95% CI: −0.42, 0.35) in the C5 inhibitor group. In order to factor out the effect of transfusions, if a patient had a transfusion during the randomised treatment period, the Hb values 30 days following the transfusion were excluded and Hb data were imputed.

The effect of iptacopan on Hb was early and sustained from Day 28, whereas Hb remained unchanged in the C5 inhibitor group from baseline throughout the randomised treatment period (Figure 9).

Figure 9: APPLY-PNH: Least squares means of CFB in Hb between baseline and Day 168 (FAS)



Source: Novartis, Data on file, APPLY-PNH CSR, Figure 11.5 (93).
CFB is analysed using a MMRM which includes randomisation strata, age indicator variable of age ≥45 years, sex, treatment, visit, baseline Hb, timepoint as fixed effects, treatment*timepoint and timepoint*baseline Hb as interaction terms. The correlations between visits within patients were modelled using an unstructured covariance matrix. Error bars represent 95% confidence intervals.
Abbreviations: Bas, baseline; b.i.d, twice daily; CFB, change from baseline; CSR, clinical study report; FAS, full analysis set; Hb, haemoglobin; LNP023, iptacopan; MMRM, mixed model of repeated measures.

B.2.6.2.2.3 Change from baseline in FACIT-Fatigue scores

All FACIT scales are scored so that a high score is better. Mean (SD) FACIT-Fatigue score at baseline was 34.7 points (9.82) in the iptacopan group and 30.8 points (11.45) in the C5 inhibitor group. Iptacopan was statistically significantly superior to C5 inhibitor therapy for CFB in FACIT-Fatigue score as mean of visits between Day 126 and Day 168 with an adjusted mean difference of +8.29 points (95% CI: 5.28, 11.29, unadjusted two-sided p<0.0001). The adjusted mean CFB was +8.59 points

(95% CI: 6.72, 10.47) in the iptacopan group vs +0.31 points (95% CI: −2.20, 2.81) in the C5 inhibitor group (Table 16).

Table 16: APPLY-PNH: CFB† in FACIT-Fatigue scores between Day 126 and Day 168 (FAS)

	Iptacopan 200 mg BD N=62	C5 inhibitor N=35
n	62	31
Adjusted mean (95%CI)	8.59 (6.72, 10.47)	0.31 (–2.20, 2.81)
Adjusted mean difference (95% CI)	8.29 (5.28, 11.29)	–
Two-sided p-value	<0.001	–

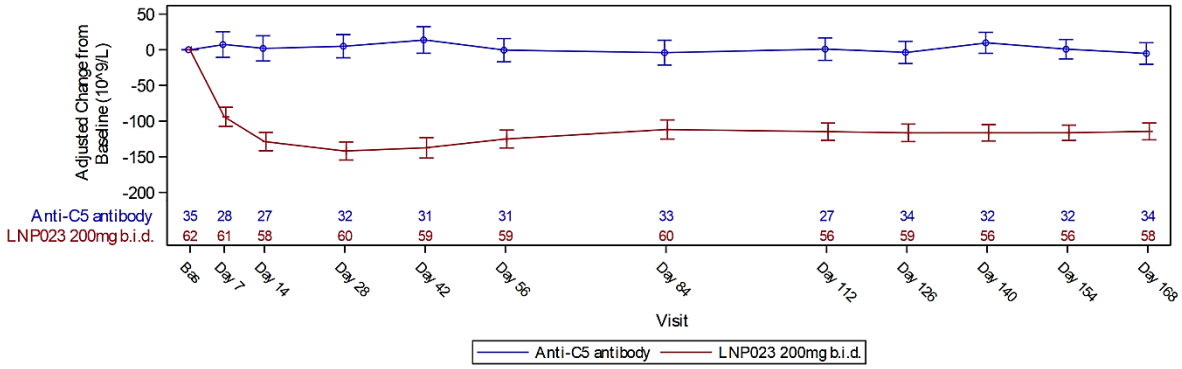
Source: Novartis, Data on file, APPLY-PNH CSR, Table 11.9 (93).
†Change from baseline was analysed using a mixed model of repeated measures which included randomization strata, age indicator variable of age ≥45 years, sex, treatment, visit, baseline FACIT-Fatigue score, timepoint as fixed effects, treatment*timepoint and timepoint*baseline FACIT-Fatigue score as interaction terms. The correlations between visits within patients were modelled using an unstructured covariance matrix.
Abbreviations: BD, twice daily; CFB, change from baseline; CI, confidence interval; CSR, clinical study report; FACIT, Functional Assessment of Chronic Illness Therapy; FAS, full analysis set; n, number of patients with values non-missing / not imputed as per the intercurrent event handling strategy.

B.2.6.2.2.4 Change from baseline in absolute reticulocyte counts (10^9/L)

Baseline mean (SD) absolute reticulocyte counts (a biomarker of EVH) was 193.22 (83.637) x 10^9/L in the iptacopan group and 190.59 (80.922) x 10^9/L in the C5 inhibitor group. Iptacopan was statistically significantly superior to C5 inhibitor therapy for CFB in absolute reticulocyte counts as mean of visits between Day 126 and Day 168, with an adjusted mean difference of –116.26 x 10^9/L (95% CI: –132.17, –100.36; unadjusted two-sided p<0.0001). The adjusted mean CFB in absolute reticulocyte counts was –115.89 x 10^9/L (95% CI: –126.49, –105.30) in the iptacopan group vs 0.37 x 10^9/L (95% CI: –13.03, 13.77) in the C5 inhibitor group.

As illustrated in Figure 10, the effect of iptacopan on absolute reticulocyte counts was seen as early as Day 7, whereas there was almost no change from baseline in the C5 inhibitor group throughout the randomised treatment period.

Figure 10: APPLY-PNH: Least squares means of CFB† in absolute reticulocyte counts (10^9/L) between baseline and Day 168 (FAS)



Source: Novartis, Data on file, APPLY-PNH CSR, Figure 11.7 (93).
†Change from baseline was analysed using a mixed model of repeated measures which included randomisation strata, age indicator variable of age >= 45 years, sex, treatment, visit, baseline FACIT-Fatigue score, timepoint as fixed effects, treatment*timepoint and timepoint*baseline FACIT-Fatigue score as interaction terms. The correlations between visits within patients were modelled using an unstructured covariance matrix.
Abbreviations: Bas, Baseline; b.i.d, twice daily; CFB, change from baseline; CSR, clinical study report; FAS, full analysis set; LNP023, iptacopan.

B.2.6.2.2.5 Change from baseline in LDH levels (U/L)

Baseline mean (SD) LDH (a biomarker of IVH) was 269.1 (70.14) U/L in the iptacopan group and 272.7 (84.8) U/L in the C5 inhibitor group. At baseline, very few patients had significant residual IVH, with four (6.5%) patients in the iptacopan group and three (8.6%) patients in the C5 inhibitor group having LDH >1.5 x ULN.

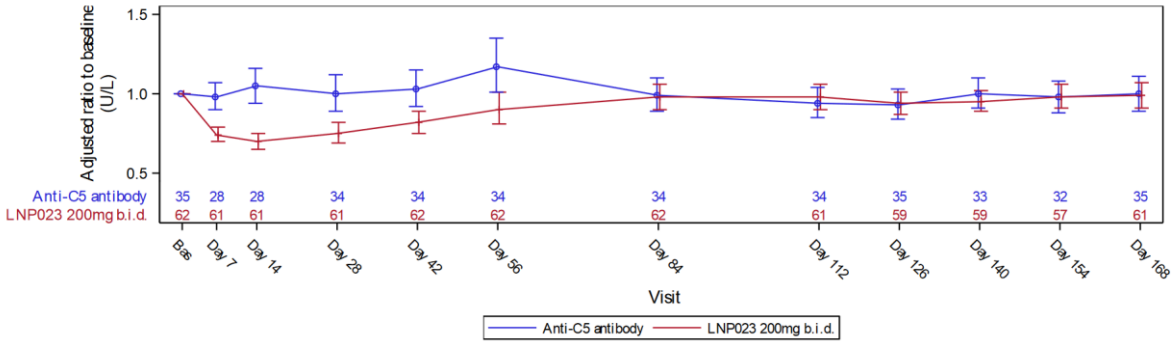
Iptacopan was not statistically significantly superior to C5 inhibitor therapy for percent reduction in LDH based on the average of the log transformed ratio to baseline in each treatment group estimated between Day 126 and Day 168 (Figure 11). The adjusted geometric mean ratio in LDH in the iptacopan group relative to the C5 inhibitor group was 0.99 (95% CI: 0.89, 1.10; unadjusted two-sided p=0.8345), demonstrating a minimal CFB in either group (Table 17).

Table 17: APPLY-PNH: Log-transformed LDH (U/L) ratio to baseline (assessed between Day 126 and Day 168)† (FAS)

	Iptacopan 200 mg BD N=62	C5 inhibitor N=35
n	62	35
Geometric adjusted mean (95%CI)	0.96 (0.90, 1.03)	0.98 (0.89, 1.07)
Geometric mean ratio (95% CI)	0.99 (0.89, 1.10)	–
% Reduction (95% CI)	1.15 (–10.18, 11.32)	–
Two-sided p-value	0.8345	–

Source: Novartis, Data on file, APPLY-PNH CSR, Table 11.13 (93).
†Log transformed ratio to baseline is analysed using a mixed model of repeated measures which was stratified by randomisation strata, and includes age indicator variable of age >=45 years, sex, treatment, visit, log-transformed baseline LDH level, timepoint as fixed effects, treatment*timepoint and timepoint*log- transformed baseline LDH level as interaction terms. The correlations between visits within patients were modelled using an unstructured covariance matrix. The log transformation used refers to the natural log (base of e). Results are back-transformed and expressed as geometric means.
Abbreviations: BD, twice daily; CI, confidence interval; CSR, clinical study report; FAS, full analysis set; LDH, lactate dehydrogenase.

Figure 11: APPLY-PNH: Least squares geometric means of LDH ratio to baseline – between baseline and Day 168† (FAS)



Source: Novartis, Data on file, APPLY-PNH CSR, Figure 11.8(93).
†Log transformed ratio to baseline is analysed using a mixed model of repeated measures which was stratified by randomisation strata, and includes age indicator variable of age ≥45 years, sex, treatment, visit, log-transformed baseline LDH level, timepoint as fixed effects, treatment*timepoint and timepoint*log- transformed baseline LDH level as interaction terms. The correlations between visits within patients were modelled using an unstructured covariance matrix. The log transformation used refers to the natural log (base of e). Results are back-transformed and expressed as geometric means.
Abbreviations: Bas, Baseline; b.i.d, twice daily; CSR, clinical study report; FAS, full analysis set; LDH, lactate dehydrogenase; LNP023, iptacopan.

B.2.6.2.2.6 Rate of clinical breakthrough haemolysis

Treatment with iptacopan was statistically significantly superior to C5 inhibitor therapy for the annualised adjusted rate of clinical BTH[e] with a rate ratio of 0.10 (95% CI: 0.02, 0.61; unadjusted two-sided p=0.0118). The adjusted annualised rate

[e] Clinical BTH was 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.

of clinical BTH was 0.07 (95% CI: 0.02, 0.31) in the iptacopan group vs 0.67 (95% CI: 0.26, 1.72) in the C5 inhibitor group (Table 18). Two clinical BTH events were reported in 2/62 patients (3.2 %) in the iptacopan group vs 11 clinical BTH events in 6/35 patients (17.1 %) in the C5 inhibitor group.

Table 18: APPLY-PNH: Number (%) of patients with clinical BTH events by treatment between baseline and Day 168† (FAS)

	Iptacopan 200 mg BD N=62	C5 inhibitor N=35
Number of patients with ≥1 event‡, n (%)	2 (3.2)	6 (17.1)
Adjusted annual BTH rate (95% CI)	0.07 (0.02, 0.31)	0.67 (0.26, 1.72)
Rate difference (95% CI)	–0.60 (–1.24, 0.04)	–
Rate ratio (95% CI)	0.10 (0.02, 0.61)	–
p-value	0.01183	–
Hb levels decrease ≥2 g/dL (vs latest assessment, or within 15 days), n (%)	2 (3.2)	4 (11.4)
LDH levels >1.5-times ULN and increased as compared with the last 2 assessments	2 (3.2)	6 (17.1)
Number of patients with ≥1 sign or symptom	1 (1.6)	6 (17.1)
Dysphagia	0	4 (11.4)
Fatigue	1 (1.6)	5 (14.3)
Painful crisis	0	3 (8.6)
Gross haemoglobinuria	0	3 (8.6)
Other signs or symptoms	0	4 (11.4)

Source: Novartis, Data on file, APPLY-PNH CSR, Table 11.15 (93).
†Adjusted annual rates of clinical Breakthrough Haemolysis events are from negative binomial model. The model included randomisation strata (prior anti-C5 treatment, transfusion history), sex, age (indicator of age ≥45 years), indicator variable of baseline Hb ≥9 g/dL as factors, and log (Day 1 till minimum (end of study, end of randomised treatment period) in years) as offset. ‡A patient with multiple occurrences of an event under one treatment is counted only once for that treatment.
Abbreviations: BD, twice daily; BTH, breakthrough haemolysis; CI, confidence interval; CSR, clinical study report; FAS, full analysis set; Hb, haemoglobin; LDH, lactate dehydrogenase; ULN, upper limit of normal.

B.2.6.2.2.7 Occurrences of MAVEs

Between Day 1 and Day 168, one patient in the iptacopan group had a MAVE (transient ischemic attack), translating into an adjusted annualised rate of 0.03% (95% CI: 0.00, 0.25). The rate ratio was not estimable due to the absence of any event in the C5 inhibitor group; the rate difference was 0.03 (95% CI: –0.03, 0.10; unadjusted two-sided p=0.31731).

B.2.6.2.3 *Exploratory endpoints*

B.2.6.2.3.1 Number and units of RBC transfusions

The summary of patients requiring RBC transfusions in the randomised treatment period is presented in Table 19.

Between Day 1 and Day 168, 8/62 patients (12.9%) in the iptacopan group and 21/35 patients (60%) in the C5 inhibitor group required transfusions at least once.

Five patients (8.1%) in the iptacopan group and 19 (54.3%) in the C5 inhibitor group received ≥1 transfusion. Among patients who received transfusions, the mean number of transfusions per patient was 1.4 (SD: 0.89) in the iptacopan group and 4.9 (SD: 3.97) in the C5 inhibitor group.

Among the patients who were transfused, the mean number of units of RBC transfused per patient was 2.2 (SD: 1.64) in the iptacopan group and 8.2 (SD: 6.73) in the C5 inhibitor group; the median was 2.0 units (range: 1, 5) in the iptacopan group and 7.0 units (range: 1, 28) in the C5 inhibitor group.

Table 19: APPLY-PNH: pRBC transfusions between Day 1 and Day 168 (FAS)

Characteristic	Iptacopan 200 mg BD N=62	C5 inhibitor N=35
Number of patients meeting criteria for transfusions ≥ once, n (%)	8 (12.9)	21 (60.0)
Number of patients receiving transfusions ≥ once, n (%)	5 (8.1)	19 (54.3)
Number of transfusions per patient, n	5	19
Mean (SD)	1.4 (0.89)	4.9 (3.97)
Number of units of pRBC transfused per patient, n	5	19
Mean (SD)	2.2 (1.64)	8.2 (6.73)
Hb level as reported prior to pRBC transfusion† (g/dL), n	10	101
Mean (SD)	6.96 (0.969)	7.37 (1.018)

Source: Novartis, Data on file, APPLY-PNH CSR, Table 14.2.3.3.3
†Based on recalculated Hb value. Total number of meeting transfusion criteria. Patient is counted multiple times if transfusion criteria was met multiple times.
Abbreviations: BD, twice daily; CSR, clinical study report; FAS, full analysis set; Hb, haemoglobin; PNH, paroxysmal nocturnal haemoglobinuria; pRBC, packed red blood cell; SD, standard deviation.

B.2.6.2.3.2 PNH-related signs and symptoms

At baseline, 39/62 (62.9%) patients in the iptacopan group and 24/35 (68.6%) patients in the C5 inhibitor group reported PNH signs and symptoms. At the end of

the randomised treatment period (Day 168), 15/62 (24.2%) in the iptacopan group and 20/35 (57.1%) in C5 inhibitor group reported ≥1 PNH related sign or symptom.

Feeling weak or tired was the most frequently reported symptom, affecting 51.6% of patients in the iptacopan group vs 65.7% of patients in the C5 inhibitor group at baseline. At Day 168 this changed to 19.4% of patients in the iptacopan group vs 54.2% of patients in C5 inhibitor group.

Shortness of breath was reported for 29% of patients in the iptacopan group vs 34.3% of patients in the C5 inhibitor group at baseline. This changed at Day 168 to 6.5% of patients in the iptacopan group and 28.5% of patients in the C5 inhibitor group.

Haemoglobinuria was reported for 16.1% of patients in the iptacopan group vs 11.5% of patients in the C5 inhibitor group at baseline. At Day 168, this changed to 0% in the iptacopan group vs 14.3% in the C5 inhibitor group.

B.2.6.2.4 *Other exploratory endpoints*

The results of other exploratory endpoints (including haematological parameters and PROs) are provided in Appendix O.

B.2.7 Subgroup analysis

This submission covers the full population of the planned marketing authorisation. Pre-specified subgroup analyses of the primary endpoints of APPOINT-PNH and APPLY-PNH are presented in Appendix E.

B.2.8 Meta-analysis

Meta-analyses were not considered appropriate as the two trials included in the submission contain two different populations, complement inhibitor-naïve patients (APPOINT-PNH) and complement inhibitor-experienced patients with residual anaemia (APPLY-PNH).

B.2.9 Indirect and mixed treatment comparisons

Indirect treatment comparisons (ITCs) for the complement inhibitor-naïve population, where the efficacy of iptacopan is informed by a single-arm trial (APPOINT-PNH), were conducted vs C5 inhibitors based on published clinical trials. In addition, real-world evidence was used for a separate ITC in this population. In the complement inhibitor-experienced population, direct evidence of iptacopan vs C5 inhibitors is available from the APPLY-PNH study; an ITC was conducted against pegcetacoplan based on published clinical trial data. A summary of the ITC methods and key results is presented in the following sections, with Appendix D providing full details of the methodology and detailed results.

Of note, results of the ITCs are not utilised in the economic model, since the definition of model health states required the consideration of Hb and transfusion outcomes in combination. Section B.3.3.2 describes how estimates of treatment efficacy in the form of transition probabilities were derived for the economic model.

B.2.9.1 Complement inhibitor-naïve population: ITC using clinical trial data

B.2.9.1.1 *Comparator studies*

Among the clinical trials identified in the SLR (Section B.2.1), Study 301 (47) and TRIUMPH (83) were considered potentially suitable for an unanchored ITC against the single-arm APPOINT-PNH study in the complement inhibitor-naïve population. Other studies identified in the SLR included interventions which are not relevant comparators in the population of interest (87, 90, 91), investigated non-licensed dosage regimens (86, 88), or differed substantially from APPOINT-PNH in terms of analysis timepoint (12, 52, or 102 weeks, vs APPOINT-PNH 24 weeks) (81, 82, 84, 85). All studies identified by the SLR are summarised in Table 12 in Appendix D.

Study 301 (47), a recent pivotal trial for ravulizumab in PNH, was a randomised controlled trial (RCT) in complement inhibitor-naïve patients that compared ravulizumab with eculizumab. Based on discussion with UK clinical experts (101), this study was selected as the most appropriate comparator study for the ITC since the study population most closely matched APPOINT-PNH and best reflects complement inhibitor-naïve patients seen in UK clinical practice. TRIUMPH (83), an

older placebo-controlled eculizumab study, only included patients who had received ≥4 transfusions during the previous 12 months, which is not representative of the current UK target population (101). Study 301 was also preferred over TRIUMPH due to its inclusion of ravulizumab, as the most relevant comparator, and the larger sample size (101). A comparison of APPOINT-PNH, Study 301, and TRIUMPH study designs as well as results from the ITC of APPOINT-PNH vs TRIUMPH are provided in Appendix D.

B.2.9.1.2 *ITC methods summary*

Given that APPOINT-PNH was a single-arm trial, a population-adjusted unanchored ITC was conducted, leveraging individual patient data (IPD) for iptacopan from APPOINT-PNH and published summary-level data for ravulizumab and eculizumab from Study 301 (47). The analysis followed the general approach outlined by the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18 for population-adjustment (102). No patients were excluded from the APPOINT-PNH dataset due to a high degree of overlap in study eligibility criteria; the difference in Hb inclusion criteria could not be addressed since Study 301 included a broader population. IPD from APPOINT-PNH were reweighted using entropy balancing (103) to adjust for differences between the APPOINT-PNH and Study 301 populations. The adjustment factors (age, sex, % transfusion free in prior 12 months, baseline LDH, history of MAVE) were validated by UK clinicians (101). Baseline Hb could not be included in the reweighting since the analysis did not converge.

The reweighted APPOINT-PNH outcomes were then compared with the Study 301 outcomes. Prior to the analysis, the APPOINT-PNH endpoint data were adjusted to align with Study 301 trial definitions where needed and feasible. Notably, for the transfusion avoidance endpoint this involved inclusion of transfusions from Day 1, rather than from Day 14 onwards as in the APPOINT-PNH study definition. ITCs were conducted for key endpoints included in both trials; this excluded the haematological responder endpoints from APPOINT-PNH as well as CFB in Hb, which were not reported for Study 301. Full details of endpoint alignment are given in Appendix D.

B.2.9.1.3 *Results*

B.2.9.1.3.1 Comparison of pre-treatment characteristics before and after weighting

A comparison of APPOINT-PNH patient characteristics before and after reweighting to balance baseline characteristics with the Study 301 population is presented in Table 20. Reweighting reduced the effective sample size (ESS) from 40 to 31 patients. Of note is the difference in baseline Hb between trials (unweighted standardised mean difference [SMD]: 0.983; weighted SMD: 1.127); adjusting for the difference was not possible as the analysis failed to converge.

Table 20: Comparison of baseline characteristics between Study 301 and APPOINT-PNH, before and after weighting

Baseline Characteristics	Study 301	APPOINT-PNH Unweighted		APPOINT-PNH Weighted†	
	N = 246	N=40	SMDs	ESS=31	SMDs
Age, years: mean (SD)	45.5 (15.7)	42.1 (15.8)	0.216	45.5 (15.7)	0.000
LDH, U/L: mean (SD)	1,606.4 (752.7)	1,698.8 (683.3)	0.129	1,606.4 (684.7)	0.000
Transfusion free, 12 months prior: n (%)	44 (17.9%)	13 (32.5%)	0.342	17.8%	0.000
History of MAVE, n (%)	42 (17.1%)	5 (12.5%)	0.129	17.1%	0.001
Sex, male: n (%)	134 (54.5%)	23 (57.5%)	0.061	54.5%	0.001
Weight, kg: mean (SD)	68.7 (15.2)	70.1 (12.7)	0.100	68.6 (12.3)	0.005
Height, cm: mean (SD)	166.2 (9.8)	168.2 (9.1)	0.208	167.1 (9.0)	0.100
Race, white: n (%)	94 (38.2%)	12 (30%)	0.174	28.4%	0.210
Hb, g/dL: mean (SD)	9.5 (1.6)	8.15 (1.09)	0.983	7.9 (1.2)	1.127
Baseline FACIT-Fatigue score: mean (SD)	NR	32.8 (10.2)	NA	32.3 (10.0)	NA
Reticulocyte count: mean (SD), per mm^3	NR	154,325 (63,666)	NA	143,231 (609,11)	NA

Green = SMD ≤ 0.1 (small difference); Yellow = 0.1 > SMD ≤ 0.2 (moderate difference); Red = SMD > 0.2 (substantial difference). These conservative thresholds were informed by Austin 2009 and 2011 (104, 105).
†Reweights APPOINT-PNH data to balance with Study 301 on age (means and SD), proportion of males, LDH level at baseline (mean and SD), transfusion free 12 months prior, and history of MAVE;
Abbreviations: ESS, effective sample size; FACIT, Functional Assessment of Chronic Illness Therapy; Hb, haemoglobin; LDH, lactate dehydrogenase; MAVE, major adverse vascular event; NA, not applicable; NR, not reported; SD, standard deviation; SMD, standardised mean difference.

B.2.9.1.3.2 Overview of ITC results

Table 21 presents a summary of the ITC results of APPOINT-PNH vs Study 301. Iptacopan-treated patients had a significantly greater reduction in LDH from baseline compared with ravulizumab or eculizumab (mean difference <0). Results for the transfusion avoidance and CFB in FACIT-Fatigue outcomes were not statistically significant, while the point estimates favoured iptacopan over ravulizumab or eculizumab for both outcomes.

Table 21: Overview of results for iptacopan vs ravulizumab or eculizumab in the complement inhibitor-naïve population: ITC using APPOINT-PNH vs Study 301

	Transfusion avoidance	% CFB in LDH	CFB in FACIT-Fatigue score
Iptacopan (ESS=31†)	78.6%	% CFB = –85.08 (95% CI –87.84, –82.32)	CFB =10.85 (95% CI 7.23, 14.47)
Ravulizumab (N=125)	73.5%	% CFB = –76.84 (95% CI –79.96, –73.73)	CFB = 7.07 (95% CI 5.55, 8.60)
Eculizumab (N =121)	66.1%	% CFB = –76.02 (95% CI –79.20, –72.83)	CFB = 6.40 (95% CI 4.85, 7.96)
Iptacopan (ESS=31†) vs ravulizumab (N=125)	OR = 1.32 (95% CI 0.47, 3.73) p=0.6011	**MD = –8.24 (95% CI –13.28, –3.20) p=0.0013**	MD = 3.78 (95% CI –1.38, 8.94), p=0.1514
Iptacopan (ESS=31†) vs eculizumab (N =121)	OR = 1.88 (95% CI 0.67, 5.28) p=0.2281	**MD = –9.06 (95% CI –14.14, –3.98) p=0.0005**	MD = 4.45 (95% CI –0.72, 9.62), p=0.0918

OR >1 implies higher odds of remaining transfusion-free for iptacopan vs ravulizumab or eculizumab; MD >0 implies higher LDH for iptacopan vs ravulizumab or eculizumab; MD >0 implies higher FACIT Fatigue score for iptacopan vs ravulizumab or eculizumab; **Bold** values indicate statistical significance and corresponds to a two-tailed p-value <0.05.
† APPOINT-PNH results using Study 301 endpoint definitions and population adjusted to balance with Study 301 on age (means and SD), proportion of males, transfusion free 12 months prior, baseline LDH (mean and SD), and history of MAVE.
Abbreviations: CFB, change from baseline; CI, confidence interval; ESS, effective sample size; FACIT, Functional Assessment of Chronic Illness Therapy; ITC, indirect treatment comparison; LDH, lactate dehydrogenase; MAVE, major adverse vascular event; MD, mean difference (in CFB); OR, odds ratio; SD, standard deviation.

B.2.9.1.3.3 Uncertainties of ITC of APPOINT-PNH vs Study 301

Due to the single-arm design of APPOINT-PNH, only an unanchored ITC was feasible. In addition, study inclusion criteria differed with regards to presence of anaemia. While all patients in APPOINT-PNH were required to have Hb <10 g/dL at baseline, Study 301 only required patients to have at least one PNH-related symptom at study entry. Anaemia (Hb <10 g/dL) was only one of the eligible symptoms, and therefore non-anaemic patients could also be included in Study 301. This difference is reflected in mean (SD) Hb at baseline of 9.5 (1.6) g/dL in Study 301 vs 8.15 (1.09) g/dL in APPOINT-PNH before population adjustments; weighting the APPOINT-PNH population to align with Study 301 on other characteristics further increased the difference (APPOINT-PNH 7.9 [1.2] g/dL after weighting). Due to non-convergence, the difference in baseline Hb could not be adjusted for, and results of associated outcomes should be interpreted with caution. Since Study 301 did not report Hb endpoints, no ITCs could be conducted on Hb outcomes.

B.2.9.2 Complement inhibitor-naïve population: ITC using real world evidence (APPEX)

B.2.9.2.1 *APPEX: Real-world evidence study design*

The APPEX study (106) was a research collaboration between Novartis and two hospital centres, one in the UK (PNH centre in Leeds) and one in France, that used retrospective, non-interventional secondary de-identified IPD from a real-world setting with longitudinal measurements of haematologic outcomes. Data collection occurred between 2007 and 2022; laboratory data were collected during routine visits and thus reflect real-world clinical practice (106). The objective of the APPEX study was to evaluate haematological response occurring after initiation of C5 inhibitor treatment in previously complement inhibitor-naïve adult patients with PNH with anaemia (baseline Hb <10 g/dL). The study protocol was registered on ClinicalTrials.gov under NCT05842486 (107).

Since the APPEX study was designed to contextualise findings of the iptacopan single-arm APPOINT-PNH trial in a target trial framework, the primary and secondary endpoints as well as patient eligibility criteria were aligned with those of the APPOINT-PNH trial (89, 106). The dataset was comprised of all patients from the French centre who met the eligibility criteria and had baseline and post-baseline measurements, and a cohort of UK patients randomly selected from those meeting the eligibility criteria (106) (full APPEX inclusion/exclusion criteria are provided in Appendix D).

The APPEX study was assessed for risk of bias as per the NICE real-world evidence (RWE) framework (108). Completed tables are provided in Appendix D.

B.2.9.2.2 *ITC methods summary*

IPD were available from both the APPOINT-PNH trial and the APPEX real-world cohort. The analysis approach was a population-adjusted comparison of iptacopan vs C5 inhibitors using data for iptacopan from APPOINT-PNH and data for C5 inhibitors from the APPEX real-world cohort (106).

Observed outcomes from patients in APPEX were weighted using a propensity score model to balance baseline confounding variables and propensity scores between the

APPEX cohort and the APPOINT-PNH trial cohort. Confounding variables included in the propensity score based on expert input were transfusion needs (implemented as total RBC units transfused during the six months prior to index date), baseline Hb, baseline reticulocyte count, ongoing aplastic anaemia/bone marrow disease, and history of MAVE, as well as age and sex as linear terms. A doubly robust augmented inverse probability weighted (AIPW) estimator used both the inverse probability weights derived from the propensity score model and the outcome model predictions from regression modelling response to C5 inhibitors in APPEX using the APPOINT-PNH patients' individual covariate values (106).

Assessment windows for the analysis were implemented to maximise the data available from APPEX, enabling contribution from most patients in the real-world dataset, whilst remaining close to APPOINT-PNH endpoints. APPEX Hb assessments between 100 and 200 days, transfusion occurrence between 15 and 200 days, and LDH measurements between 15 and 200 days were included in the analysis. For Hb, since the assessment window still excluded six patients, sensitivity analyses were conducted with two alternative assessment windows of 40–200 days and 100–230 days (106).

Further details regarding APPEX study design, data, and analysis methods reported as per the NICE RWE framework (108) are provided in Appendix D.

B.2.9.2.3 *Results*

B.2.9.2.3.1 Comparison of pre-treatment characteristics before and after weighting

The total number of patients included in the retrospective APPEX real-world cohort was 92. Of these, 85 patients were included in the analysis (one patient was considered a screening failure, one patient had no documented data on occurrence of transfusions, and five patients did not have baseline reticulocyte measurements). Of patients included in the analysis, 47 patients were from France and 38 were from the UK. In total, 84 patients in the APPEX cohort had been treated with eculizumab, and 1 with ravulizumab (106).

A comparison of APPEX patient characteristics before and after reweighting to balance baseline characteristics with the APPOINT-PNH population is presented in

Table 22. After reweighting, patient characteristics were generally well balanced, with most SMDs <±0.10 (106).

Table 22: Comparison of baseline characteristics between APPEX and APPOINT-PNH, before and after weighting

Characteristic Categories/statistics	Before weighting			After weighting	
	APPOINT-PNH trial cohort (N=40)	APPEX real-world cohort (N=85)	SMD	APPEX real-world cohort (N=41)	SMD
Age, years: mean (SD)	42.1 (15.85)	47.8 (19.07)	−0.362	42.5 (17.47)	−0.023
Sex, male: n (%)	23 (57.5)	34 (40.0)	0.354	22 (53.8)	0.074
Baseline Hb, g/dL: mean (SD)	8.2 (1.09)	8.4 (1.27)	−0.200	8.1 (1.49)	0.035
Number of transfusions in the 24 weeks prior to index date: mean (SD)	2.2 (2.25)	1.9 (2.93)	0.114	2.5 (3.65)	–0.148
Number of units of RBC transfused in the 24 weeks prior to index date: mean (SD)	3.98 (4.08)	3.24 (4.04)	0.181	4.01 (4.66)	–0.009
Transfusions in the 24 weeks prior to index date, yes: n (%)	28 (70.0)	49 (57.6)	0.270	25 (61.1)	0.195
Number of transfusions in the 24 weeks prior to index date among patients who had a transfusion: mean (SD)	3.1 (2.09)	3.3 (3.21)	–0.103	4.1 (3.93)	–0.476
Number of transfusions in the 24 weeks prior to index date among patients who had a transfusion: n (%)					
<2	7 (25.0)	16 (32.7)	–0.177	7 (26.1)	–0.025
≥2	21 (75.0)	33 (67.3)	0.177	18 (73.9)	0.025
Number of units of RBC transfused in the 24 weeks prior to index date among patients who had a transfusion: mean (SD)	5.7 (3.74)	5.6 (3.86)	0.018	6.6 (4.33)	–0.239
Absolute reticulocyte counts, $\times 10^9$/litre: mean (SD)	154.3 (63.67)	149.3 (83.73)	0.079	155.3 (91.28)	–0.015
History of MAVE, yes: n (%)	5 (12.5)	15 (17.6)	–0.156	5 (12.9)	0.013
Ongoing aplastic anaemia, yes: n (%)	16 (40.0)	18 (21.2)	0.384	15 (36.7)	0.068

Abbreviations: Hb, haemoglobin; MAVE, major adverse vascular event; RBC, red blood cells; SD, standard deviation; SMD, standardised mean difference, defined as the difference in mean or proportion estimates between the APPOINT-PNH trial and APPEX real-world cohorts (trial - real-world) divided by the SD in the trial cohort.

B.2.9.2.3.2 Overview of ITC results

AIPW estimates were derived for APPOINT-PNH study patients to estimate what would have happened to APPOINT-PNH patients had they been treated with C5 inhibitors instead of iptacopan. These results were then compared with the iptacopan results from APPOINT-PNH. Results show greater improvements across outcomes with iptacopan than with C5 inhibitors (Table 23). The AIPW estimates and sensitivity analyses are provided in Appendix D.

Table 23: Overview of results for iptacopan vs C5 inhibitors in the complement inhibitor-naïve population: ITC using APPOINT-PNH vs APPEX

Endpoint	Estimate	Iptacopan vs C5 inhibitors, average treatment effect (95% CI)§
≥2 g/dL increase in Hb from baseline† in the absence of RBC transfusions‡	Difference in proportions (%)	68.4 (41.0, 95.8)
Hb levels ≥12 g/dL† in the absence of RBC transfusions‡	Difference in proportions (%)	53.5 (31.6, 75.5)
Transfusion avoidance‡	Difference in proportions (%)	38.9 (15.1, 62.6)
% CFB in LDH (U/L)‡	Ratio of % levels to baseline	0.52 (0.40, 0.67)
CFB in reticulocyte count (x10⁹/L)¶	Difference in CFB	–75.8 (–107.2, –44.4)

†Endpoint for C5 inhibitors included measurements between Day 100 and Day 200 (mean of all available measurements); ‡Endpoint for C5 inhibitors included measurements between Day 15 and Day 200; ¶Endpoint for C5 inhibitors included measurements between Day 1 and Day 200.
§Estimates of differences between treatments derived as average treatment effect in the treated using debiased 4-fold cross-fitting of orthogonalised scores from efficient influence function; confidence bounds comparisons including multiple imputations in APPOINT-PNH are combined using Rubin's combination rules.
Abbreviations: CFB, change from baseline; CI, confidence interval; Hb, haemoglobin; ITC, indirect treatment comparison; LDH, lactate dehydrogenase; RBC, red blood cell.

B.2.9.2.4 *Uncertainties of ITC of APPOINT-PNH vs APPEX*

Given that APPOINT-PNH was a single-arm trial, only an unanchored ITC was feasible. Data from the APPEX real-world cohort has high relevance given that the included patients were treated in the UK and France. However, the difference between irregular measurement practices in real-world clinical practice, which may in some cases be driven by clinical events, as opposed to regularly scheduled measurements in clinical trials, introduced uncertainty in the ITC.

B.2.9.3 Complement inhibitor-experienced population

B.2.9.3.1 *Comparator studies*

Among the clinical trials identified in the SLR (Section B.2.1), the pegcetacoplan PEGASUS study (49) was considered potentially suitable for an ITC against the APPLY-PNH study in the complement inhibitor-experienced population with residual anaemia. Other clinical trials identified in the SLR but not considered for the ITC were a trial investigating iptacopan as an add-on to eculizumab (92), which does not correspond to the expected iptacopan licence, and a trial for danicopan (94), which is not considered to be a comparator for this submission (Table 1). All studies identified by the SLR are summarised in Table 13 in Appendix D.

PEGASUS was a Phase 3 RCT evaluating the efficacy and safety of pegcetacoplan vs eculizumab in patients with PNH with residual anaemia (Hb <10.5 g/dL) despite eculizumab therapy for ≥3 months (49). Upon study inclusion, all patients continued to receive their current dose of eculizumab plus the addition of twice-weekly pegcetacoplan (1,080 mg). Only after completion of this 4-week run in period (Day –28 to Day 0) patients were randomised to pegcetacoplan monotherapy (eculizumab was withdrawn) or eculizumab monotherapy (pegcetacoplan was withdrawn). The randomised controlled period had a duration of 16 weeks (Day 0 to Day 112).

The key eligibility criteria for the APPLY-PNH and PEGASUS studies were similar with few clinically meaningful differences (Appendix D) (101). Some eligibility criteria were broader for APPLY-PNH, which were addressed by removing patients who would not have been eligible for PEGASUS.

B.2.9.3.2 *ITC methods summary*

B.2.9.3.2.1 Population adjustment

A population-adjusted ITC was conducted using IPD from APPLY-PNH and published summary-level data from PEGASUS (49).

As an initial step to account for differences in the study populations, patients who would not have been eligible to enrol in PEGASUS were excluded from the APPLY-PNH dataset. It was not possible to match the APPLY-PNH population to PEGASUS with regards to the Hb inclusion criterion, since the PEGASUS population was broader (Hb <10.5 g/dL vs APPLY-PNH <10 g/dL). Following removal of patients from the APPLY-PNH dataset, the IPD were reweighted using entropy balancing (103) to adjust for differences between the APPLY-PNH and PEGASUS populations. The adjustment factors were baseline Hb, sex, % transfusion free in prior 12 months, screening reticulocytes, baseline LDH, and age; these were validated by UK clinicians (101). Due to the resulting substantial drop in ESS, a sensitivity analysis was carried out whereby no patients were removed on the basis of the PEGASUS exclusion criteria for BMI and reticulocyte count, and differences in age and sex were not adjusted for, based on feedback from UK clinicians (101).

B.2.9.3.2.2 Alignment of endpoints

It was noted that the timeframe for endpoints reported for PEGASUS include the run-in period for key outcomes. Change in Hb was measured from the start of the 4-week run-in up to Week 16 of the randomised, controlled period, which was a total of 20 weeks (Day –28 to Day 112 = 140 days). Similarly, it was noted that for the pegcetacoplan arm, at the end of the 16-week randomised phase patients had received a total of 20 weeks of pegcetacoplan treatment (as add-on to eculizumab in the 4-week run-in – which is consistent with the pegcetacoplan SmPC (23) – followed by 16 weeks monotherapy). To match time on treatment for the ITCs, the analysis used the equivalent time period for APPLY-PNH endpoints (i.e. Day 0 to Day 140 from APPLY-PNH; Day –28 to Day 112 from PEGASUS). UK clinicians and health economists considered this alignment of timeframes appropriate (101).

In addition, APPLY-PNH endpoint data were adjusted to align with PEGASUS definitions where needed and feasible. ITCs were conducted for key endpoints included in both trials; this excluded the haematological responder endpoints from APPLY-PNH, which were not reported for PEGASUS. Full details of endpoint alignment are given in Appendix D.

B.2.9.3.2.3 Comparison approach

The initially planned approach was an anchored ITC comparing iptacopan with pegcetacoplan using the C5 inhibitor control arms of APPLY-PNH (eculizumab/ravulizumab) and PEGASUS (eculizumab) as linking treatment. Clinicians advised that eculizumab and ravulizumab could generally be considered sufficiently similar to allow an anchored comparison (101). However, there were concerns that patients in the eculizumab arm in PEGASUS had received 4 weeks of pegcetacoplan treatment during the run-in period of the study before switching back to eculizumab monotherapy. Patients in the control arm of APPLY-PNH had remained on C5 inhibitor monotherapy, which may impact the similarity of the control arms. When analysing the data, even after differences in trial populations and endpoint definitions had been adjusted for, stark differences between control arms of APPLY-PNH and PEGASUS remained for most outcomes, which could not be explained by clinicians (101). Therefore, an unanchored ITC was conducted, using the same approach as the ITC vs Study 301 in the complement inhibitor-naïve population (Section B.2.9.1.2). The iptacopan arm from APPLY-PNH was compared

with the pegcetacoplan arm from PEGASUS after reweighting the APPLY-PNH data to balance pre-treatment characteristics between the studies. While results of the anchored ITC are presented alongside results from the unanchored ITC, these should be interpreted with caution due to potential bias in the anchored comparison arising from the PEGASUS study run-in.

Full methodological details are provided in Appendix D.

B.2.9.3.3 *Results*

B.2.9.3.3.1 Comparison of pre-treatment characteristics before and after reweighting

Of the 62 patients randomised to iptacopan in APPLY-PNH, eight patients (Table 24) were removed from the dataset prior to the reweighting step as patients would not have met the PEGASUS inclusion criteria.

Table 24: Patients in APPLY-PNH study that were not eligible for PEGASUS study

Criteria†	Iptacopan N=62	Eculizumab or ravulizumab N=35
BMI ≥ 35.0 kg/m^2	3 (4.8%)	3 (8.6%)
Platelet count ≤ 50 × 10^9/L at screening	1 (1.6%)	2 (5.7%)
Absolute reticulocyte counts <1 x ULN (30–120 x 10^{-9}/L) at screening	4 (6.5%)	6 (17.1%)
Total excluded	**8 (12.9%)**	**10 (28.6%)**

†Patients included in APPLY-PNH that would not be eligible for PEGASUS based on these criteria.
Abbreviations: BMI, body mass index; ULN, upper limit of normal.

The remaining 54 APPLY-PNH patients were then reweighted to balance pre-treatment characteristics with the PEGASUS population (Table 25). After reweighting, the studies were well balanced for the adjustment factors Hb, LDH, age, reticulocytes, sex, and % transfusion free in previous 12 months, as well as for duration of C5 inhibitor treatment.

Table 25: Comparison of baseline characteristic between iptacopan (APPLY-PNH) and pegcetacoplan (PEGASUS): ITT population (N= 62), and analysis set (N = 54) before and after weighting

Characteristics	Pegcetacoplan (PEGASUS)	Iptacopan (APPLY-PNH)					
		ITT		ITC analysis dataset† Unweighted		ITC analysis dataset† Weighted‡	
	N=41	N=62	SMDs	N=54	SMDs	ESS=15	SMDs
Hb, g/dL: mean (SD)¶	8.7 (1.1)	8.9 (0.6)	0.196	8.8 (0.7)	0.158	8.7 (1.1)	0.000
LDH (U/L): mean (SD)	257.5 (97.6)	269.1 (70.1)	0.137	263.5 (71.5)	0.070	257.5 (73.5)	0.000
Age, years: mean (SD)	50.2 (16.3)	51.7 (16.9)	0.091	51.7 (16.6)	0.092	50.2 (16.5)	0.001
Screening reticulocytes (10^9/L): mean (SD)	217.5 (75.0)	204.0 (84.1)	0.169	210.7 (84.1)	0.086	217.6 (76.3)	0.002
Sex female: n (%)	27 (65.9)	43 (69.4)	0.075	37 (68.5)	0.057	66%	0.003
Transfusion free, 12 months prior: n (%)	10 (24.4)	25 (40.3)	0.346	22 (40.7)	0.354	24%	0.008
Duration of C5 inhibitor, years: mean (SD)	5.5 (3.9)	3.8 (3.5)	0.460	3.8 (3.7)	0.437	5.5 (4)	0.008
Screening platelet count (10^9/L): mean (SD)	166.6 (98.3)	160.9 (55.9)	0.071	167.4 (55.1)	0.010	152.1 (66.3)	0.173
FACIT-F score: mean (SD)	32.2 (11.4)	34.7 (9.8)	0.234	35.1 (10.1)	0.274	35.2 (10.9)	0.270
Time since diagnosis, years: mean (SD)	8.7 (7.4)	11.9 (9.8)	0.362	11.9 (9.6)	0.372	11 (7)	0.310
BMI (kg/m^2): mean (SD)	26.7 (4.3)	24.9 (5.0)	0.385	24.5 (4.3)	0.523	25.1 (4.4)	0.355
History of aplastic anaemia: n (%)	11 (26.8)	9 (14.5)	0.308	8 (14.8)	0.299	12.7%	0.360
Race, white: n (%)	24 (58.5)	48 (77.4)	0.413	42 (77.8)	0.422	34.7 (84.3)	0.594
≥4 transfusions of pRBCs, 12 months prior: n (%)	21 (51.2)	16 (25.8)	0.541	15 (27.8)	0.494	20.1%	0.686
History of MAVE: n (%)	NR	12 (19.4)	NA	11 (20.4)	NA	14.6%	NA

Green = SMD ≤0.1 (small difference); Yellow = 0.1 > SMD ≤ 0.2 (moderate difference); Red = SMD > 0.2 (substantial difference). These conservative thresholds were informed by Austin 2009 and 2011 (104, 105).

†8 patients removed from the APPLY-PNH iptacopan dataset, who were not eligible for PEGASUS based on criteria for reticulocyte count, platelet count and BMI; ‡Reweights APPLY-PNH data to balance with PEGASUS on baseline Hb per PEGASUS definition, sex, proportion transfusion-free within 12 months prior to baseline, reticulocyte count at screening, baseline LDH, and age; ¶Baseline Hb was calculated as per PEGASUS definition, as an average of values recorded prior to run-in dosing including local and central laboratory values.

Abbreviations: BMI, body mass index; ESS, effective sample size; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; ITT, intent-to-treat; LDH, lactate dehydrogenase; MAVE, major adverse vascular event; NA, not applicable; NR, not reported; pRBC packed red blood cell; SD, standard deviation; SMD, standardised mean difference.

B.2.9.3.3.2 Overview of ITC results

Table 26 presents a summary of the unanchored and anchored ITCs for iptacopan based on APPLY-PNH vs pegcetacoplan based on PEGASUS. The unanchored ITCs for CFB in Hb and transfusion avoidance favoured iptacopan compared with pegcetacoplan; all results were statistically significant. The anchored ITC point estimate favoured pegcetacoplan for CFB in Hb excluding post-transfusion data, while the point estimates for CFB in Hb including post-transfusion data, and transfusion avoidance, favoured iptacopan; none of the estimates were statistically significant. However, results of the anchored ITCs for CFB in Hb excluding post-transfusion data, and transfusion avoidance, should be interpreted with caution due to large, unexplained differences in the C5 inhibitor control arms between APPLY-PNH and PEGASUS. Results of sensitivity analyses are presented in Appendix D. These were generally consistent with the primary analyses. Results for additional outcomes of LDH and FACIT-Fatigue are also presented in Appendix D.

Table 26: Overview of results for iptacopan vs pegcetacoplan in the complement inhibitor-experienced population: ITC using APPLY-PNH vs PEGASUS

	CFB in Hb, excluding post-transfusion data (95% CI)	CFB in Hb, including post-transfusion data (95% CI)	Transfusion avoidance
Iptacopan (ESS=15†)	[redacted]	[redacted]	[redacted]
Pegcetacoplan (N=41)	2.37 (1.66, 3.08)	2.66 (2.17, 3.15)	85.4%
Eculizumab/ ravulizumab APPLY-PNH (ESS=7†)	[redacted]	[redacted]	[redacted]
Eculizumab PEGASUS (N=39)	*–1.47 (–2.78, –0.16)*	*–0.03 (–0.54, 0.48)*	*15.4%*
Unanchored ITC results			
Iptacopan vs pegcetacoplan	**MD [redacted] (95% CI [redacted]) p=0.014**	**MD [redacted] (95% CI [redacted]) p=0.011**	**OR [redacted] (95% CI [redacted]) p<0.001**
Anchored ITC results			
Iptacopan vs pegcetacoplan	MD –[redacted] (95% CI –[redacted]) p=0.837	MD [redacted] (95% CI –[redacted]) p=0.151	OR [redacted] (95% CI [redacted]) p=0.090

MD >0 implies higher value for iptacopan vs pegcetacoplan; OR >1 implies higher odds for iptacopan vs pegcetacoplan; **Bold** values indicate statistical significance and corresponds to a two-tailed p-value <0.05.
†APPLY-PNH results using PEGASUS endpoint definitions and population adjusted, reweighted to balance with

PEGASUS on baseline Hb (mean and SD), proportion of females, proportion transfusion-free within 12 months prior, screening reticulocyte (mean and SD), baseline LDH (mean and SD), and age (mean and SD).
Abbreviations: CFB, change from baseline; CI, confidence interval; ESS, effective sample size; Hb, haemoglobin; ITC, indirect treatment comparison; LDH, lactate dehydrogenase; MD, mean difference (in CFB); OR, odds ratio.

B.2.9.3.4 *Uncertainties of ITC of APPLY-PNH vs PEGASUS*

While the narrower eligibility criteria of the APPLY-PNH population with regards to Hb at baseline (Hb <10.0 g/dL vs PEGASUS Hb <10.5 g/dL) could not be addressed in the analysis, the difference in baseline Hb was adjusted for. However, the population adjustments led to a substantial loss in sample size, from 62 patients included in the iptacopan arm of APPLY-PNH to an ESS of only 15, thereby limiting the robustness of the ITC results. Sensitivity analyses with fewer adjustment factors did not result in meaningful increases of the ESS (Appendix D). In addition, due to concerns about the lack of similarity between the C5 inhibitor comparator arms of APPLY-PNH and PEGASUS, given the PEGASUS run-in period during which patients randomised to eculizumab also received pegcetacoplan, a non-anchored ITC was considered potentially more appropriate, which represents another limitation of the analysis.

B.2.10 Adverse reactions

B.2.10.1 APPOINT-PNH

Safety data is presented for the core treatment period and the overall study period. The overall study period includes data from the 24-week core treatment period plus the extension treatment period until the data cut-off date (2nd Nov 2022).

B.2.10.1.1 *Adverse reactions*

B.2.10.1.1.1 Overview of adverse events

In the core treatment period, 37/40 patients (92.5%) had ≥1 adverse event (AE) (Table 27). The majority of AEs were mild or moderate, with only 1/40 patients (2.5%) with a severe AE. Fourteen patients (35.0%) had AEs that were suspected to be treatment related by the investigator. Four patients (10.0%) experienced serious adverse events (SAE), none of them were fatal. None of the patients discontinued iptacopan treatment or had a dose interruption due to AEs. There were no deaths or discontinuations due to AEs in the study.

In the extension treatment period until the data cut-off date (2nd Nov 2022), there were no additional patients who experienced ≥1 AE when compared with the core treatment period (Table 27). There were no deaths, and no study drug discontinuations or interruptions due to AEs. However, there were additional AEs reported during the extension treatment period in the same patients who had AEs during the core treatment period.

Table 27: APPOINT-PNH: Overview of AEs until the data cut-off date (2nd Nov 2022) (SAS)

	Iptacopan 200 mg BD, N=40 n (%)	
	Core treatment period (24 weeks)	**Overall (core + extension treatment period until cut-off date)**
AEs	37 (92.5)	37 (92.5)
Suspected to be treatment related	14 (35.0)	16 (40.0)
Severe AEs	1 (2.5)	3 (7.5)
Suspected to be treatment related	0	1 (2.5)
SAEs	4 (10.0)	6 (15.0)
Suspected to be treatment related	0	1 (2.5)
Fatal SAEs	0	0
AEs leading to treatment discontinuation	0	0
AEs leading to dose interruption	0	0
AEs requiring additional therapy	24 (60.0)	30 (75.0)

Source: Novartis, Data on file, APPOINT-PNH CSR, Table 12.1 (89).
Abbreviations: AE, adverse event; BD, twice daily; CSR, clinical study report; SAE, serious adverse event; SAS, safety analysis set.

The most commonly reported AEs were headache (core treatment period: 27.5%; overall period: 30.0%), COVID-19 (core treatment period: 15.0%; overall period: 17.5%), and upper respiratory tract infections (core treatment period: 12.5%; overall period: 15.0%) (Table 28).

Table 28: APPOINT-PNH: Most common TEAEs (≥5% of patients in any treatment period) by preferred term until the data cut-off date (2nd Nov 2022) (SAS)

	Iptacopan 200 mg BD, N=40 n (%)	
	Core treatment period (24 weeks)	**Overall (core + extension treatment period until cut-off date)**
Number of patients with ≥1 event	**37 (92.5)**	**37 (92.5)**
Headache	11 (27.5)	12 (30.0)
COVID-19	6 (15.0)	7 (17.5)

	Iptacopan 200 mg BD, N=40 n (%)	
	Core treatment period (24 weeks)	Overall (core + extension treatment period until cut-off date)
Upper respiratory tract infection	5 (12.5)	6 (15.0)
Diarrhoea	3 (7.5)	5 (12.5)
Iron deficiency	3 (7.5)	5 (12.5)
Vomiting	2 (5.0)	3 (7.5)
Pyrexia	2 (5.0)	3 (7.5)
Hyperlipidaemia	2 (5.0)	2 (5.0)
Cataract	2 (5.0)	2 (5.0)
Abdominal pain	2 (5.0)	2 (5.0)
Constipation	2 (5.0)	2 (5.0)
Nausea	2 (5.0)	2 (5.0)
Conjunctivitis	2 (5.0)	2 (5.0)
Blood glucose increased	2 (5.0)	2 (5.0)
Periarthritis	2 (5.0)	2 (5.0)
Renal impairment	2 (5.0)	2 (5.0)
Epistaxis	2 (5.0)	2 (5.0)
Nasal congestion	2 (5.0)	2 (5.0)
Dermatitis allergic	2 (5.0)	2 (5.0)
Vision blurred	1 (2.5)	2 (5.0)
Asthenia	1 (2.5)	2 (5.0)
Chest pain	1 (2.5)	2 (5.0)
Contusion	1 (2.5)	2 (5.0)
Amylase increased	1 (2.5)	2 (5.0)
C-reactive protein increased	1 (2.5)	2 (5.0)
Lipids abnormal	1 (2.5)	2 (5.0)
Ureterolithiasis	0	2 (5.0)
Heavy menstrual bleeding	1 (2.5)	2 (5.0)

Source: Novartis, Data on file, APPOINT-PNH CSR, Table 12.3 (89).
Abbreviations: BD, twice daily; CSR, clinical study report; PNH, paroxysmal nocturnal haemoglobinuria; SAS, safety analysis set; TEAE, treatment-emergent adverse event.

B.2.10.1.1.2 Serious adverse events

SAEs were reported in 4/40 patients (10.0%): cataract (mild), COVID-19 (moderate), pneumonia bacterial (severe), and type 2 diabetes mellitus (moderate) were reported in one patient each. None of the SAEs were suspected to be related to iptacopan treatment by the investigator.

In the extension treatment period, SAEs were reported in two additional patients (one case of COVID-19 [mild] which was followed by a severe BTH event, and one case of pneumonia [severe]).

B.2.10.1.1.3 Deaths

As of the data cut-off date, no deaths were reported in the overall study period.

B.2.10.1.1.4 Adverse events of special interest

The adverse events of special interest (AESI) for iptacopan are based on its mechanism of action, preclinical safety studies and clinical studies, and include serious or severe infections, infections caused by encapsulated bacteria, haemolysis and thrombosis events (Table 29).

In the core treatment period, no patient had clinical BTH. In the extension treatment period, one patient had a mild COVID-19 infection (Day 213 to Day 220) that was not suspected to be related to iptacopan treatment. Five days after hospitalisation for COVID-19 infection the patient developed a severe BTH (Day 218 to Day 281) and was treated in the intensive care unit. This patient had a second occurrence of BTH at Day 299 that was nonserious and of moderate intensity. In both instances, the BTH was not suspected to be related to iptacopan treatment and treatment was continued.

Table 29: APPOINT-PNH: Overview of AESI until the data cut-off date (2nd Nov 2022) (SAS)

	Iptacopan 200 mg BD, N=40 n (%)	
	Core treatment period (24 weeks)	**Overall (core + extension treatment period until cut-off date)**
Severe or serious infections	**2 (5.0)**	**4 (10.0)**
COVID-19 infections	1 (2.5)	2 (5.0)
Pneumonia bacterial	1 (2.5)	1 (2.5)
Pneumonia	0	1 (2.5)
Infections capsular bacteria	**1 (2.5)**	**2 (5.0)**
Pneumonia bacterial	1 (2.5)	1 (2.5)
Staphylococcal skin infection	0	1 (2.5)
PNH haemolysis and thrombosis	**1 (2.5)**	**2 (5.0)**
Blood creatinine increased	1 (2.5)	1 (2.5)
BTH	0	1 (2.5)

	Iptacopan 200 mg BD, N=40 n (%)	
	Core treatment period (24 weeks)	**Overall (core + extension treatment period until cut-off date)**
Testicular effects	**1 (2.5)**	**1 (2.5)**
Blood follicle stimulating hormone increased	1 (2.5)	1 (2.5)
Dihydrotestosterone decreased	1 (2.5)	1 (2.5)
Thyroid changes	**1 (2.5)**	**1 (2.5)**
Reverse tri-iodothyronine increased	1 (2.5)	1 (2.5)

Source: Novartis, Data on file, APPOINT-PNH CSR, Table 12.7 (89).
Abbreviations: AESI, adverse event of special interest; BD, twice daily; BTH, breakthrough haemolysis; CSR, clinical study report; PNH, paroxysmal nocturnal haemoglobinuria; SAS, safety analysis set.

B.2.10.2 APPLY-PNH

Safety data is presented for the 24-week randomised period and the treatment extension period. The iptacopan combined safety set (n=95) includes data from the 24-week randomised treatment period and the extension treatment period until the data cut-off date (26th Sep 2022), starting from the first administration of iptacopan.

B.2.10.2.1 *Adverse reactions*

B.2.10.2.1.1 Overview of adverse events

In the randomised treatment period, the proportion of patients experiencing an AE was comparable between the iptacopan and C5 inhibitor treatment groups (iptacopan: 82.3%; C5 inhibitor: 80.0%). The proportion of patients with severe AEs was low in both groups (iptacopan: 4.8%; C5 inhibitor: 8.6%) (Table 30). A total of 16/62 patients (25.8%) in the iptacopan treatment group and 3/35 patients (8.6%) in the C5 inhibitor group reported AEs suspected to be related to the study drug by the investigator. Overall, 6/62 (9.7%) patients in the iptacopan group and 5/35 (14.3%) patients in the C5 inhibitor treatment group experienced SAEs. One SAE in the iptacopan group (blood creatine phosphokinase increase) was suspected to be related to iptacopan. None of the SAEs had a fatal outcome. There were no AEs leading to treatment discontinuation or treatment interruption.

Overall, 78.9% (75/95) of patients in the iptacopan combined safety set experienced AEs. Most of the AEs reported were mild or moderate in severity.

Of the 75 patients with AEs reported in the iptacopan combined safety analysis, 21 (22.1%) had AEs which were suspected to be related to iptacopan by the investigator. Overall, 12/95 (12.6%) patients experienced SAEs. None of the SAEs had a fatal outcome or led to interruption or discontinuation of treatment with iptacopan.

Table 30: APPLY-PNH: Overview of AEs until the data cut-off date (26th Sep 2022) (SAS)

	Randomised treatment period		Combined iptacopan safety analysis
	Iptacopan 200 mg BD N=62 n (%)	C5 inhibitor N=35 n (%)	N=95 n (%)
AEs	**51 (82.3)**	**28 (80.0)**	**75 (78.9)**
Suspected to be treatment related	16 (25.8)	3 (8.6)	21 (22.1)
Severe AEs	**3 (4.8)**	**3 (8.6)**	**8 (8.4)**
Suspected to be treatment related	0	0	1 (1.1)
SAEs	**6 (9.7)**	**5 (14.3)**	**12 (12.6)**
Suspected to be treatment related	1 (1.6)	0	2 (2.1)
Fatal SAEs	**0**	**0**	**0**
AEs leading to treatment discontinuation	**0**	**0**	**0**
AEs leading to interruption	**0**	**0**	**0**
AEs requiring additional therapy	**40 (64.5)**	**18 (51.4)**	**62 (65.3)**

Source: Novartis, Data on file, APPLY-PNH CSR, Table 12.1 and Table 12.12 (93).
A patient with multiple occurrences of an AE under one treatment is counted only once.
Abbreviations: AE, adverse event; BD, twice daily; CSR, clinical study report; SAE, serious adverse event; SAS, safety analysis set.

The most common AE reported in the iptacopan group was headache (16.1%), while in the C5 inhibitor group, COVID-19 was the most common (25.7%). The AEs with the largest risk differences in the randomised period between the iptacopan and C5 inhibitor groups were COVID-19 and BTH, both were more frequent in patients treated with C5 inhibitors than in patient treated with iptacopan, and headaches, which were more frequent in the iptacopan group (Table 31).

Table 31: APPLY-PNH: Most common AEs (≥ 5% of patients in any treatment group) by preferred term between baseline and Day 168 (SAS)

	Randomised treatment period		Risk difference (95% CI)
	Iptacopan 200 mg BD N=62 n (%)	C5 inhibitor N=35 n (%)	
Number of patients with ≥1 event	**51 (82.3)**	**28 (80.0)**	**2.26 (–14.05, 18.57)**
Headache	10 (16.1)	1 (2.9)	13.27 (2.58, 23.96)
Diarrhoea	9 (14.5)	2 (5.7)	8.80 (–2.86, 20.46)
Nasopharyngitis	7 (11.3)	2 (5.7)	5.58 (–5.43, 16.58)
Nausea	6 (9.7)	1 (2.9)	6.82 (–2.38, 16.02)
Arthralgia	5 (8.1)	1 (2.9)	5.21 (–3.53, 13.95)
COVID-19	5 (8.1)	9 (25.7)	–17.65 (–33.64, –1.66)
Urinary tract infection	5 (8.1)	1 (2.9)	5.21 (–3.53, 13.95)
Abdominal pain	4 (6.5)	1 (2.9)	3.59 (–4.64, 11.83)
Blood LDH increased	4 (6.5)	3 (8.6)	–2.12 (–13.23, 8.99)
Dizziness	4 (6.5)	0	6.45 (0.34, 12.57)
Back pain	3 (4.8)	2 (5.7)	–0.88 (–10.24, 8.49)
BTH	2 (3.2)	6 (17.1)	–13.92 (–27.15, –0.68)
Pyrexia	2 (3.2)	3 (8.6)	–5.35 (–15.61, 4.92)
Sinusitis	2 (3.2)	3 (8.6)	–5.35 (–15.61, 4.92)
Upper respiratory tract infection	2 (3.2)	3 (8.6)	–5.35 (–15.61, 4.92)
Extravascular haemolysis	0	2 (5.7)	–5.71 (–13.40, 1.98)

Source: Novartis, Data on file, APPLY-PNH CSR, Table 12.3 (93).
Abbreviations: AE, adverse event; BD, twice daily; BTH, breakthrough haemolysis; CI, confidence interval; CSR, clinical study report; LDH, lactate dehydrogenase; SAS, safety analysis set.

The most commonly reported AEs in iptacopan-treated patients in the combined safety analysis were COVID-19 (23.2%), headache (12.6%), and nasopharyngitis (12.6%) (Table 32).

Table 32: APPLY-PNH: Most common AE (≥5% of patients) by preferred term until the data cut-off date (26th Sep 2022) (Combined iptacopan SAS)

	Iptacopan 200 mg BD N=95 n (%)
Number of patients with ≥1 event	**75 (78.9)**
COVID-19	22 (23.2)
Headache	12 (12.6)
Nasopharyngitis	12 (12.6)
Diarrhoea	11 (11.6)
Nausea	9 (9.5)
Arthralgia	7 (7.4)
Urinary tract infection	6 (6.3)
Abdominal pain	5 (5.3)
Blood LDH increased	5 (5.3)
BTH	5 (5.3)
Hypertension	5 (5.3)
Thrombocytopenia	5 (5.3)

Source: Novartis, Data on file, APPLY-PNH CSR, Table 12.14 (93).
Abbreviations: AE, adverse event; BD, twice daily; BTH, breakthrough haemolysis; CSR, clinical study report; LDH, lactate dehydrogenase; SAS, safety analysis set.

B.2.10.2.1.2 Serious adverse events

Overall, 6/62 patients (9.7%) in the iptacopan treatment group and 5/35 patients (14.3%) in the C5 inhibitor treatment group experienced SAEs in the randomised treatment period (Table 33).

The only SAE which was suspected to be related to study medication was reported in the iptacopan group. The SAE was a large increase in creatine phosphokinase that the investigator suspected could be related to a drug-drug interaction of concomitant cyclosporin and/or eltrombopag with iptacopan.

Table 33: APPLY-PNH: Overview of SAEs in the randomised treatment period between baseline and Day 168 (SAS)

	Randomised treatment period	
	Iptacopan 200 mg BD N=62 n (%)	**C5 inhibitor N=35 n (%)**
Number of patients with ≥1 event	**6 (9.7)**	**5 (14.3)**
Blood and lymphatic system disorders	0	2 (5.7)
BTH	0	1 (2.9)
Extravascular haemolysis	0	1 (2.9)
Cardiac disorders	1 (1.6)	0
Sinus node dysfunction	1 (1.6)	0
Hepatobiliary disorders	0	1 (2.9)
Jaundice	0	1 (2.9)
Infections and infestations	2 (3.2)	3 (8.6)
COVID-19	1 (1.6)	2 (5.7)
Pyelonephritis	1 (1.6)	0
Urinary tract infection	1 (1.6)	0
Arthritis bacterial	0	1 (2.9)
Intervertebral discitis	0	1 (2.9)
Sepsis	0	1 (2.9)
Investigations	1 (1.6)	1 (2.9)
Blood creatine phosphokinase increased	1 (1.6)	0
Influenza A virus test positive	0	1 (2.9)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	2 (3.2)	0
Basal cell carcinoma	1 (1.6)	0
Myelodysplastic syndrome	1 (1.6)	0
Nervous system disorders	1 (1.6)	0
Transient ischaemic attack	1 (1.6)	0
Renal and urinary disorders	0	1 (2.9)
Acute kidney injury	0	1 (2.9)
Bilirubinuria	0	1 (2.9)

Source: Novartis, Data on file, APPLY-PNH CSR, Table 12.6 (93).
Abbreviations: BD, twice daily; BTH, breakthrough haemolysis; CSR, clinical study report; SAE, serious adverse event; SAS, safety analysis set.

In the combined safety analysis set, 12/95 iptacopan-treated patients (12.6%) experienced SAEs, compared with 6/62 patients (9.7%) in the iptacopan treatment group in the randomised treatment period (Table 34).

Table 34: APPLY-PNH: Overview of SAEs until the data cut-off date (26th Sep 2022) (Combined iptacopan SAS)

	Combined iptacopan safety analysis N=95 n (%)
Number of patients with ≥1 event	**12 (12.6)**
Cardiac disorders	1 (1.1)
Sinus node dysfunction	1 (1.1)
Gastrointestinal disorders	1 (1.1)
Pancreatolithiasis	1 (1.1)
Infections and infestations	5 (5.3)
COVID-19	1 (1.1)
Cellulitis	1 (1.1)
Pyelonephritis	1 (1.1)
Septic shock	1 (1.1)
Systemic infection	1 (1.1)
Urinary tract infection	1 (1.1)
Investigations	2 (2.1)
Blood creatine phosphokinase increased	1 (1.1)
Platelet count decreased	1 (1.1)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	2 (2.1)
Basal cell carcinoma	1 (1.1)
Myelodysplastic syndrome	1 (1.1)
Nervous system disorders	1 (1.1)
Transient ischaemic attack	1 (1.1)
Reproductive system and breast disorders	1 (1.1)
Ovarian cyst	1 (1.1)

Source: Novartis, Data on file, APPLY-PNH CSR, Table 12.16 (93).
Abbreviations: CSR, clinical study report; SAE, serious adverse event; SAS, safety analysis set.

B.2.10.2.1.3 Deaths

There were no deaths in the study.

B.2.10.2.1.4 Adverse events of special interest

In the randomised treatment period, fewer AESI occurred in the iptacopan arm vs the C5 inhibitors (25.8% vs 31.4%; risk difference: –5.6; 95% CI: –24.47, 13.22; Table 35). In the iptacopan arm, the most common AESI were PNH haemolysis and thrombosis (16.1%), decreased platelets (6.5%), and serious or severe infections (3.2%). In the C5 inhibitor arm, the most common AESIs were PNH haemolysis and thrombosis (28.6%), and serious or severe injections (8.6%).

In the combined safety analysis set, 25.3% of patients experienced an AESI (Table 36). The most common AESIs were in the combined safety set were PNH haemolysis and thrombosis (12.6%), decreased platelets (9.5%), and serious or severe injections (5.3%).

Table 35: APPLY-PNH: Overview of AESI – between baseline and Day 168 (SAS)

	Randomised treatment period		Risk difference (95% CI)
	Iptacopan 200 mg BD N=62 n (%)	C5 inhibitor N=35 n (%)	
Number of patients with ≥1 event	**16 (25.8)**	**11 (31.4)**	**–5.62 (–24.47, 13.22)**
Serious or severe infections	2 (3.2)	3 (8.6)	–5.35 (–15.61, 4.92)
COVID-19	1 (1.6)	2 (5.7)	–4.10 (–12.41, 4.20)
Pyelonephritis	1 (1.6)	0	1.61 (–1.52, 4.75)
Urinary tract infection	1 (1.6)	0	1.61 (–1.52, 4.75)
Arthritis bacterial	0	1 (2.9)	–2.86 (–8.38, 2.66)
Intervertebral discitis	0	1 (2.9)	–2.86 (–8.38, 2.66)
Sepsis	0	1 (2.9)	–2.86 (–8.38, 2.66)
Infections caused by encapsulated bacteria	1 (1.6)	0	1.61 (–1.52, 4.75)
Bronchitis haemophilus	1 (1.6)	0	1.61 (–1.52, 4.75)
PNH haemolysis and thrombosis	10 (16.1)	10 (28.6)	–12.44 (–29.99, 5.10)
Blood LDH increased	4 (6.5)	3 (8.6)	–2.12 (–13.23, 8.99)
BTH	2 (3.2)	6 (17.1)	–13.92 (–27.15, –0.68)
Blood creatinine increased	1 (1.6)	0	1.61 (–1.52, 4.75)
Haemoglobinuria	1 (1.6)	0	1.61 (–1.52, 4.75)
Hemiparesis	1 (1.6)	0	1.61 (–1.52, 4.75)
Ocular icterus	1 (1.6)	0	1.61 (–1.52, 4.75)
Transient ischaemic attack	1 (1.6)	0	1.61 (–1.52, 4.75)
Extravascular haemolysis	0	2 (5.7)	–5.71 (–13.40, 1.98)
Jaundice	0	1 (2.9)	–2.86 (–8.38, 2.66)
Testicular effects	1 (1.6)	0	1.61 (–1.52, 4.75)
Dihydrotestosterone decreased	1 (1.6)	0	1.61 (–1.52, 4.75)
Thyroid changes	1 (1.6)	0	1.61 (–1.52, 4.75)
Hypothyroidism	1 (1.6)	0	1.61 (–1.52, 4.75)
Decreased platelets	4 (6.5)	0	6.45 (0.34, 12.57)
Thrombocytopenia	3 (4.8)	0	4.84 (–0.50, 10.18)
Platelet count decreased	1 (1.6)	0	1.61 (–1.52, 4.75)

Source: Novartis, Data on file, APPLY-PNH CSR, Table 12.7 (93).
Abbreviations: AESI, adverse event of special interest; BD, twice daily; BTH, breakthrough haemolysis; CI, confidence interval; CSR, clinical study report; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal haemoglobinuria; SAS, safety analysis set.

Table 36: APPLY-PNH: Overview of AESI – overall treatment period (Combined iptacopan SAS)

	Combined iptacopan safety analysis N=95 n (%)
Number of patients with ≥1 event	**24 (25.3)**
Serious or severe infections	5 (5.3)
COVID-19	1 (1.1)
Cellulitis	1 (1.1)
Pyelonephritis	1 (1.1)
Septic Shock	1 (1.1)
Systemic infection	1 (1.1)
Urinary tract infection	1 (1.1)
Infections capsular bacteria	1 (1.1)
Bronchitis haemophilus	1 (1.1)
PNH haemolysis and thrombosis	12 (12.6)
Blood LDH increased	5 (5.3)
BTH	5 (5.3)
Blood creatinine increased	1 (1.1)
Extravascular haemolysis	1 (1.1)
Haemoglobin decreased	1 (1.1)
Haemoglobinuria	1 (1.1)
Hemiparesis	1 (1.1)
Ocular icterus	1 (1.1)
Transient ischaemic attack	1 (1.1)
Testicular effects	1 (1.1)
Dihydrotestosterone decreased	1 (1.1)
Thyroid changes	1 (1.1)
Hypothyroidism	1 (1.1)
Decreased platelets	9 (9.5)
Thrombocytopenia	5 (5.3)
Platelet count decreased	4 (4.2)

Source: Novartis, Data on file, APPLY-PNH CSR, Table 12.17 (93).
Abbreviations: AESI, adverse event of special interest; BD, twice daily; BTH, breakthrough haemolysis; CI, confidence interval; CSR, clinical study report; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal haemoglobinuria; SAS, safety analysis set.

B.2.11 Ongoing studies

Iptacopan for the treatment of PNH is also being evaluated in two ongoing studies: NCT04747613 and APPULSE.

NCT04747613 is a single-arm, open-label, multicentre, roll-over extension study to characterise long-term safety, tolerability and efficacy of iptacopan in PNH, and to

provide access to iptacopan to patients who have completed Novartis-sponsored Phase 2 or 3 studies with iptacopan in PNH (109).The estimated study completion date of NCT04747613 is June 2026.

APPULSE (NCT05630001) is a single-arm, open-label, multicentre trial evaluating the efficacy and safety of iptacopan in adult patients with PNH with a mean Hb level ≥10 g/dL while being treated with a C5 inhibitor and then switch to iptacopan (110). The estimated study completion date of APPULSE is January 2025.

B.2.12 Interpretation of clinical effectiveness and safety evidence

Iptacopan is a novel proximal complement inhibitor and expected to be the first oral monotherapy for the treatment of adult patients with PNH who are complement inhibitor-naïve or complement inhibitor-experienced with residual anaemia.

Results from two Phase 3 trials provide evidence on the clinical efficacy of iptacopan as twice daily oral treatment for PNH. The results consistently demonstrate clinically meaningful improvements with iptacopan in both complement inhibitor-naïve patients and in complement inhibitor-experienced patients with residual anaemia across a range of efficacy endpoints, including haematological and clinical outcomes as well as patient symptoms such as fatigue. As such, in a clinical advisory board meeting, UK clinicians expressed that they would feel confident offering iptacopan to most patients with PNH (50).

In the complement inhibitor-naïve population, 92.2% (95% CI: 82.5, 100.0) of patients treated with iptacopan in the APPOINT-PNH trial had a sustained increase in Hb levels from baseline of ≥2 g/dL in the absence of RBC transfusions. This was replicated in complement inhibitor-experienced patients with residual anaemia, with the APPLY-PNH RCT demonstrating superiority vs C5 inhibitors for both a sustained increase in Hb levels from baseline of ≥2 g/dL (difference in marginal proportions iptacopan vs C5 inhibitors 80.3%; 95% CI: 71.3, 87.6) and a sustained Hb level of ≥12 g/dL (difference in marginal proportions iptacopan vs C5 inhibitors 67.0%; 95% CI: 56.3, 76.9), in the absence of RBC transfusions. In both trials, the clinically significant improvements in anaemia shown by the primary endpoints were robust

and consistent across subgroups, demonstrating the consistency of treatment response to iptacopan throughout the PNH population (Appendix E). UK clinicians agreed that Hb normalisation was an important outcome (50).

The clinically meaningful benefits of iptacopan are further substantiated by a range of complementary secondary endpoints of high clinical relevance (50), including transfusion avoidance, which were also used in clinical trials of other complement inhibitors. In APPOINT-PNH, no patients required RBC transfusions between Day 14 and the end of the core treatment period (Day 168). In APPLY-PNH, the treatment difference in marginal proportions of patients not requiring transfusions between Day 14 and Day 168 was 70.3% (iptacopan vs C5 inhibitors; 95% CI: 52.6, 84.9), with statistically significantly superiority demonstrated for iptacopan over C5 inhibitor therapy. The transfusion avoidance demonstrated in APPOINT-PNH and APPLY-PNH has potential positive implications for patient burden, as transfusions are associated with decreased health-related quality of life (HRQoL), increased risks and complications (such as iron overload), and can result in decreased productivity (51).

In the complement inhibitor-naïve population, the therapeutic benefit with iptacopan was achieved by rapid and sustained control of IVH as evidenced by the reduction in LDH (CFB greater than –83% at any visit after Day 7), which constitutes a key treatment goal for clinicians (50), and also inhibiting the emergence of C3-mediated EVH. In the complement inhibitor-experienced population, IVH control was maintained after switching from a C5 inhibitor to iptacopan, and rapid control of EVH was achieved, as evidenced by the reduction in reticulocyte counts seen as early as Day 7. This demonstrates that iptacopan addresses complement-mediated haemolysis overall, both IVH and EVH. The therapeutic benefit of iptacopan is further supported by the low number of BTH events in both trials.

Consistent with the improvement in anaemia and control of haemolysis with iptacopan treatment, patient-reported fatigue improved in both complement inhibitor-naïve and -experienced patients. In both populations, the adjusted mean change from baseline in the FACIT-Fatigue score exceeded the pre-specified 5-point threshold, and by the end of the treatment periods the level of fatigue was comparable to that of the general population (66).

Furthermore, iptacopan had a favourable safety profile and was generally well tolerated with no discontinuations due to AEs both in complement inhibitor-naïve patients in APPOINT-PNH, and complement inhibitor-experienced patients in APPLY-PNH.

Consistent with other ultra-rare conditions, evidence generation in PNH is associated with challenges that may affect the reliability of clinical study results. The sample sizes of the Phase 3 trial arms (APPOINT-PNH: iptacopan N=40; APPLY-PNH: iptacopan N=62, C5 inhibitors N=35) are similar to those supporting the pegcetacoplan appraisal (PEGASUS: pegcetacoplan N=41, eculizumab N=39) (20). In addition, the sample size in APPLY-PNH was sufficient to demonstrate statistically significant superior improvements in key efficacy endpoints vs C5 inhibitors.

Both Phase 3 trials included sites within the UK, however, in the APPOINT-PNH trial, 65% of the study population was from Asia. Clinicians participating in a UK advisory board were confident that iptacopan is expected to work similarly in the UK population and that the study results are generalisable to UK patients with PNH (50). Other than ethnicity, the only difference between the APPOINT-PNH population and UK patients highlighted by clinicians was the lower proportion of patients with a history of thrombosis in the trial, although the study population was considered comparable to UK patients regarding a history of aplastic anaemia (50).

Although the single-arm design of APPOINT-PNH is a limitation, which was also highlighted by clinicians (50), the response rates for the clinical endpoints were high in absolute terms. For example, 100% of patients remained transfusion-free on iptacopan between Day 14 and the end of the core treatment period (Day 168). To contextualise these results, ITCs were conducted, comparing iptacopan data from APPOINT-PNH to C5 inhibitor data from clinical trials as well as real-world evidence from the UK and France (Section B.2.9.1, Section B.2.9.2, Appendix D). Results from these ITCs in the complement inhibitor-naïve population consistently favoured iptacopan over C5 inhibitors, although not all results were statistically significant. Limitations of the ITCs included differences in the trial populations that could not be adjusted for (Hb in ITC vs Study 301, since the analysis did not converge) as well as irregular measurements, reflecting routine clinical practice, in the APPEX real-world study.

For the treatment-experienced population with anaemia, evidence for the efficacy and safety of iptacopan is available from the randomised, active comparator-controlled study, APPLY-PNH. Approximately one third of the C5 inhibitor arm patients in APPLY-PNH were receiving ravulizumab, which is the most frequently used treatment in UK clinical practice (50) and thus the most relevant comparator for this submission. A subgroup analysis of APPLY-PNH by type of C5 inhibitor found no difference in the iptacopan treatment effect size vs ravulizumab or eculizumab. Although the APPLY-PNH trial did not include pegcetacoplan as a comparator, use of pegcetacoplan in UK clinical practice to date remains low, with clinicians predicting that it is unlikely to increase with availability of iptacopan as an oral proximal inhibitor (50). While the ITCs vs pegcetacoplan were associated with methodological challenges because of the differences between the APPLY-PNH and PEGASUS C5 inhibitor control arms, the results mostly favoured iptacopan over pegcetacoplan. However, it should be noted that none of the ITC results informed the economic model since the definition of model health states required the consideration of Hb and transfusion outcomes in combination, and transition probabilities were derived independently (Section B.3.3.2).

Taken together, the results of the iptacopan clinical trial programme and the ITCs demonstrate that treatment with iptacopan results in clinically meaningful improvements in outcomes, and was generally well tolerated. Iptacopan may therefore offer patients with PNH an effective, orally administered, treatment option.

B.3 Cost effectiveness

The cost-effectiveness analysis showed that iptacopan (200 mg twice daily, oral capsule) is a cost-effective treatment option for the treatment of paroxysmal nocturnal haemoglobinuria (PNH)

- The economic analysis considered two subpopulations of adults with PNH, in line with the available trial evidence and expected iptacopan licence
  - Adult patients with PNH who are naïve to treatment with complement inhibitors and have haemolysis with clinical symptom(s) (i.e. complement inhibitor-naïve)
  - Adult patients with PNH who have been treated with a complement inhibitor and have anaemia (i.e. complement inhibitor-experienced with residual anaemia)
- The economic model was based on a semi-Markov structure and comprised health states defined by anaemia and transfusions
- Transition probabilities were derived from individual patient data (IPD) where available, or taken from the literature
  - For complement inhibitor-naïve patients, transition probabilities were derived from APPOINT-PNH for iptacopan and from APPEX real-world data for C5 inhibitors. APPEX data was reweighted to match the APPOINT-PNH population
  - For complement inhibitor-experienced patients, transition probabilities were derived from APPLY-PNH data for iptacopan and C5 inhibitors, and taken from a publication for pegcetacoplan, based on the PEGASUS trial. APPLY-PNH data was reweighted to match the PEGASUS population
- Utility values were estimated from pooled APPOINT-PNH and APPLY-PNH EQ-5D-5L data, which was mapped to EQ-5D-3L
- Base-case analyses (using iptacopan patient access scheme [PAS] price and comparator list prices) indicate that iptacopan is expected to be a cost-effective option for the treatment of PNH
  - In the complement inhibitor-naïve population, iptacopan is cost-effective vs eculizumab and ravulizumab ([redacted])
  - In the complement inhibitor-experienced population, iptacopan is cost-effective vs ravulizumab and pegcetacoplan ([redacted]). Compared with eculizumab, iptacopan is associated with £[redacted] increased costs and 1.73 incremental QALYs, resulting in an ICER above the threshold range (£[redacted]); this is related to patients discontinuing iptacopan switching to ravulizumab, and iptacopan is expected to be cost-effective vs eculizumab once the ravulizumab PAS price is considered.

B.3.1 Published cost-effectiveness studies

A systematic literature review (SLR) was conducted to identify cost-effectiveness studies from the published literature. A summary of the included cost-effectiveness studies relevant to the decision problem is provided in Table 37. A complete description of the SLR methods is presented in Appendix G.

Table 37: Summary list of published cost-effectiveness studies

Study, Year	Intervention/ comparator	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Quist et al 2023 (111)	Ravulizumab/ eculizumab	This study was a cost-utility Markov model comparing ravulizumab and eculizumab from a Dutch societal perspective, with a lifetime horizon and 2-week cycle length Two cohorts of adult patients with PNH were considered (see patient population column) 11 health states were included • 8 related to BTH events (with distinction between BTH events related to suboptimal free C5 inhibition vs related to complement-amplifying condition) • 2 related to mortality (natural/background and PNH-related) • Spontaneous remission	Adult patients with PNH who were • Cohort 1: naïve to treatment with a complement inhibitor • Cohort 2: clinically stable on eculizumab for ≥6 months (labelled dose)	Incremental QALYs, ravulizumab vs eculizumab • Aggregate population: 1.57 • Cohort 1: 1.60 • Cohort 2: 1.57	Incremental costs (EUR), ravulizumab vs eculizumab • Aggregate population: –€266,833 • Cohort 1: –€306,071 • Cohort 2: –€263,266	Ravulizumab vs eculizumab • Aggregate population: dominant • Cohort 1: dominant • Cohort 2: dominant
CADTH 2022 (a) (112)	Pegcetacoplan/ eculizumab, ravulizumab	This HTA submission presented a cost-utility Markov model comparing pegcetacoplan with eculizumab and ravulizumab from a Canadian payer perspective, with a lifetime horizon at a maximum of 51.2 years and a 4-week cycle length The efficacy of ravulizumab was considered to be equivalent to eculizumab Four health states were modelled:	Adults patients with PNH who had an inadequate response to C5 inhibitors (eculizumab or ravulizumab)	Incremental QALYs • Pegcetacoplan vs ravulizumab: 1.96 • Pegcetacoplan vs eculizumab: 3.07	Incremental costs (CAD) • Pegcetacoplan vs ravulizumab: $48,227 • Pegcetacoplan vs eculizumab: –$1,484,848	• Pegcetacoplan vs ravulizumab: $24,636 • Pegcetacoplan vs eculizumab: dominant *CADTH Appraisal – deterministic*

Study, Year	Intervention/ comparator	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
		• Transfusion avoidance Hb <10.5 g/dL • Transfusion avoidance Hb ≥10.5 g/dL • Transfusion required • Death				• Pegcetacoplan vs ravulizumab: $111,038 • Pegcetacoplan vs eculizumab: dominant *CADTH Appraisal – probabilistic* • Pegcetacoplan vs ravulizumab: $62,144 • Pegcetacoplan vs eculizumab: dominant
CADTH 2022 (b) (113)	Ravulizumab/ eculizumab	This HTA submission presented a cost-utility Markov model comparing ravulizumab with eculizumab from a Canadian payer perspective, with a lifetime horizon and a 2-week cycle length 11 health states were included: • 8 related to BTH events (with distinction between BTH events related to suboptimal free C5 inhibition vs related to complement-amplifying condition)	Adults with PNH who were • Cohort 1: treatment-naïve • Cohort 2: clinically stable on eculizumab	Incremental QALYs, ravulizumab vs eculizumab: • Aggregate population: 0.92 • Cohort 1: 0.78 • Cohort 2: 0.93 *CADTH appraisal* Aggregate population: 0	Incremental costs (CAD), ravulizumab vs eculizumab: • Aggregate population: –$42,858 • Cohort 1: –$66,425 • Cohort 2: –$41,617 *CADTH appraisal* Aggregate	Ravulizumab vs eculizumab: • Aggregate population: dominant • Cohort 1: dominant • Cohort 2: dominant *CADTH appraisal* Aggregate population:

Study, Year	Intervention/ comparator	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
		• 2 related to mortality (natural/background and PNH-related) • Spontaneous remission			population: $-13,386	dominant
Hakimi et al 2022 (114)	Pegcetacoplan/ ravulizumab	This study was a cost-utility Markov model comparing pegcetacoplan and ravulizumab from a UK payer perspective, with a lifetime horizon and a 4-week cycle length Five health states were included • Transfusion dependent • Transfusion avoidant Hb high (Hb ≥10.5 g/dL) • Transfusion avoidant Hb low (Hb <10.5 g/dL) • Spontaneous remission • Death	Adult patients with PNH whose anaemia was insufficiently controlled (Hb <10.5 g/dl) despite ≥3 months treatment with eculizumab	Incremental QALYs, pegcetacoplan vs ravulizumab: 1.75 *NCPE-adjusted base case* 0.01	Incremental costs (GBP), pegcetacoplan vs ravulizumab: –£251,510 *NCPE-adjusted base case* €-620,118	Pegcetacoplan vs ravulizumab: dominant *NCPE-adjusted base case* Pegcetacoplan vs ravulizumab: dominant
NCPE 2022 (115)	Ravulizumab/ eculizumab	This HTA submission presented a cost-utility state-transition model comparing ravulizumab with eculizumab from the perspective of the Irish healthcare system, with a lifetime horizon, and a 2-week cycle length The modelled health states were not reported	Adults patients with PNH	Incremental QALYs, ravulizumab vs eculizumab: 0.94	Incremental costs (EUR), ravulizumab vs eculizumab: –€621,262	Ravulizumab vs eculizumab: dominant
NICE TA778, 2022 (20)	Pegcetacoplan/ eculizumab, ravulizumab	This HTA submission presented a cost-utility Markov model comparing pegcetacoplan with eculizumab and ravulizumab. The economic analysis used a UK NHS and PSS perspective, with a lifetime horizon (maximum: 51	Adult patients with PNH whose anaemia is not sufficiently controlled after treatment with a C5 inhibitor for ≥3 months	Total QALYs: redacted	Total costs (GBP): redacted	• Pegcetacoplan vs ravulizumab: dominant • Pegcetacopla

Study, Year	Intervention/ comparator	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
		years), and a 4-week cycle length with half-cycle correction. The model assumes equal efficacy between ravulizumab and eculizumab in the PEGASUS trial population. Four health-states were included • No transfusion and Hb <10.5 g/dL • No transfusion and Hb ≥10.5 g/dL • Transfusion required • Death				n vs eculizumab: dominant
PBAC 2022 (116)	Pegcetacoplan/ ravulizumab, eculizumab	This HTA submission presented a cost-utility Markov model comparing pegcetacoplan with eculizumab and ravulizumab with a 51.2-year time horizon and a 4-week cycle length with half-cycle correction The submission assumed non-inferiority between ravulizumab and eculizumab within the target population Four health states were modelled • No transfusion and Hb <10.5 g/dL • No transfusion and Hb ≥10.5 g/dL • Transfusion required • Dead	Patients with PNH and inadequate clinical response to C5 inhibitor treatment (Hb <10.5 g/dL after ≥3 months of stable treatment)	Incremental QALYs: • Pegcetacoplan vs eculizumab: 1.24 • Pegcetacoplan vs ravulizumab: 1.24	Incremental costs (AUD): • Pegcetacoplan vs eculizumab: redacted • Pegcetacoplan vs ravulizumab: NR	• Pegcetacoplan vs eculizumab: dominant • Pegcetacoplan vs ravulizumab: dominant
SMC 2451, 2022 (117)	Pegcetacoplan/ ravulizumab, eculizumab	This HTA submission presented a cost-utility Markov model comparing pegcetacoplan with ravulizumab and eculizumab from the perspective of the	Adult patients with PNH who were anaemic after treatment with a C5 inhibitor for ≥3 months	NR, only LYs reported	NR	• Pegcetacoplan vs eculizumab: £376,078[†]

Study, Year	Intervention/ comparator	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
		UK NHS and social services, with a 51-year time horizon. Four health states were included • No transfusion and Hb <10.5 g/dL • No transfusion and Hb ≥10.5 g/dL • Transfusion required • Death				• Pegcetacoplan vs ravulizumab: dominant[†]
NICE TA698, 2021 (19)	Ravulizumab/ eculizumab	This HTA submission presented a cost-utility state-transition model comparing ravulizumab with eculizumab from the perspective of the UK NHS and PSS, with a lifetime horizon, and a 2-week cycle length without half-cycle correction. Ten health states were included • Eight BTH health states • Spontaneous remission (included in scenario analysis only) • Death	Adult patients with PNH who: • Had haemolysis with clinical symptom(s) indicative of high disease activity • Were clinically stable after treatment with eculizumab for ≥6 months	Total QALYs: redacted	Total costs (GBP): redacted	Ravulizumab vs eculizumab: dominant
SMC 2305, 2021 (118)	Ravulizumab/ eculizumab	This HTA submission presented both a CMA and a CUA The CMA assumed no difference in clinical effectiveness between ravulizumab and eculizumab and was a simple comparison of acquisition and administration costs The CUA used a state-transition model from the perspective of the UK NHS and social services, with a lifetime	Adults patients with PNH	Incremental QALYs, ravulizumab vs eculizumab: 0.97	• CUA, incremental costs (GBP): NR • CMA, incremental costs (GBP; at list price) £1,470,784	Ravulizumab vs eculizumab, at PAS price: dominant

Study, Year	Intervention/ comparator	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
		horizon (maximum: 50 years) Ten health states were included • Different categories of BTH (including complement amplifying condition associated, incomplete C5 inhibition related, and modelling the history of previous BTH events) • Two health states assumed patients required an increased dose of eculizumab for the remainder of the time horizon following two incomplete C5 inhibition related BTH events • Background mortality was assumed constant with the general population, and spontaneous remission and PNH-specific mortality were only modelled in the scenario analyses				
O'Connell et al 2020 (119)	Ravulizumab/ eculizumab	This study was a CUA using a Markov state-transition model to compare ravulizumab and eculizumab, from a US payer perspective with lifetime horizon and a 2-week cycle length. 11 health states were included • 8 related to BTH events (with distinction between BTH events related to suboptimal free C5 inhibition vs related to complement-amplifying condition) • 2 related to mortality (natural/background and PNH-	Adults with PNH who were • Cohort 1: naïve to eculizumab (initiating labelled dosing at the start of the model) • Cohort 2: clinically stable on approved maintenance dose of eculizumab (900mg every 2 weeks) • Cohort 3: clinically stable on off-label use of a higher maintenance	Incremental QALYs, ravulizumab vs eculizumab • Total population: 1.67 • Cohort 1: 1.19 • Cohort 2: 1.71 • Cohort 3: 1.71	Mean incremental costs (USD), ravulizumab vs eculizumab • Total population: –$1,673,465 • Cohort 1: –$1,804,568 • Cohort 2: –$1,661,792 • Cohort 3: –$3,894,428	Ravulizumab vs eculizumab: • Total population: dominant • Cohort 1: dominant • Cohort 2: dominant • Cohort 3: dominant

Study, Year	Intervention/ comparator	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
		related) • Spontaneous remission	dose of eculizumab (92.5% on 1,200mg and 7.5% on 1,500mg, every 2 weeks, based on data on file)			
O'Connell et al 2019 (120)	Ravulizumab/ eculizumab	This study was a CUA comparing ravulizumab with eculizumab from a German payer perspective, with a lifetime horizon The type of model used was not reported	Adults with PNH who were • Cohort 1: naïve to eculizumab • Cohort 2: stable on eculizumab labelled dosage • Cohort 3: stable on a higher dosage of eculizumab	Incremental QALYs, ravulizumab vs eculizumab: 0.53	Mean incremental costs (EUR), ravulizumab vs eculizumab: –€1,906,440	Ravulizumab vs eculizumab: dominant

†Assumed to be reported as ICER (per QALY); however, table in the SMC summary document is unclear as incremental LYs reported in table with no incremental QALYs.

Abbreviations: BTH, breakthrough haemolysis; AUD, Australian dollar; CAC, complement-amplifying condition; CAD, Canadian dollar; CADTH, Canadian Agency for Drugs and Technologies in Health; CMA, cost-minimisation analysis; CUA, cost-utility analysis; EUR, euro; GBP, Great British Pound; Hb, haemoglobin; HTA, health technology assessment; ICER, incremental cost-effectiveness ratio; LY, life year; NCPE, National Centre for Pharmacoeconomics; NHS, National Health Service; PAS, patient access scheme; PBAC, Pharmaceutical Benefits Advisory Committee; PNH, paroxysmal nocturnal haemoglobinuria; PSS, personal social services; QALYs, quality-adjusted life years; SMC, Scottish Medicines Consortium; UK, United Kingdom; US, United States; USD, United States dollar.

B.3.2 Economic analysis

No existing economic evaluations of iptacopan were identified in the cost-effectiveness SLR (Section B.3.1); as such, a *de novo* cost-effectiveness model (CEM) has been developed.

B.3.2.1 Patient population

In line with the Phase 3 trials (APPOINT-PNH and APPLY-PNH) (89, 93) and the expected marketing authorisation, this cost-effectiveness analysis includes two populations of adult patients with paroxysmal nocturnal haemoglobinuria (PNH):

1) Adult patients with PNH who are naïve to treatment with complement inhibitors and have haemolysis with clinical symptom(s) (i.e. complement inhibitor-naïve).

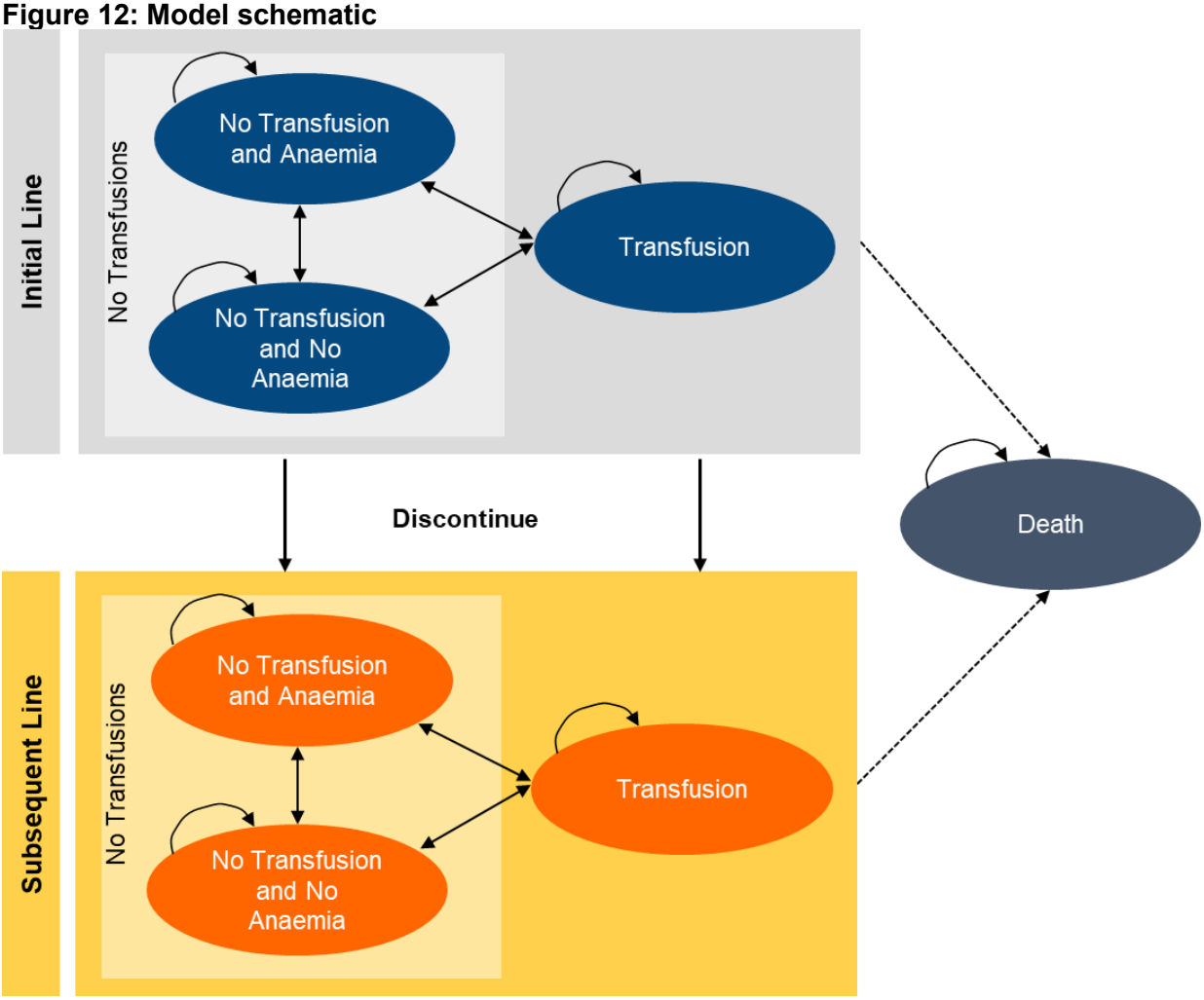
2) Adult patients with PNH who have been treated with a complement inhibitor and have anaemia (i.e. complement inhibitor-experienced with residual anaemia).

B.3.2.2 Model structure

The model was developed in Microsoft® Excel and structured as a semi-Markov model to capture all costs and outcomes associated with iptacopan and comparator treatments (Figure 12). Since mortality is derived from life-tables and the per cycle probability of death thus changes over time, the model is considered a semi-Markov model. The model comprises four mutually exclusive health states:

- No transfusion and no anaemia: patients who are not receiving transfusions and do not have anaemia
- No transfusion and anaemia: patients who are not receiving transfusions and have anaemia
- Transfusion: patients who receive transfusions
- Death: death due to any cause; terminal health state.

Figure 12: Model schematic



A similar model structure was used in the pegcetacoplan appraisal where it was assumed that presence of anaemia and blood transfusion requirements together represent different levels of disease (20, 114). The model structure was validated with UK clinical and health economic experts (101).

Patient characteristics at baseline were based on the APPOINT-PNH and APPLY-PNH trials (Section B.3.3.1). During each cycle, patients either remained in their current health state or moved to another health state based on transition probabilities derived from APPLY-PNH, APPOINT-PNH, APPEX, or published literature (Section B.3.3.2).

A subsequent line of therapy was modelled with the same three health states based on anaemia and transfusion status. After discontinuing their initial complement inhibitor, patients transitioned to another complement inhibitor and continued that

therapy for the remainder of the time horizon. Different treatment discontinuation approaches were included in the model (Section B.3.3.3).

Death could occur from any health state, with the probability of death being age- and sex-specific.

B.3.2.2.1 *Time horizon*

As PNH is a chronic disease, a lifetime time horizon was considered appropriate for the model, consistent with previous models for PNH identified by the SLR (Table 37) (19, 20, 114, 119-124). To reflect this, the model adopts a lifetime time horizon, continuing up to age 100, which leads to time horizons of 58 years in complement-inhibitor-naïve patients, and 49 years in complement-inhibitor-experienced patients, given a starting age of 42.1 and 51.0 years based on APPOINT-PNH and APPLY-PNH, respectively (89, 93).

B.3.2.2.2 *Cycle length*

The model used a 4-week cycle length which was considered appropriate to account for health events and changes in patients' health state. This cycle length also best captured the variations in dosing regimens across treatments. The same cycle length was also used in the pegcetacoplan model (20, 114). A half-cycle correction was applied using the life table method to account for uncertainty in the timing of transitions within the cycle period, where the time in each cycle was estimated using the average number of patients at the start and end of the cycle.

B.3.2.2.3 *Discounting*

In the base case, a discount rate of 3.5% per annum was applied in line with the National Institute for Health and Care Excellence (NICE) reference case (125). A discount rate for costs and health outcomes of 0% was explored in scenario analyses (Section B.3.10.2).

B.3.2.2.4 *Perspective*

The analysis was conducted from the perspective of the National Health Service (NHS) and personal social services (PSS) in England and Wales, in line with the NICE reference case (125).

B.3.2.3 Features of the economic analysis

Key features of the economic analysis and a comparison to previous NICE appraisals of PNH treatments are outlined in Table 38.

Table 38: Features of the economic analysis

Factor	Previous appraisals		Current appraisal	
	TA698 (ravulizumab)	TA778 (pegcetacoplan)	Chosen values	Justification
Patient population	Adults with PNH who have haemolysis with clinical symptom(s) indicative of high disease activity or whose disease is clinically stable after having eculizumab for ≥6 months	Adults with PNH whose anaemia is not sufficiently controlled after treatment with a C5 inhibitor	Adults with PNH: • Complement inhibitor-naïve patients who have haemolysis with clinical symptom(s) • Complement inhibitor-experienced patients with anaemia despite treatment with a complement inhibitor	Aligned with the available evidence and the anticipated licence for iptacopan (Table 1).
Model structure	Semi-Markov model	Semi-Markov model	Semi-Markov model	In line with NICE reference case (125) and previous appraisals (19, 20).
Health states	10 health states: • Eight BTH health states • Death • Spontaneous remission (included in scenario analysis only)	Four health states: • No transfusion and Hb ≥10.5 g/dL • No transfusion and Hb <10.5 g/dL • Transfusion • Death	Four health states: • No transfusion and no anaemia • No transfusion and anaemia • Transfusion • Death In the base case, no anaemia was defined as Hb ≥10.5 g/dL and anaemia was defined as Hb <10.5 g/dL.	Iptacopan is comparable to pegcetacoplan in terms of mechanism of action (proximal complement inhibitor) and has demonstrated benefit over C5 inhibitors in improving anaemia and reducing blood transfusion requirements, which UK clinicians consider important outcomes (50, 93). UK clinical and health economic experts confirmed that the model structure of TA778, which defined health states as a combination of Hb levels and transfusions, was more appropriate to compare iptacopan vs current SoC than the BTH-based model structure used in TA698 (101). Therefore,

Factor	Previous appraisals		Current appraisal	
	TA698 (ravulizumab)	TA778 (pegcetacoplan)	Chosen values	Justification
				the model structure of TA778 was adopted in this submission. In the base case, no transfusion was stratified based on patients' Hb level above or below a threshold level of 10.5g/dL in line with TA778 (20), which was validated by clinical opinion as appropriate for capturing differences in HRQoL between health states (101).
Time horizon	Lifetime	Lifetime	Lifetime	In line with NICE reference case (125)
Cycle length	2 weeks	4 weeks	4 weeks	The chosen cycle length is consistent with TA778 (20). In addition, the cycle period is aligned with the visit schedule in APPOINT-PNH and APPLY-PNH trials, where Hb data was collected at least every 4 weeks (89, 93). A half cycle correction was applied.
Perspective	NHS and PSS	NHS and PSS	NHS and PSS	In line with NICE reference case (125)
Discounting per year of costs and utilities	3.5% per annum	3.5% per annum	3.5% per annum	In line with NICE reference case (125)
Health effects	QALYs and life years	QALYs and life years	QALYs and life years	In line with NICE reference case (125)
Treatment waning effect?	None	None	None	Not considered appropriate in line with prior appraisals (19, 20).
Source of clinical efficacy and	Study 301 (NCT02946463) and Study 302	PEGASUS trial (49)	APPOINT-PNH and APPLY-PNH trials (89, 93), APPEX study (106),	APPOINT-PNH and APPLY-PNH are the primary sources of evidence for iptacopan in PNH; APPLY-PNH was also used as a

Factor	Previous appraisals		Current appraisal	
	TA698 (ravulizumab)	TA778 (pegcetacoplan)	Chosen values	Justification
safety	(NCT03056040) (46, 47)		and published clinical evidence (PEGASUS trial (49, 114))	source for C5 inhibitors in the experienced population. The APPEX study served as source for C5 inhibitor efficacy in the naïve population due to access to IPD, which was required for generation of transition probabilities. Pegcetacoplan efficacy and safety was informed by the most appropriate source identified in the SLR (PEGASUS trial) and transition probabilities were taken from a published source (114).
Source of utilities	EORTC QLQ-C30 data from Study 301 and Study 302 (46, 47) mapped to EQ-5D-3L utility estimates, using the Longworth et al. mapping algorithm (126)	EORTC QLQ-C30 data from the PEGASUS trial (49) mapped to EQ-5D-3L utilities using the Longworth et al. mapping algorithm (126)	EQ-5D-5L utilities from APPOINT-PNH and APPLY-PNH (89, 93) mapped to EQ-5D-3L utilities using the Hernández et al mapping algorithm (127).	In line with NICE reference case (125), EQ-5D-3L utilities were used in this submission, mapped from EQ-5D-5L. Utilities used in prior submissions (19, 20) were mapped from EORTC to EQ-5D-3L, since the clinical trials informing the submissions did not collect EQ-5D data. Utilities based on EORTC data from APPOINT-PNH and APPLY-PNH have been used in scenario analysis.
Source of costs	Standard UK sources including eMIT and MIMS for drug costs, and NHS reference costs	BNF for drug costs, NHS reference costs for disease management unit costs, and clinical expert opinion	BNF for drug costs, NHS reference costs for disease management unit costs, and clinical expert opinion	In line with NICE reference case (125), previous appraisals (19, 20), and input from clinicians (50).

Abbreviations: BTH, breakthrough haemolysis; BNF, British National Formulary; eMIT, electronic market information tool; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D, European Quality of Life 5 Dimensions; EQ-5D-3L/ -5L, European Quality of Life 5 Dimensions 3 Level Version/ 5 Level Version; EVH, extravascular haemolysis; Hb, haemoglobin; IPD, individual patient data; MIMS, Monthly Index of Medical Specialties; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PNH, paroxysmal nocturnal haemoglobinuria; PSS, Personal social services; QALY, Quality-adjusted life-years; QoL, quality of life; SoC, standard of care; UK, United Kingdom.

B.3.2.4 Intervention technology and comparators

B.3.2.4.1 *Intervention*

The intervention considered in this analysis is iptacopan with a dose of 200 mg BD (oral capsules).

B.3.2.4.2 *Comparators*

The final scope states that the comparators for iptacopan include:

- Eculizumab
- Ravulizumab
- Pegcetacoplan
- Danicopan with a C5 inhibitor (subject to NICE ongoing appraisal).

Pegcetacoplan is only an option for patients who continue to have anaemia after ≥3 months of treatment with a C5 inhibitor, as per TA778 (20), and has therefore only been considered as a comparator in the complement inhibitor-experienced population.

Danicopan with a C5 inhibitor has not been considered since it does not currently have a licence and is not expected to become established NHS clinical practice prior to the appraisal of iptacopan by committee.

Table 39 summarises PNH treatment indications and dosing regimens of the intervention and comparators.

Table 39: Treatment indications and dosing regimens

Comparators	Indication	Dosing	Source

Iptacopan	Expected indication
	• Indicated for the treatment of adult patients with PNH:
	  • who have haemolysis with clinical symptom(s), or
	  • who are anaemic after treatment with a complement inhibitor
		• Oral
		• 200 mg BD
			Draft SmPC (Appendix C)

Eculizumab	• Indicated in adults and children for the treatment of PNH. Evidence of	• IV infusion • For adult patients (≥18 years of age), 4-week	SmPC (42)

Comparators	Indication	Dosing	Source
	clinical benefit is demonstrated in patients with haemolysis with clinical symptom(s) indicative of high disease activity, regardless of transfusion history	initial phase followed by maintenance phase: • Initial phase: • 600 mg QW for first 4 weeks • Maintenance phase: • 900 mg for the fifth week, followed by 900 mg Q2W	
Ravulizumab	• Indicated in the treatment of adult and paediatric patients with a body weight of 10 kg or above with PNH: • in patients with haemolysis with clinical symptom(s) indicative of high disease activity • in patients who are clinically stable after having been treated with eculizumab for at least the past 6 months	• IV infusion • For adult patients (≥18 years of age), loading dose followed by maintenance doses Q8W starting 2 weeks after loading dose • Dosing by weight: • ≥40 to <60 kg: • Loading: 2,400 mg • Maintenance: 3,000 mg • ≥60 to <100 kg: • Loading: 2,700 mg • Maintenance: 3,300 mg • ≥100 kg: • Loading: 3,000 mg • Maintenance: 3,600 mg	SmPC (45)
Pegcetacoplan	• Indicated in the treatment of adult patients with PNH who are anaemic after treatment with a C5 inhibitor for ≥3 months	• SC infusion • 1,080 mg twice weekly (on Day 1 and Day 4 of each week) • Patients switching from a C5 inhibitor • First 4 weeks, pegcetacoplan 1,080 mg twice weekly in addition to current dose of C5 inhibitor • After 4 weeks, discontinue C5 inhibitor • Dose adjustment (if LDH >2 x ULN) • Dosing regimen may be changed to 1,080 mg every third day (Day 1, Day 4, Day 7, Day 10, etc.)	SmPC (23)

Abbreviations: BD, twice daily; IV, intravenous; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal haemoglobinuria; Q2W, every two weeks; Q8W, every eight weeks; QW, once weekly; SC, subcutaneous; SmPC, summary of product characteristics; ULN, upper limit of normal.

In the economic model, eculizumab and ravulizumab are assumed to have equivalent efficacy, in line with the approach adopted in the pegcetacoplan appraisal [TA778] (20). Ravulizumab was created from eculizumab by targeted substitution of four amino acids, resulting in a longer terminal half-life, and Study 301 and Study 302 demonstrated the non-inferiority of ravulizumab vs eculizumab as treatments for PNH (46, 47). In TA698 the committee considered that eculizumab and ravulizumab were similarly effective (19) and in TA778 the committee agreed that the assumption of equal efficacy in the model was reasonable (20). UK clinicians and health economists consulted during the preparation of this submission also considered this assumption appropriate (101).

B.3.3 Clinical parameters and variables

B.3.3.1 Patient characteristics

Patient characteristics at baseline (Table 40) and initial distribution of patients across health states (Table 41) were based on APPOINT-PNH and APPLY-PNH trial data (89, 93).

Table 40: Patient characteristics in the APPOINT-PNH and APPLY-PNH trials

Patient characteristic	Complement inhibitor-naïve patients	Complement inhibitor-experienced patients
Mean age, SD (years)	42.1 (15.8)	51.0 (16.8)
Proportion male (%)	57.5%	30.9%
Mean body weight, (SD), kg	70.1 (12.7)	71.6 (18.8)
Proportion of patients by weight category (%)	≥40 to <60 kg: 17.5% ≥60 to <100 kg: 80.0% ≥100 kg: 2.5%	≥40 to <60 kg: 26.8% ≥60 to <100 kg: 66.0% ≥100 kg: 7.2%

Abbreviations: SD, standard deviation.

Table 41: Distribution of patients at baseline

Health state	Complement inhibitor-naïve patients	Complement inhibitor-experienced patients
No Transfusion and No Anaemia	0%	0%
No Transfusion and Anaemia	75.0%	75.3%
Transfusion	25.0%	24.7%

B.3.3.2 Transition probabilities

B.3.3.2.1 *Methodology*

Transition probabilities were derived from individual patient data (IPD) where available. Where IPD was not available (i.e. for pegcetacoplan), published transition probabilities were used. As such, when deriving transition probabilities from IPD, it was necessary to follow the methods applied in the published literature (114) to ensure comparability between treatments.

B.3.3.2.1.1 Complement inhibitor-experienced population

IPD from APPLY-PNH were used to derive health state transition probabilities for iptacopan and C5 inhibitors (eculizumab/ravulizumab) in the complement inhibitor-experienced population, for health states defined as: 1) No transfusion and no anaemia; 2) No transfusion and anaemia; and 3) Transfusion. The transfusion health state was defined as receipt of packed RBC transfusion within 4 weeks prior to a study visit. All available haemoglobin (Hb) values were used to allow patients to move to and from the anaemia health state, in line with the pegcetacoplan model (20, 114).

Transition probabilities were derived in line with the methods described by Hakimi et al (114). A multinomial logistic regression model was fit using health state as a dependent variable and lagged health state (i.e. health state 4 weeks prior), treatment (i.e. iptacopan, C5 inhibitor therapy), time from first dose (measured in weeks) to study visit as well as interactions for time × treatment and time × lagged health state as independent variables. The multinomial model was fit using data from study visits collected over 4-week intervals (up to the end of the randomised controlled period at Day 168) to align with the cycle length of the economic model. To adjust for differences between trial populations, the model was fit using patient weights from the indirect treatment comparison (ITC) described in Section B.2.9.3 to align the APPLY-PNH data to the PEGASUS trial population (base case; a scenario analysis explored unweighted transition probabilities). The fitted model was used to predict the probability of being in each health state conditional on study visit, lagged health state, and treatment arm. These predicted probabilities were then averaged over study visits by lagged health state and treatment arm.

In the base-case analysis, pooled C5 inhibitor arm data were used to obtain a single set of transition probabilities, assuming that the treatments are similarly effective (Section B.3.2.4.2). A scenario analysis used separate sets of transition probabilities for eculizumab and ravulizumab.

In the absence of head-to-head data comparing iptacopan with pegcetacoplan or access to pegcetacoplan IPD, transition probabilities for pegcetacoplan were sourced from the literature, as reported by Hakimi et al from the PEGASUS trial (114). Since this submission uses the same health states as the pegcetacoplan model, the pegcetacoplan transition probabilities reported in the literature could be used in the model. A scenario analysis also explored use of transition probabilities from the PEGASUS trial for C5 inhibitors as used in the pegcetacoplan model and reported by Hakimi et al (114) (see Section B.3.10.2).

B.3.3.2.1.2 Complement inhibitor-naïve population

IPD from APPOINT-PNH were used to derive health state transition probabilities for iptacopan in the complement inhibitor-naïve population, using similar methods as for APPLY-PNH (detailed in Section B.3.3.2.1.1). Since APPOINT-PNH was a single-arm trial with iptacopan as the only treatment, the multinomial model was specified without treatment or time × treatment. The fitted model was used to predict the probability of being in each health state conditional on study visit and lagged health state. These predicted probabilities were then averaged over study visits by lagged health state.

Data for C5 inhibitors (eculizumab/ravulizumab) in treatment-naïve patients were not available from the iptacopan clinical trials, and no suitable published transition probabilities were identified for C5 inhibitors in this population. Generation of transition probabilities from published summary data of clinical trials, such as Study 301, was not feasible as assigning a patient's health state requires data on both Hb and transfusion status in combination. IPD was thus required to generate transition probabilities for the model.

IPD for C5 inhibitors in the naïve population were available from the APPEX study, a real-world retrospective cohort of patients in the UK and France (Section B.2.9.2). These data were used to derive transition probabilities for C5 inhibitors in the naïve

population using the same methods as were applied for APPOINT-PNH. Since APPEX data were collected in real-world routine clinical practice, Hb values were subject to high levels of missing information across consecutive four-week periods. To address this, missing information for Hb was imputed using last observation carried forward (LOCF) prior to fitting the multinomial logistic regression model. A scenario analysis is presented using transition probabilities generated without data imputation. APPEX data were reweighted to match the APPOINT-PNH population (Section B.2.9.2); a scenario analysis explored unweighted transition probabilities.

B.3.3.2.1.3 Haemoglobin threshold for anaemia

Two Hb thresholds were considered when defining anaemia: 1) <10.0 g/dL, to align with the inclusion criteria in APPLY-PNH and APPOINT-PNH (89, 93); and 2) <10.5 g/dL, to align with the definition used in the pegcetacoplan model (78, 114). UK clinicians considered both thresholds as acceptable to define anaemia (50, 101).

Where IPD were available, transition probabilities were derived using both thresholds. In order to maintain a consistent definition across all treatment lines and interventions in the model, the base-case analysis for both populations used a threshold of <10.5 g/dL to define anaemia because the only transition probabilities published for pegcetacoplan were based on this threshold (114).

B.3.3.2.2 *Transition probabilities applied in the analysis*

B.3.3.2.2.1 Complement inhibitor-naïve population

Table 42 presents the health state transition probabilities derived from APPOINT-PNH (iptacopan) and APPEX (C5 inhibitors), which were used in the base-case analysis for the complement inhibitor-naïve population. Transition probabilities used in scenario analyses are presented in Appendix P.

Table 42: Health state transition probabilities for the complement inhibitor-naïve population

From	To		
	No Transfusion and No Anaemia	No Transfusion and Anaemia	Transfusion
Iptacopan			
No Transfusion and No Anaemia	99.1%	0.9%	0.0%
No Transfusion and Anaemia	49.4%	48.2%	2.4%
Transfusion	18.0%	80.1%	1.9%
C5 inhibitors (eculizumab/ravulizumab)			
No Transfusion and No Anaemia	90.1%	9.4%	0.5%
No Transfusion and Anaemia	10.2%	87.9%	1.9%
Transfusion	0.5%	78.4%	21.1%

Anaemia defined as Hb <10.5 g/dL.
Abbreviations: Hb, haemoglobin.

B.3.3.2.2.2 Complement inhibitor-experienced population

Health state transition probabilities derived from APPLY-PHN (iptacopan and C5 inhibitors) and as reported from PEGASUS (pegcetacoplan) (114) which were used in the base-case analysis for the complement inhibitor-experienced population are shown in Table 43. Transition probabilities used in scenario analyses are presented in Appendix P.

Table 43: Health state transition probabilities for the complement inhibitor-experienced population

From	To		
	No Transfusion and No Anaemia	No Transfusion and Anaemia	Transfusion
Iptacopan			
No Transfusion and No Anaemia	97.8%	2.2%	0.0%
No Transfusion and Anaemia	50.6%	48.2%	1.2%
Transfusion	56.7%	39.6%	3.7%
C5 inhibitors (eculizumab/ravulizumab)			
No Transfusion and No Anaemia	47.0%	52.9%	0.1%
No Transfusion and Anaemia	8.0%	65.2%	26.8%
Transfusion	6.1%	33.8%	60.1%
Pegcetacoplan			
No Transfusion and No Anaemia	96.6%	3.1%	0.3%
No Transfusion and Anaemia	49.1%	43.7%	7.2%
Transfusion	61.2%	26.6%	12.2%

Anaemia defined as Hb <10.5 g/dL.
Abbreviations: Hb, haemoglobin.

B.3.3.2.2.3 Maintenance of treatment effect

Health state transition probabilities were based on efficacy data up to Week 24. It was assumed that the treatment effect observed during that time is maintained

throughout the duration of therapy for each treatment. This assumption was applied to all treatments in the model. This approach aligns with the pegcetacoplan model that also assumed that transition probabilities based on data up to Week 16 were applicable for the duration of treatment (20, 114).

B.3.3.3 Discontinuation and subsequent therapy

PNH is a chronic disease, requiring lifelong treatment with complement inhibitors (23, 42, 45, 101, 128) (Appendix C). Lifelong treatment was assumed accordingly in the model; where patients discontinued one complement inhibitor, a switch to another complement inhibitor was modelled. A maximum of one subsequent therapy was included, in line with clinical and health economic expert advice (101).

Continuous discontinuation was included for iptacopan and pegcetacoplan in the base case analysis. The annual probability of discontinuation was informed by treatment-specific all-cause discontinuation rates from clinical trials, and it was assumed that patients would discontinue from all health states equally. In all cases it was assumed that patients discontinuing would switch to ravulizumab, based on UK clinical input (50, 101). For complement inhibitor-experienced patients, the annual probabilities of discontinuation for iptacopan and pegcetacoplan were based on data from APPLY-PNH and PEGASUS (80), respectively; data were adjusted to reflect 52-week discontinuation.

In the iptacopan arm of APPLY-PNH, during the 24-week randomised treatment period, there was one discontinuation in 28.66 patient-years of follow-up, giving a discontinuation probability of 3.43% per year.

Four out of 13 discontinuations during pegcetacoplan treatment in PEGASUS were attributed to breakthrough haemolysis (BTH) (80). However, in UK clinical practice, BTH is not a reason for discontinuation of pegcetacoplan (50, 101), and these four cases were excluded from the calculation. One further discontinuation was due to death (from COVID-19), and this has also been excluded, to avoid double counting since mortality is considered separately. There was a reported median of 215 days of exposure in PEGASUS (80), thus 8 discontinuations in 45.48 patients-years of follow-up, giving an annual discontinuation probability of 16.13%.

No discontinuations were observed with iptacopan in APPOINT-PNH up to Week 24, and so the discontinuation rate from the iptacopan arm in APPLY-PNH has conservatively been applied also for the complement inhibitor-naïve population.

In the complement inhibitor-naïve population, it was assumed that a proportion of patients receiving eculizumab or ravulizumab who still had anaemia or were receiving transfusions at 6 months would switch to pegcetacoplan (i.e. one-time discontinuation for patients in the Transfusion or No transfusion and anaemia states). This is reflective of UK clinical practice (50, 101). While the NICE recommendation states that patients who have anaemia after ≥3 months of treatment with a C5 inhibitor may switch to pegcetacoplan (20), UK clinicians advised that in practice such a switch would usually occur at around 6 months (101). UK clinicians also advised that among those eligible to switch, only 20–30% of patients would switch to pegcetacoplan in clinical practice, with the remaining patients staying on their C5 inhibitor treatment, mainly due to patient preference (50).

Complement inhibitor-experienced patients receiving eculizumab or ravulizumab were assumed not to discontinue and thus remain on the same treatment throughout the time horizon. This was based on assumptions that in the experienced population, any patients that wanted to switch to pegcetacoplan would have done so already, and patients require lifelong complement inhibitor treatment to control haemolysis and manage the risk of thrombosis (42, 45, 101). Of note, for simplicity, no switches between eculizumab and ravulizumab were modelled; however, it should be kept in mind that eculizumab is for most patients only considered a short- to medium-term treatment option during family planning and/or pregnancy, given the availability of extensive long-term safety data, with patients eventually switching (back) to ravulizumab longer-term (101).

Transition probabilities for patients switching to pegcetacoplan were taken from PEGASUS. For patients switching to ravulizumab, transition probabilities were based on APPEX. It was assumed that the health state that patients discontinued from in the initial treatment line was the health state that patients entered in the subsequent line of therapy. A summary of treatment discontinuation in the model base case is provided in Table 44. A scenario analysis explored no treatment discontinuation for all treatments (Section B.3.10.2).

Table 44: Treatment discontinuation and subsequent therapy in the base case

Initial therapy	Discontinuation type	Discontinuation probability	Subsequent therapy	Source
Complement inhibitor-naïve population				
Iptacopan	Continuous	3.43% per year	Ravulizumab	Assumed equal to experienced population
Eculizumab	One-time	30% of patients in 'Transfusion' or 'No Transfusion and Anaemia' health states at 6 months	Pegcetacoplan	UK clinical advisory board (50); Expert input in model validation calls (101)
Ravulizumab	One-time	30% of patients in 'Transfusion' or 'No Transfusion and Anaemia' health states at 6 months	Pegcetacoplan	UK clinical advisory board (50); Expert input in model validation calls (101)
Complement inhibitor-experienced population				
Iptacopan	Continuous	3.43% per year	Ravulizumab	APPLY-PNH (24 weeks) (93); UK clinical advisory board (50)
Eculizumab	No discontinuation	NA	NA	Expert input in model validation calls (101)
Ravulizumab	No discontinuation	NA	NA	Expert input in model validation calls (101)
Pegcetacoplan	Continuous	16.13% per year	Ravulizumab	PEGASUS (48 weeks) (80), excluding 4 discontinuations due to BTH and one due to death based on UK clinical advisory board input (50); Expert input in model validation calls (101)

Abbreviations: BTH, breakthrough haemolysis; NA, not applicable; UK, United Kingdom.

B.3.3.4 Safety and BTH

BTH was incorporated into the model as a discrete event associated with a one-off cost and disutility. For iptacopan, the rate of BTH was taken from APPOINT-PNH for complement inhibitor-naïve patients and from APPLY-PNH for complement inhibitor-

experienced patients (89, 93). For eculizumab and ravulizumab, the rate of BTH events was taken from Study 301 (47) for complement inhibitor-naïve patients, and from APPLY-PNH for complement inhibitor-experienced patients (93). For pegcetacoplan, the rate of BTH events was taken from PEGASUS (48-week data) (80). The rate of BTH events in summarised in Table 45.

Table 45: Summary of BTH event rates

Treatment	Annualised BTH rates	
	Complement inhibitor-naïve	Complement inhibitor-experienced
Iptacopan	0.00	0.07
Eculizumab	0.21	0.67
Ravulizumab	0.08	0.67
Pegcetacoplan	NA	0.13

Abbreviations: BTH, breakthrough haemolysis. NA, not applicable (pegcetacoplan is not licensed or used in complement inhibitor-naïve patients).

Additionally, the model considered treatment-emergent serious adverse events (SAE) occurring in ≥3% of patients in any arm of the key trials relevant for the decision problem (APPOINT-PNH, APPLY-PNH, PEGASUS, Study 301) (89, 93, 129, 130). SAEs were selected because they were expected to have more meaningful disutility and cost implications than total adverse events (AE). The only SAEs with a frequency of ≥3% in any treatment arm were anaemia (eculizumab arm in PEGASUS), haemolysis (pegcetacoplan arm in PEGASUS and C5 inhibitor arm in APPLY-PNH), and COVID-19 (C5 inhibitor arm in APPLY-PNH) (93, 130). Since anaemia and haemolysis are already captured in the model, through the health states (Section B.3.2.2) and via modelling of BTH, including them as SAEs would double count their impact. COVID-19 has been excluded as an SAE because it is not an adverse reaction to a treatment and was not a risk for earlier trials. Therefore, no additional SAEs were included in the analysis.

B.3.3.5 Mortality

Long-term survival data suggest that patients with PNH receiving eculizumab have comparable survival to the age-adjusted general population (131). Therefore, in the model, the probability of death was based on general population mortality. The same approach was used in the ravulizumab and pegcetacoplan appraisals, which was considered appropriate by the Evidence Review Group (ERG) in both cases, with no objections raised by the NICE committees (19, 20).

Mortality is the same from all model health states, with the probability changing over time based on patient age and assumed equal for all treatments. General population mortality data were obtained from the most recent England and Wales life tables (132). The annual probabilities of death by sex and age were converted to rates of death. The rates were weighted based on the proportion of males in the model and then converted to per cycle probabilities of death by age. The model uses the sex-weighted per cycle probability of death based on the mean patient age at each cycle.

B.3.4 Measurement and valuation of health effects

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

Health state utility values used in the analysis were estimated from APPOINT-PNH and APPLY-PNH IPD (89, 93). Mapped EQ-5D-3L utilities (Table 46) were derived from EQ-5D-5L responses collected at Day 1 (defined as baseline) and at all other visits where patients completed the EQ-5D questionnaire (i.e. Day 14, 42, 84, 126, 140, 154, and 168).

Table 46: Mapped utility values, mean (standard deviation)

Visit	APPOINT-PNH	APPLY-PNH iptacopan	APPLY-PNH C5 inhibitor
Screening	0.77 (0.21)	0.79 (0.17)	0.74 (0.20)
Day 1	0.77 (0.17)	0.79 (0.17)	0.69 (0.28)
Day 14	0.85 (0.15)	0.85 (0.12)	0.77 (0.21)
Day 42	0.86 (0.13)	0.88 (0.12)	0.70 (0.19)
Day 84	0.88 (0.15)	0.88 (0.13)	0.75 (0.17)
Day 126	0.88 (0.16)	0.87 (0.12)	0.75 (0.17)
Day 140	0.89 (0.12)	0.86 (0.13)	0.72 (0.26)
Day 154	0.87 (0.15)	0.87 (0.13)	0.75 (0.24)
Day 168	0.90 (0.10)	0.88 (0.11)	0.72 (0.26)

B.3.4.2 Mapping

EQ-5D-3L utilities for the UK were obtained by applying the mapping function from Hernandez Alava et al. (2020) (133) to EQ-5D-5L responses from APPOINT-PNH (89) and APPLY-PNH (93). EQ-5D-3L utilities were summarised descriptively by treatment arm for patients with complete EQ-5D-5L responses at baseline.

EORTC-QLQ-C30 data was also collected in APPOINT-PNH and APPLY-PNH. This data was mapped to EQ-5D-3L utility values using the Longworth et al., 2014 (126) algorithm and used in a scenario analysis.

B.3.4.3 Health-related quality of life studies

B.3.4.3.1 *Description of identified studies*

The SLR identified 10 studies that met the pre-defined inclusion criteria. A complete description of the identified studies is presented in Appendix H.

B.3.4.4 Adjustment for general population utility values

In line with the NICE manual (125), utility values applied in the model were adjusted for age, using general population utility values for the UK derived from the HSE 2014 dataset reported by Hernandez-Alava et al, 2022 (134). A multiplicative method was used to adjust utility values in each cycle.

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

The model used to estimate health state utility values was a mixed linear model for repeated measures, which was fit to all utility values obtained at Day 1 (defined as baseline) and all other visits where patients completed the EQ-5D questionnaire (i.e. Day 14, 42, 84, 126, 140, 154 and 168). Patient-visit observations with missing Hb values were discarded from model fitting. Data from APPLY-PNH and APPOINT-PNH were pooled for model fitting to enhance sample size and precision of model coefficients. A total of 960 observations were available across the two trials.

Model selection was performed among all models adjusting for health state and study visit using information criteria such as the Akaike information criterion (AIC) and Bayesian information criterion (BIC). Baseline utility and treatment were found to be statistically significant in model runs, so these covariates were included in the final model. Additionally, a study covariate differentiating patients in APPLY-PNH from those in APPOINT-PNH was also incorporated. This covariate generally had a small and statistically insignificant coefficient, suggesting that the difference in mean utilities for the iptacopan arm of APPLY-PNH and APPOINT-PNH could be expected a priori to be small. Nevertheless, models were fit separately for each study to

confirm that utility estimates by health state for the iptacopan arm did not differ substantially between APPOINT-PNH and APPLY-PNH. Finally, additional demographic variables, such as age and sex, did not improve model fit and thus were not included in the final model. All models were fit using random individual-level intercepts to account for correlation in utility values within patients across visits. The models were fit using the lme4 package in R.

Covariates included in the final model, selected for best fit, were health state, treatment (iptacopan vs C5 inhibitors), baseline utility value, follow-up visit, and study (APPLY-PNH vs APPOINT-PNH). Coefficient estimates are shown in Table 47.

Table 47: Multivariable regression results for selected utility model

Covariate	Point Estimate	SE	Lower 95% CI	Upper 95% CI
Intercept	0.793	0.028	0.738	0.848
Health state (reference: Transfusion)				
No transfusion and Anaemia	0.003	0.014	–0.025	0.031
No transfusion and No Anaemia	0.026	0.017	–0.007	0.058
Treatment (iptacopan vs C5 inhibitors)	0.071	0.022	0.028	0.114
Baseline utility	0.488	0.038	0.413	0.563
Study (APPLY–PNH vs APPOINT-PNH)	–0.019	0.018	–0.055	0.017
Follow–up visit				
Baseline	–0.076	0.016	–0.107	–0.045
Day 14	–0.026	0.014	–0.054	0.002
Day 42	–0.013	0.013	–0.039	0.013
Day 84	–0.003	0.013	–0.029	0.023
Day 126	–0.012	0.013	–0.039	0.014
Day 140	–0.019	0.013	–0.045	0.007
Day 154	–0.010	0.013	–0.036	0.016

Anaemia defined as Hb <10.5 g/dL.
Abbreviations: CI, confidence interval; Hb, haemoglobin; SE, standard error.

After fitting the model to the pooled data, predicted utilities were computed for all patients in APPLY-PNH and APPOINT-PNH, conditional on study enrolment, study visit, health state at study visit, baseline utility, and treatment. Treatment-specific means and SDs of the predicted utilities were then pooled by treatment arm across studies, study visit, and observed baseline utilities. Treatment-independent means and SDs of utilities were similarly derived by pooling across studies, study visits, observed baseline utilities, and treatment arms; these were used in a scenario analysis.

Model-generated utility predictions which were used in the base-case analysis for both populations are shown in Table 48. Within each health state, patients treated with iptacopan were predicted to experience better health-related quality of life (HRQoL) compared with those treated with C5 inhibitors. This could be due to patients treated with iptacopan having higher mean Hb levels (Section B.2.6.2.2.2) and experiencing less fatigue (Section B.2.6.2.2.3), which may not be fully accounted for in the definition of anaemia health states using a Hb threshold of 10.5 g/dL. In addition, patients treated with iptacopan may have experienced better HRQoL associated with the oral mode of administration vs intravenous (IV) infusions with C5 inhibitors. In the model, utility values for pegcetacoplan were assumed equal to iptacopan, which is considered a conservative assumption (Section B.3.12).

The utility values used in scenario analyses are presented in Appendix P.

Table 48: Health state utility values

Health State	Iptacopan		C5 inhibitors	
	Mean	SE	Mean	SE
No Transfusion and No Anaemia	0.879	0.098	0.775	0.126
No Transfusion and Anaemia	0.819	0.102	0.743	0.182
Transfusion	0.800	0.102	0.695	0.182

Note: Iptacopan health state utility values were also applied to pegcetacoplan. Anaemia defined as Hb <10.5 g/dL.
Abbreviations: Hb, haemoglobin; SE, standard error.

B.3.4.5.1 *Disutility associated with mode of administration*

Iptacopan is the only oral therapy included in the analysis, with C5 inhibitors being administered via IV infusion and pegcetacoplan via subcutaneous (SC) infusion. These infusions can be burdensome for patients, as they take time to administer and can be difficult to plan around (50, 78, 135).

Previous appraisals have included a utility decrement for frequent IV infusions with eculizumab (dosing every 2 weeks [Q2W]) (19, 20). The committee in the ravulizumab appraisal accepted that there was a benefit on utility for ravulizumab (dosing every 8 weeks [Q8W]) over eculizumab (Q2W) which was reflected in the trial data and this was also adopted in the pegcetacoplan appraisal, where a disutility of –0.025 was applied for eculizumab (19, 20). This has not been applied in the base-case analysis here, as treatment-dependent utilities are being used, but is considered in a scenario analysis which uses treatment-independent utilities.

No data were identified quantifying a potential disutility associated with 8-weekly IV infusion for ravulizumab, or with twice weekly SC infusion for pegcetacoplan. The latter can be time consuming for patients, with a typical infusion time of approximately 30 minutes if using two sites, or approximately 60 minutes if using one site (23). As such, the potential positive impact on patients' quality of life from receiving an oral treatment with iptacopan vs the currently available infusion treatments, is not fully captured within quality-adjusted life years (QALY) (Section B.3.12).

B.3.4.5.2 *Breakthrough haemolysis*

Similar to the approach used in the ravulizumab appraisal, a utility decrement associated with BTH was incorporated into the analysis. The appraisal reports this as a disutility of 0.11, based on data from Study 301, alongside an average duration of a complement-amplifying condition (CAC)-related BTH event of 14 days (19).

This time-adjusted per cycle disutility was then multiplied by the per cycle probability of BTH (Section B.3.3.4) to obtain the BTH-related disutility per cycle for each treatment (Table 49).

Table 49: Disutility associated with BTH per cycle

	Complement inhibitor-naïve population	Complement inhibitor-experienced population
Iptacopan	0.00000	–0.00002
Eculizumab	–0.00007	–0.00022
Ravulizumab	–0.00003	–0.00022
Pegcetacoplan†	NA	–0.00004

†Pegcetacoplan is not licensed or used in complement inhibitor-naïve patients.
Abbreviations: BTH, breakthrough haemolysis; NA, not applicable.

The utility values used in the cost-effectiveness analysis are summarised in Table 50.

Table 50: Summary of utility values for cost-effectiveness analysis

State	Utility value, mean (SE)	95% CI	Reference in submission (section and page number)	Justification
Health state utility values for iptacopan and pegcetacoplan				
No Transfusion and No Anaemia	0.879	0.858, 0.899	Section B.3.4.5, page 122	Based on trial data from APPOINT-PNH and APPLY-PNH. Pegcetacoplan has been assumed equivalent to iptacopan.
No Transfusion and Anaemia	0.819	0.794, 0.843		
Transfusion	0.800	0.774, 0.825		
Health state utility values for C5 inhibitors				
No Transfusion and No Anaemia	0.775	0.748, 0.801	Section B.3.4.5, page 122	Based on trial data from APPOINT-PNH and APPLY-PNH.
No Transfusion and Anaemia	0.743	0.715, 0.770		
Transfusion	0.695	0.666, 0.724		
Disutility for eculizumab administration (scenario analysis)				
Disutility	–0.025	NA	Section B.3.4.5.1, page 124	In line with previous appraisals (19, 20)
BTH disutility				
BTH	–0.11	–0.188, –0.041	Section B.3.4.5.2, page 125	In line with TA698 (19)

Abbreviations: AE, adverse effect; BTH, breakthrough haemolysis; CI, confidence interval; NA, not applicable; SE, standard error.

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

Methods and results of the SLR conducted as part of the appraisal for the identification of relevant cost and health care resource use data are presented in Appendix I.

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 *Acquisition costs*

Treatment acquisition costs were estimated based on treatment dosing regimens and corresponding drug prices. The dosing regimens for each treatment and the proportion of patients receiving each are provided in Table 51.

The dosing regimen for iptacopan was based on the dosing used in APPLY-PNH and APPOINT-PNH and the expected licensed dosing regimen (200 mg BD).

For eculizumab, based on clinical practice, some patients were assumed to receive higher than label maintenance doses. For the complement inhibitor-naïve population, it was assumed that patients would start the model on a loading dose (as per SmPC) and then receive the label maintenance dose (i.e. 900 mg every 14 days) (42) up to 6 months, at which time some patients would switch to higher maintenance doses, if required to achieve sufficient complement inhibition. In the base case, the proportion of patients receiving each maintenance dose after 6 months was based on the proportions of patients receiving these doses at baseline in APPLY-PNH. For the complement inhibitor-experienced population, it was assumed that at the start of the model, patients who required higher maintenance doses were already on such a dose. As above, the proportions of patients receiving each maintenance dose were based on the proportions of patients receiving each dose at baseline in APPLY-PNH. Weighted average drug costs were calculated based on the proportions receiving each dose. A similar approach was taken in the pegcetacoplan submission, using data from the PEGASUS trial (20, 114). A scenario analysis considered clinical expert responses provided in the UK medical advisory board (50).

Ravulizumab dosing is weight based (45). As such, in the base case, the proportion of patients in each weight category from APPLY-PNH and APPOINT-PNH were used to inform dosing; a weighted average cost was calculated. A scenario analysis was conducted using clinical expert responses from the UK medical advisory board (50). A dose increase was not considered for ravulizumab. For the complement inhibitor-naïve population, patients started the model on a loading dose then received the maintenance dose according to the label. Complement inhibitor-experienced patients were assumed to start the model on the maintenance dose.

The pegcetacoplan SmPC recommends an overlap transition period for patients switching to pegcetacoplan from C5 inhibitors (23); patients are recommended to initiate pegcetacoplan while continuing their C5 inhibitor therapy at the current dose for 4 weeks. For the base-case analysis in the complement inhibitor-experienced population, it was assumed that 12% and 88% of patients were switching from eculizumab and ravulizumab, respectively (Table 51). These proportions were based

on clinical expert responses provided in the UK medical advisory board (50) and were used to calculate a weighted average cost of C5 inhibitors for the 4-week overlap that was then added to the cost of pegcetacoplan in the first cycle. As ravulizumab is administered every 8 weeks, no additional cost was applied as it was assumed all patients would switch within 4 weeks of their last dose.

For pegcetacoplan, the base-case analysis assumed that all patients receive the standard dose of pegcetacoplan at 1,080 mg twice weekly, in line with the dosing in the PEGASUS study as source of pegcetacoplan efficacy data. However, this underestimates the costs associated with pegcetacoplan treatment in clinical practice, since some patients require and receive infusions with shorter dosage intervals (23, 50). Therefore, up-dosing of pegcetacoplan was considered in a scenario analysis for a proportion of patients after 6 months of treatment based on clinical expert responses provided in the UK medical advisory board (50). It was assumed that 83% of patients received the standard dose of pegcetacoplan at 1,080 mg twice weekly, 10% of patients were assumed to receive 1,080 mg every third day and the remaining 7% of patients received 1,080 mg thrice weekly (50).

Table 51: Treatment dosing assumed in the base case

Treatments	Dosing regimen	Proportion of patients	Source
Iptacopan (oral)	200 mg BD	100%	Draft SmPC (Appendix C)
Eculizumab (IV infusion)	***Loading***		
	600 mg QW for first 4 weeks	100%	SmPC (42)
	Maintenance		
	900 mg Q2W starting at Week 5 (label dose)	81.0%	SmPC; APPLY-PNH (42, 93)
	1,200 mg Q2W starting at Month 6 (up dose)	17.5%	
	1,500 mg Q2W starting at Month 6 (up dose)	1.5%	

Treatments	Dosing regimen	Proportion of patients	Source
Ravulizumab (IV infusion)	***Loading***		
	≥40 to <60 kg: 2,400 mg at Week 0	• Naïve: 17.5% • Experienced: 26.8%	SmPC; APPOINT-PNH; APPLY-PNH (45, 89, 93)
	≥60 to <100 kg: 2,700 mg at Week 0	• Naïve: 80.0% • Experienced: 66.0%	
	≥100 kg: 3,000 mg at Week 0	• Naïve: 2.5% • Experienced: 7.2%	
	Maintenance		
	≥40 to <60 kg: 3,000 mg Q8W starting at Week 2	• Naïve: 17.5% • Experienced: 26.8%	SmPC; APPOINT-PNH; APPLY-PNH (45, 89, 93)
	≥60 to <100 kg: 3,300 mg Q8W starting at Week 2	• Naïve: 80.0% • Experienced: 66.0%	
	≥100 kg: 3,600 mg Q8W starting at Week 2	• Naïve: 2.5% • Experienced: 7.2%	
Pegcetacoplan (SC infusion)	***Switching from C5 inhibitors***		
	1,080 mg twice weekly in addition to eculizumab for 4 weeks	12%	SmPC (23, 50)
	1,080 mg twice weekly in addition to ravulizumab for 4 weeks	88%	
	Maintenance		
	1,080 mg twice weekly starting at week 5 (label dose)	100%	SmPC (23)

Abbreviations: BD, twice a day; IV, intravenous; Q2W, every two weeks; Q8W, every eight weeks; QW, once weekly; SC, subcutaneous; SmPC, summary of product characteristics.

Details of dosing regimens applied in scenario analyses are presented in Appendix P.

Unit costs for each treatment are provided in Table 52. Acquisition costs for all comparators are list prices; drug costs were obtained from the BNF (136). Drug wastage was not considered in the model because the required dosing for all treatments does not result in wastage.

Table 52: Drug acquisition costs

Treatment	Formulation size	Price per pack	Pack size	Source
Iptacopan (list price)	200 mg	£[redacted]	56	Novartis
Iptacopan (PAS price)	200 mg	£[redacted]	56	Novartis
Eculizumab	300 mg	£3,150.00	1	BNF (136)
Ravulizumab	300 mg	£4,533.00	1	BNF (137)
Pegcetacoplan	1,080 mg	£3,100.00	1	BNF (138)

Note: All comparator costs at list price.
Abbreviations: BNF, British National Formulary; PAS, patient access scheme.

The model applies cycle-specific drug costs for the first six cycles to capture unique loading doses and switches to up-doses in cycle seven (where applicable). Thereafter, an average subsequent cycle cost is applied.

Costs differ for the complement inhibitor-naïve and -experienced populations because loading doses are included for the complement inhibitor-naïve population. As described above, for the complement inhibitor-experienced population, patients receiving eculizumab and ravulizumab were assumed to start on maintenance doses (accounting for eculizumab up-dosing for a proportion of patients) and patients receiving pegcetacoplan were assumed to have a 4-week overlap with C5 inhibitors (patients switching from eculizumab only). Patients that switched treatments during the model time horizon were assumed to incur the cost of any required loading dose.

The annual costs per patient associated with the first year of treatment and subsequent years are summarised in Table 53 for each therapy. Costs for eculizumab and ravulizumab are weighted based on the proportion of patients receiving each dose (Table 51).

Table 53: Annual drug acquisition costs

Treatment	Complement inhibitor-naïve population		Complement inhibitor-experienced population	
	First year cost	Subsequent year cost	First year cost	Subsequent year cost
Iptacopan (list price)	£[redacted]	£[redacted]	£[redacted]	£[redacted]
Iptacopan (PAS price)	£[redacted]	£[redacted]	£[redacted]	£[redacted]
Eculizumab	£261,942	£263,391	£263,391	£263,391
Ravulizumab	£360,905	£320,788	£319,428	£319,428
Pegcetacoplan	NA†	NA†	£324,823	£323,507

Note: All comparator costs at list price.
†Pegcetacoplan is not licensed or used in complement inhibitor-naïve patients.
Abbreviations: NA, not applicable, PAS, patient access scheme.

B.3.5.1.2 *Treatment administration costs*

Treatment administration costs in the analysis are based on the route of administration (i.e. oral for iptacopan, IV infusion for C5 inhibitors, and SC infusion for pegcetacoplan) and the site of care (i.e. clinic or home). No administration costs were assigned to iptacopan as an oral therapy.

For the IV infusions eculizumab and ravulizumab, administration costs were included for the first dose in the complement inhibitor-naïve population, as the first dose is

administered in hospital. Subsequent doses are administered through a homecare service and costs are assumed to be covered by the manufacturer (19, 20). Resource utilisation for the first in-hospital administration has been derived from the ravulizumab appraisal, assuming 35 minutes of Band 6 nurse specialist time for administration, with an additional 1 hour of observation time, and 15 minutes of Band 7 pharmacist specialist time (19). Staff costs were taken from the Personal Social Services Research Unit (PSSRU) 2022 (139).

The pegcetacoplan SmPC states the SC infusions can be self-administered, following training from a qualified healthcare professional (23). Therefore, a one-time training cost was applied, consisting of one in-clinic self-administration training, which was assumed to be 20 minutes of nurse specialist time, and two in-home self-administration trainings, which were assumed to be 30 minutes of community nurse time, based on the assumptions used in the pegcetacoplan appraisal (20). Staff costs were taken from the PSSRU 2022 (139).

Table 54 summarises the staff costs applied in the model and Table 55 summarises the cost of treatment administration or training applied in the first cycle of the model.

Table 54: Staff costs for treatment administration

Staff	Hourly cost	Source
Band 6 nurse specialist (hospital-based)	£53	PSSRU 2022 (139)
Band 7 pharmacist specialist (hospital-based)	£64	
Band 6 nurse	£57	

Abbreviations: PSSRU, Personal Social Services Research Unit.

Table 55: Treatment administration costs

Treatment	Administration cost (Cycle 1)
Iptacopan	£0
Eculizumab and ravulizumab	£99.92
Pegcetacoplan	£74.67

B.3.5.2 Health-state unit costs and resource use

The model includes healthcare resource use associated with routine patient monitoring, including physician visits and laboratory tests, and interventions. Resource use costs varied by treatment and health state.

B.3.5.2.1 *Resource use by treatment*

Table 56 presents treatment-related resource use associated with vaccinations, antibiotics, and iron overload treatment (chelation therapy or venesection). The unit costs and data sources for treatment-related and health state-related resources are summarised in Table 57.

Vaccinations are required for patients upon initiation of treatment with complement inhibitors as per the SmPCs. For all therapies included in the analysis, vaccinations against *Neisseria (N.) meningitidis* types A, C, W, Y, and B are required (23, 42, 45) (Appendix C). For the proximal inhibitors iptacopan and pegcetacoplan, vaccinations are also required for *Streptococcus (S.) pneumoniae* and *Haemophilus (H.) influenzae type B* (Appendix C) (23). The UK National PNH Service recommends vaccination for *N. meningitidis* every 5 years, while *S. pneumoniae* and *H. influenzae type B* are recommended to be revaccinated according to current medical guidelines (140). Vaccination guidelines from the UK Department of Health and Social Care Green Book recommend revaccination for *S. pneumoniae* every 5 years for at-risk patient populations and no additional vaccines for *H influenzae type B* (141). As such, all patients were assumed to receive vaccinations for *N. meningitidis* every 5 years, and patients treated with iptacopan and pegcetacoplan receive one vaccination for *H. influenzae type B* and a vaccination for *S. pneumoniae* every 5 years.

The National PNH Service recommends prophylactic antibiotics, specifically penicillin (500 mg BD), for all patients treated with compliment inhibitors (140). It was assumed that all patients would receive penicillin 500 mg BD, in line with previous appraisals (19, 20).

A proportion of patients treated with C5 inhibitors require on-going chelation therapy to manage iron overload. The proportion of patients receiving chelation therapy was based on the concomitant use amongst patients in APPLY-PNH (17.5%) (93). An average dose of deferasirox 21 mg/kg once daily was assumed based on the pegcetacoplan appraisal (20, 142). The average patient weight was derived from APPOINT-PNH and APPLY-PNH (Table 40).

Clinical advisors at the UK advisory board stated that patients receiving proximal inhibitor treatment can undergo monthly venesection rather than iron chelation. While the required duration of venesection depends on the level of iron overload prior to starting proximal inhibitor treatment, advisors were aligned that venesection can usually be stopped after around 12 months (50). As such, for iptacopan and pegcetacoplan, the cost of monthly venesection for 12 months, rather than cost of chelation therapy, has been incorporated for the proportion of patients that received chelation therapy in APPLY-PNH (17.5%) (93). This cost was applied as a one-off cost in the first cycle. This is aligned with the approach taken in the pegcetacoplan appraisal, where the cost of ongoing chelation therapy was applied for C5 inhibitors, with venesection for 1 year applied for pegcetacoplan (20). A scenario analysis excluding the cost of iron chelation and venesection has been explored.

Table 58 summarises the total treatment-related resource use costs per cycle used in the model for each treatment; these were calculated using the information summarised in Table 56 for the frequency of use and in Table 57 for the unit cost per resource, with all resources being summed to give the overall cost.

Table 56: Treatment-related resource use

		Iptacopan	Eculizumab	Ravulizumab	Pegcetacoplan
***Neisseria Meningitidis* vaccine**	Proportion of patients	100%	100%	100%	100%
	Annual frequency	0.2	0.2	0.2	0.2
***Streptococcus Pneumoniae* vaccine**	Proportion of patients	100%	0%	0%	100%
	Annual frequency	0.2	0	0	0.2
***Haemophilus Influenzae type B* vaccine**	Proportion of patients	100%	0%	0%	100%
	Annual frequency	One-off cost	0	0	One-off cost
Penicillin (twice daily)	Proportion of patients	100%	100%	100%	100%
	Annual frequency	365	365	365	365
Chelation therapy	Proportion of patients	0%	17.5%	17.5%	0%
	Annual frequency	0	365	365	0
Venesection	Proportion of patients	17.5%	0%	0%	17.5%
	Annual frequency	12 (1st year only)	0	0	12 (1st year only)

Table 57: Treatment-related resource use unit costs

Resource	Cost	Source
Neisseria meningitidis vaccine	£105	Bexsero vaccine suspension for injection 0.5 ml pre-filled syringes (GlaxoSmithKline UK Ltd) (£75.00); Nimenrix vaccine powder and solvent for solution for injection 0.5 ml pre-filled syringes (Pfizer Ltd) (£30.00); BNF (143)
Streptococcus pneumoniae vaccine	£49.10	Prevenar 13 vaccine suspension for injection 0.5 ml pre-filled syringes (Pfizer Ltd); BNF (143)
Haemophilus influenzae type B vaccine	£37.76	Menitorix vaccine powder and solvent for solution for injection 0.5 ml vials (GlaxoSmithKline UK Ltd); BNF (143)
Antibiotics	£0.15/day	Phenoxymethylpenicillin 250 mg tablets (Crescent Pharma Ltd) (£1.05 per 28 tablets); BNF (143)
Chelation therapy	£9.76/day	21 mg/kg. Deferasirox 360 mg tablets (£70.11 per 30 tablets); eMIT (144)
Venesection	£26.50	30 minutes of specialist nurse time, based on pegcetacoplan TA778 (20). £53 per hour, PSSRU 2022 (139)

Abbreviations: BNF, British National Formulary; UK, United Kingdom.

Table 58: Treatment-related resource use costs per cycle

	One-off cost in the first cycle	Per cycle costs
Iptacopan	£97.61	£6.56
Eculizumab	£0.00	£53.64
Ravulizumab	£0.00	£53.64
Pegcetacoplan	£97.61	£6.56

B.3.5.2.2 *Resource use by health state*

Table 60 summarises the resources that were considered by health state, including blood transfusions, haematologist visits, and blood tests. Resource use by health state was assumed not to differ between treatments, based on clinical expert opinion provided in the UK medical advisory board (50). It was assumed that all patients in the transfusion health state would receive one transfusion per cycle, in line with the assumption made in. The frequency of haematologist visits and blood tests was based input from UK clinical experts (50). It was assumed that patients in the no transfusion health states had a haematologist visit approximately every 6 months and patients in the transfusion health state had a visit every 2 months. Blood tests were assumed to be required at each haematologist visit for patients in the no transfusion health states, and prior to every transfusion in the transfusion health state. A scenario analysis using health state resource use from the pegcetacoplan appraisal (20) was also considered.

As with treatment-related resource use, costs per cycle were calculated using the information summarised in Table 60 for the frequency of use and Table 59 for the unit cost per resource, with all resources being summed to give the overall cost for each health state. Table 61 summarises the total resource use costs per cycle by health state used in the model.

Table 59: Health state related resource use unit costs

Resource	Cost	Source
Blood transfusion	£694.96	Single Plasma Exchange or Other Intravenous Blood Transfusion, 19 years and over, Total HRGs (SA44A); National Schedule of NHS Costs 2021/22, NHS (145)
Haematologist visit	£200.81	Clinical Haematology Service, Total Outpatient Attendance Data, Consultant Led (Service code 303); National Schedule of NHS Costs 2021/22, NHS (145)
Blood test	£2.96	Haematology (DAPS05); National Schedule of NHS Costs 2021/22, NHS (145)

Abbreviations: NHS, National Health Service.

Table 60: Health state-related resource use

	Blood transfusion		Haematologist visit		Blood test	
	Proportion of patients	Frequency per cycle	Proportion of patients	Frequency per cycle	Proportion of patients	Frequency per cycle
No transfusion and No Anaemia	0%	0	100%	0.15	100%	0.15
No transfusion and Anaemia	0%	0	100%	0.15	100%	0.15
Transfusion	100%	1	100%	0.5	100%	1

Table 61: Health state-related resource use costs per cycle

Health state	Cost per cycle
No transfusion and No Anaemia	£ 30.57
No transfusion and Anaemia	£ 30.57
Transfusion	£ 798.32

B.3.5.3 Breakthrough haemolysis

Some BTH events may require blood transfusions; costs of these are assumed to be captured within the costs of the transfusion health state (following TA778) (20).

For severe BTH events, a one-off dose of eculizumab (900 mg) may be considered, based on advisory board input (50). This was included for 10% of BTH events in the model, at a cost of £9,450 per event. A scenario analysis excluded these costs.

B.3.6 Severity

Severity weights are not expected to be applicable for this submission. Table 62 and Table 63 summarise the QALY shortfall in the complement inhibitor-naïve and -experienced populations, respectively. Expected QALYs were generated using England and Wales lifetables (131) and general population utility values for the UK derived from the HSE 2014 dataset reported by Hernandez-Alava et al, 2022 (134).

Table 62: QALY shortfall in the complement inhibitor-naïve population

Treatment	Expected general population QALYs	Total QALYs in the model	Absolute shortfall	Proportional shortfall
Eculizumab	18.02	15.54	2.48	0.14
Ravulizumab		15.55	2.47	0.14

Abbreviations: QALY, quality-adjusted life year.

Table 63: QALY shortfall in the complement inhibitor-experienced population

Treatment	Expected general population QALYs	Total QALYs in the model	Absolute shortfall	Proportional shortfall
Eculizumab	15.54	12.69	2.85	0.18
Ravulizumab		12.69	2.85	0.18
Pegcetacoplan		13.35	2.19	0.14

Abbreviations: QALY, quality-adjusted life year.

B.3.7 Uncertainty

PNH is an ultra-rare disease and generating comparative efficacy data can be challenging as the number of patients included in clinical trials is typically small. While the methods applied to generate comparative efficacy data for this submission are in line with best practice, the nature of the disease leads to uncertainty in the estimates.

B.3.8 Summary of base-case analysis inputs and assumptions

B.3.8.1 Summary of base-case analysis inputs

A summary of base-case analysis inputs is provided in Table 64.

Table 64: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
General parameters			
Discount rate, costs	3.5%	Fixed	B.3.2.3
Discount rate, outcomes	3.5%	Fixed	
Time horizon	Lifetime	Fixed	
Baseline age, complement inhibitor-naïve	42.1	Fixed	B.3.3.1
% male, complement inhibitor-naïve	57.5%	Fixed	
Body weight, complement inhibitor-naïve	70.1	Fixed	
Baseline age, complement inhibitor-experienced	51.0	Fixed	
% male, complement inhibitor-experienced	30.9%	Fixed	
Body weight, complement inhibitor-experienced	71.6	Fixed	
Transition probabilities			
Iptacopan, complement inhibitor-naïve	Multinomial logistic regression using APPOINT-PNH data	Dirichlet	Table 42
Eculizumab, complement inhibitor-naïve	Multinomial logistic regression using APPEX data matched to APPOINT-PNH		
Ravulizumab, complement inhibitor-naïve			
Iptacopan, complement inhibitor-experienced	Multinomial logistic regression using APPLY-PNH data matched to PEGASUS	Dirichlet	Table 43
Eculizumab, complement inhibitor-experienced			
Ravulizumab, complement inhibitor-experienced			
Pegcetacoplan, complement inhibitor-experienced	Multinomial logistic regression using PEGASUS data as		

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
	reported in Hakimi et al (114)		
Discontinuation			
Iptacopan, complement inhibitor-naïve	3.43%	Beta distribution	B.3.3.3
Eculizumab, complement inhibitor-naïve	30%		
Ravulizumab, complement inhibitor-naïve	30%		
Iptacopan, complement inhibitor-experienced	3.43%		
Pegcetacoplan, complement inhibitor-experienced	16.13%		
BTH, annual rate			
Iptacopan, complement inhibitor-naïve	0.00	Log-normal distribution	B.3.3.4
Eculizumab, complement inhibitor-naïve	0.21		
Ravulizumab, complement inhibitor-naïve	0.08		
Iptacopan, complement inhibitor-experienced	0.07		
Eculizumab, complement inhibitor-experienced	0.67		
Ravulizumab, complement inhibitor-experienced	0.67		
Pegcetacoplan, complement inhibitor-experienced	0.13		
Mortality			
Mortality	England and Wales lifetables	Fixed	B.3.3.5
Utility values			
No transfusion, no anaemia, iptacopan and pegcetacoplan	0.879	Beta distribution	B.3.4.5
No transfusion, anaemia, iptacopan and pegcetacoplan	0.819		
Transfusion, iptacopan and pegcetacoplan	0.800		
No transfusion, no anaemia, C5 inhibitors	0.775		
No transfusion, anaemia, C5 inhibitors	0.743		
Transfusion, C5 inhibitors	0.695		

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Disutility for BTH	–0.11	Normal distribution	
Treatment costs			
Iptacopan (PAS price)	£[redacted]	Fixed	B.3.5.1.1
Eculizumab	£3,150.00		
Ravulizumab	£4,533.00		
Pegcetacoplan	£3,100.00		
Administration costs			
Eculizumab	£99.92	Fixed	B.3.5.1.2
Ravulizumab	£99.92		
Pegcetacoplan	£74.67		
Other costs			
Treatment-related resource use	Table 56, Table 57, Table 58	Fixed	B.3.5.2.1
Health state resource use	Table 59, Table 60, Table 61	Fixed	B.3.5.2.2
Cost of BTH treatment	£9,450	Fixed	B.3.5.3
Proportion of BTH events treated	10%	Fixed	

Abbreviations: BTH, breakthrough haemolysis; C5, complement component 5; CI, confidence interval; PAS, patient access scheme; SC, subcutaneous.

B.3.8.2 Assumptions

A summary of base case assumptions is provided in Table 65.

Table 65: Assumptions

Assumption	Justification
Eculizumab and ravulizumab have comparable efficacy	Ravulizumab was created from eculizumab by targeted substitution of four amino acids, resulting in a longer terminal half-life, and Study 301 and Study 302 demonstrated the non-inferiority of ravulizumab vs eculizumab as treatments for PNH (46, 47). The assumption of comparable efficacy is aligned with conclusions in previous NICE appraisals and was considered appropriate according to UK clinicians and health economists (19, 20, 101).
Transition probabilities are maintained throughout the duration of treatment	This approach aligns with the pegcetacoplan model that also assumed that transition probabilities based on trial data up to Week 16 were applicable for the duration of treatment (20, 114). No waning was applied in the ravulizumab model (19).
In the complement inhibitor-naïve population, 30% of patients treated with eculizumab or ravulizumab who continue to have anaemia or	This is aligned with the clinical pathway and expert opinion. Not all eligible patients switch to pegcetacoplan, and those that do tend to switch at around 6 months (50, 101).

Assumption	Justification
are transfusion dependent at 6 months will switch to pegcetacoplan	
Patients that discontinue iptacopan or pegcetacoplan switch to ravulizumab	Clinical experts explained that ravulizumab accounted for the majority of C5 inhibitor use, and patients discontinuing a proximal inhibitor would most likely switch to ravulizumab (or be considered for a clinical trial) (50, 101).
Mortality is in line with the general population	This is aligned with previous appraisals (19, 20).
Iptacopan has a benefit on HRQoL over C5 inhibitors, beyond that captured by health state membership	The utility regression model predicted that within each health state, patients treated with iptacopan experience better HRQoL vs those treated with C5 inhibitors (treatment covariate statistically significant). This could be due to patients treated with iptacopan having higher mean Hb levels and experiencing less fatigue, which may not be fully accounted for in the definition of anaemia health states using a Hb threshold of 10.5 g/dL. In addition, patients treated with iptacopan may have experienced better HRQoL associated with the oral mode of administration vs IV infusions with C5 inhibitors. In the model, utility values for pegcetacoplan (SC infusion) were assumed equal to iptacopan, which is considered a conservative assumption.
Patients treated with eculizumab may receive higher than label maintenance doses	In clinical practice, some patients receive a higher eculizumab dose to achieve sufficient C5 inhibition. This was applied in previous appraisals (19, 20) and was confirmed by clinical experts consulted at an advisory board to reflect UK clinical practice (50).
There are no on-going administration costs to the NHS for any treatment	Iptacopan is administered orally and is not expected to incur any administration costs. For C5 inhibitors, ongoing administration costs are covered by the manufacturer (homecare service). Patients were assumed to be able to self-administer pegcetacoplan.
10% of BTH events incur the cost of a one-off dose of eculizumab	Some BTH events may require blood transfusions; costs of these are assumed to be captured within the costs of the transfusion health state (following TA778) (20). A one-off dose of eculizumab is assumed for patients with severe BTH events.
Patients treated with iptacopan or pegcetacoplan do not require iron chelation therapy and instead receive a 12-month course of venesections	Patients treated with iptacopan and pegcetacoplan are less transfusion dependent and do not continue to accumulate iron after switching from a C5 inhibitor. This was in line with clinical expert opinion (50) and TA778 (20).

Abbreviations: BTH, breakthrough haemolysis; C5, complement component 5; Hb, haemoglobin; HRQoL, health-related quality of life; NHS, National Health Service; PNH, paroxysmal nocturnal haemoglobinuria; TA, technology appraisal; UK, United Kingdom.

B.3.9 Base-case results

B.3.9.1 Base-case incremental cost-effectiveness analysis results

In the complement inhibitor-naïve population (Table 66), using the iptacopan PAS price and comparator list prices, iptacopan is cost-effective vs eculizumab and ravulizumab ([redacted]).

In the complement inhibitor-experienced population with residual anaemia (Table 68), using the iptacopan PAS price and comparator list prices, iptacopan is cost-effective vs ravulizumab and pegcetacoplan ([redacted]). Compared with eculizumab, iptacopan is more costly and more effective, with an ICER above the threshold range ([redacted]); this is related to patients discontinuing iptacopan switching to ravulizumab, and iptacopan is expected to be cost-effective vs eculizumab once the ravulizumab PAS price is considered in the analysis.

Table 67 and Table 69 present the net health benefit (NHB) for the complement inhibitor-naïve and -experienced populations, respectively. Iptacopan has a positive net health benefit in all comparisons, except when compared with eculizumab in the complement inhibitor-experienced population. However, when the net price for ravulizumab is applied it is expected that iptacopan will have a positive net health benefit also in this comparison.

Table 66: Base-case results, complement inhibitor-naïve population (iptacopan PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
Iptacopan (PAS price)	[redacted]	21.05	16.60	–	–	–	–	–
Eculizumab	[redacted]	21.05	15.54	[redacted]	0.00	–1.06	[redacted]	[redacted]
Ravulizumab	[redacted]	21.05	15.55	[redacted]	0.00	–1.05	[redacted]	[redacted]

Analysis uses PAS price for iptacopan and list price for comparators.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 67: Net health benefit, complement inhibitor-naïve population (iptacopan PAS price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Iptacopan (PAS price)	[redacted]	16.60	–	–	–	–
Eculizumab	[redacted]	15.54	[redacted]	–1.06	[redacted]	[redacted]
Ravulizumab	[redacted]	15.55	[redacted]	–1.05	[redacted]	[redacted]

Analysis uses PAS price for iptacopan and list price for comparators.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 68: Base-case results, complement inhibitor-experienced population (iptacopan PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
Eculizumab	[redacted]	18.89	12.69	–	–	–	–	–
Iptacopan (PAS price)	[redacted]	18.89	14.42	[redacted]	0.00	1.73	[redacted]	[redacted]
Ravulizumab	[redacted]	18.89	12.69	[redacted]	0.00	0.00	[redacted]	[redacted]
Pegcetacoplan	[redacted]	18.89	13.35	[redacted]	0.00	0.67	[redacted]	[redacted]

Analysis uses PAS price for iptacopan and list price for comparators.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 69: Net health benefit, complement inhibitor-experienced population (iptacopan PAS price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Eculizumab	[redacted]	12.69	–	–	–	–
Iptacopan (PAS price)	[redacted]	14.42	[redacted]	1.73	[redacted]	[redacted]
Ravulizumab	[redacted]	12.69	[redacted]	0.00	[redacted]	[redacted]
Pegcetacoplan	[redacted]	13.35	[redacted]	0.67	[redacted]	[redacted]

Analysis uses PAS price for iptacopan and list price for comparators.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; PAS, patient access scheme; QALY, quality-adjusted life year.

B.3.10 Exploring uncertainty

B.3.10.1 Probabilistic sensitivity analysis

Joint parameter uncertainty was explored through probabilistic sensitivity analysis (PSA), in which all parameters are assigned distributions and varied jointly. 10,000 Monte Carlo simulations were recorded. Where the covariance structure between parameters was known, correlated random draws were sampled from a multivariate normal distribution. Results were plotted on a cost-effectiveness plane (CEP) and a cost-effectiveness acceptability curve (CEAC) was generated.

In the complement inhibitor-naïve population, PSA results (Table 70) are congruent with the deterministic results, and iptacopan remains cost-effective ([redacted]) at the iptacopan PAS price and comparator list prices. Figure 13 presents the cost-effectiveness plane. The CEAC (Figure 14) shows that iptacopan [redacted] was cost-effective in [redacted]% of simulations at a willingness-to-pay (WTP) threshold of £20,000 per QALY, and [redacted]% of simulations at a WTP threshold of £30,000 per QALY.

Table 70: PSA results, complement inhibitor-naïve population (iptacopan PAS price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
Iptacopan (PAS price)	[redacted]	16.58	-	-	-	-
Eculizumab	[redacted]	15.54	[redacted]	-1.05	[redacted]	[redacted]
Ravulizumab	[redacted]	15.54	[redacted]	-1.04	[redacted]	[redacted]

Analysis uses PAS price for iptacopan and list price for comparators.
Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

Figure 13: Cost-effectiveness plane, complement inhibitor-naïve population

Abbreviation: QALY, quality-adjusted life year.

Figure 14: Cost-effectiveness acceptability curve, complement inhibitor-naïve population

In the complement inhibitor-experienced population, PSA results (Table 71) are congruent with the deterministic results, and iptacopan remains cost-effective vs ravulizumab and pegcetacoplan ([redacted]). The ICER vs eculizumab is above the threshold range ([redacted]), but iptacopan is expected to be cost-effective once the ravulizumab PAS price is considered in the analysis (Section B.3.9.1). Figure 15 presents the cost-effectiveness plane. The CEAC (Figure 16) shows that iptacopan [redacted] cost-effective at a WTP threshold of £20,000 per QALY in [redacted]% of simulations and at a WTP threshold of £30,000 in [redacted]% of simulations.

Table 71: PSA results, complement inhibitor-experienced population (iptacopan PAS price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
Eculizumab	[redacted]	12.69	-	-	-	-
Iptacopan (PAS price)	[redacted]	14.40	[redacted]	1.71	[redacted]	[redacted]
Ravulizumab	[redacted]	12.69	[redacted]	0.00	[redacted]	[redacted]
Pegcetacoplan	[redacted]	13.36	[redacted]	0.67	[redacted]	[redacted]

Analysis uses PAS price for iptacopan and list price for comparators.
Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

Figure 15: Cost-effectiveness plane, complement inhibitor-experienced population

Abbreviation: QALY, quality-adjusted life year.

Figure 16: Cost-effectiveness acceptability curve, complement inhibitor-experienced population

B.3.10.2 Scenario analysis

Table 72 summarises the different scenario analyses considered, with results of the scenario analyses presented in Table 73 for the complement inhibitor-naïve population and Table 74 for the complement inhibitor-experienced population. All scenarios have been run using the PAS price for iptacopan and list prices for comparators.

Table 72: Summary of scenario analyses considered

Area of uncertainty	Base case	Scenario	Population	Section
Definition of anaemia	Hb <10.5 g/dL	Hb <10 g/dL	Both	B.3.3.2.1.3
C5 inhibitor efficacy	Pooled C5 inhibitor arm data from APPLY-PNH	Separate eculizumab / ravulizumab data from APPLY-PNH	Experienced†	B.3.3.2.1
Transition probabilities	Transition probabilities for complement inhibitor-naïve patients treated with C5 inhibitors have population weights applied to match the APPOINT-PNH population. Transition probabilities for complement inhibitor-experienced patients treated with iptacopan or C5 inhibitors have population weights applied to match the PEGASUS population.	Transition probabilities without population weights applied	Both	B.3.3.2.1
Transition probabilities for C5 inhibitors	APPEX data with LOCF	APPEX data without data imputation	Naïve	B.3.3.2.1.2
Transition probabilities for C5 inhibitors	Transition probabilities from APPLY-PNH	Transition probabilities from PEGASUS	Experienced	B.3.3.2.1.1
Comparator dosing	Based on trial data • Eculizumab up-dosing based on APPLY-PNH • Ravulizumab dosing based on weight categories in APPOINT-	Based on UK clinical input • Eculizumab up-dosing based on clinical input • Ravulizumab dosing based on clinical input	Both	B.3.5.1.1

	PNH and APPLY-PNH populations • Pegcetacoplan standard dose based on PEGASUS (no up-dosing) o 1080 mg twice weekly	• Pegcetacoplan up-dosing based on clinical input o 1080 mg twice weekly (83%) o 1080 mg every 3 days (10% o 1080 mg thrice weekly (7%)		
Discontinuations	Including discontinuation and treatment switch	Excluding discontinuation and treatment switch for all treatments	Both	B.3.3.3
Discontinuations	Including discontinuation and treatment switch	Excluding discontinuation and treatment switch for iptacopan (to reflect no discontinuations in APPOINT-PNH)	Naïve	B.3.3.3
Utilities	Treatment-dependent utilities	Treatment-independent (pooled) utilities, including a disutility for eculizumab	Both	B.3.4.5
Utilities	Mapped from EQ-5D-5L	Mapped from EORTC QLQ-C30	Both	B.3.4.5
Resource utilisation	Advisory board input	Pegcetacoplan TA778 assumptions	Both	B.3.5.2.2
Resource utilisation	Including cost of chelation therapy and venesection for iron overload	Excluding cost of chelation therapy and venesection for iron overload	Both	B.3.5.2.1
Cost of BTH treatment	One-off eculizumab dose for 10% of BTH events	Exclude BTH treatment (nobody receives one-off eculizumab dose)	Both	B.3.5.3
Discount rate	3.50%	0%	Both	B.3.2.2.3

†A similar scenario was not possible for the naïve population, as only one of 85 patients in the APPEX C5 inhibitor cohort received ravulizumab.
Abbreviations: C5, complement component 5; Hb, haemoglobin; LOCF, last observation carried forward; TA, technology appraisal; UK, United Kingdom.

Table 73: Scenario analyses for iptacopan in the complement inhibitor-naïve population (iptacopan PAS price)

Scenario	Iptacopan vs eculizumab			Iptacopan vs ravulizumab		
	Inc. costs	Inc. QALYs	ICER	Inc. costs	Inc. QALYs	ICER
Base case	[redacted]	**1.06**	[redacted]	[redacted]	**1.05**	[redacted]
Definition of anaemia	[redacted]	1.07	[redacted]	[redacted]	1.06	[redacted]
No imputation for APPEX data	[redacted]	1.16	[redacted]	[redacted]	1.15	[redacted]
Unweighted transition probabilities	[redacted]	1.06	[redacted]	[redacted]	1.05	[redacted]
Comparator dosing	[redacted]	1.06	[redacted]	[redacted]	1.05	[redacted]
No discontinuation for any treatment	[redacted]	2.40	[redacted]	[redacted]	2.38	[redacted]
No discontinuation for iptacopan	[redacted]	1.93	[redacted]	[redacted]	1.92	[redacted]
Treatment independent utilities	[redacted]	0.48	[redacted]	[redacted]	0.44	[redacted]
EORTC QLQ-C30 utilities	[redacted]	1.06	[redacted]	[redacted]	1.05	[redacted]
No BTH cost	[redacted]	1.06	[redacted]	[redacted]	1.05	[redacted]
No chelation therapy or venesection	[redacted]	1.06	[redacted]	[redacted]	1.05	[redacted]
TA778 resource use	[redacted]	1.06	[redacted]	[redacted]	1.05	[redacted]
No discounting	[redacted]	1.52	[redacted]	[redacted]	1.50	[redacted]

Analysis uses PAS price for iptacopan and list price for comparators.
Abbreviations: BTH, breakthrough haemolysis; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TA, technology appraisal.

Table 74: Scenario analyses for iptacopan in the complement inhibitor-experienced population (iptacopan PAS price)

Scenario	Iptacopan vs eculizumab			Iptacopan vs ravulizumab			Iptacopan vs pegcetacoplan		
	Inc. costs	Inc. QALYs	ICER	Inc. costs	Inc. QALYs	ICER	Inc. costs	Inc. QALYs	ICER
Base case	[redacted]	**1.73**	[redacted]	[redacted]	**1.73**	[redacted]	[redacted]	**1.07**	[redacted]
Definition of anaemia	[redacted]	1.58	[redacted]	[redacted]	1.58	[redacted]	[redacted]	0.98	[redacted]
Unweighted transition probabilities	[redacted]	1.65	[redacted]	[redacted]	1.65	[redacted]	[redacted]	1.02	[redacted]
C5 inhibitor efficacy by treatment	[redacted]	1.50	[redacted]	[redacted]	2.11	[redacted]	[redacted]	1.30	[redacted]
C5 inhibitor efficacy from PEGASUS	[redacted]	1.84	[redacted]	[redacted]	1.84	[redacted]	[redacted]	1.13	[redacted]
Comparator dosing	[redacted]	1.73	[redacted]	[redacted]	1.73	[redacted]	[redacted]	1.07	[redacted]
No discontinuation	[redacted]	2.60	[redacted]	[redacted]	2.60	[redacted]	[redacted]	0.03	[redacted]
Treatment independent utilities	[redacted]	1.19	[redacted]	[redacted]	1.15	[redacted]	[redacted]	0.71	[redacted]
EORTC QLQ-C30 utilities	[redacted]	1.62	[redacted]	[redacted]	1.62	[redacted]	[redacted]	1.00	[redacted]
No BTH cost	[redacted]	1.73	[redacted]	[redacted]	1.73	[redacted]	[redacted]	1.07	[redacted]
No chelation therapy or venesection	[redacted]	1.73	[redacted]	[redacted]	1.73	[redacted]	[redacted]	1.07	[redacted]
TA778 resource utilisation	[redacted]	1.73	[redacted]	[redacted]	1.73	[redacted]	[redacted]	1.07	[redacted]
No discounting	[redacted]	2.59	[redacted]	[redacted]	2.59	[redacted]	[redacted]	1.80	[redacted]

Analysis uses PAS price for iptacopan and list price for comparators.
Abbreviations: BTH, breakthrough haemolysis; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TA, technology appraisal.

B.3.10.3 Summary of sensitivity analyses results

Sensitivity analyses are mostly well aligned with the deterministic base-case results. Outputs of the PSA are well aligned with the deterministic base case and the model does not exhibit a large amount of non-linearity.

Scenario analyses for the complement inhibitor-naïve population show that the relative effectiveness of iptacopan in the model base case is conservative, with only the scenario using treatment-independent utility values showing a reduction in incremental QALYs vs the base case. At the iptacopan PAS price and comparator list prices, iptacopan remains cost-effective vs ravulizumab in all scenario analyses, and vs eculizumab in all but two scenarios at a WTP threshold of £30,000 per QALY. The first of these is the scenario without discounting applied. The second is the scenario using APPEX data without imputation to inform transition probabilities for C5 inhibitors; however, same as in the complement inhibitor-experienced population base case (Section B.3.9.1), this is related to discontinuations and iptacopan is expected to be cost-effective in this scenario after the PAS price for ravulizumab is applied. The scenario using unweighted transition probabilities showed minimal changes in results.

Discontinuation is also a key driver of results in the complement inhibitor-experienced population, with the scenario that demonstrates the largest change in incremental QALYs vs the base case being the one excluding discontinuation. When discontinuation is not applied, the incremental QALYs vs C5 inhibitors increase, while total QALYs of iptacopan and pegcetacoplan become similar.

In the complement inhibitor-experienced population, the scenario analysis using unweighted transition probabilities for iptacopan and the C5 inhibitors shows only a small impact on results, as do scenarios using alternative sources for transition probabilities. The scenario using differential efficacy for C5 inhibitors suggests an increase in total QALYs for eculizumab and a decrease for ravulizumab, however the sample sizes used to inform these estimates were small and estimates of transition probabilities may be implausible.

As the model is sensitive to discontinuation rates, it is also highly sensitive to prices of comparator treatments. The incremental cost for iptacopan compared with

eculizumab in the complement inhibitor-experienced population is driven by patients discontinuing iptacopan and switching to ravulizumab, which has been included at its list price. Similarly, in the complement inhibitor-naïve population, costs for eculizumab and iptacopan are impacted by the proportion of patients discontinuing treatment and switching to more expensive therapies.

B.3.11 Subgroup analysis

No additional subgroup analyses have been conducted.

B.3.12 Benefits not captured in the QALY calculation

Fatigue is one of the main patient-reported symptoms of PNH (6) and evidence of improvements in fatigue with iptacopan is available from the clinical trials (FACIT-Fatigue endpoint; Sections B.2.6.1.2.7 and B.2.6.2.2.3). Standard generic HRQoL instruments used for generating health state utility values for economic modelling may not be able to capture the full impact of fatigue on patients' HRQoL. In particular, the EQ-5D has been shown to have low sensitivity to the impact of fatigue on HRQoL (146, 147). Consequently, benefits of iptacopan in terms of reducing fatigue may not be fully captured in QALYs based on health state utility values generated from EQ-5D, as presented in this submission.

Additionally, benefits in terms of convenience of oral administration vs current IV/SC infusions may not be fully captured in the QALY calculation. Patients have reported that IV infusions can have a negative impact on QoL with patients worried about their veins, the need for frequent cannulations, and disruptions to their work or study and family life (78). Similarly, while self-administered SC infusion of pegcetacoplan may be less disruptive than healthcare professional-administered IV infusion of C5 inhibitors, it can still be time consuming, with infusions required twice a week and a typical infusion time of approximately 30 minutes if using two sites, or approximately 60 minutes if using one site (23). The health state utility values used in the economic model base case differ between iptacopan and C5 inhibitors, but for pegcetacoplan the same values as for iptacopan were used, in the absence of data. This is conservative and likely underestimates incremental QALYs of iptacopan vs pegcetacoplan, given that studies in other disease areas have demonstrated higher utility values associated with oral treatments vs SC infusions (148-150).

The impact of reduced need for blood transfusions on NHS direct costs is captured in the economic model, however there may also be a wider benefit for the NHS as it frees up healthcare professional time and blood for other purposes.

An effective oral treatment may also have benefits on workplace productivity. Time off work may be required for infusion of IV and SC treatments, and anaemia-related fatigue and the requirement for blood transfusions can impact patients' productivity. The potential for patients and carers to start or return to work or study, if they receive an effective treatment that addresses both intravascular haemolysis (IVH) and extravascular haemolysis (EVH) and does not require them to miss work or study to receive/administer infusions, was also highlighted by the patient group in the iptacopan draft scope consultation (135).

B.3.13 Validation

B.3.13.1 Validation of cost-effectiveness analysis

B.3.13.1.1 *Internal validation*

Quality control of the economic model was performed by the model developers and by health economists not involved in the development of the model. This included cell-by-cell checks and logical checks.

The approach to modelling was validated with UK clinical and economic experts. Two clinical experts and two health economists were consulted in two separate calls with one clinician and one health economist each (101). Expert input was sought on:

- Sources of clinical evidence and approaches to analysing them
- Key prognostic factors and treatment effect modifiers for population adjustments
- Model structure
- Treatment discontinuations
- Utility values
- Key model assumptions.

B.3.13.1.2 *External model validation*

A meaningful comparison of model outcomes with previous NICE appraisals is challenging, as most model outputs have been redacted. However, a comparison can be made with published cost-effectiveness analyses. The cost-effectiveness analysis published by Hakimi et al (114) compares pegcetacoplan to ravulizumab in complement inhibitor-experienced patients with residual anaemia, using an analysis that is closely aligned with the pegcetacoplan NICE appraisal TA778 (20). The model structure used in this submission is also closely aligned with the TA778 model and so outcomes of these analyses should be comparable. Table 75 presents modelled outcomes for pegcetacoplan and ravulizumab from this analysis and from Hakimi et al (114).

Table 75: Comparison of model outcomes with Hakimi et al

Outcome	Ravulizumab		Pegcetacoplan	
	Modelled outcome	Hakimi et al (114)	Modelled outcome	Hakimi et al (114)
Total costs	[redacted]	£6,660,676	[redacted]	£6,409,166
Total QALYs	12.686	12.942	13.351	14.694

Abbreviations: QALY, quality-adjusted life-year.

Modelled outcomes for ravulizumab are comparable to those from Hakimi et al. Both costs and QALYs in this analysis are slightly smaller, however this may be explained by the population characteristics, with patients in the Hakimi et al analysis being younger (48.8 years vs 51.0 years) and thus expected to live longer, and having a higher mean weight (75.3 kg vs 71.6 kg), and expected to accrue more costs.

Costs for pegcetacoplan are also comparable between analyses, though there is a larger difference in health outcomes for pegcetacoplan, with this analysis producing fewer QALYs. This is largely driven by discontinuation, as the Hakimi et al analysis assumes 2.44% of patients discontinue at 16 weeks due to BTH, but does not model discontinuation beyond this point (114).

There is also a difference in incremental outcomes, with the Hakimi et al analysis predicting a cost-saving with pegcetacoplan compared with ravulizumab. This is possibly also driven by discontinuation, and differences in patients' weight. In this analysis, using the weight distribution from APPLY-PNH ravulizumab has a lower

average acquisition cost per year than pegcetacoplan at list price (Table 53), though in a heavier population this may not be the case.

When the differences in input parameters are accounted for, the difference in outcomes between the analyses is smaller, and incremental results are more closely aligned, with pegcetacoplan dominating ravulizumab (Table 76). This analysis aligns baseline characteristics (age, weight, and proportion male), transition probabilities for ravulizumab, discontinuation and utility values with Hakimi et al (114).

Table 76: Comparison of model outcomes with Hakimi et al when matching inputs

Outcome	Ravulizumab		Pegcetacoplan	
	Modelled outcome	Hakimi et al (114)	Modelled outcome	Hakimi et al (114)
Total costs	[redacted]	£6,660,676	[redacted]	£6,409,166
Total QALYs	13.077	12.942	14.663	14.694

Abbreviations: QALY, quality-adjusted life-year.

B.3.14 Interpretation and conclusions of economic evidence

This cost-effectiveness analysis estimates that in complement inhibitor-naïve patients with PNH, iptacopan is more effective than eculizumab or ravulizumab and produces more QALYs than either comparator. When using its PAS price and comparator list prices, iptacopan is cost-effective compared to both eculizumab and ravulizumab. In complement inhibitor-experienced patients, iptacopan remains the most effective option, and when using its PAS price and comparator list prices it is cost-effective compared to ravulizumab and pegcetacoplan. Compared with eculizumab, iptacopan has an ICER above the threshold range ([redacted]). However, scenario analysis has shown that the incremental cost is driven by the cost of ravulizumab as subsequent therapy in patients who discontinue iptacopan. When PAS prices are applied for comparators, iptacopan is expected to be cost-effective vs all comparator in both patient populations.

The analysis has been conducted in line with the NICE reference case and is based on efficacy data from the two iptacopan Phase 3 clinical trials, APPOINT-PNH and APPLY-PNH (89, 93), which included UK patients and are generalisable to UK clinical practice (50). The analysis is based on a previously accepted model structure

(20), which provides a high level of comparability with the most recent NICE appraisal in PNH, and key model inputs and assumptions have been informed by or validated with UK clinicians and health economists (50, 101).

The key weakness of this analysis is that not all transition probabilities could be informed by head-to-head trial data, which introduces uncertainty into the analysis. The PSA demonstrates that results are stable to parameter uncertainty. In both the complement inhibitor-naïve and complement inhibitor-experienced populations, PSA results are well matched with the deterministic analysis. Scenario analyses were conducted to address the uncertainty introduced by using transition probabilities derived from sources other than the iptacopan Phase 3 trials. In the complement inhibitor-naïve population a key source of uncertainty is the APPEX real-world data, informing C5 inhibitor efficacy, and its comparability to APPOINT-PNH. In the base case, the APPEX data was reweighted to better match the APPOINT-PNH population; while this can introduce additional uncertainty, there are minimal differences between weighted and unweighted results. There is also uncertainty introduced by missing Hb data in APPEX, with irregular measurements reflecting data collection in clinical practice, and imputation (LOCF) applied in the base case. However, a scenario analysis using transition probabilities without imputation shows that there is only a small impact on efficacy. While there is a larger impact on costs when comparing with eculizumab, this is driven by the proportion of patients that discontinue and switch to another treatment that is associated with higher drug costs, and the impact of this is expected to be reduced when PAS prices for all comparators are considered. In the complement inhibitor-experienced population, reweighting is carried out to reduce bias in the comparison vs pegcetacoplan. Scenario analysis demonstrates that there are only minor differences in results with and without weights applied.

The results of the analyses indicate that, at its PAS price, iptacopan is expected to be a cost-effective treatment option for PNH, in both complement inhibitor-naïve patients and complement inhibitor-experienced patients with residual anaemia. This conclusion is supported by sensitivity analyses, providing reassurance that iptacopan is a cost-effective use of NHS resources.

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Appendices

All appendices are provided as separate documents.

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

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

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

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

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Price details of treatments included in the submission

Appendix L: Checklist of confidential information

Appendix M: APPOINT-PNH and APPLY-PNH additional trial methodology

Appendix N: APPOINT-PNH additional results

Appendix O: APPLY-PNH additional results

Appendix P: Additional data for scenario analyses

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Iptacopan for treating paroxysmal nocturnal haemoglobinuria [ID6176]

Summary of Information for Patients (SIP)

October 2023

File name	Version	Contains confidential information	Date
ID6176_Iptacopan_PNH_NICE_SIP	1	No	26th Oct 2023

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic: Iptacopan Brand name: The brand name for iptacopan is yet to be decided.

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Iptacopan is intended to be used by adult patients with paroxysmal nocturnal haemoglobinuria (PNH). Two groups of patients are being considered by the National Institute of Health and Care Excellence (NICE): 1. Adults with PNH who have not received previous treatment with complement inhibitors who have haemolysis (destruction of red blood cells) with clinical symptoms 2. Adults with PNH who have received previous treatment with a complement inhibitor, but who still have anaemia.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Iptacopan does not currently have a marketing authorisation in Great Britain (Document B, Section B.1.2, Table 2: Technology being evaluated).

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

During the last 12 months, PNH Support (a patient group dedicated to people with PNH), has received a total of £1,740.50 from Novartis for consultancy services (participation in global patient insights panel).

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

PNH is a very rare blood disease (sometimes referred to as an ultra-orphan disease) where blood cells (red blood cells or white blood cells) are vulnerable to being attacked by a particular part of the body's immune system called "the complement system". There are an estimated 926 people in England living with PNH (1).

The process by which red blood cells are destroyed is called haemolysis and is responsible for many of the symptoms of the disease. Common symptoms and complications include fatigue (a feeling of constant exhaustion), dark or reddish urine, anaemia (when the blood has a reduced ability to carry oxygen due to having low haemoglobin), smooth muscle dystonia (where smooth muscles, such as the ones in the gut, contract uncontrollably), thrombosis (when blood clots inside a blood vessel and obstructs the flow of blood), high blood pressure, and chronic kidney disease (2-10).

Not all people with PNH experience the same signs and symptoms of PNH, and not all people have the same symptoms consistently. Some people have no (or few) symptoms and others may be affected by a number of different symptoms. Over time, the symptoms experienced by a person with PNH can change. Some people only experience symptoms when an episode of severe haemolysis occurs (which is often triggered by an infection), while others may experience symptoms all the time.

The symptoms of PNH are burdensome and result in people with PNH having a lower quality of life compared with the general population (11). Fatigue is the most common symptom, affecting approximately 80% of people with PNH (3), with fatigue having a direct impact on quality of life (12).Fatigue is often caused by anaemia, which can be managed by blood transfusions temporarily raising blood haemoglobin levels. However, needing regular transfusions also has a negative impact on patients' quality of life (13, 14).

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

PNH can take some time to be accurately diagnosed. As the symptoms experienced by people with PNH can vary, people are often seen by a wide range of specialist doctors (for example, hepatologists who treat people with liver, gallbladder, bile ducts, and pancreas issues, gastroenterologists who are digestive system doctors, or cardiologists who treat issues to do with the cardiovascular system) before it is recognised that the symptoms are due to a blood and bone marrow problem. Once this happens, the patient will be referred to a haematologist (a specialist blood doctor) (15).

To diagnose PNH, a doctor will send a blood sample to a laboratory where it will be checked for PNH blood cells using a method called flow cytometry (15, 16), which shows the proportions of red and white PNH cells, and normal red and white blood cells, in the blood.

There are no additional diagnostic tests required before starting treatment with iptacopan.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

The treatment pathway for patients with PNH in the UK is managed by the National PNH Service (17). The National PNH Service consists of two designated centres: St James's University Hospital in Leeds, and King's College Hospital in London. There are also several outreach clinics across England and one in Scotland, while in Wales and Northern Ireland, haematologists in Cardiff and Belfast manage their patients under the direction of the National PNH Service (17). After diagnosis of PNH, patients are managed in collaboration between the National PNH Service and the haematologist who referred the patient to the National PNH Service (17).

Some people with PNH receive treatment with a category of medicines called complement inhibitors. This includes:

- Terminal complement inhibitors (C5 inhibitors)
    - Eculizumab (18), administered by intravenous (through a vein) infusion every 2 weeks
    - Ravulizumab (19), administered by intravenous infusion every 8 weeks
- Proximal complement inhibitor (C3 inhibitor)
    - Pegcetacoplan (20, 21), administered by subcutaneous (under the skin) infusion, twice a week.

Terminal complement inhibitors work by blocking a part of the immune system called the complement system, at a terminal (late stage) part of the process, that in PNH is responsible for attacking the blood cells (22). By blocking the complement system at this stage, these treatments reduce or stop the destruction of the PNH blood cells that occurs within blood vessels (known as 'intravascular haemolysis'), as well as preventing other complications due to unregulated complement activity (22).

Proximal complement inhibitors work by blocking the complement pathway at an earlier stage than the terminal complement inhibitors, which reduces or stops the destruction of the PNH blood cells that occurs both within blood vessels ('intravascular haemolysis'), and

outside blood vessels (for instance, in the liver or spleen; known as ‘extravascular haemolysis’) (22).

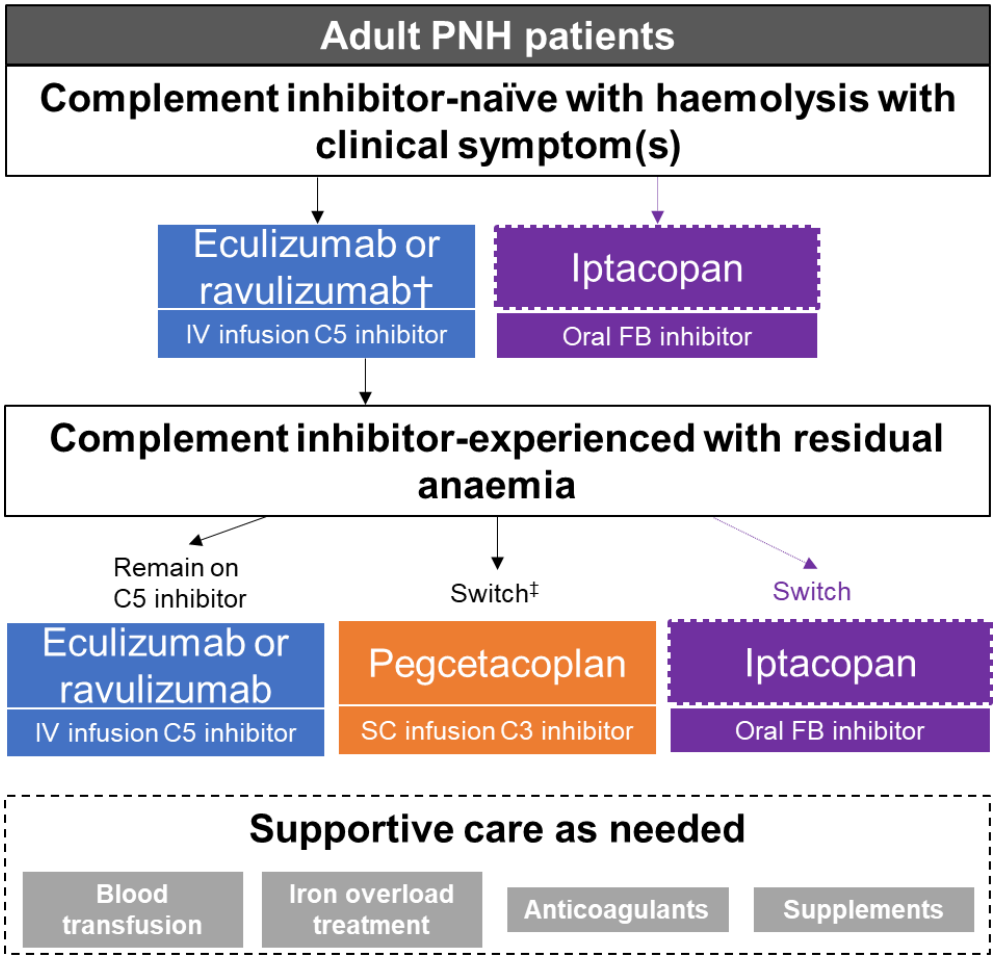
In 2022, approximately one third (339) of the people with PNH living in England were receiving treatment with complement inhibitors (1). People usually start treatment with a C5 inhibitor (either eculizumab or ravulizumab). If patients still have anaemia after 3 months of treatment with one of the C5 inhibitors, they can either remain on a C5 inhibitor, or switch to pegcetacoplan (a C3 inhibitor).

Although currently available treatments have improved disease outcomes and overall survival, these treatments require infusions, which may be uncomfortable and time-consuming to receive.

Treatment of PNH can also include the use of several supporting treatments, to help manage a patient’s symptoms or the side effects of treatment. These include blood transfusions, iron overload treatment (which reduces the amount of iron in the blood), and anticoagulants (which make the blood less sticky and less likely to clot), and vitamin supplements.

Iptacopan is being assessed by NICE as a potential new treatment option for people with PNH, in patients who have not received previous treatment with complement inhibitors, or in patients who have received previous treatment with a complement inhibitor, but who still have anaemia. The potential future treatment pathway (showing the proposed use of iptacopan) is summarised in Figure 1.

Figure 1: Future anticipated treatment pathway for PNH with iptacopan



Source: NICE TA698 (23), NICE TA778 (20) and proposed positioning for iptacopan.
†Ravulizumab is also recommended for patients whose disease is clinically stable after having eculizumab for ≥6 months (NICE TA698) (23); ‡Pegcetacoplan is recommended for patients who have anaemia after ≥3 months of treatment with a C5 inhibitor (NICE TA778) (20).
Abbreviations: C3, complement component 3; C5, complement component 5; FB, Factor B; IV, intravenous; PNH, paroxysmal nocturnal haemoglobinuria; SC, subcutaneous.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Debilitating fatigue is a common symptom, affecting approximately 80% of people with PNH (6). In people with PNH treated with C5 inhibitors, fatigue is the most common symptom, reported by 73% of patients at time of diagnosis (12). When measuring levels of fatigue, people with PNH usually have lower scores (indicating worse fatigue) than the general population. People with PNH also have lower quality of life than the general population, with cognitive problems (memory loss, confusion, brain fog, problems concentrating, difficulty focusing on tasks) reported by 48% of participants in a survey (12).

People also report that PNH affects their ability to work. In one study, 15% of people treated with C5 inhibitors reported that they had stopped working, 21% had changed to flexible working hours, and 11% had reduced their work responsibilities due to PNH (24). Amongst people with PNH who were employed, 9% reported absenteeism (not being at work) and 26% reported presenteeism (being at work, but not fully functioning or experiencing loss of productivity). This is supported by data from a separate study which found that amongst working people with PNH, 98% report that their work is affected, on average, for 27% of their weekly working time (12). This same study also found that over the previous week 84% of people reported that their normal daily activity was negatively impacted for 37% of their waking time (12).

Although the data on the burden placed on carers of people with PNH are limited, the substantial symptom burden experienced by people with PNH (11), suggests that family members and carers may need to provide additional support with daily activities and medical appointments (13).

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

The complement system is a part of the body's immune system which acts as the first line of defence against infections. In people with PNH, the complement system destroys the PNH blood cells, a process called haemolysis (22). As described in Section 2c, current treatments (eculizumab, ravulizumab, and pegcetacoplan) work by blocking this process at different stages (either at a proximal [early stage] or terminal [later stage]).

Similar to pegcetacoplan, iptacopan is a proximal complement inhibitor. However, it targets a different part of the complement pathway, a protein called Factor B. By inhibiting the complement pathway at this stage, iptacopan can reduce or stop the destruction of blood cells that occurs both within blood vessels, and outside blood vessels (for instance, in the liver or spleen) (25-27).

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Iptacopan is not intended to be used in combination with any other medicine.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

PNH is a chronic condition, and treatment will be lifelong.

Iptacopan is taken twice a day as a 200 mg capsule that is swallowed. Iptacopan has no special storage conditions, so it does not need to be kept in the fridge.

Importantly, iptacopan is the first complement inhibitor for PNH that is an oral treatment. Iptacopan differs from the other currently available treatments (eculizumab, ravulizumab, and pegcetacoplan) which are administered as infusions. Eculizumab and ravulizumab (C5 inhibitors) are infused intravenously (through a vein), pegcetacoplan (C3 inhibitor) is infused subcutaneously (under the skin). Infusion times are typically 1 hour for eculizumab (every 2 weeks) and ravulizumab (every 8 weeks) (28), and 30 mins–1 hour for pegcetacoplan (twice a week) (29). Eculizumab and ravulizumab both need to be administered by a nurse. Pegcetacoplan can be self-administered by patients with PNH after they have been trained how to do so by a nurse.

Whilst ravulizumab offers longer gaps between infusions compared with eculizumab (every 8 weeks instead of every 2 weeks), and pegcetacoplan is an infusion treatment that can be self-administered, iptacopan is an oral treatment and would avoid the need for needles and infusion time.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The clinical trials providing evidence for iptacopan in PNH are two Phase 3 trials called APPOINT-PNH (in patients who have not received previous treatment with complement inhibitors) and APPLY-PNH (in patients who have received previous treatment with complement inhibitors, but who still have anaemia). In both studies, patients received iptacopan oral capsules at a dose of 200 mg twice daily, the same dose being assessed by NICE.

The APPOINT-PNH trial (NCT04820530) was a multicentre, single-arm (meaning only iptacopan was provided, there was no comparator treatment), open-label trial (meaning

people knew they were receiving iptacopan), with sites in Europe (including the UK) and Asia, which finished in April 2023. People could take part in APPOINT-PNH if:

- They were over 18 years of age with a diagnosis of PNH
- They had a blood haemoglobin level under 10 g/dL and a blood lactate dehydrogenase level over 1.5 times the upper limit of normal
- They had been vaccinated against *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae*
- They had not previously been treated with a complement inhibitor.

Patients received iptacopan for 24 weeks (core treatment period), and could then continue treatment for a further 24 weeks (extension treatment period). A total of 40 patients participated in APPOINT-PNH.

The APPLY-PNH trial (NCT04558918) was a multicentre, randomised (meaning people were allocated at random to one of two groups, either iptacopan, or a C5 inhibitor [eculizumab or ravulizumab]), open-label, active comparator-controlled trial (meaning that iptacopan was compared with treatments, in this case eculizumab and ravulizumab, that are used in clinical practice in England), with sites in Europe (including the UK), Asia, and North and South America which finished in March 2023. People could take part in APPLY-PNH if:

- They were over 18 years of age with a diagnosis of PNH
- They had a blood haemoglobin level under 10 g/dL
- They had been vaccinated against *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae*
- They had been on C5 inhibitor treatment (either eculizumab or ravulizumab) for at least 6 months prior to the trial.

At the start of the APPLY-PNH trial, patients either discontinued their existing treatment (eculizumab or ravulizumab) and switched to iptacopan, or continued treatment with either eculizumab or ravulizumab, for 24 weeks (the randomised treatment period). Following this, all patients received iptacopan for a further period of 24 weeks (the extension treatment period). A total of 97 patients participated in APPLY-PNH; 62 receiving iptacopan and 35 receiving C5 inhibitors during the first 24 weeks of the trial.

Iptacopan for the treatment of PNH is also being evaluated in two ongoing studies:

- NCT04747613 (NCT04747613) is a single arm, open-label, multicentre, roll-over extension study (when patients from one trial subsequently take part in another, related trial) investigating the long-term safety, tolerability, and efficacy of

iptacopan in PNH. It provides access to iptacopan for patients who have already completed previous Phase 2 or 3 studies with iptacopan in PNH funded by Novartis, the manufacturer of iptacopan (30). The estimated study completion date is June 2026.

- APPULSE (NCT05630001) is a single-arm, open-label, multicentre trial evaluating the efficacy and safety of iptacopan in adult patients with PNH with haemoglobin over 10 g/dL while being treated with a C5 inhibitor, who then switch to iptacopan (31). The estimated study completion date is January 2025.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Efficacy evidence from the clinical trials

The APPOINT-PNH and the APPLY-PNH trials demonstrated that iptacopan results in significant improvements in efficacy outcomes for patients who have not been previously treated with a complement inhibitor (Document B, Section B.2.6.1) and for patients who have previously been treated with a complement inhibitor and still have anaemia (Document B, Section B.2.6.2).

Haemoglobin levels

Both trials met their key endpoints, with iptacopan demonstrating a significant increase in the proportion of patients achieving at least a 2 g/dL increase in their haemoglobin level without needing a blood transfusion, as well as a significant increase in the proportion of patients achieving haemoglobin levels of at least 12 g/dL. These are important outcomes for people with PNH, as they represent blood haemoglobin levels close to normal (32).

In APPOINT-PNH, 92.2% of patients (95% confidence interval [CI]: 82.5, 100.0) had a sustained increase of ≥2 g/dL in their blood haemoglobin, and 62.8% of patients (95% CI: 47.5, 77.5) achieved sustained haemoglobin levels of ≥12 g/dL.

In APPLY-PNH, 82.3% of patients receiving iptacopan and 2.0% of patients receiving C5 inhibitors achieved a sustained increase of ≥2 g/dL in their blood haemoglobin, a difference of 80.3% (95% CI: 71.3, 87.6; p<0.0001). Furthermore, 68.8% of patients

receiving iptacopan and 1.8% of patients receiving C5 inhibitors achieved a sustained increase of ≥2 g/dL in their blood haemoglobin, a difference of 67.0% (56.3, 76.9; p<0.0001).

Intravascular and extravascular haemolysis

Destruction of red blood cells can happen either in the blood vessels (intravascular haemolysis), or outside the blood circulatory system such as in the liver or spleen (extravascular haemolysis). Whilst this cannot be measured directly, biochemical markers in the bloodstream can be measured to see if these processes are happening. In previously untreated patients (APPOINT-PNH), intravascular haemolysis was brought under control as seen in the reduction of lactate dehydrogenase from previously high levels. In patients who had previously been treated with a C5 inhibitor (APPLY-PNH), control of intravascular haemolysis was maintained with iptacopan treatment as evidenced by the stable (normal) level of lactate dehydrogenase, while extravascular haemolysis was reduced as demonstrated by the improvements in reticulocyte counts. The effects of iptacopan were seen early (from 7 days after starting treatment) and sustained to the end of the trials. In APPLY-PNH, the effect of iptacopan on lactate dehydrogenase was similar to the effect of the C5 inhibitors, and the effect of iptacopan on reticulocyte counts was significantly improved compared with the C5 inhibitors.

Breakthrough haemolysis

Breakthrough haemolysis (an increase in haemolysis and the reappearance of PNH symptoms) is the return of haemolytic activity (the destruction of blood cells). Low numbers of patients experienced breakthrough haemolysis while they were treated with iptacopan. At the time when the data was analysed, 1 patient (2.5%) in the APPOINT-PNH study had had breakthrough haemolysis (during the extension period), and in the APPLY-PNH study 2 patients (3.2%) treated with iptacopan compared with 6 patients (17.1%) treated with C5 inhibitors had had breakthrough haemolysis.

Blood transfusions

Treatment with iptacopan reduced the need for blood transfusions. In APPOINT-PNH, no patients required a blood transfusion after they had been on iptacopan for at least 14 days. In APPLY-PNH, after the first 14 days of the clinical trial, only 2 out of 62 patients (3.2%) in the iptacopan group required a blood transfusion compared with 21 out of 35 patients (60%) in the C5 inhibitor group.

Efficacy evidence using trial data and statistical analyses

The design of the clinical trials means that iptacopan has not been compared directly with all comparator treatments in a clinical trial setting. Instead, statistical methods known as indirect treatment comparisons (ITC) were used to compare iptacopan with:

- Eculizumab and ravulizumab (C5 inhibitors) in patients who have not received previous treatment with complement inhibitors
- Pegcetacoplan in patients who have received treatment with complement inhibitors, but who still have anaemia.

In patients who have not received previous treatment with complement inhibitors, one ITC compared iptacopan data from the APPOINT-PNH study with eculizumab and ravulizumab data from another published study (Study 301). The results showed that iptacopan-treated patients had a statistically significant greater reduction in lactate dehydrogenase (a biochemical marker for red blood cell destruction within blood vessels) from baseline compared with ravulizumab or eculizumab. The results also suggested that the proportion of patients not requiring blood transfusions was higher with iptacopan, and that patients receiving iptacopan had greater improvements in their fatigue, but the results were not statistically significant so this is uncertain. A second ITC compared iptacopan data from the APPOINT-PNH study with C5 inhibitor data from 84 patients treated with eculizumab and 1 patient treated with ravulizumab outside clinical trials, in real world clinical practice in the UK (38 patients) and France (47 patients) (APPEX study). This ITC showed greater improvements in haemoglobin levels, lactate dehydrogenase, and reticulocyte counts (a biochemical marker for red blood cell destruction outside blood vessels), and a reduced need for blood transfusions with iptacopan compared with C5 inhibitors.

In patients who have received previous treatment with complement inhibitors, but who still have anaemia, an ITC was conducted to compare iptacopan data from the APPLY-PNH study with pegcetacoplan data from the PEGASUS study. The results of most analyses suggested that iptacopan-treated patients had greater improvements in haemoglobin levels and needed fewer blood transfusions than patients treated with pegcetacoplan, but the results varied depending on the type of analysis used so this is uncertain.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Quality of life was measured in the iptacopan clinical trials using a number of different measures:

- Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue): A short, 13-item questionnaire that measures a person's level of fatigue during their usual daily activities over the past week
- European Organization for the Research and Treatment of Cancer quality of life questionnaire (EORTC-QLQ C30): A questionnaire that measures patients' physical, psychological, and social functions
- EQ-5D-5L: A questionnaire used to assess five areas: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

These questionnaires were completed by patients participating in the clinical trials before starting treatment and again several times during the trial.

Fatigue is a key symptom for people with PNH, with 80% reporting the presence of debilitating fatigue (3). In the APPOINT-PNH and APPLY-PNH clinical trials, fatigue as measured by the FACIT-Fatigue questionnaire improved for patients treated with iptacopan. Improvements were seen as early as 7 days after starting iptacopan treatment, and by the end of the 24-week treatment periods, fatigue had decreased to a level comparable to that of the general population without PNH.

Patient responses in the EORTC-QLQ C30 questionnaire demonstrated improvements with iptacopan treatment in categories including fatigue, pain, dyspnoea (shortness of breath) and overall quality of life in both the APPOINT-PNH and APPLY-PNH studies.

Data from patient responses to the EQ-5D questionnaire in the APPOINT-PNH and APPLY-PNH trials is used in the economic model, however it is recognised that this questionnaire may not fully capture the impact of fatigue on patients' quality of life (33, 34) (see Section 3i; Value and economic considerations).

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

In both the APPOINT-PNH and APPLY-PNH trials, iptacopan had a favourable safety profile and was generally well tolerated. There were no deaths, and no patients stopped treatment or interrupted treatment due to adverse events (side effects) in either trial.

In patients who have not been previously treated with complement inhibitors (APPOINT-PNH), the majority of adverse events were mild or moderate. The most commonly reported adverse events by patients treated with iptacopan were headaches, COVID-19, and upper respiratory tract infections.

In patients who have previously been treated with a complement inhibitor and still have anaemia (APPLY-PNH), the majority of adverse events were mild or moderate. In the iptacopan treated patients, the most commonly reported adverse events were headaches, diarrhoea, and nasopharyngitis (commonly caused by the common cold), while in patients treated with a C5 inhibitor, the most common adverse events were COVID-19 and breakthrough haemolysis.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Iptacopan is a novel proximal complement inhibitor and is expected to be the first oral option for the treatment of adult patients with PNH who have not been previously treated with a complement inhibitor, and those who have previously been treated with a complement inhibitor and still have anaemia.

Results from the two Phase 3 trials (APPOINT-PNH and APPLY-PNH) provide evidence on the effectiveness of iptacopan as a twice daily oral treatment for PNH. The results consistently show the impact of iptacopan across a range of outcomes including:

- Increased haemoglobin levels (improvement in anaemia)

- Lower risk of haemolysis (destruction of blood cells), both within blood vessels (intravascular haemolysis) and outside blood vessels (extravascular haemolysis)
- Reduced need for blood transfusions
- Improved patient symptoms such as fatigue
- Improved quality of life.

Furthermore, results from the two Phase 3 trials demonstrated that iptacopan had a favourable safety profile and was generally well tolerated. No patients stopped iptacopan treatment due to side effects.

As an oral therapy for PNH, iptacopan may offer patients a convenient way of taking their medicine. Current C5 inhibitors, eculizumab and ravulizumab, and the C3 inhibitor, pegcetacoplan, are administered as infusions which require needles, may need visits from a nurse (C5 inhibitors), and can be time consuming.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

As with all treatments, there can be side effects. Side effects that patients receiving iptacopan may experience include (35):

- Most common (more than or equal to 1 in 10 patients receiving treatment) – diarrhoea, abdominal pain, upper respiratory tract infection, or headache
- Common (between more than or equal to 1 in 100 to less than 1 in 10 patients receiving treatment) – decreased platelet count (reduced levels of a type of blood cell called platelets which help the body form clots to stop/prevent bleeding), nausea, bacterial pneumonia infection, urinary tract infection, bronchitis (inflammation of the bronchi in the lungs), arthralgia (joint stiffness), or dizziness.

However, in the APPOINT-PNH and APPLY-PNH clinical trials no patients stopped treatment or had a treatment interruption because of side effects of treatment.

The complement system is part of the body's immune system that fights infection. Complement inhibitors work by blocking the complement system. In people with PNH receiving treatment with a complement inhibitor, this means that some bacteria (*Neisseria meningitidis*, *Streptococcus pneumoniae,* and *Haemophilus influenzae*) are harder for the

body to fight, and patients might be at higher risk of getting certain illnesses. In order to reduce the increased risk of infection, patients can receive preventative antibiotics, and vaccines. All patients with PNH currently already receiving a complement inhibitor must be vaccinated. Depending on the type of complement inhibitor, this can include vaccinations against meningococcal infections, pneumococcal infections, and *Haemophilus influenzae* (29, 36, 37). Vaccination is also a requirement before beginning treatment with iptacopan.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

How the health economic model reflects the condition

The health economic model captures the impact of PNH and PNH treatments by modelling the probability of moving between 'health states'. The health economic model is used to assess the benefits of treatment which a patient may experience, the impact of any side effects, and the cost to the NHS, through using different treatments for PNH. To simplify reality and allow an assessment to be made, the model uses health states which help to define some of these outcomes.

In this submission, these health states are based on the presence of anaemia and the requirement for blood transfusions, which together represent different levels of disease. The model has four health states: 'No transfusion and no anaemia', 'No transfusion and anaemia', 'Transfusion', and 'Death'. The model looks at discrete time periods (called cycles). In each 4-week cycle, patients will either move to a different health state or stay in the same health state. How patients move through health states depends on the treatment they receive, and is based on each treatment's clinical data. The model also looks at the impact of breakthrough haemolysis on costs and quality of life.

Modelling how much a treatment extends life

People with PNH have a life expectancy comparable to people without PNH (the general population). The model assumes that life expectancy is the same for all patients regardless of the treatment they receive.

Modelling how much a treatment improves quality of life

Patients' quality of life will be affected by symptoms and complications of PNH. These include fatigue, having blood transfusions, anaemia, and breakthrough haemolysis. These are all associated with a reduction in quality of life, and are considered in the economic model, although it may not have been possible to consider the full impact of fatigue.

Clinical data showed that patients treated with iptacopan had, on average, higher haemoglobin levels and experienced less fatigue compared with patients treated with C5 inhibitors. How treatments are administered – C5 inhibitors as intravenous infusions and iptacopan as oral therapy – may also have an impact on quality of life. This is reflected in the health economic model by better quality of life scores for patients treated with iptacopan compared with patients treated with C5 inhibitors. However, the potential impact of subcutaneous infusions (pegcetacoplan) on patients' quality of life could not be considered in the analysis because no suitable data was available for inclusion in the model.

Modelling how the costs of treatment differ with the new treatment

Costs in the model come from the cost of treatments and the cost of managing the disease. Treatment costs include the cost for the NHS to buy treatments, and the costs associated with administration. Disease management costs include vaccines, preventative antibiotics, treatments to reduce excess iron, anticoagulants, blood transfusions, healthcare professional visits, and blood tests.

Uncertainty

All economic modelling is associated with uncertainty. There are uncertainties around the haemoglobin levels used to define anaemia, efficacy data for the C5 inhibitors, dosing of the comparator treatments, numbers of patients discontinuing treatments, quality of life data, and amounts of healthcare resources used.

To assess the impact of these uncertainties, values for these data inputs were varied and the model calculations re-run.

Cost-effectiveness results

The cost-effectiveness results are based on calculations using an iptacopan price with a confidential discount which has been offered to the NHS, and the published prices of the comparators (eculizumab, ravulizumab, pegcetacoplan). Each comparator may also have a confidential discounted price, which could not be considered in the analysis because the discount is not known to Novartis, the manufacturer of iptacopan.

Based on the results of the cost-effectiveness model, it is expected that:

- In people with PNH who have not received previous treatment with complement inhibitors, iptacopan is a cost-effective treatment option, when compared with eculizumab and ravulizumab
- In people with PNH who have received previous treatment with complement inhibitors but who still have anaemia, iptacopan is a cost-effective treatment option, when compared with eculizumab, ravulizumab, and pegcetacoplan

Additional factors

Not all benefits of treatment could be captured in the model. Fatigue is one of the main patient-reported symptoms of PNH (6), and the APPOINT-PNH and APPLY-PNH clinical trials have demonstrated improvements in fatigue with iptacopan. However, the standard instrument used to measure quality of life (the EQ-5D questionnaire) has been shown to not react sensitively to improvements in fatigue (33, 34). This means that these improvements in fatigue may not be fully reflected in the model results.

Additionally, the model does not capture the benefits associated with the convenience of the oral administration of iptacopan over the requirement for subcutaneous infusion of pegcetacoplan. Although studies in other disease areas have shown improved quality of life with oral treatments compared with subcutaneous infusion treatments, data in patients with PNH was not available. The model therefore cautiously assumes that administration of pegcetacoplan does not have a negative impact on quality of life compared with administration of iptacopan.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations. If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Innovation

Iptacopan is expected to be the first complement inhibitor treatment for PNH that is administered as an oral treatment. This offers patients with PNH a potentially more convenient treatment option than currently available treatments that are administer by intravenous (through a vein) or subcutaneous (under the skin) infusion.

QALY benefits not captured in the QALY calculation

The full benefits of the oral administration of iptacopan may not be captured in the calculation of quality-adjusted life years (QALY, a measure combing length of life and quality of life). Patients have reported that intravenous infusion can have a negative impact on quality of life with them being worried about their veins, the need for frequent cannulations (a process where a small plastic tube called a cannula is inserted into a vein), and disruptions to their work or study and family life (38). Similarly, lower quality of life is expected with the self-administered subcutaneous infusion of pegcetacoplan because of the frequent infusion regimen required (twice a week), and every infusion lasting 30-60 minutes. However, no data relating to quality of life with subcutaneous infusion specifically in people with PNH could be identified. In addition, the health economic model does not include the potential benefits of an oral treatment on a person's ability to work or study.

Fatigue is one of the main patient-reported symptoms of PNH (6). However, the improvements in fatigue observed in the clinical trials may not be fully reflected in the results of the health economic model. This is because the standard instruments used to measure quality of life are not very sensitive to changes in fatigue (33, 34).

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
Currently, all available treatments for PNH are administered as an infusion, either intravenously (into a vein) or subcutaneously (under the skin) (29, 36, 39). As infusion requires a needle, people with needle phobia may be disadvantaged. Although pegcetacoplan can be self-administered, some people may find this difficult. This may particularly affect people with dexterity (the ability to use the hands skilfully), visual, or cognitive (relating to the brain's functioning, including thinking, reasoning, and remembering) disabilities. Subcutaneous infusions may also be unsuitable for some people that are classified as obese, as their body may absorb pegcetacoplan differently (40, 41).

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
Further information on PNH • The National PNH service: https://pnhserviceuk.co.uk/patient-information/ Further information on NICE and the role of patients: • Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE • NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE • EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/ • EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf

- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Absenteeism: Not being at work

Active comparator-controlled trial: A study design that compares the effect of treatment A (in this case iptacopan) with another treatment that is currently used to treat the disease (in this case either eculizumab or ravulizumab)

Adverse event: A side effect of a drug or other therapy. Adverse events may be mild, moderate, or severe.

Anaemia: When the blood has a reduced ability to carry oxygen due to low levels of haemoglobin

Anticoagulants: A treatment which makes the blood less sticky and less likely to clot

Breakthrough haemolysis: An increase in haemolysis and the reappearance of PNH symptoms whilst on treatment

C3 inhibitor: Complement inhibitor treatments that work by blocking complement activity at the C3 stage

C5 inhibitor: Complement inhibitor treatments that work by blocking complement activity at the C5 stage

Cardiologist: A doctor who treats issues to do with the cardiovascular system

Clinical trial/clinical study: A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease. They are carefully designed, reviewed, and completed, and need to be approved before they can start.

Cognitive: relating to the brain's functioning, including thinking, reasoning, and remembering

Complement inhibitor: A treatment blocking the complement system (a part of the immune system)

Complement system: Part of the immune system that destroys bacteria and other foreign cells

Dexterity: The ability to use the hands skilfully

Dyspnoea: Shortness of breath

Eculizumab: A terminal complement inhibitor (C5 inhibitor) that is administered by an intravenous infusion every 2 weeks

Efficacy: The measurement of a medicine's desired effect under ideal conditions, such as in a clinical trial

EORTC-QLQ C30: A questionnaire that measures patients' physical, psychological, and social functions

EQ-5D-5L: A questionnaire used to assess five areas: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression

Extravascular haemolysis: The destruction of red blood cells outside blood vessels, for example in the liver or spleen

FACIT-Fatigue: A short, 13-item questionnaire that measures a person's level of fatigue during their usual daily activities over the past week

Fatigue: A feeling of constant exhaustion

Gastroenterologist: A doctor who specialises in the digestive system

Haematologist: A doctor who specialises in blood disorders

Haemolysis: The destruction of red blood cells

Hepatologist: A doctor who specialises in liver, gallbladder, bile ducts, and pancreas issues

Indirect treatment comparisons (ITC): A statistical method used to compare treatments which are not directly compared in a trial

Intravascular haemolysis: The destruction of red blood cells inside the blood vessels

Intravenous: Giving medicines through a needle or tube inserted into a vein

Iptacopan: A proximal complement inhibitor (Factor B inhibitor), that is administered orally (by swallowing) twice a day

Iron overload treatment: Treatment which reduces the amount of iron in the blood

Lactate dehydrogenase: A biochemical marker for red blood cell destructions within blood vessels

National PNH Service: A specialised service in the NHS to provide support and care to patients with PNH across the UK

National Institute for Health and Care Excellence (NICE): an independent organisation set up by the Government to decide which drugs and treatments are available on the NHS in England

Open-label: In open-label trials, both the researchers and people taking part know what treatment is being given

Overall survival: How long people live

Pegcetacoplan: A proximal complement inhibitor (C3 inhibitor) that is administered by subcutaneous infusion twice a week

PNH Support: A patient group dedicated to people with PNH

Presenteeism: Being at work, but not fully functioning or experiencing a loss of productivity

Proximal complement inhibitor: A treatment blocking the complement system (a part of the immune system) at an early stage

Quality-adjusted life year: A measure of disease burden that includes the length and quality of life

Quality of life: A measure of the overall enjoyment and happiness of life including aspects of an individual's sense of well-being and ability to carry out activities of daily living

Randomised: People were allocated at random to one of two groups, in this case, either iptacopan, or a C5 inhibitor

Ravulizumab: A terminal complement inhibitor (C5 inhibitor) that is administered by an intravenous infusion every 8 weeks

Reticulocyte counts: A biochemical marker for red blood cell destruction outside blood vessels

Roll-over extension: When patients from one trial subsequently take part in another, related trial

Single-arm: A clinical trial design where only one treatment is provided with no comparator group

Smooth muscle dystonia: Where smooth muscles, such as the ones in the gut, contract uncontrollably

Subcutaneous: Giving medicines through a needle inserted under the skin

Terminal complement inhibitor: A treatment blocking the complement system (a part of the immune system) at a late stage

Thrombosis: When blood clots inside a blood vessel and obstructs the flow of blood

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Iptacopan for treating paroxysmal nocturnal haemoglobinuria [ID6176]

Clarification questions

December 2023

File name	Version	Contains confidential information	Date
ID6176_Iptacopan_PNH_NICE_Clarification questions response_[REDACTED]	1	Redacted	4th Dec 2023

Section A: Clarification on effectiveness data

Clinical effectiveness evidence

A1. Please clarify whether participants with current significant aplastic anaemia were eligible for inclusion in the APPOINT-PNH and APPLY-PNH studies. Please also provide the definition of "history of aplastic anaemia" used by these studies.

Both APPOINT-PNH and APPLY-PNH excluded patients with laboratory evidence of bone marrow failure (reticulocytes <100x10^9/L, platelets <30x10^9/L, neutrophils <0.5x10^9/L) (1, 2), which covers patients with severe aplastic anaemia (defined by modified Camitta criteria as: marrow cellularity <25% (or 25–50% with <30% residual haematopoietic cells), plus at least 2 of: (i) neutrophils <0.5x10^9/L, (ii) platelets <20x10^9/L (iii), reticulocyte count <20x10^9/L) (3).

Patients with current aplastic anaemia not meeting the exclusion criteria, as well as patients with a history of aplastic anaemia – unless they received a haematopoietic stem cell transplantation – were eligible for inclusion in APPOINT-PNH and APPLY-PNH (1, 2). Among the patients enrolled in APPOINT-PNH, 40% had a history of aplastic anaemia (1); in APPLY-PNH, 14.4% of patients had a history of aplastic anaemia (2).

The pivotal trials of pegcetacoplan and ravulizumab applied similar patient eligibility criteria (4-6).

A2. Please provide the APPLY-PNH subgroup analysis by type of C5 inhibitor.

Subgroup analyses for the primary endpoints, including by type of C5 inhibitor, were provided in Appendix E of the company submission (please see revised version of Appendix E following the APPLY-PNH data updates uploaded along with the addendum to the company evidence submission). Forest plots for the secondary endpoints are provided in the file A2_APPLY-PNH_Subgroups_Secondary endpoints_[CON] in the supplementary files pack. Table 1 provides an overview of subgroup analysis results by type of C5 inhibitor. Please note that due to time limitations, subgroup analyses for the secondary endpoints could not be re-run

following the data changes in APPLY-PNH in time for the clarification questions response and thus represent data from the original analysis; however, as shown in the addendum to the company evidence submission, impact of the APPLY-PNH data updates on estimates was minimal.

Results of the ravulizumab subgroup in particular should be interpreted with caution, due to the small sample size of 12 patients. The treatment effect of iptacopan was consistent across eculizumab and ravulizumab subgroups.

Table 1: Summary of subgroup analysis results from APPLY-PNH by type of C5 inhibitor

Endpoint	Subgroup[#]	C5 inhibitor (N=35)		Iptacopan (N=62)		Difference iptacopan vs C5 inhibitor
Primary endpoints						
		n/M	Marginal proportion (95% CI)	n/M	Marginal proportion (95% CI)	Difference in marginal proportions (95% CI)
Increase in Hb levels ≥2 g/dL from baseline	Eculizumab	0/23	3.2 (1.7, 7.3)	33/38	83.8 (73.2, 92.5)	80.6 (69.5, 88.9)
	Ravulizumab	0/12	1.9 (1.3, 15.0)	18/22	78.7 (64.8, 90.7)	76.7 (57.3, 84.8)
Hb levels ≥12 g/dL	Eculizumab	0/23	2.7 (1.3, 8.2)	27/38	67.9 (54.5, 80.4)	65.3 (50.8, 77.2)
	Ravulizumab	0/12	2.9 (1.3, 18.0)	15/22	69.2 (52.3, 83.7)	66.3 (42.4, 78.9)
Secondary endpoints						
Transfusion avoidance		n/M	Marginal proportion (95% CI)	n/M	Marginal proportion (95% CI)	Difference in marginal proportions (95% CI)
	Eculizumab*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Ravulizumab*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		M	Adjusted mean (95% CI)	M	Adjusted mean (95% CI)	Adjusted mean difference (95% CI)
Change from baseline in Hb	Eculizumab*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Ravulizumab*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline in FACIT-Fatigue	Eculizumab*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Ravulizumab*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline in absolute reticulocyte counts	Eculizumab*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Ravulizumab*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		M	Geometric adjusted mean (95% CI)	M	Geometric adjusted mean (95% CI)	Geometric mean ratio (95% CI)
LDH ratio to baseline (log-transformed)	Eculizumab*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Ravulizumab*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		n/M	Adjusted annualised rate (95% CI)	n/M	Adjusted annualised rate (95% CI)	Rate ratio (95% CI)
Annualised clinical BTH rate	Eculizumab*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Ravulizumab*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

#Subgroup by C5 inhibitor medication history – 6 months prior to randomisation. For the C5 inhibitor arm, this corresponds to the treatment received during the study. *Subgroup results from original APPLY-PNH primary analysis, prior to data changes.
Abbreviations: BTH: breakthrough haemolysis; CI: confidence interval; Hb: haemoglobin; LDH: lactate dehydrogenase; M: number of patients in the subgroup.

A3. Please clarify whether there are any longer-term data on iptacopan available from either a more recent data cut for APPOINT-PNH or APPLY-PNH, or the extension programme (NCT04747613).

Longer-term data supporting this appraisal is now available from the APPOINT-PNH and APPLY-PNH trials, with summaries of the 48-week patient disposition, efficacy, and safety data provided below.

APPOINT-PNH: 48-week results

Patient disposition

Patients who benefitted from treatment and had completed the 24-week core treatment period were offered to continue iptacopan treatment for another 24 weeks during the extension treatment period (i.e. a total of 48 weeks). All 40 patients who were enrolled in APPOINT-PNH completed the core treatment period, and entered and completed the extension treatment period.

Clinical effectiveness

Efficacy results for the entire 48-week study duration of APPOINT-PNH are summarised in Table 2, demonstrating clinically meaningful benefits of iptacopan treatment. After 48 weeks, 97.4% of patients had a ≥2 g/dL increase from baseline in haemoglobin (Hb); the percentage of patients with Hb ≥12 g/dL was 79.5%. Of note, haematological response endpoints in the 48-week analysis included all Hb values irrespective of red blood cell (RBC) transfusions, whereas the primary analysis at 24 weeks required the absence of transfusions as an integral part of the endpoints. However, only one of 40 patients required a transfusion between Day 14 and Day 336, resulting in a marginal proportion of patients avoiding transfusion of 97.5% (95% CI: 92.5, 100.0). Change from baseline in Hb, lactate dehydrogenase (LDH), absolute reticulocyte counts, and FACIT-Fatigue were maintained up to Day 336 (Figure 1 to Figure 4), demonstrating sustained inhibition of intravascular and extravascular haemolysis as well as improvements in anaemia and fatigue. While no patients had experienced clinical breakthrough haemolysis (BTH) during the core treatment period, 2/40 patients (5.0%) had one clinical BTH event each in the extension treatment period. Calculated over the entire 48-week study duration, this results in an adjusted annualised clinical BTH rate of 0.05 (95% CI: 0.01, 0.17). No

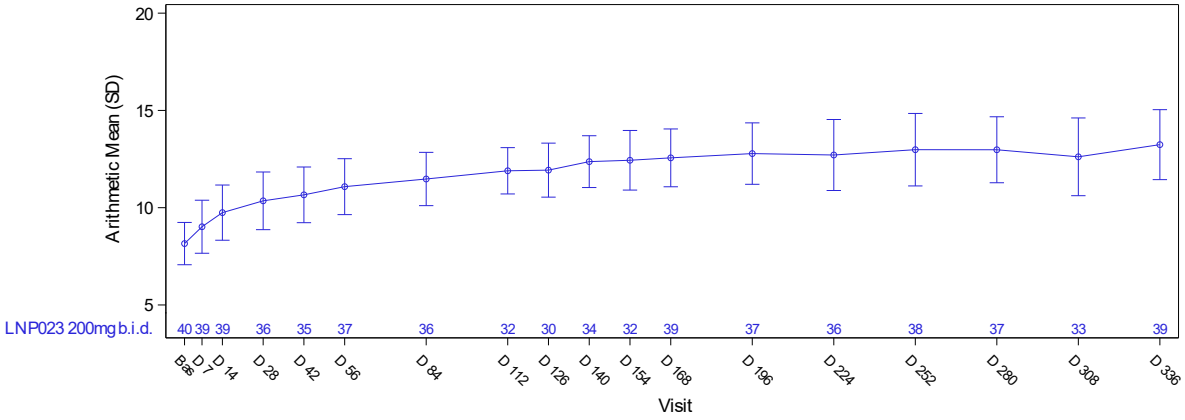
patients experienced a major adverse vascular event (MAVE) over the 48-week study duration.

Table 2: APPOINT-PNH: Summary of 48-week efficacy results

Endpoint	Summary measure	
≥2 g/dL increase from baseline in Hb, irrespective of transfusions, at Day 336	n/M (%)	38/39 patients (97.4%)
Hb ≥12 g/dL, irrespective of transfusions, at Day 336	n/M (%)	31/39 patients (79.5%)
Transfusion avoidance†	Marginal proportion (95% CI)	97.5% (95% CI: 92.5%, 100.0%)
Change from baseline in Hb levels (g/dL)‡	Mean (SD)	+5.09 g/dL (SD: 2.010 g/dL)
Change from baseline in LDH levels (U/L)‡	Mean (SD)	−1393.3 U/L (SD: 652.15 U/L)
Clinical BTH	Adjusted annualised rate (95% CI)¶	0.05 (95% CI: 0.01, 0.17)
Change from baseline in absolute reticulocyte counts (10^9/L)‡	Mean (SD)	−76.55 10^9/L (SD: 50.149 10^9/L)
Change from baseline in FACIT-Fatigue scores‡	Mean (SD)	+10.4 points (SD: 10.14 points)
MAVEs	Adjusted annualised rate (95% CI)¶	0.00 (95% CI: 0.00, 0.09)

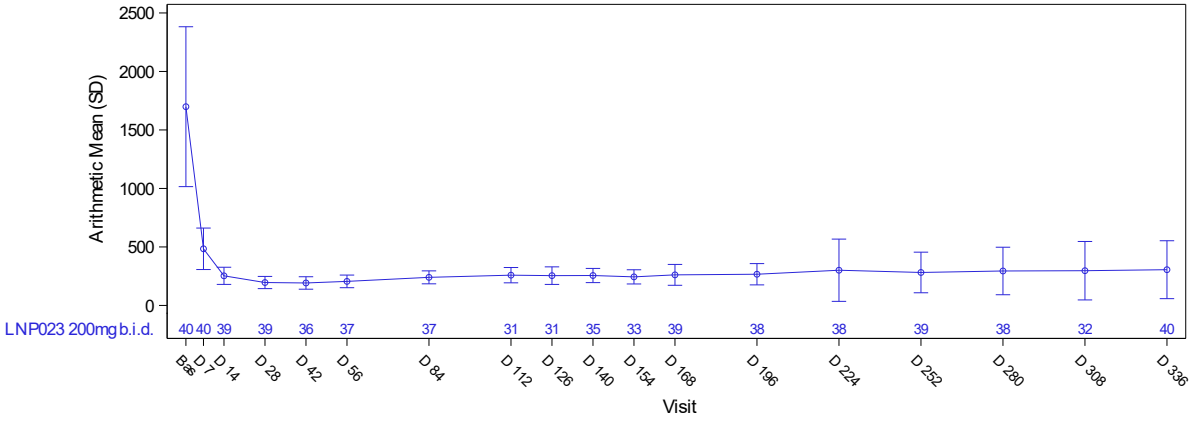
Source: Novartis data on file, 48-week APPOINT-PNH CSR (2023) (7)
†Marginal proportion of patients not receiving or not requiring transfusions between Day 14 and Day 336. The marginal proportion of responders was computed using simple proportion, based on observed data. The 95% CI was obtained using the bootstrap method; ‡Summary statistics for change from baseline up to Day 336; ¶Between Day 1 and Day 336.
Abbreviations: BTH, breakthrough haemolysis; CI, confidence interval; FACIT-Fatigue, Functional Assessment Of Chronic Illness Therapy – Fatigue; Hb, haemoglobin; LDH, lactate dehydrogenase; M, number of patients with evaluable/non-missing data; MAVE, major adverse vascular event; n, number of patients meeting the specified criterion; SD, standard deviation.

Figure 1: APPOINT-PNH: Arithmetic mean (SD) of Hb (g/dL) by visit up to Day 336 (FAS)



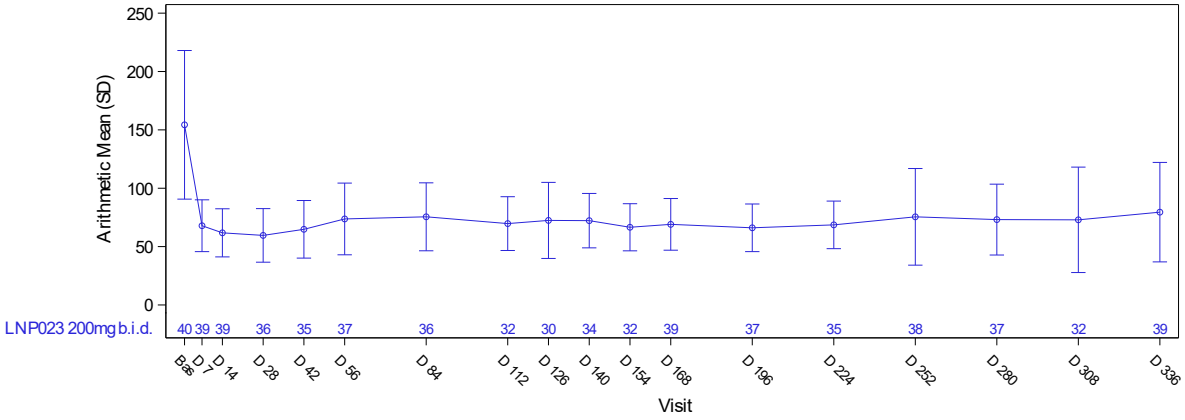
Source: Novartis data on file, 48-week APPOINT-PNH CSR (2023) (7)
At each visit-window, only patients with a value at both baseline and that visit-window are included.
Abbreviations: Bas = baseline; FAS, full analysis set; Hb, haemoglobin; SD, standard deviation.

Figure 2: APPOINT-PNH: Arithmetic mean (SD) of LDH (U/L) by visit up to Day 336 (FAS)



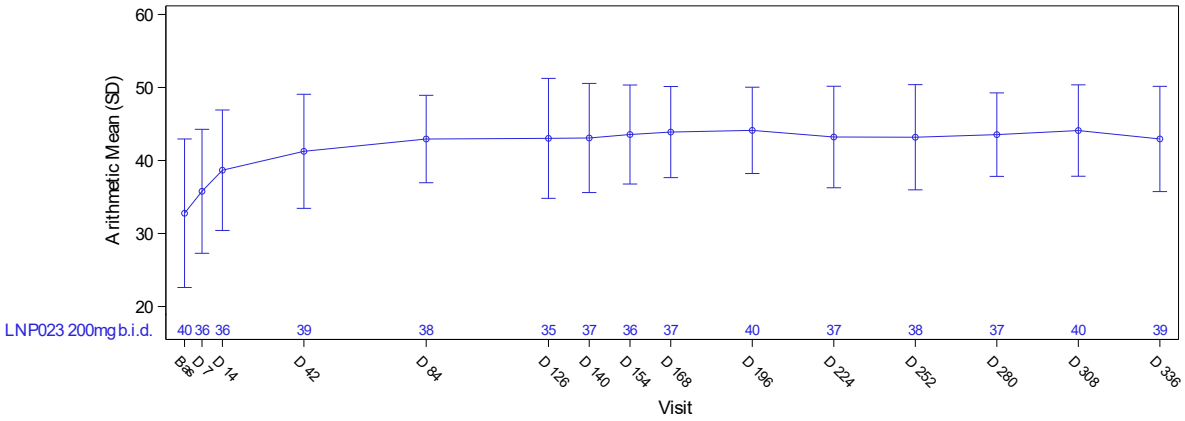
Source: Novartis data on file, 48-week APPOINT-PNH CSR (2023) (7)
At each visit-window, only patients with a value at both baseline and that visit-window are included.
Abbreviations: Bas = baseline; FAS, full analysis set; LDH, lactate dehydrogenase; SD, standard deviation.

Figure 3: APPOINT-PNH: Arithmetic mean (SD) of absolute reticulocyte counts (10^9/L) by visit up to Day 336 (FAS)



Source: Novartis data on file, 48-week APPOINT-PNH CSR (2023) (7)
At each visit-window, only patients with a value at both baseline and that visit-window are included.
Abbreviations: Bas = baseline; FAS, full analysis set; SD, standard deviation.

Figure 4: APPOINT-PNH: Arithmetic mean (SD) of FACIT-Fatigue scores by visit up to Day 336 (FAS)



Source: Novartis data on file, 48-week APPOINT-PNH CSR (2023) (7)
At each visit-window, only patients with a value at both baseline and that visit-window are included.
Abbreviations: Bas = baseline; FAS, full analysis set; SD, standard deviation.

Safety

During the entire 48-week study, iptacopan was well tolerated, with the majority of treatment-emergent adverse events (AEs) being mild or moderate. Overall, 37/40 patients (92.5%) experienced at least one AE, and 17/40 patients (42.5%) experienced AEs that were suspected by the Investigator to be treatment related. Four of the 40 patients (10.0%) experienced severe AEs and 8/40 (20.0%) experienced SAEs, and of these, 2 patients (5.0%) experienced SAEs suspected by the Investigator to be treatment related (Table 3). The most frequently reported AEs were headache (30.0% of patients), COVID-19 (22.5%), upper respiratory tract

infection (17.5%), and diarrhoea (15.0%). There were no discontinuations or dose interruptions due to AEs, and there were no MAVEs or deaths.

Table 3: APPOINT-PNH: Overview of AEs in 48 weeks (Safety set)

Category	Iptacopan 200 mg BD N=40 n (%)
Adverse events	**37 (92.5)**
Suspected to be treatment-related	17 (42.5)
Severe AEs	**4 (10.0)**
Suspected to be treatment-related	1 (2.5)
SAEs	**8 (20.0)**
Suspected to be treatment-related	2 (5.0)
Fatal SAEs	**0**
Suspected to be treatment-related	0
AEs leading to treatment discontinuation	**0**
AEs leading to dose interruption	**0**
AEs requiring additional therapy	**33 (82.5)**

Source: Novartis data on file, 48-week APPOINT-PNH CSR (2023) (7)
Abbreviations: AE, adverse event; BD, twice daily; SAE, serious adverse event.

APPLY-PNH: 48-week results

Patient disposition

In APPLY-PNH, patients were randomised in an 8:5 ratio to receive either iptacopan (N=62) or C5 inhibitor treatment (N=35) during the 24-week randomised treatment period. Upon completion of the 24-week randomised treatment period, patients randomised to the C5 inhibitor arm were offered to switch to iptacopan and enter the 24-week treatment extension period. Patients in the iptacopan arm who benefitted from treatment and had completed the 24-week randomised treatment period on study treatment were offered to continue iptacopan for another 24 weeks during the treatment extension period (i.e. a total of 48 weeks).

One of 62 patients had discontinued iptacopan due to pregnancy during the randomised period. Of the 61 patients who completed the randomised period on iptacopan treatment, all 61 patients chose to continue iptacopan in the extension period, during which one patient discontinued iptacopan due to pregnancy. One patient from the C5 inhibitor arm did not enter the treatment extension period due to the investigator's decision (patient's clinical condition). All other 34 patients from the

C5 inhibitor arm entered the treatment extension period and completed 24 weeks of iptacopan treatment. Overall, 94 out of 95 patients who entered the extension period completed the treatment extension period on iptacopan.

Clinical effectiveness

Efficacy results of the APPLY-PNH 48-week analysis are summarised in Table 4, demonstrating clinically meaningful benefits of iptacopan treatment both in patients randomised to the iptacopan arm and treated for overall 48 weeks, as well as patients who switched from C5 inhibitor to iptacopan at the start of the 24-week treatment extension period.

After 48 weeks of iptacopan treatment, 86.4% of patients randomised to the iptacopan arm had a ≥2 g/dL increase from baseline in Hb; the percentage of patients with Hb ≥12 g/dL was 67.8%. Among the patients who switched from C5 inhibitor to iptacopan at the start of the treatment extension period and were treated with iptacopan for 24 weeks, the proportion of patients achieving these haematological response endpoints were 72.4% and 58.6%, respectively. Of note, haematological response endpoints in the 48-week analysis included all Hb values irrespective of RBC transfusions, whereas the primary analysis at 24 weeks required the absence of transfusions as an integral part of the endpoints. However, the large majority of patients did not require transfusions after 14 days of iptacopan treatment, with the proportion of transfusion-avoidant patients in the iptacopan arm 91.9% (Day 14 to Day 336) and in the C5 inhibitor-to-iptacopan arm 94.1% (Day 14 to Day 168 of iptacopan treatment).

Change from baseline in Hb, FACIT-Fatigue and absolute reticulocyte counts as well as control of LDH were maintained in the iptacopan arm over the 48-week treatment duration up to Day 336 (Figure 5 to Figure 8). For patients switching from C5 inhibitor to iptacopan at the start of the treatment extension period, Hb, FACIT-Fatigue and absolute reticulocyte counts improved rapidly within four weeks of starting iptacopan treatment, and reached similar levels as those of patients treated with iptacopan for 48 weeks (Figure 5 to Figure 7). Inhibition of intravascular haemolysis (LDH endpoint) was maintained following the switch to iptacopan (Figure 8).

Occurrences of clinical BTH and MAVE with iptacopan treatment were low, with adjusted annualised event rates estimated as 0.11 (95% CI: 0.05, 0.23) for BTH and 0.04 (95% CI: 0.01, 0.13) for MAVE, based on events observed in all patients since initiation of iptacopan treatment.

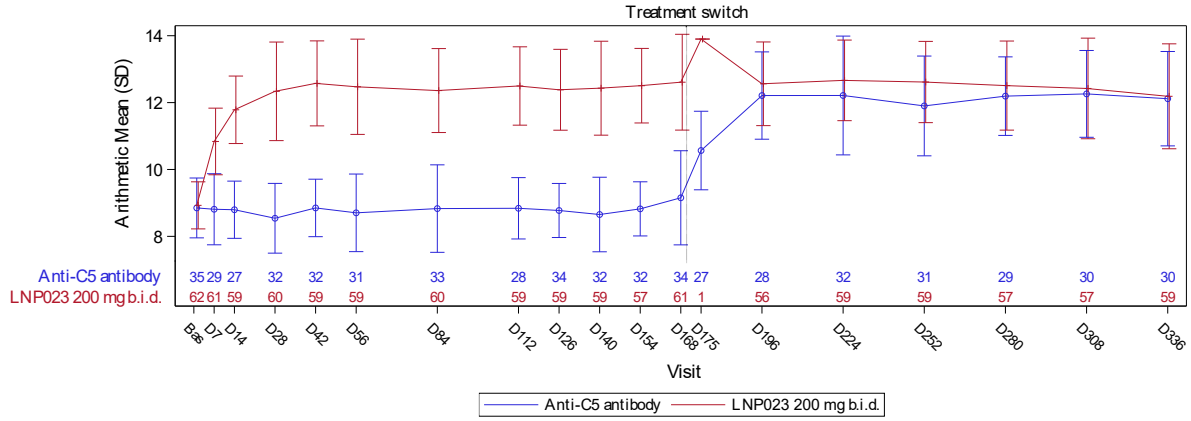
Table 4: APPLY-PNH: Summary of efficacy results at the 48-week analysis

Endpoint	Arm[#]	Time	Summary measure	
		Iptacopan exposure	Patients achieving the haematological response endpoint (n/M (%))	
≥2 g/dL increase from baseline in Hb, irrespective of transfusions	Iptacopan	48 weeks	51/62 (86.4)	
	C5 inhibitor to iptacopan	24 weeks[III]	21/34 (72.4)	
Hb ≥12 g/dL, irrespective of transfusions	Iptacopan	48 weeks	40/62 (67.8)	
	C5 inhibitor to iptacopan	24 weeks[III]	17/34 (58.6)	
		Iptacopan exposure	Adj mean CFB (95% CI) at Day 336	Adj mean difference in CFB (95% CI): Day 336 vs Day 168
Change from baseline* in Hb level (g/dL)[†]	Iptacopan	48 weeks	+3.35 (3.04, 3.67)	−0.41 (−0.80, −0.01)
	C5 inhibitor to iptacopan	24 weeks[III]	+3.36 (2.94, 3.79)	+3.02 (2.49, 3.56)
Change from baseline[‡] in FACIT-Fatigue score	Iptacopan	48 weeks	+9.80 (8.04, 11.56)	+0.73 (−1.14, 2.60)
	C5 inhibitor to iptacopan	24 weeks[III]	+10.96 (8.58, 13.34)	+10.79 (8.12, 13.47)
Change from baseline[§] in absolute reticulocyte counts (10^9/L)	Iptacopan	48 weeks	−106.26 (−117.57, −94.96)	+9.92 (−4.40, 24.25)
	C5 inhibitor to iptacopan	24 weeks[III]	−107.95 (−123.18, −92.73)	−102.29 (−121.57, −83.02)
		Iptacopan exposure	Geometric adj mean ratio to baseline (95% CI) at Week 48	Geometric adj mean ratio (95% CI): Day 336 vs Day 168
Ratio to baseline[‖] in log-transformed LDH (U/L)	Iptacopan	48 weeks	1.11 (1.02, 1.22)	1.12 (1.00, 1.25)
	C5 inhibitor to iptacopan	24 weeks[III]	0.99 (0.88, 1.11)	0.99 (0.85, 1.15)

		Time period	Patients not requiring an RBC transfusion since 2 weeks after initiation of iptacopan monotherapy (n [%])	
Transfusion avoidance¶	Iptacopan	Day 14 to Day 336	57 (91.9)	
	C5 inhibitor to iptacopan	Day 182 to Day 336 (iptacopan)	32 (94.1)**	
		Time period	n/N	Overall adj annualised rate of events since initiation of iptacopan monotherapy, including both treatment arms (95% CI)
Clinical BTH††	Iptacopan	Baseline to Day 336	6/62	0.11 (0.05, 0.23)
	C5 inhibitor to iptacopan	Day 169 to Day 336 (iptacopan)	1/34	
MAVEs	Iptacopan	Baseline to Day 336	2/62	0.04 (0.01, 0.13)
	C5 inhibitor to iptacopan	Day 169 to Day 336 (iptacopan)	1/34	

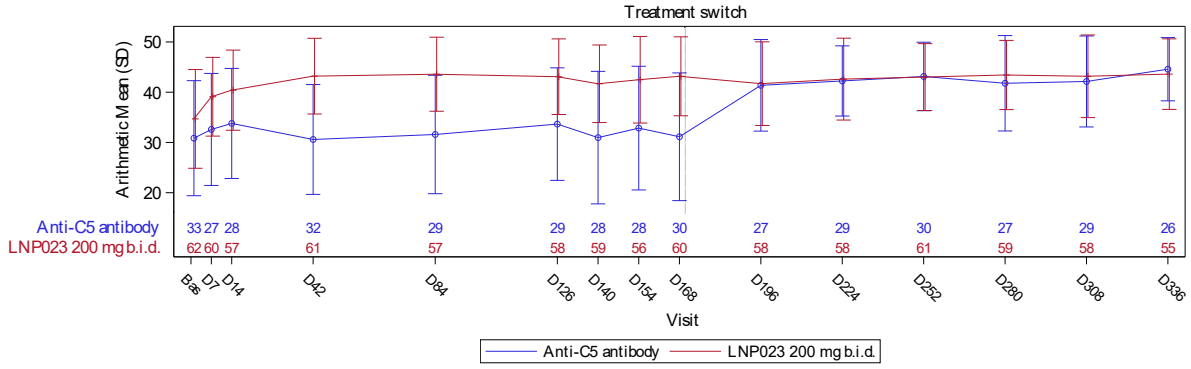
Source: Novartis data on file, 48-week APPLY-PNH CSR (2023) (8)
Iptacopan N=62; C5 inhibitor to iptacopan N=35; *Mean (SD) baseline Hb levels were 8.93 (0.70) and 8.85 (0.89) g/dL in the iptacopan and C5 inhibitor-to-iptacopan arms, respectively; †Analysis includes all central lab Hb data, including post-transfusion data; ‡Mean (SD) baseline FACIT-F scores were 34.7 (9.8) and 30.8 (11.5) in the iptacopan and C5 inhibitor-to-iptacopan arms, respectively; §Mean (SD) baseline absolute reticulocyte counts were 193.2 (83.6) and 190.6 (80.9) × 10^9/L in the iptacopan and C5 inhibitor-to-iptacopan arms, respectively; ‖Mean (SD) baseline LDH levels were 269.1 (70.1) and 272.7 (84.8) U/L in the iptacopan and C5 inhibitor-to-iptacopan arms, respectively; ¶Defined as neither receiving nor meeting the criteria to receive a packed RBC transfusion; **34 of 35 patients in the C5 inhibitor-to-iptacopan arm received iptacopan in the treatment extension period; ††Events that met the protocol-specified criteria for clinical BTH; ‖‖ Received iptacopan from Day 169 to Day 336 (treatment extension period).
Abbreviations: Adj, adjusted; BTH, breakthrough haemolysis; CFB, change from baseline; CI, confidence interval; Hb, haemoglobin; LDH, lactate dehydrogenase; M, number of patients with evaluable/non-missing data; MAVE, major adverse vascular event; n, number of patients with event; N, number of patients treated with iptacopan; RBC, red blood cells; SD, standard deviation.

Figure 5: APPLY-PNH: Arithmetic mean (SD) of Hb (g/dL) by visit up to Day 336 (FAS)



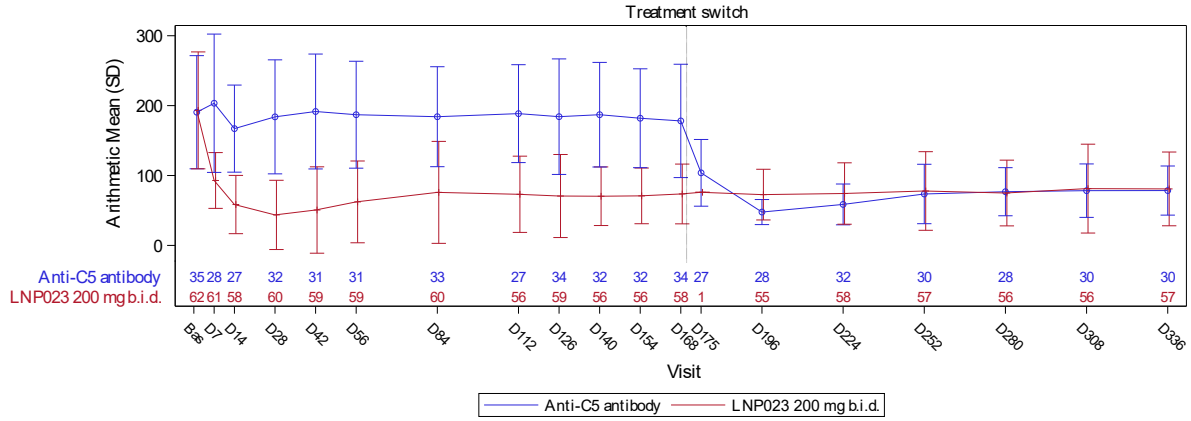
Source: Novartis data on file, 48-week APPLY-PNH CSR (2023) (8)
At each visit-window, only patients with a value at both baseline and that visit-window are included.
Abbreviations: Bas = baseline; FAS, full analysis set; Hb, haemoglobin; SD, standard deviation.

Figure 6: APPLY-PNH: Arithmetic mean (SD) of FACIT-Fatigue scores by visit up to Day 336 (FAS)



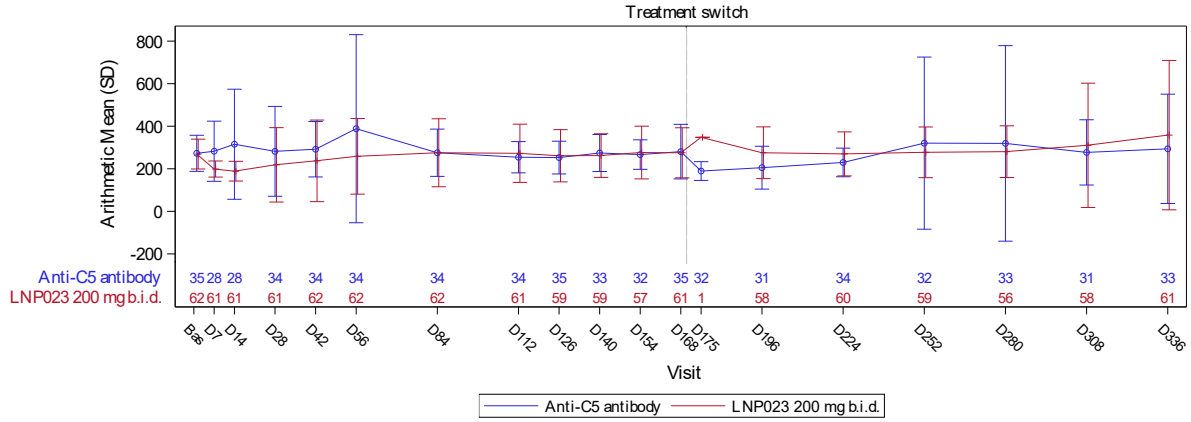
Source: Novartis data on file, 48-week APPLY-PNH CSR (2023) (8)
At each visit-window, only patients with a value at both baseline and that visit-window are included.
Abbreviations: Bas = baseline; FAS, full analysis set; SD, standard deviation.

Figure 7: APPLY-PNH: Arithmetic mean (SD) of absolute reticulocyte counts (10^9/L) by visit up to Day 336 (FAS)



Source: Novartis data on file, 48-week APPLY-PNH CSR (2023) (8)
At each visit-window, only patients with a value at both baseline and that visit-window are included.
Abbreviations: Bas = baseline; FAS, full analysis set; SD, standard deviation.

Figure 8: APPLY-PNH: Arithmetic mean (SD) of LDH (U/L) by visit up to Day 336 (FAS)



Source: Novartis data on file, 48-week APPLY-PNH CSR (2023) (8)
At each visit-window, only patients with a value at both baseline and that visit-window are included.
Abbreviations: Bas = baseline; FAS, full analysis set; LDH, lactate dehydrogenase; SD, standard deviation.

Safety

Overall, iptacopan was well-tolerated. No new safety signals were observed in the treatment extension period.

Most patients had an AE during the entire 48-week study period, and the proportions were comparable between patients randomised to iptacopan (93.5%) and all patients who received iptacopan (88.5%) (Table 5). The majority of all patients who received iptacopan had mild or moderate AEs. A total of 9.7% (6/62) of patients randomised to iptacopan had severe AEs, with an additional 3 patients randomised to C5

inhibitors having severe AEs after they switched to iptacopan. The most commonly reported AEs were COVID-19 (27.1% among all patients who received iptacopan), headache (14.6%), diarrhoea (12.5%), nasopharyngitis (12.5%), and nausea (11.5%). AEs suspected to be related to study medication were reported in 27.4% of patients randomised to iptacopan and in 21.9% of all patients who received iptacopan. SAEs were reported in 14.5% of patients randomised to iptacopan and in 13.5% of all patients who received iptacopan.

Three MAVEs occurred in three patients whilst on iptacopan treatment, of which two were transient ischemic attacks (TIAs) and one was portal vein thrombosis following discontinuation of anti-coagulant therapy by the patient. None of the MAVEs were considered to be related to iptacopan treatment by the investigator and all patients continued with iptacopan treatment.

There were no deaths and no study drug discontinuations due to AEs, indicating favourable tolerability in the target population.

Table 5: APPLY-PNH: Overview of AEs in patients treated with iptacopan 200 mg BD (Combined Safety Analysis Set)

Category	Iptacopan 200 mg BD N=62 n (%)	Combined iptacopan safety analysis N=96 n (%)
Adverse events	**58 (93.5)**	**85 (88.5)**
Suspected to be treatment-related	17 (27.4)	21 (21.9)
Severe AEs	**6 (9.7)**	**9 (9.4)**
Suspected to be treatment-related	0	1 (1.0)
SAEs	**9 (14.5)**	**13 (13.5)**
Suspected to be treatment-related	0	1 (1.0)
Fatal SAEs	**0**	**0**
AEs leading to treatment discontinuation	**0**	**0**
AEs leading to dose interruption	**1 (1.6)**	**1 (1.0)**
AEs requiring additional therapy	**53 (85.5)**	**73 (76.0)**

Source: Novartis data on file, 48-week APPLY-PNH CSR (2023) (8)
Abbreviations: AE, adverse event; BD, twice daily; SAE, serious adverse event.

A4. Please explain the large difference in % female participants between the APPOINT-PNH (42.5%) and the APPLY-PNH (69.1%) trials.

While international PNH registry data demonstrates a slightly higher incidence of PNH in females (53%) vs males (47%) (9), the percentages of female patients in the APPOINT-PNH (42.5%) and the APPLY-PNH (69.1%) trials are within the range observed in other PNH clinical trials identified in the SLR (Table 6), where the proportion of female patients ranged from 23.1% (Study 201; N=26) (10) to 83.3% (Kulasekararaj 2021; N=12) (11). In larger trials with at least 40 patients, the range was closely aligned with the APPOINT-PNH and APPLY-PNH range, with 44.0% female patients in Jang 2023 (N=50) (12), and 61.3% female patients in PEGASUS (N=80) (4).

The lower proportion of female patients in APPOINT-PNH could be related to the high proportion of patients from study sites in Asia (65%), with a previous meta-analysis demonstrating a significantly lower proportion of female PNH patients in Asian countries (44.9%) than in Western countries (54.9%) (13).

Subgroup analyses for APPOINT-PNH and APPLY-PNH (Appendix E) did not show any significant differences in iptacopan treatment effect between female and male patients.

Table 6: Proportion of female patients in clinical trials identified by the clinical effectiveness SLR

Trial (key reference)	Intervention	Comparator	N	% female
Trials evaluating complement inhibitor-naïve PNH patients				
Hillmen 2004 (14)	Eculizumab	—	11	45.5%
SHEPHERD Brodsky 2008 (15)	Eculizumab	—	97	50.5%
TRIUMPH Hillmen 2006 (16)	Eculizumab	Placebo	87	59.8%
Eculizumab extension study (including patients from Hillmen 2004, SHEPHERD, and TRIUMPH) Hillmen 2007 (17)	Eculizumab	—	195	54.4%
AEGIS Kanakura 2011 (18)	Eculizumab	—	29	51.7%

Trial (key reference)	Intervention	Comparator	N	% female
Study 201 Roth 2018 (10)	Ravulizumab	—	26	23.1%
Study 301 Lee 2019 (6)	Ravulizumab	Eculizumab	246	45.5%
Wong 2019 (19)	Pegcetacoplan	—	20	NR
Jang 2022 (20)	Iptacopan 25 mg BD	Iptacopan 50 mg BD	13	53.8%
APPOINT-PNH CSR (1)	Iptacopan	—	40	42.5%
Risitano 2021 (21)	Danicopan	-—	10	NR
Jang 2023 (12)	SB12 (eculizumab biosimilar) to eculizumab	Eculizumab to SB12 (eculizumab biosimilar)	50	44.0%
Trials evaluating complement inhibitor-experienced PNH patients with anaemia				
PEGASUS Hillmen 2021 (4)	Pegcetacoplan	Eculizumab	80	61.3%
Risitano 2021 (22)	Iptacopan + eculizumab	—	10	30.0%
APPLY-PNH CSR (2)	Iptacopan	C5 inhibitors (eculizumab, ravulizumab)	97	69.1%
Kulasekararaj 2021 (11)	Danicopan + eculizumab	—	12	83.3%

Abbreviations: BD, twice daily; CSR, clinical study report; NR, not reported; SLR, systematic literature review.

Indirect treatment comparisons (ITC)

A5. Please clarify why a randomly selected cohort of UK participants was included in APPEX rather than all UK participants meeting the inclusion criteria (section B.2.9.2.1).

A preliminary assessment using information on the expected degree of overlap in patient characteristics between real-world data and APPOINT-PNH trial data indicated an estimated reduction of effective sample size by up to 52%. The APPEX protocol hence specified a target sample size of 75–90 patients with evaluable data for the primary endpoint in order to achieve precision equivalent to a sample size of 35–40 patients in the APPOINT-PNH trial (23).

The two participating study sites in the UK and France were therefore asked to extract and share data for 40–60 patients each. Since the UK site had data for more

patients, records for the patient number required for the study were selected at random, to minimise the risk of selection bias.

A UK clinician with no involvement in the APPEX study was consulted during the preparation of the clarification questions response. Upon review of the patients' baseline characteristics, the clinician confirmed that the patients included in the APPEX real-world cohort were largely representative of PNH patients commencing C5 inhibitor therapy in current UK clinical practice, with the only exception being the proportion of patients with a history of MAVE which tends to be higher in the UK.

A6. Please clarify why breakthrough haemolysis (BTH) was not included as an outcome in the indirect treatment comparisons.

In the APPOINT-PNH study in complement inhibitor-naïve patients, there were zero patients with BTH events on iptacopan during the 24-week core treatment period (up to Day 168) (1), making an ITC of BTH rates in the naïve population infeasible. The APPEX study had included BTH as an exploratory objective, but no ITC was undertaken and BTH data from the APPEX real-world cohort was summarised in a descriptive manner only. 15 events were observed in 10/85 patients (11.8%) up to Day 200 after starting C5 inhibitor treatment; the adjusted annualised BTH event rate was estimated as 0.30 (95% CI 0.16, 0.65) (23).

In the complement inhibitor-experienced population, BTH events for iptacopan and pegcetacoplan were rare. In APPLY-PNH, two clinical BTH events were reported in 2/62 patients (3.2%) in the iptacopan arm during the 24-week randomised controlled period, with an adjusted annualised event rate of 0.07 (95% CI: 0.02, 0.31) (2). While BTH was a secondary endpoint in APPLY-PNH, PEGASUS did not have any pre-specified BTH endpoint and BTH events were reported as AEs only. During the 16-week randomised controlled period, 4/41 patients (9.8%) were reported to have BTH while on pegcetacoplan (4). Due to the small number of observed events, any ITC would likely have been considerably underpowered. In addition, since BTH events were only captured as AEs in PEGASUS, no uniform definition may have been applied across events, and any definition applied in PEGASUS may have differed from the clinical BTH criteria in APPLY-PNH (a decrease in Hb of ≥2 g/dL (compared to the latest assessment, or within 15 days) *and/or* presence of signs or symptoms,

and LDH level >1.5 x ULN and increased as compared to the last 2 assessments) (2), further limiting the validity of any ITC.

A7. Please provide all codes and datasets (including APPOINT-PNH, APPLY-PNH) used in the ITC analyses, both in the C5 complement naïve and experienced populations.

While code used for the ITCs can be provided to the EAG, to protect patient information and adhere to legal and ethical compliance, clinical trial datasets cannot be shared to third parties without a rigorous approval process and subject to data access agreements, which is not feasible within the timeline and scope of a single technology appraisal process. Although it is not possible to share the individual patient level data with the EAG, Novartis will endeavour to conduct analyses requested by the EAG.

R code demonstrating the functional code and analytic steps undertaken to conduct the ITCs vs published clinical trials including calculation of ITC weights and derivation of weighted contrasts is provided in the file 'A7_R codes excerpt - ITCs, experienced population base case' in the supplementary files pack. The code also demonstrates post-estimation extraction of point estimates, robust standard errors, confidence intervals, and p-values. Code is presented for the base case outcomes for the experienced population. Similar code was used for scenarios in the experienced population and for ITCs in the naïve population. For ITCs in the naïve population, code demonstration for anchored ITCs is not relevant as APPOINT-PNH was a single-arm trial without a common comparator.

Code for the APPEX study including the comparative effectiveness assessment is provided in the file 'A7_APPEX code' in the supplementary files pack.

A8. Please confirm and justify which method was used to undertake the anchored ITC in the C5 complement experienced population.

The anchored ITC estimates were derived by leveraging the arm-based weights from the unanchored ITC. Anchored ITCs for iptacopan vs pegcetacoplan were computed as the difference between (a) the reweighted outcome for iptacopan minus the reweighted outcome for the C5 inhibitor control arm of APPLY-PNH and (b) the published estimate of the outcome for pegcetacoplan minus that of the C5 inhibitor

control arm of PEGASUS. Consequently, the anchored ITC analysis performed may be viewed as in line with a weighted form of contrast-based evidence synthesis methods described in the NICE TSD2 (24), which differs from a Bucher ITC which does not incorporate weights.

A9. In the C5 complement naïve population ITC (APPOINT-PNH vs Study 301, and APPOINT – PNH vs TRIUMPH), baseline haemoglobin (Hb) could not be adjusted for due to non-convergence (Company Submission Document B, section B.2.9.1.2 and Appendix D section D.4.3.5.1). Also, adjusting for baseline Hb led to a small effective sample size (ESS) (ITC of APPLY vs PEGASUS - Document B, section B.2.9.3.4). Could this be a problem related to non-overlapped population? Could there be other confounders or factors that need to be adjusted for? Please comment on this.

Hb inclusion criteria differed among the studies included in the ITC in the complement inhibitor-naïve population. In APPOINT-PNH, patients were required to have Hb <10 g/dL. For Study 301 eligible patients may have had Hb ≥10 g/dL, provided other PNH symptoms were present (e.g. fatigue). For the TRIUMPH study, patients were required to have Hb <10.5 g/dL. Therefore, Study 301 and TRIUMPH will likely have included some patients with baseline Hb ≥10 g/dL, with no counterpart in the APPOINT-PNH population. Prior to implementing population adjustments for the ITC, the population mean and SD baseline Hb of all studies were compared (Table 7). The standardised mean differences (SMD) in baseline Hb between Study 301 and APPOINT-PNH as well as TRIUMPH and APPOINT-PNH were interpreted to be substantial differences (SMD >0.2). An attempt was made to include baseline Hb in the population adjustment, but no weights could be estimated as the model did not converge. Novartis acknowledges that this is a limitation of the ITCs vs Study 301 and TRIUMPH, and results especially for Hb and transfusion endpoints should be interpreted with caution due to substantial differences in baseline Hb values that could not be adjusted for. Reticulocyte counts (ITCs vs Study 301 and vs TRIUMPH) and MAVE (ITC vs TRIUMPH) were other factors that could not be adjusted for as baseline data were not reported for the comparator studies.

The APPEX real-world evidence study in the complement inhibitor-naïve population was designed under a target trial framework, and thus mirrored the Hb inclusion criterion of APPOINT-PNH (Hb <10 g/dL). Due to sufficient overlap between the baseline Hb distributions in APPEX and APPOINT-PNH, this variable could be included in the population adjustment and the SMD was 0.035 after reweighting (Table 7).

Table 7: Baseline Hb level before and after adjustment in studies included in complement inhibitor-naïve population ITCs

	Comparator study	**APPOINT-PNH Unweighted** (N=40)		**APPOINT-PNH Weighted** (vs Study 301 ESS=31, vs TRIUMPH ESS=10)	
	Baseline Hb, mean (SD)	**Baseline Hb, mean (SD)**	**SMDs**	**Baseline Hb, mean (SD)**	**SMDs**
Study 301 (N=246)	9.5 (1.6)	8.15 (1.09)	0.983	7.9 (1.2)	1.127
TRIUMPH (N=43)	10 (0.2)	8.15 (1.09)	2.36	8.4 (1.1)	2.05
	APPOINT-PNH (N=40)	**APPEX Unweighted** (N=85)		**APPEX Weighted** (ESS=41)	
	Baseline Hb, mean (SD)	**Baseline Hb, mean (SD)**	**SMDs**	**Baseline Hb, mean (SD)**	**SMDs**
APPOINT-PNH (N=40)	8.15 (1.09)	8.4 (1.27)	−0.200	8.1 (1.49)	0.035

Interpretation: Green = SMD ≤ 0.1 (small difference); Yellow = 0.1 > SMD ≤ 0.2 (moderate difference); Red = SMD > 0.2 (substantial difference) (25, 26).
Abbreviations: ESS, effective sample size; SD, standard deviation; SMD, standardised mean difference

In the complement inhibitor-experienced population ITC of APPLY-PNH vs PEGASUS, Hb inclusion criteria also differed between trials, with patients in APPLY-PNH required to have Hb <10 g/dL and patients in PEGASUS Hb <10.5 g/dL. Therefore, there may have been some patients in the PEGASUS study with baseline Hb ≥10 g/dL, with no counterpart in the APPLY-PNH population.

Prior to the adjustment the population mean and SD for baseline Hb were compared (Table 8). Despite the difference in inclusion criteria, baseline mean Hb was very similar between the two studies, with 8.9 g/dL in APPLY-PNH and 8.7 g/dL in PEGASUS, although the SD showed more variance in PEGASUS. Due to sufficient overlap between the baseline Hb distributions, this variable could be included in the adjustment and the SMD was <0.0001 after reweighting.

Table 8: Baseline Hb level before and after adjustment in studies included in complement inhibitor-experienced population ITC

	Comparator study	APPLY-PNH: Iptacopan – ITT, unweighted (N=62)		APPLY-PNH: Iptacopan – Weighted (ESS=15)	
	Baseline Hb, mean (SD)	Baseline Hb, mean (SD)	SMDs	Baseline Hb, mean (SD)	SMDs
PEGASUS: Pegcetacoplan (N=41)	8.7 (1.1)	8.9 (0.7)‡	0.186	8.7 (1.1)	0.000

Interpretation: Green = SMD ≤ 0.1 (small difference); Yellow = 0.1 > SMD ≤ 0.2 (moderate difference); Red = SMD > 0.2 (substantial difference) (25, 26).
‡ Baseline Hb as per PEGASUS trial definition.
Abbreviations: ESS, effective sample size; SD, standard deviation; SMD, standardised mean difference

A10. In Appendix D of the company submission (page 60, D.4.4.2.1), the company state that "Potential confounders and prognostic factors were identified through systematic literature review and expert advice…". Please provide details.

As part of the APPEX study, a literature review was conducted by [redacted] in October 2022 to identify potential confounders in PNH. Data sources searched included MEDLINE, Embase, Cochrane Database of Systematic Reviews, and websites of several national and international societies, to identify guidelines, systematic reviews, and observational studies. Further details including search terms and inclusion/exclusion criteria by study type are available in the file A10_Documentation of Literature Research_Confounder PNH in the supplementary files pack. Title/abstracts were screened by two independent reviewers, followed by full text screening of records considered potentially eligible based on title/abstract screening. Disagreements at each screening stage were resolved by discussion.

Overall, 40 records (37 full-text publications) meeting the eligibility criteria were identified (see file A10_Literature review confounders_Included studies in the supplementary files pack). Information pertaining to potential prognostic factors for PNH was extracted from the identified studies and summarised for discussion with clinical experts (23). A meeting with three clinical experts (the APPEX principal investigators of the two participating centres in the UK and France as well as one clinical expert from [redacted]

[redacted]) to review the candidate list of potential confounders took place in January 2023. Following the meeting, a list of the main factors was produced and reconfirmed with the clinical experts by majority rule (Table 9) (23). Most of the factors considered (very) important could be implemented in the APPEX analysis, with a few exceptions due to insufficient data available in the real-world data (Table 9) (23).

Table 9: Baseline factors and their importance for the APPEX analysis

Baseline factor	Importance to account for in APPEX analysis, based on input from clinical experts	Feasibility to include in APPEX analysis
Medical history: transfusions	Very important	Implemented as total number of packed RBC transfused 24 weeks prior to index date
Medical history: thromboembolic events	Very important	Implemented as history of MAVEs
Medical history: aplastic anaemia	Very important	Implemented as ongoing aplastic anaemia/ neutropenia/ bone marrow failure with modified coding to match APPOINT-PNH study
Medical history: bone marrow failure	Very important	
Medical history: infections	Very important	Not included – incomplete real world data
Signs and symptoms	Very important	Not included – incomplete real world data
Medical history: renal disease	Important	Not included – incomplete real world data
Haematology/biochemistry: haemoglobin	Important	Implemented as baseline haemoglobin
Haematology/biochemistry: LDH	Important	Not included – incomplete real world data
Haematology/biochemistry: reticulocytes	Important	Implemented as baseline reticulocyte count
Age	Less important	Included to account for unmeasured confounding
Sex	Less important	Included to account for unmeasured confounding
Medical history: year of PNH diagnosis	Less/not important	Not included, not important
PNH clone size	Not important	Not included, not important
Medical history: leukopenia	Not important	Not included, not important
Medical history: neutropenia	Not important	Not included, not important
Medical history: anaemia	Not important	Not included, not important
Medical history: inflammatory conditions	Not important	Not included, not important
Medical history: MDS/ AML	Not important	Not included, not important

Medical history: additional treatment requirement	Not important	Not included, not important

Source: APPEX Study Report (23), Section 4.1.2, Appendix 16.1.9, Section 2 Confounder review, Table 4-1 (page 860)
Abbreviations: AML, acute myeloid leukaemia; LDH, lactate dehydrogenase; MAVE, major adverse vascular event; MDS, myelodysplastic syndrome; PNH, paroxysmal nocturnal haemoglobinuria; RBC, red blood cell.

In addition to the confounder review conducted as part of the APPEX study, adjustment factors for all ITCs were validated with two UK clinicians and two UK health economists consulted in preparation of the submission (27).

A11. In the APPEX section in Appendix D of the company submission (page 61, D.4.4.2.2), please specify which covariates were adjusted for.

For the APPEX ITC, the final model applied to the estimation of the propensity score used glmboost and included total RBC units transfused during six months prior to index date, baseline Hb, baseline reticulocyte count, ongoing aplastic anaemia/bone marrow disease, and history of MAVE, as well as age and sex as linear terms (Company submission, B.2.9.2.2, page 72).

Section B: Clarification on cost-effectiveness data

Treatment effectiveness used in the economic model

The effectiveness of the treatments used in the model are based on the transition probabilities reported in Table 42 and Table 43 of the company submission, informing the complement inhibitor-naïve and experienced populations, respectively.

There appears to be no link in the company submission between the statistical analysis of endpoints (primary, secondary and exploratory) of the trials, reported in Section B.2.4 of the company submission, and the transition probabilities between the health states used in the model.

B1. Please provide a comprehensive comparison and validation of the transition probabilities derived from the trials with the outcomes of the trials.

A comparison and validation of the results is essential to show that the transitions between the health states in the model are in line with the primary

and secondary outcomes of the trial, and expectations for the complement inhibitor-naïve and experienced populations for each treatment.

Two clinical outcomes are reflected in the modelled transition probabilities: the requirement for transfusion and anaemia. Although both outcomes were also captured in clinical trial endpoints, the way data are utilised by the economic model differs.

A direct comparison of modelled transfusion outcomes with transfusion outcomes from the clinical trials is challenging, as the transfusion endpoints used in trials typically focus on the proportion of patients that are transfusion-avoidant or transfusion-dependent over the trial duration, without consideration whether transfusion-dependent patients receive transfusions once or at multiple timepoints during the trial. The model, on the other hand, incorporates data on all patients receiving transfusions in 4-week time periods, thereby considering that some patients had multiple transfusions. The model is a semi-Markov model and does not track the history of transfusions. Therefore, it is not possible to directly compare model outputs on the proportion of patients in 'No transfusion' health states at any given timepoint with the proportion of patients considered transfusion-avoidant over the entire trial duration as reported in clinical trial endpoints.

Similarly, the outputs of the economic model related to anaemia cannot be easily compared with endpoints from the clinical trials. Several clinical trials reported haemoglobin (Hb) endpoints as change from baseline in Hb. The iptacopan trials also included endpoints assessing the proportion of patients with an increase from baseline in Hb of ≥2 g/dL, or the proportion of patients with Hb ≥12 g/dL, without requiring a transfusion. These endpoints were not utilised for the economic model since this would have precluded a comparison vs pegcetacoplan, due to lack of suitable reported data. The economic model therefore followed the only structure that allowed inclusion of pegcetacoplan on the basis of published transition probabilities, considering a threshold of Hb <10.5 g/dL when defining anaemia. A direct comparison of Hb trial endpoints and model results on anaemia is thus not feasible.

In place of a comparison of primary and secondary endpoints from the clinical trials with outcomes of the economic model, a comparison between observed and

predicted health state membership over 24 weeks is presented below. (The model was set to not include discontinuation for this analysis). Table 10 presents observed health state occupancy in APPOINT-PNH (based on count data derived from individual patient data [IPD]) in comparison to the modelled health state occupancy in the iptacopan arm of the model for the treatment-naïve population between Week 0 and Week 24. This shows that the distribution of patients across health states in the trial and economic model is well-aligned. At Day 28 (the end of the first cycle), there are more patients in the transfusion state in the clinical trial than in the model, however beyond this point there were no transfusions observed in APPOINT-PNH and the rate of transfusion in the economic model is similarly low.

Table 11 compares C5 inhibitor outcomes observed in the APPEX study (after imputation of missing Hb values) to those in the C5 inhibitor arm of the model for the naïve population over 24 weeks. Again, the modelled outcomes are well aligned with the observed data. While there are more transfusions in the model over the first 3 cycles, this is driven by the baseline distribution of patients, with 100% of patients in the APPEX data being in the 'No transfusion and anaemia' state at baseline, while in the model 25% of patients started in the transfusion state based on APPOINT-PNH. After 8 weeks the number of transfusions is better aligned between the model and the observed data.

Table 10: Comparison of observed and predicted health state occupancy up to Day 168 for iptacopan in APPOINT-PNH

	No transfusion and no anaemia		No transfusion and anaemia		Transfusion	
	Observed	**Predicted**	**Observed**	**Predicted**	**Observed**	**Predicted**
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 56	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 84	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 112	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 140	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 168	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 11: Comparison of observed and predicted health state occupancy up to Day 168 for C5 inhibitors in APPEX

	No transfusion and no anaemia		No transfusion and anaemia		Transfusion	
	Observed	**Predicted**	**Observed**	**Predicted**	**Observed**	**Predicted**

Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 56	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 84	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 112	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 140	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 168	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 12 and Table 13 compare observed health state occupancy from APPLY-PNH to the modelled outcomes for the treatment-experienced population with residual anaemia for iptacopan and C5 inhibitors, respectively. In both comparisons the proportion of patients in the transfusion state is well aligned between the observed data and the model. In the iptacopan arm the model does not reflect the speed at which patients enter the 'No transfusion and no anaemia' state, but the distribution is well aligned from Day 112. In the C5 inhibitor arm, the model appears to slightly overstate the proportion of patients without anaemia across the course of the observed data, driven by the higher value at Day 168. This was also highlighted by a UK clinician, who reviewed model predictions up to 5 years, as high compared to clinical experience in this population (see response to question B8). The model can therefore be considered to be conservative. No comparison was made for pegcetacoplan, as health state occupancy in PEGASUS over time has not been reported. The UK clinician consulted on longer-term predictions confirmed these to be in line with expectations based on the trial data (see B8).

Table 12: Comparison of observed and predicted health state occupancy up to Day 168 for iptacopan in APPLY-PNH

	No transfusion and no anaemia		No transfusion and anaemia		Transfusion	
	Observed	Predicted	Observed	Predicted	Observed	Predicted
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 56	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 84	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 112	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 140	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 168	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 13: Comparison of observed and predicted health state occupancy up to Day 168 for C5 inhibitors in APPLY-PNH

	No transfusion and no anaemia		No transfusion and anaemia		Transfusion	
	Observed	Predicted	Observed	Predicted	Observed	Predicted
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 56	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 84	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 112	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 140	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 168	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Overall, as reported in the response to question B8, the long-term predictions of the model are expected to have good clinical validity.

Transition probabilities

B2. Please provide comprehensive details on the methodology used to derive the transition probabilities from the individual participant data (IPD) for iptacopan and C5 inhibitors (eculizumab/ravulizumab), including details on covariates included in the multinomial logistic regression model and reasons for the choice of included and excluded covariates; interactions terms; and

model assumptions. Please provide justification for the choice of models and what measures of fit were performed.

As outlined in section B.3.3.2 of the company submission, transition probabilities were derived in line with the methods described by Hakimi et al (28). This approach was selected to increase comparability between iptacopan and pegcetacoplan, and to this end it was decided *a priori* to use the same set of model covariates as was applied in the analysis of PEGASUS. As a result of this, a single model specification was applied across all analyses and model fit was not considered.

In the complement inhibitor-experienced population, IPD from APPLY-PNH were used to derive transition probabilities for iptacopan and C5 inhibitors (eculizumab/ravulizumab). All post-transfusion Hb values were used, so transition probabilities to and from the transfusion health state could be derived (i.e., transfusion was not considered a permanent state), in line with the pegcetacoplan model. To derive the transition probabilities, a multinomial logistic regression model was fit using health state as a dependent variable and prior health state (i.e., health state four weeks prior), treatment (iptacopan, C5 inhibitor), time from first dose (measured in weeks) to study visit as well as interactions for time × treatment and time × prior health state, allowing for transition probabilities to vary over time by treatment and starting health state. The multinomial logistic regression model was fit using data from study visits at 4-week intervals (i.e., Day 28, 56, 84, 112, 140, 168) to align with the cycle length of the economic model. The fitted model was used to predict the probability of being in each health state conditional on study visit, prior health state, and treatment arm. These predicted probabilities were then averaged over study visits by prior health state and treatment arm.

IPD from APPOINT-PNH were used to derive health state transition probabilities for iptacopan in the complement inhibitor-naïve population, using similar methods as described above for APPLY-PNH. In this case, the multinomial logistic regression model was fit using health state as a dependent variable and prior health state (i.e., health state four weeks prior), time from first dose (measured in weeks) to study visit as well as an interaction for time × prior health state, allowing for transition probabilities to vary over time across starting health states. Since APPOINT-PNH was a single-arm trial with iptacopan as the only treatment, the multinomial model

was specified without treatment or time × treatment, as coefficients for these terms cannot be obtained without a control arm. The fitted model was used to predict the probability of being in each health state conditional on study visit and prior health state. These predicted probabilities were then averaged over study visits by prior health state.

B3. Please provide the number of participants (or sample size) included in the multinomial logistic regression model at each study visit (collected over 4-week intervals up to the end of the randomised controlled period at Day 168) for each health state transition and for each treatment (i.e., iptacopan and C5 inhibitors)

The number of patients with data available to generate transition probabilities (information on prior health state and health state at study visit) as well as the number of patients with missing transition data is provided in

Table 14 for the complement inhibitor-naïve population and in Table 15 for the complement inhibitor-experienced population.

For transition probabilities informed by clinical trial data from APPOINT-PNH and APPLY-PNH, the number of patients with missing transition data was low. In the real-world source APPEX, which informed transition probabilities for the C5 inhibitors in the naïve population, the proportion of patients with missing transition data ranged from 56–92% across 4-week windows (mean: 81.5%). A large proportion of missing data for estimation of transition probabilities for 4-week cycles was to be expected from the dataset, given that Hb does not tend to be measured on a monthly basis in clinical practice. To address this limitation, last observation carried forward (LOCF) was applied for missing Hb values in the estimation of transition probabilities utilised in the base case (see response to Question B4). Data could be imputed for all patients with missing values; as a result, the dataset used for deriving base case transition probabilities from APPEX contained no missing data.

Table 14: Number of participants informing health state transitions in the complement inhibitor-naïve population

		Health state at visit				
Visit	**Prior health state**	**No transfusion and anaemia**	**No transfusion and no anaemia**	**Transfusion**	**Total observed**	**Missing**
Iptacopan (APPOINT-PNH; N=40)						
Week 4	No transfusion and anaemia	[redacted]	[redacted]	[redacted]	37	3
	No transfusion and no anaemia	[redacted]	[redacted]	[redacted]		
	Transfusion	[redacted]	[redacted]	[redacted]		
Week 8	No transfusion and anaemia	[redacted]	[redacted]	[redacted]	31	9
	No transfusion and no anaemia	[redacted]	[redacted]	[redacted]		
	Transfusion	[redacted]	[redacted]	[redacted]		
Week 12	No transfusion and anaemia	[redacted]	[redacted]	[redacted]	36	4
	No transfusion and no anaemia	[redacted]	[redacted]	[redacted]		
	Transfusion	[redacted]	[redacted]	[redacted]		
Week 16	No transfusion and anaemia	[redacted]	[redacted]	[redacted]	34	6
	No transfusion and no anaemia	[redacted]	[redacted]	[redacted]		
	Transfusion	[redacted]	[redacted]	[redacted]		
Week 20	No transfusion and anaemia	[redacted]	[redacted]	[redacted]	35	5
	No transfusion and no anaemia	[redacted]	[redacted]	[redacted]		
	Transfusion	[redacted]	[redacted]	[redacted]		
Week 24	No transfusion and anaemia	[redacted]	[redacted]	[redacted]	37	3
	No transfusion and no anaemia	[redacted]	[redacted]	[redacted]		
	Transfusion	[redacted]	[redacted]	[redacted]		

C5 inhibitors (APPEX; N=85)[#]						
Week 4	No transfusion and anaemia	[redacted]	[redacted]	[redacted]	37	48[#]
	No transfusion and no anaemia	[redacted]	[redacted]	[redacted]		
	Transfusion	[redacted]	[redacted]	[redacted]		
Week 8	No transfusion and anaemia	[redacted]	[redacted]	[redacted]	12	73[#]
	No transfusion and no anaemia	[redacted]	[redacted]	[redacted]		
	Transfusion	[redacted]	[redacted]	[redacted]		
Week 12	No transfusion and anaemia	[redacted]	[redacted]	[redacted]	16	69[#]
	No transfusion and no anaemia	[redacted]	[redacted]	[redacted]		
	Transfusion	[redacted]	[redacted]	[redacted]		
Week 16	No transfusion and anaemia	[redacted]	[redacted]	[redacted]	10	75[#]
	No transfusion and no anaemia	[redacted]	[redacted]	[redacted]		
	Transfusion	[redacted]	[redacted]	[redacted]		
Week 20	No transfusion and anaemia	[redacted]	[redacted]	[redacted]	13	72[#]
	No transfusion and no anaemia	[redacted]	[redacted]	[redacted]		
	Transfusion	[redacted]	[redacted]	[redacted]		
Week 24	No transfusion and anaemia	[redacted]	[redacted]	[redacted]	15	70[#]
	No transfusion and no anaemia	[redacted]	[redacted]	[redacted]		
	Transfusion	[redacted]	[redacted]	[redacted]		
Week 28	No transfusion and anaemia	[redacted]	[redacted]	[redacted]	7	78[#]
	No transfusion and no anaemia	[redacted]	[redacted]	[redacted]		
	Transfusion	[redacted]	[redacted]	[redacted]		

#Missing data in APPEX prior to imputation of missing Hb values using LOCF. Following data imputation, the number of participants with missing data was 0 for all timepoints.

Table 15: Number of participants informing health state transitions in the complement inhibitor-experienced population

		Health state at visit				
Visit	**Prior health state**	**No transfusion and anaemia**	**No transfusion and no anaemia**	**Transfusion**	**Total observed**	**Missing**
Iptacopan (APPLY-PNH; N=62)						
Week 4	No transfusion and anaemia	[redacted]	[redacted]	[redacted]	59	3
	No transfusion and no anaemia	[redacted]	[redacted]	[redacted]		
	Transfusion	[redacted]	[redacted]	[redacted]		
Week 8	No transfusion and anaemia	[redacted]	[redacted]	[redacted]	58	4
	No transfusion and no anaemia	[redacted]	[redacted]	[redacted]		
	Transfusion	[redacted]	[redacted]	[redacted]		
Week 12	No transfusion and anaemia	[redacted]	[redacted]	[redacted]	60	2
	No transfusion and no anaemia	[redacted]	[redacted]	[redacted]		
	Transfusion	[redacted]	[redacted]	[redacted]		
Week 16	No transfusion and anaemia	[redacted]	[redacted]	[redacted]	59	3
	No transfusion and no anaemia	[redacted]	[redacted]	[redacted]		
	Transfusion	[redacted]	[redacted]	[redacted]		
Week 20	No transfusion and anaemia	[redacted]	[redacted]	[redacted]	58	4
	No transfusion and no anaemia	[redacted]	[redacted]	[redacted]		
	Transfusion	[redacted]	[redacted]	[redacted]		

Week 24	No transfusion and anaemia	[redacted]	[redacted]	[redacted]	60	2
	No transfusion and no anaemia	[redacted]	[redacted]	[redacted]		
	Transfusion	[redacted]	[redacted]	[redacted]		
C5 inhibitors (APPLY-PNH; N=35)						
Week 4	No transfusion and anaemia	[redacted]	[redacted]	[redacted]	33	2
	No transfusion and no anaemia	[redacted]	[redacted]	[redacted]		
	Transfusion	[redacted]	[redacted]	[redacted]		
Week 8	No transfusion and anaemia	[redacted]	[redacted]	[redacted]	31	4
	No transfusion and no anaemia	[redacted]	[redacted]	[redacted]		
	Transfusion	[redacted]	[redacted]	[redacted]		
Week 12	No transfusion and anaemia	[redacted]	[redacted]	[redacted]	31	4
	No transfusion and no anaemia	[redacted]	[redacted]	[redacted]		
	Transfusion	[redacted]	[redacted]	[redacted]		
Week 16	No transfusion and anaemia	[redacted]	[redacted]	[redacted]	28	7
	No transfusion and no anaemia	[redacted]	[redacted]	[redacted]		
	Transfusion	[redacted]	[redacted]	[redacted]		
Week 20	No transfusion and anaemia	[redacted]	[redacted]	[redacted]	32	3
	No transfusion and no anaemia	[redacted]	[redacted]	[redacted]		
	Transfusion	[redacted]	[redacted]	[redacted]		
Week 24	No transfusion and anaemia	[redacted]	[redacted]	[redacted]	32	3
	No transfusion and no anaemia	[redacted]	[redacted]	[redacted]		
	Transfusion	[redacted]	[redacted]	[redacted]		

B4. Please indicate how much missing data in each four-week period was imputed in order to estimate the transition probabilities from the multinomial logistic regression models.

The number of patients with missing transition data (information on prior health state and/or health state at study visit) at each timepoint is provided in the response to Question B3,

Table 14 (naïve population) and Table 15 (experienced population).

No data was imputed in the estimation of transition probabilities from APPOINT-PNH and APPLY-PNH, due to the small number of patients with missing data.

In the estimation of base case transition probabilities from the real-world evidence source APPEX, last observation carried forward (LOCF) was applied for missing Hb values, due to larger amounts of data missing for 4-weekly intervals, reflecting less frequent Hb measurement in routine clinical practice compared with clinical trials with regular study visits. With LOCF applied for missing Hb values, patients were allocated to either the 'No transfusion and Anaemia' or 'No transfusion and No Anaemia' health state based on their last recorded Hb value carried forward, unless a transfusion was recorded in the current interval, in which case they were assigned to the 'Transfusion' state. After imputation there were no missing data. A scenario analysis without data imputation (i.e. complete cases analysis) was presented in the company submission; however, such a scenario likely overpredicts the transitions into the 'Transfusion' health state where data are less likely to be missing.

B5. Please provide details on how the multinomial logistic regression model was fit using patient weights from the indirect treatment comparisons described in Section B.2.9.3 of the company submission to align the APPLY-PNH data to the PEGASUS trial population. Please clarify whether this weighting has been applied to the transition probabilities for both iptacopan and C5 inhibitors or just iptacopan from APPLY-PNH. Similarly, please provide details on how the APPEX data was reweighted to match the APPOINT-PNH population.

To adjust the health state transition probabilities from APPLY-PNH to the PEGASUS trial population, weights derived via the ITC (company submission, Section B.2.9.3) were used. In brief, patients who would not have been eligible for inclusion in PEGASUS were removed from the IPD of APPLY-PNH. Afterwards, the remaining patients from APPLY-PNH were weighted within treatment arm to match the marginal distribution of baseline Hb, sex (% female), proportion of patients transfusion-free within 12 months prior, reticulocyte count at screening, baseline LDH, and age in the PEGASUS population. The weights obtained from this approach were used as estimation weights when fitting the multinomial logistic regression

model for health states. Weights were applied to both the iptacopan and C5 inhibitor arms.

To adjust the health state transition probabilities from APPEX to the APPOINT-PNH population, propensity score based inverse probability of treatment weights (IPTW) were used. Propensity scores were estimated for using a gradient boosting model applied to a generalised linear model with logistic loss function. The model was fit using pooled IPD from APPOINT-PNH and APPEX, specified with treatment (iptacopan, C5 inhibitor) as the dependent variable and the following baseline variables as predictors: total red blood cell (RBC) units transfused during six months prior to index date, baseline Hb, baseline reticulocyte count, ongoing aplastic anaemia/bone marrow disease, history of MAVE, age, and sex. After fitting the model, individual-level predicted propensity scores were used to calculate average treatment effect on the treated (ATT) weights for each patient in APPEX, assigning more weight to patients from APPEX who more closely resembled patients from APPOINT-PNH. These weights were then used as estimation weights when fitting the multinomial logistic regression model for health states.

B6. Please clarify how uncertainty was captured in the estimates from the multinomial logistic regression model.

Uncertainty in the transition probabilities from the multinomial logistic model was captured using a Dirichlet distribution to vary transition probabilities for each health state simultaneously. This approach was selected in preference to methods that varied parameters in the multinomial logistic models directly as it allows the transition probabilities in each arm to be varied in the same manner, as the regression model parameters and variance-covariance matrices are not available for pegcetacoplan transition probabilities.

B7. In the absence of head-to-head data comparing iptacopan with pegcetacoplan, please provide an indirect treatment comparison of the transition probabilities for iptacopan and pegcetacoplan from APPLY-PNH and PEGASUS trial populations, using C5 inhibitors as the common comparator. Please provide full details on the methods for the estimation of relative effect

for all transitions and the corresponding results for the transition probabilities when applied to an appropriate baseline.

Feasibility to conduct an ITC of transition probabilities from APPLY-PNH and PEGASUS was limited by Novartis not having access to IPD from PEGASUS and technical difficulties in estimating multinomial outcomes from aggregated data. Utilising published transition probability matrices for pegcetacoplan and C5 inhibitors from PEGASUS and transition probability matrices for iptacopan and C5 inhibitors derived from APPLY-PNH IPD, an attempt was made to calculate the point estimates for the conditional probabilities, however this relied on a comparison of individual transitions. As transition probabilities for each state are interdependent, this analysis did not produce sensible results as the resulting transition probabilities did not sum to 1. More complex methods such as constructing pseudo-IPD from the published PEGASUS transition probabilities were not considered feasible within the time available to respond to the clarification questions.

In addition, validity of any transition probabilities for iptacopan and pegcetacoplan from APPLY-PNH and PEGASUS derived from an ITC of transition probabilities using the C5 inhibitor trial arms as the common comparator would likely be severely limited by large differences observed in the outcomes of C5 inhibitor arms across the two trials, which suggest that the C5 inhibitor arms of the trials may not be sufficiently similar to allow for an anchored comparison.

Table 16 compares the transition probabilities for C5 inhibitors from PEGASUS (as published in Hakimi et al (28); utilised in a scenario analysis in the company submission) and APPLY-PNH (estimated from IPD; utilised in the model base case). In the PEGASUS transition probabilities, patients treated with C5 inhibitors are much more likely to enter the Transfusion state than patients treated with C5 inhibitors in APPLY-PNH. Patients treated with C5 inhibitors in PEGASUS are also much less likely to enter or remain in the ‘No anaemia’ state than patients treated with C5 inhibitors in APPLY-PNH.

Table 16: Comparison of transition probabilities for C5 inhibitors in PEGASUS and APPLY-PNH

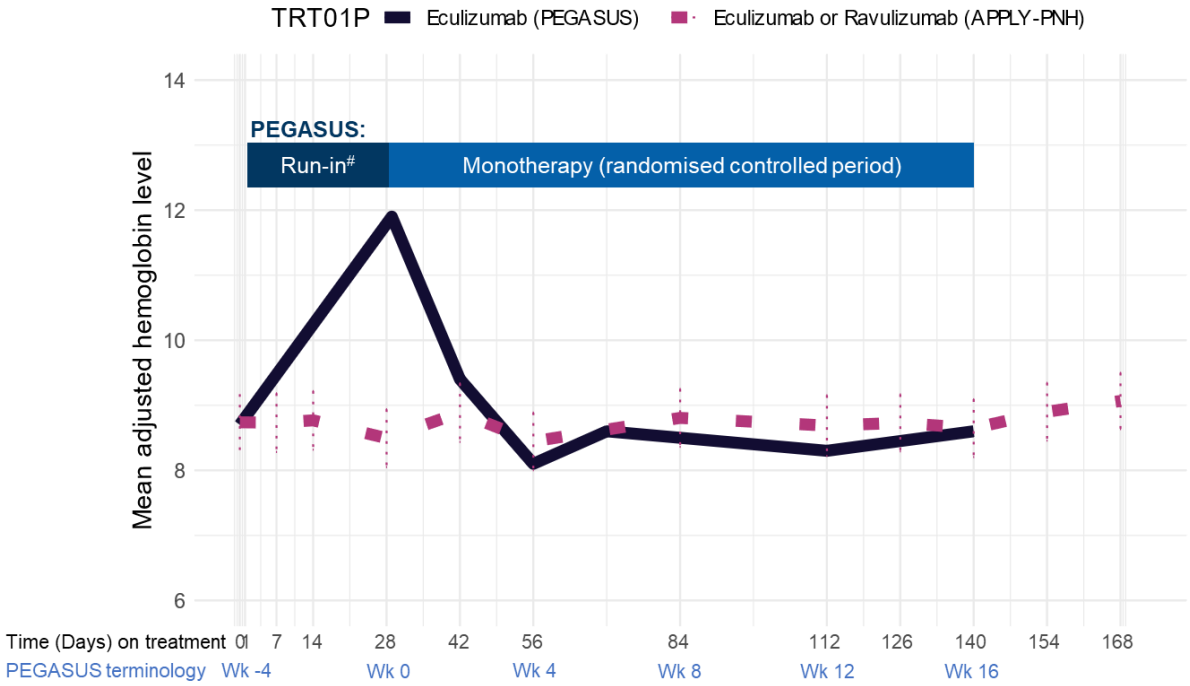
From	To		
	No Transfusion and No Anaemia	No Transfusion and Anaemia	Transfusion
PEGASUS			
No Transfusion and No Anaemia	3.0%	74.2%	22.8%
No Transfusion and Anaemia	0.1%	65.2%	34.7%
Transfusion	0.1%	40.4%	59.5%
APPLY-PNH			
No Transfusion and No Anaemia	45.5%	47.9%	6.6%
No Transfusion and Anaemia	7.7%	65.7%	26.6%
Transfusion	6.2%	33.6%	60.2%

In the economic model, this results in predictions of 0% of C5 inhibitor-treated patients being in the 'No transfusion and no anaemia' health state after 24 weeks of treatment based on PEGASUS data, compared with 11% of C5 inhibitor-treated patients based on APPLY-PNH data. Similarly, 46% of C5 inhibitor-treated patients were in the Transfusion health state at 24 weeks based on PEGASUS data, compared with 37% based on APPLY-PNH data. The model prediction that C5 inhibitor-treated patients in PEGASUS were less likely to become transfusion avoidant than C5 inhibitor-treated patients in APPLY-PNH aligns with the results of the respective clinical trials, with 6/39 (15.4%) of patients meeting the transfusion avoidance endpoint in PEGASUS (4) vs 14/35 (40.0%) of patients in APPLY-PNH (estimated as 39.3% after aligning endpoint definition with PEGASUS and adjusting for differences in trial populations; see ITC section, Update to Table 26 in the Addendum). (Please note that the percentages of model outputs and clinical trial endpoints are not directly comparable; see explanations in response to question B1).

As highlighted in the ITC section of the company submission (Document B, section B.2.9.3.2.3 and Appendix D, section D.4.5.4), there are concerns about the lack of similarity between the C5 inhibitor comparator arms of APPLY-PNH and PEGASUS, given the PEGASUS run-in period during which patients randomised to eculizumab also received pegcetacoplan for 4 weeks, before switching back to eculizumab monotherapy. In the APPLY-PNH study, patients randomised to the C5 inhibitor arm continued the same C5 inhibitor treatment as prior to the trial, as monotherapy (without addition of iptacopan at any time).

Figure 9 shows the development of mean Hb for the C5 inhibitor arms over time in APPLY-PNH (pink dashed lined) and PEGASUS (blue solid line). Mean Hb for C5 inhibitor-treated patients in APPLY-PNH remained stable throughout the trial. In PEGASUS, on the other hand, mean Hb in the C5 inhibitor arm sharply increased with addition of pegcetacoplan during the 4-week run-in period, followed by a steep decline upon withdrawal of pegcetacoplan, and eventually returning to baseline levels approximately 6 weeks after patients' return to eculizumab monotherapy (4).

Figure 9: Mean Hb over time for C5 inhibitor control arms in APPLY-PNH (C5 inhibitor monotherapy) and PEGASUS (eculizumab including 4-week combination therapy with pegcetacoplan in run-in)



During the run-in period, all patients in PEGASUS received eculizumab + pegcetacoplan.
APPLY-PNH data aligned to PEGASUS endpoint definition. PEGASUS data from Hillmen et al 2021, Figure 2A (4).
Abbreviations: Wk, week.

While the manufacturer of pegcetacoplan took a cautious approach when deriving the transition probabilities from PEGASUS in only utilising data from Weeks 4-16 of the randomised controlled period (28), it is Novartis' understanding that the peculiar Hb pattern as a consequence of the run-in period will still have impacted the transition probabilities, by inclusion of the prior 4-weeks' health state as a covariate in the multinomial logistic regression model (28) (i.e. Week 0-4 of the randomised period as prior health state to inform current health state at Week 4). It is assumed that this may be the primary reason for transition of 74.2% of patients from the 'No

anaemia' state to the 'Anaemia' state, and 22.8% of patients from the 'No anaemia' state to the 'Transfusion' state in the PEGASUS transition probability matrix, compared with only 47.9% and 6.6%, respectively, in the APPLY-PNH transition probability matrix (Table 16).

In conclusion, while it was not feasible from a technical perspective within the time available to derive transition probabilities for iptacopan and pegcetacoplan from an ITC using C5 inhibitors as the common comparator, such analysis would not be expected to produce valid results given the observed differences in comparator arm transition probabilities.

A UK clinician consulted during the preparation of the clarification questions response considered the model predictions for iptacopan and pegcetacoplan as reasonable (see response to question B8).

B8. Please provide details on the validation of the transition probabilities derived from the trials with expert clinical opinion.

Final transition probabilities were not available when model validation calls with clinical experts and health economists were conducted in preparation of the submission, and were thus not included in the original validation.

One UK clinical expert was consulted in November 2023 during preparation of the clarification questions response. The clinician was selected on the basis of being an experienced consultant haematologist at one of the two centres of the National PNH Service and had also participated in the previously held UK advisory board and model and ITC validation calls. Information presented by Novartis during a 1-hour call included the distribution of patients across health states at baseline, transition probability matrices for each treatment (based on corrected 24-week data), and model outputs in the form of a graph for each treatment showing the distribution of patients across health states up to 5 years of treatment (longer-term graphs were not presented since the distribution reached a stable state after a maximum of 2 years for all treatments). When producing the model outputs, treatment discontinuation was set to zero for all treatments, in order to exclude the impact of treatment switches. Information was presented separately for the treatment-naïve population and the treatment-experienced population with residual anaemia on C5 inhibitors.

The clinician confirmed overall good face validity of the model predictions in terms of patient distribution across health states, for all treatments in both populations. In the treatment-naïve population, for C5 inhibitors the model predicts approximately 55% of patients in the model steady state to not require transfusions and be non-anaemic (defined as Hb ≥10.5 g/dL in the model base case), which reflects experience with C5 inhibitors in clinical practice. The model further predicts that approximately 12% of patients treated with C5 inhibitors require transfusions long-term, which was considered relatively low compared to UK clinical experience of approximately 20%; the model can thus be considered conservative. For iptacopan, the clinician agreed that model outputs were aligned with expectations based on the clinical trial results.

For the treatment-experienced population with residual anaemia on a C5 inhibitor, the model predicts that around 35% of patients require transfusions with continued C5 inhibitor treatment. The clinician advised that while this proportion would be considered too high for the overall population, it is a realistic estimate for a population with partial response to a C5 inhibitor, i.e. the modelled population of interest, and reflects outcomes seen in UK clinical practice. The model also predicts that around 10% of patients reach the non-anaemic state with continued C5 inhibitor treatment, which the clinician considered might be too optimistic; the model can thus again be considered conservative. Model outputs for pegcetacoplan show a substantially more favourable health state distribution compared to C5 inhibitors, which the clinician agreed aligns well with the available data. Model predictions for iptacopan are similar to pegcetacoplan, with slightly better results predicted for iptacopan, which the clinician considered plausible based on the trial data of both products.

Baseline distribution

B9. Please clarify how the baseline distribution of 25% and 24.7% for participants who require transfusions was derived from the APPOINT-PNH and APPLY-PNH trials, respectively (e.g., number of participants receiving transfusions over what time period?).

The proportion of patients in the Transfusion health state at baseline was derived from APPOINT-PNH and APPLY-PNH trial data based on the proportion of patients who had received transfusion(s) in the 4 weeks prior to baseline. For APPOINT-

PNH, this was 25.0% of patients; for APPLY-PNH, the proportion of patients has been updated to 25.8% following the data corrections.

Discontinuation rates and compliance

B10. Please justify the assumption that people would discontinue treatment at an equal rate from all health states, based on treatment-specific all-cause discontinuation rates from clinical trials.

The assumption that discontinuation would occur at an equal rate from all health states was applied for iptacopan and pegcetacoplan. For pegcetacoplan, no information was available which health state patients were in at the time of pegcetacoplan discontinuation. The PEGASUS study publication (29) specified treatment-emergent adverse events as the reason for discontinuation in the PEGASUS study in 12 out of 13 cases (see response to Question B11).

For iptacopan, a decision was made to assume that discontinuation would occur at an equal rate from all health states since all discontinuations in the Phase 3 trials were unrelated to treatment efficacy (two discontinuations due to pregnancy; see response to Question B11).

For the C5 inhibitors eculizumab and ravulizumab, discontinuation in the naïve population was only applied for patients in the ‘Transfusion’ and ‘No transfusion and anaemia’ health states, in order to model a proportion of patients switching to pegcetacoplan due to insufficient response to a C5 inhibitor (see response to Question B12).

B11. Please explain why a higher annual discontinuation rate is expected on treatment with pegcetacoplan (16.13%) compared to treatment with iptacopan (3.43%). Please clarify the reasons for discontinuations in the APPLY-PNH and PEGASUS trials. Please compare the rates of discontinuation from the trials with those observed in NHS practice for pegcetacoplan and C5 inhibitors, or expected to be observed for iptacopan.

Discontinuation rates of iptacopan and pegcetacoplan were informed by the respective Phase 3 trials. In APPOINT-PNH, no patients discontinued iptacopan over the 48-week study duration (7). In APPLY-PNH, one patient each discontinued iptacopan in the randomised treatment period (Week 0-24) and the extension treatment period (Week 25-48), both due to pregnancy (8). In PEGASUS, overall 13 patients discontinued pegcetacoplan over the 48-week study duration; 12 due to a treatment-emergent AE, and one due to physician's decision associated with an AE (29). Reasons for discontinuation are listed in Table 17. No patients discontinued C5 inhibitor treatment in APPLY-PNH or PEGASUS.

Table 17: Reasons for discontinuation of iptacopan and pegcetacoplan in Phase 3 trials

Treatment (Study)	Study period	Reason for discontinuation
Iptacopan (APPOINT-PNH)	Core and extension treatment period	NA (no discontinuations)
Iptacopan (APPLY-PNH)	Randomised treatment period	Pregnancy
	Extension treatment period	Pregnancy
Pegcetacoplan (PEGASUS)	Randomised controlled period	Breakthrough haemolysis
	Randomised controlled period	Breakthrough haemolysis
	Randomised controlled period	Breakthrough haemolysis
	Open-label period	Haemolysis
	Open-label period	Haemolytic anaemia
	Open-label period	Hypersensitivity pneumonitis
	Open-label period	Breakthrough haemolysis
	Open-label period	Acute myeloid leukaemia
	Open-label period	Diffuse large B cell lymphoma
	Open-label period	Fatal COVID-19 infection
	Open-label period	Pancytopenia[a]

	Open-label period	Bone marrow failure
	Follow-up period	Mesenteric ischaemia

Source: Novartis Data on File 2023 APPOINT-PNH 48-week CSR (7); Novartis Data on File 2023 APPLY-PNH 48-week CSR (8); PEGASUS (29)
Iptacopan (APPLY-PNH) and pegcetacoplan (PEGASUS): Each row reflects one patient discontinuing treatment. [a] discontinuation due to physician decision, but confirmed to be because of an adverse event (29)

As explained in section B.3.3.3 of the company submission, the four discontinuations in PEGASUS due to breakthrough haemolysis (BTH) were excluded from the calculation of the pegcetacoplan discontinuation rate for the economic model, since UK clinicians advised that BTH is not a reason for discontinuation of pegcetacoplan in clinical practice (27, 30). One discontinuation due to fatal COVID-19 infection was also excluded, to avoid double counting of mortality in the model. This reduced the annual probability of discontinuation with pegcetacoplan from 24.86% (based on PEGASUS observed data) to 16.13% (Table 18). A UK clinician consulted during preparation of the clarification questions response confirmed that the rationale for the implemented exclusions was reasonable and advised against excluding further discontinuations observed in PEGASUS from the calculation.

The annual probability of discontinuation for iptacopan in the company submission (3.43%) was based on 24-week data from APPLY-PNH. With 48-week data now available, an option was included in the model to utilise data from the 48-week analyses, with an annual probability of discontinuation of 2.72% (Table 18).

Table 18: Annual probability of discontinuation of iptacopan and pegcetacoplan

Treatment	Included discontinuations	Annual probability of discontinuation	Model input
Iptacopan	As observed in APPOINT-PNH – 48 weeks: 0 discontinuations	0.00%	Scenario for naïve population in company submission
	As observed in APPLY-PNH – 24 weeks: 1 discontinuation in 28.66 patient years	3.43%	Base case in company submission for experienced and naïve populations
	As observed in APPLY-PNH – 48 weeks: 2 discontinuations in 72.47 patient years	2.72%	Updated in model based on 48-week data

Pegcetacoplan	As observed in PEGASUS – 48 weeks: 13 discontinuations in 45.48 patient years	24.86%	–
	Excluding discontinuations due to BTH and fatal COVID-19 infection: 8 discontinuations in 45.48 patient years	16.13%	Base case in company submission

Data on discontinuation of pegcetacoplan in UK clinical practice is limited. [redacted] discontinued due to insufficient efficacy [redacted] due to AEs [redacted] and due to difficulties with administering the subcutaneous infusions [redacted] A UK clinician consulted during preparation of the clarification questions response also reported of cases from clinical experience in the UK and other European countries where patients had discontinued pegcetacoplan due to issues with using the infusion pump for subcutaneous administration or infusion site reactions.

The probability of discontinuation of C5 inhibitors due to insufficient response, with subsequent switch to pegcetacoplan, was assumed based on input from six clinicians of the National PNH Service (see response to B12). Apart from that, no discontinuation was assumed for C5 inhibitors since patients with PNH require lifelong complement inhibitor treatment to control haemolysis and manage the risk of thrombosis and mortality (31, 32); this was validated with UK clinicians consulted during the preparation of the submission (27) and again confirmed by the clinician consulted during the preparation of the clarification questions response.

B12. Please justify the value of 30% of people discontinuing C5 inhibitors at 24 weeks in the treatment naïve population.

Pegcetacoplan was recommended by NICE in March 2022 as an option for treating adults with PNH who have anaemia after at least 3 months of treatment with a C5 inhibitor. However, based on insights from UK clinicians, only a small proportion of eligible patients has so far switched from a C5 inhibitor to pegcetacoplan in UK clinical practice, with some patients preferring to remain on their C5 inhibitor, for

example because they do not feel comfortable with twice weekly self-infusion of pegcetacoplan (30).

The assumption that 30% of patients in the 'Transfusion' or 'No transfusion and anaemia' health states would discontinue their C5 inhibitor treatment and switch to pegcetacoplan was informed by a UK advisory board in June 2023. In response to an advisory board pre-work question, six clinicians of the National PNH Service advised that among C5 inhibitor-treated patients with a partial response or worse (Hb <10 g/dL +/- transfusions; (21)), currently, 22% (mean across all six responses; median: 18%) would switch to pegcetacoplan, which was expected to increase to 30% of patients (median: 25%) in the next 6 months (see Appendix 4. Pre-meeting survey responses, Question 1c in the UK advisory board report (30)). This was reconfirmed as a valid assumption by a UK clinician consulted during the preparation of the clarification questions response.

While the licence and NICE recommendation of pegcetacoplan allow for a switch after at least 3 months of C5 inhibitor treatment, UK clinicians advised that in clinical practice, a switch would usually only be considered after around 6 months (27).

B13. Please justify the assumption of 100% compliance to treatment with iptacopan, and clarify what is the expected effect on the effectiveness of iptacopan with a lower compliance rate, or missed doses of the oral therapy.

In APPOINT-PNH, at the data cut-off 2 November 2022, the mean (SD) relative dose intensity for iptacopan was [redacted]% ([redacted]) with relative dose intensity >90 to 100% for all 40 patients. [redacted]/40 patients ([redacted]%) had at least one missed dose. The mean (SD) cumulative duration of missed dose was [redacted] days ([redacted] days), the median (range) was [redacted] days ([redacted] days) (1)

In APPLY-PNH, at the data cut-off 26 September 2022, in the combined safety set the mean relative dose intensity for iptacopan was [redacted]% (SD: [redacted]) with [redacted]/95 patients ([redacted]%) having relative dose intensity >90 to 100%. [redacted]/95 patients ([redacted]%) in the combined safety set had at least one missed iptacopan dose, with a mean (SD) cumulative duration of missed dose of [redacted] days ([redacted] days), and a median (range) of [redacted] days ([redacted] days) (2).

In both studies, no associated AEs nor changes in haematological parameters suggestive of haemolysis were reported due to these unintentional missed dose events (1, 2).

The trial data informing the effectiveness of iptacopan in the economic model thus includes data from patients who missed some doses of iptacopan. The iptacopan cost in the model was conservatively not adjusted (i.e. assumed 100% dose intensity).

It is acknowledged that compliance to treatment tends to be higher in clinical trials than in clinical practice. However, based on information provided by UK clinicians during an advisory board, the National PNH Service ensures to educate all patients diagnosed with PNH and starting complement inhibitor therapy about the serious nature of their disease and the need to take their medication as prescribed (30). UK clinicians also reported that patients will quickly experience symptoms of PNH such as haemoglobinuria (reddish or brown urine) if they don't comply with their treatment, and this would often serve as a warning sign to ensure future treatment compliance (30).

One clinician (consultant haematologist at one of the two centres of the National PNH Service) consulted in November 2023 during preparation of the clarification questions response reiterated this, describing the extensive education provided to patients as a "masterclass" on PNH. The clinician also emphasised that most patients with PNH have first-hand experience of the devastating consequences of the disease when presenting with haemolysis and thrombosis, and are thus well aware of the severity of PNH and potential consequences if they do not adhere to their medication. The clinician further reported that most patients are members of the PNH Support patient group, which provides additional education and support to patients. The clinician, drawing on personal experience treating various haematological diseases, described patients with PNH overall as extremely diligent in managing their disease and does not see compliance being an issue.

The clinician also highlighted the aspect of ease of compliance. An oral treatment makes managing travel and holidays much easier for patients, whereas arranging infusions therapies while abroad or ensuring continuous storage of pegcetacoplan in

a fridge while travelling can present patients and healthcare professionals with practical challenges and may lead to treatment non-compliance.

Overall, while it is expected that many patients with PNH would like to receive an oral therapy, some patients will prefer other treatments with a different mode of administration and/or less frequent dosing. Iptacopan, as the first oral monotherapy for PNH, would provide an additional treatment option to choose from. UK clinicians advised that patient preference – including considerations on practicality of different modes of administration – is taken into account when selecting the right therapy for the individual patient (30). Therefore, it is considered unlikely that a patient would receive iptacopan in clinical practice if the patient themselves or the treating clinician anticipate that they will struggle with twice daily oral dosing.

At time of iptacopan launch, Novartis plans to roll out a company-funded Patient Support Programme (PSP) which patients with PNH can sign up for. The PSP is currently being developed, incorporating insights gained from the National PNH Service and PNH Support. It will include further patient education around the potential risks and symptoms of missed doses as well as (optional) reminders to support patients with the twice daily dosing regimen of iptacopan. The PSP is intended to complement the education and support provided by the National PNH Service and PNH Support and, along with monthly deliveries from the homecare provider, aims to aid adherence and compliance with iptacopan treatment.

Breakthrough haemolysis (BTH) rates

B14. Please clarify why the rates of BTH would be expected to be higher in the treatment experienced population compared to the treatment naive population (Table 45 of company submission).

No reasons could be identified why BTH event rates would be expected to be higher in the experienced population compared to the naïve population. The UK clinician consulted during the preparation of the clarification questions response suggested this difference may have occurred due to chance, considering that BTH is rare and the number of events with iptacopan during the clinical trials was small.

Updated adjusted annualised BTH rates for iptacopan are available from the 48-week analyses of APPOINT-PNH (0.05, 95% CI: 0.01, 0.17) and APPLY-PNH (0.11, 95% CI: 0.05, 0.23) and have been included in the economic model updated with the 48-week data. Given the clinician's feedback that the difference in BTH event rates between APPOINT-PNH and APPLY-PNH may have occurred by chance, a scenario based on the 48-week data explores the impact of an iptacopan BTH event rate pooled across both trials (0.09, 95% CI: 0.05, 0.17).

Health-related quality of life utility values

B15. Please provide details on numbers of participants providing EQ-5D data at each time point (baseline, Day 14, 42, 84, 126, 140, 154, and 168) for each treatment arm in the trials (reported separately for APPLY-PNH and APPOINT-PNH) to inform the mapped utility values presented in Table 46 of company submission.

The number of participants providing EQ-5D data at each time point in the APPOINT-PNH and APPLY-PNH studies is presented in Table 19. Out of the overall 1,007 available EQ-5D observations, 958 were used for the utility model;
49 observations could not be included in the utility model due to missing covariate data.

Table 19: Number of participants providing EQ-5D data in APPOINT-PNH and APPLY-PNH

Visit	APPOINT-PNH iptacopan (N=40)	APPLY-PNH iptacopan (N=62)	APPLY-PNH C5 inhibitor (N=35)
Day 1	40	60	32
Day 14	35	56	30
Day 42	39	61	33
Day 84	38	57	29
Day 126	35	58	30
Day 140	37	59	29
Day 154	36	56	29
Day 168	37	60	31

B16. Please clarify whether missing EQ-5D data was imputed and, if appropriate, please provide details on the methods used.

A linear mixed effects model with random patient-level intercepts was used to model EQ-5D data and to predict health-state utility values. The model was fit using data observed during the trials while patients were on treatment. Intermittently missing EQ-5D values over the course of treatment were not imputed as linear mixed models rely on the missing at random (MAR) assumption, which is in line with model-based imputation methods such as multiple imputation (33).

B17. Please provide comprehensive details on the methods used to estimate health state utility values, including results of model fit.

Utilities based on EQ-5D and EORTC QLQ-C30 mapped to EQ-5D were derived using the same underlying statistical model. The model was a mixed linear model for repeated measures, which was fit to all utility values obtained at Day 1 (defined as baseline), Day 14, Day 42, Day 84, Day 126, Day 140, Day 154, and Day 168. Model fitting was conducted in the set of complete cases with available covariate values and outcome values across study visits.

Data from APPLY-PNH and APPOINT-PNH were pooled for model fitting to enhance sample size and precision of model coefficients. Model selection was performed among all models adjusting for health state and study visit using information criteria such as the Akaike Information Criterion and Bayesian Information Criterion. Health states were incorporated as a forcing variable to allow for prediction of utilities by health state after model fitting.

The model selection process was conducted as part of the analysis of EQ-5D using a Hb threshold of <10.5 g/dL. Baseline utility and treatment were found to be statistically significant in model runs, so these covariates were included in the final model. Additionally, a study covariate differentiating patients in APPLY-PNH from those in APPOINT-PNH was also incorporated. This covariate generally had a small and statistically insignificant coefficient, suggesting that the difference in mean utilities for the iptacopan arm of APPLY-PNH and APPOINT-PNH could be expected a priori to be small. Nevertheless, models were fit separately for each study to confirm that utility estimates by health state for the iptacopan arm did not differ substantially between APPOINT-PNH and APPLY-PNH (see response to question

B19). Finally, additional demographic variables, such as age and sex, did not improve model fit and thus were not included in the final model. Coefficient estimates for the final model are shown below (Table 20), incorporating corrected data from APPLY-PNH. All models were fit using random individual-level intercepts to account for correlation in utility values within patients across visits.

After fitting the models to the pooled data, predicted utilities were computed for all patients in APPLY-PNH and APPOINT-PNH, conditional on study enrolment, study visit, health state at study visit, baseline utility, and treatment. Treatment-specific means and SDs of the predicted utilities were then pooled by treatment arm across studies, study visit, and observed baseline utilities. Treatment-independent means and SDs of utilities were similarly derived by pooling across studies, study visits, observed baseline utilities, and treatment arms.

Table 20: Multivariable regression results (updated) for selected utility model

Covariate	Coefficient (SE)	95% CI
Intercept	0.790 (0.028)	0.735, 0.845
Health state (reference: Transfusion)		
No transfusion and Anaemia	0.007 (0.014)	-0.021, 0.035
No transfusion and No Anaemia	0.029 (0.016)	-0.003, 0.061
Treatment (iptacopan vs C5 inhibitor)	0.071 (0.022)	0.027, 0.114
Baseline utility	0.487 (0.038)	0.412, 0.562
Study (APPLY-PNH vs APPOINT-PNH)	-0.019 (0.018)	-0.055, 0.017
Study visit (reference: Day 168)		
Baseline (Day 1)	-0.076 (0.016)	-0.107, -0.045
Day 14	-0.026 (0.014)	-0.054, 0.002
Day 42	-0.013 (0.013)	-0.039, 0.013
Day 84	-0.003 (0.013)	-0.029, 0.023
Day 126	-0.013 (0.013)	-0.039, 0.014
Day 140	-0.019 (0.013)	-0.045, 0.007
Day 154	-0.010 (0.013)	-0.036, 0.016
Model fit		
AIC	-1318.8	
BIC	-1245.8	
Marginal R^2	0.461	
Conditional R^2	0.667	

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CI, confidence interval; SE, standard error.

B18. Please clarify why missing Hb values were discarded from the mixed linear model fitting, rather than imputation of Last Observation Carried Forward as undertaken in the statistical analyses of trial endpoints.

Please note that in the primary analysis of trial endpoints in APPOINT-PNH and APPLY-PNH at the end of the 24-week core treatment period, missing Hb data were imputed based on pattern mixture models. For patients with intermittent missing data during study follow-up where reasons for missing were assumed to be unrelated to response or compliance status, their missing data were imputed under a missing at random hypothesis (1, 2).

For the utility model, although missing values were discarded from the mixed linear model fitting, patients with missing Hb values who received a transfusion within 4 weeks prior to the study visit were still assigned to the transfusion state and therefore included in linear mixed models for utility values. It should also be noted that linear mixed models require the assumption that data are missing at random (data are missing conditional on observed data), which standard multiple imputation methods also require.

B19. Please justify the pooling of data from different populations of APPLY-PNH and APPOINT-PNH to estimate health state utility values.

The health states used in the naïve and experienced populations are aligned, and data from APPOINT-PNH and APPLY-PNH were pooled to increase statistical power, as there were few observations available in some of the health states. Differences in utility between the naïve and experienced populations are expected to be driven by the proportion of patients that require transfusion, or continue to experience anaemia, but for patients receiving the same treatment, with comparable baseline characteristics and in the same health state, it is not expected that there would be a difference in utility values.

A covariate for study (APPLY-PNH vs APPOINT-PNH) was included in the regression model used to generate utility values, however this was not significant in either the base-case model, or the models applied in scenario analyses. Further model covariates included in the final model were health state, treatment, baseline utility, and study visit (see Table 20). Additional demographic variables that may

explain differences between the trials were tested in the model selection process but did not improve model fit.

Models were fit to the individual trials, with predicted utility values for iptacopan presented in Table 21. Results were generally consistent between the trials, with only small variations in health state utility values and no clear signal that utilities are higher in one population. The largest difference is in the transfusion state, however this is based on very few observations, with only 18 observations of utility values in the transfusion state in APPOINT-PNH and 29 in APPLY-PNH.

Table 21: Comparison of predicted utility values for iptacopan in individual trials

Health state	APPOINT-PNH	APPLY-PNH
No transfusion and no anaemia	0.882	0.875
No transfusion and anaemia	0.820	0.833
Transfusion	0.819	0.787

B20. Please justify the use of treatment-specific utility values by health state, based on limited comparative data from one trial only (APPLY-PNH).

The health states used in the economic model distinguish between two important factors of quality for patients with PNH, transfusion and anaemia. However, there may still be within-health state differences between treatments. This was investigated by assessing mean Hb values of patients receiving iptacopan vs patients receiving a C5 inhibitor in APPLY-PNH for each health state (

Table 22). In each health state mean Hb is significantly higher for iptacopan. The dichotomy between Hb <10.5 g/dL and ≥10.5g/dL used to define anaemia and no anaemia, respectively, thus does not account for the fact that within each health state, patients treated with iptacopan have higher mean Hb levels than those treated with C5 inhibitors.

Table 22: Difference in mean Hb between iptacopan and C5 inhibitors in APPLY-PNH for each health state

Health state	Treatment	Observations	Mean Hb (g/dL)	SD	Difference iptacopan vs C5 inhibitor within health state (g/dL)
No transfusion and no anaemia	Iptacopan	568	12.58	1.03	**1.49 (p=0.011)**
	C5 inhibitor	8	11.09	1.23	
No transfusion and anaemia	Iptacopan	50	9.58	0.80	**0.74 (p<0.001)**
	C5 inhibitor	226	8.85	0.83	
Transfusion	Iptacopan	35	10.72	1.29	**2.19 (p<0.001)**
	C5 inhibitor	110	8.53	1.23	

Abbreviations: Hb, haemoglobin; SD, standard deviation.

As a result of having higher Hb levels, patients treated with iptacopan are expected to feel less fatigued. Table 23 compares the mean FACIT-Fatigue score in each health state in APPLY-PNH for iptacopan and C5 inhibitors. In each state, the mean FACIT-Fatigue score is higher for iptacopan, indicating less fatigue, and for the 'No transfusion and anaemia' and 'Transfusion' states the difference is significant.

Table 23: Difference in mean FACIT-Fatigue score between iptacopan and C5 inhibitors in APPLY-PNH for each health state

Health state	Treatment	Observations	Mean score	SD	Difference iptacopan vs C5 inhibitor within health state
No transfusion and no anaemia	Iptacopan	396	42.61	7.84	**7.94 (p=0.166)**
	C5 inhibitor	6	34.67	11.96	
No transfusion and anaemia	Iptacopan	34	38.76	8.99	**6.02 (p=0.002)**
	C5 inhibitor	147	32.74	13.07	
Transfusion	Iptacopan	26	39.35	5.96	**7.81 (p<0.001)**
	C5 inhibitor	76	31.54	8.44	

Abbreviations: Hb, haemoglobin; SD, standard deviation.

As a result of these differences in mean Hb and FACIT-Fatigue values, it is expected that patients treated with iptacopan are likely to have higher utility values within each health state, compared with patients treated with C5 inhibitors.

In addition, the difference in mode of administration may also have contributed to higher utility values within health states for iptacopan as an oral therapy vs C5 inhibitors as intravenous (IV) infusion treatments. As described in the company submission, infusions can be burdensome for patients, as they take time to administer and can be difficult to plan around (30, 34, 35), and previous appraisals in PNH have included a utility decrement for frequent IV infusions with eculizumab (36, 37).

While comparative data is available from a single trial, it is important to assess this within the context of PNH, which is an ultra-rare disease. Despite the ultra-rare nature of the disease, the utility model included overall 958 EQ-5D observations and the treatment covariate was statistically significant (see Table 20).

B21. Please provide details on the methods used to map EORTC-QLQ-C30 data collected in APPOINT-PNH and APPLY-PNH to EQ-5D-3L utility values.

Responses to the EORTC QLQ-C30) were mapped to EQ-5D-3L utility values using the Longworth et al., 2014 algorithm (38), which was also used to estimate utility values in the NICE appraisals of ravulizumab and pegcetacoplan in PNH (36, 37).

The Longworth algorithm involves deriving an EQ-5D-3L expected utility characterised by equations (2) of Longworth et al. copied below:

$$
\begin{aligned}
&Expected(EQ-5D)\\
&\quad = 1-(Prmob2\ x\ 0.069)-(Prmob3\ x\ 0.314)-(Prcare2\ x\ 0.104)\\
&\quad -(Prcare3\ x\ 0.214)-(Pruact2\ x\ 0.036)-(Pruact3\ x\ 0.094)\\
&\quad -(Prpain2\ x\ 0.123)-(Prpain3\ x\ 0.386)-\Pr(anx2\ x\ 0.071)\\
&\quad -(\Pr anx3\ x\ 0.236)-(1-PrPerfect)x\ 0.081-PrN3\ x\ 0.236
\end{aligned}
$$

The expected utility involves determining the probability of being in each level of the various EQ-5D-5L domains, and then multiplying each probability by the standard UK tariff. The formula includes terms for the probability of being in perfect health ($PrPerfect$), i.e. the joint probability of having a response level of 1 across all EQ-5D-3L domains, and the probability of having any of the EQ-5D dimensions at level 3 ($PrN3$).

Longworth et al. used multinomial models to map each EORTC variable to EQ-5D-3L response domains levels. The model coefficients of the multinomial represent the effect of a change in an EORTC variable and the log relative risk of having a level 2 (or level 3) response compared to a level 1 (reference) response. The model coefficients were reported in Table 21 of Longworth et al. and are copied below. These coefficients were used in APPLY-PNH and APPOINT-PNH to derive patient-level *z scores (linear predictions)* for each level of each EQ-5D domain, $z_{i,k}$, with i indexing patient observations and k denoting the response level (2 or 3). The

probability of response was then calculated in accordance with a multinomial distribution by relating probabilities to *z scores* via the equation $p_k = \frac{\exp(z_k)}{\sum_{k=1}^{3} \exp(z_k)}$ where the patient indices have been dropped to simplify presentation. Note that in a multinomial model the linear prediction for the non-reference category is normalised to one for all observations.

Table 24: Predictive equations relating domains of the EORTC to EQ-5D-3L domain levels – Table 21 of Longworth et al (2014)

Variables	Mobility 2	Mobility 3	Self-care 2	Self-care 3	Usual acts 2	Usual acts 3	Pain 2	Pain 3	Anxiety/depression 2	Anxiety/depression 3
Physical functioning (SE)	−0.072*** (0.010)	−0.167*** (0.037)	−0.049*** (0.008)	−0.099 (0.119)	−0.036*** (0.010)	−0.085*** (0.014)	−0.001 (0.009)	−0.013 (0.013)	−0.014** (0.006)	−0.044*** (0.016)
Role functioning (SE)	−0.011* (0.006)	−0.007 (0.017)	−0.017*** (0.006)	−0.030 (0.023)	−0.032*** (0.007)	−0.055*** (0.010)	0.001 (0.007)	−0.001 (0.011)	0.005 (0.005)	0.019 (0.013)
Emotional functioning (SE)	0.010 (0.006)	0.024 (0.019)	0.008 (0.006)	0.008 (0.015)	0.021*** (0.007)	0.028*** (0.010)	0.009 (0.008)	0.011 (0.011)	−0.078*** (0.008)	−0.148*** (0.017)
Cognitive functioning (SE)	−0.011* (0.006)	−0.006 (0.015)	−0.010* (0.006)	−0.009 (0.029)	0.004 (0.007)	−0.001 (0.010)	0.003 (0.008)	0.015 (0.011)	−0.007 (0.006)	0.006 (0.014)
Social functioning (SE)	0.003 (0.006)	0.011 (0.016)	−0.009* (0.006)	−0.005 (0.017)	−0.021*** (0.007)	−0.034*** (0.009)	0.005 (0.008)	−0.001 (0.010)	0.006 (0.006)	0.008 (0.011)
Fatigue (SE)	0.006 (0.008)	0.002 (0.019)	−0.022*** (0.008)	−0.025 (0.027)	0.028*** (0.009)	0.033** (0.013)	0.007 (0.008)	0.006 (0.013)	−0.006 (0.007)	0.007 (0.019)
Nausea and vomiting (SE)	0.001 (0.007)	0.016 (0.018)	0.007 (0.008)	0.019 (0.029)	0.022** (0.010)	0.022* (0.013)	0.005 (0.017)	−0.004 (0.019)	−0.007 (0.008)	−0.009 (0.015)
Pain (SE)	0.023*** (0.005)	0.043*** (0.017)	0.016*** (0.005)	0.024* (0.015)	0.020*** (0.006)	0.023*** (0.008)	0.100*** (0.012)	0.164*** (0.016)	0.002 (0.004)	−0.012 (0.012)
Dyspnoea (SE)	0.002 (0.005)	0.004 (0.012)	−0.005 (0.005)	−0.015 (0.014)	−0.005 (0.006)	−0.015** (0.008)	0.010* (0.006)	0.008 (0.008)	0.000 (0.004)	−0.018 (0.011)
Sleep disturbance (SE)	0.002 (0.004)	0.010 (0.012)	0.002 (0.004)	−0.000 (0.010)	−0.001 (0.005)	−0.002 (0.007)	0.013*** (0.005)	0.021*** (0.008)	−0.003 (0.004)	0.012 (0.008)
Appetite loss (SE)	−0.009* (0.005)	0.004 (0.012)	−0.000 (0.004)	0.010 (0.013)	−0.010* (0.006)	−0.011 (0.008)	−0.013* (0.006)	−0.008 (0.009)	0.006 (0.004)	0.016* (0.009)
Constipation (SE)	−0.004 (0.005)	−0.012 (0.013)	−0.004 (0.005)	−0.009 (0.014)	−0.000 (0.005)	0.004 (0.007)	0.006 (0.006)	0.010 (0.008)	0.004 (0.004)	0.001 (0.009)
Diarrhoea (SE)	−0.005 (0.006)	0.010 (0.016)	0.003 (0.006)	0.005 (0.024)	−0.009 (0.006)	−0.011 (0.009)	−0.004 (0.008)	−0.008 (0.012)	0.002 (0.006)	0.002 (0.013)
Financial Impact (SE)	−0.001 (0.005)	−0.003 (0.010)	0.005 (0.004)	0.015 (0.010)	0.008 (0.006)	0.006 (0.008)	0.010* (0.005)	0.012 (0.008)	0.012*** (0.004)	0.015* (0.009)
Age (SE)	0.028** (0.013)	−0.021 (0.056)	0.048*** (0.015)	0.131* (0.069)					0.026** (0.011)	0.008 (0.028)
Female (SE)	−0.349 (0.251)	−1.397* (0.831)								
Constant (SE)	3.169** (1.598)	3.542 (5.250)	0.498 (1.467)	−6.619 (5.120)	3.494** (1.436)	5.675*** (1.835)	−3.255** (1.410)	−9.819*** (2.086)	4.562*** (1.316)	6.024* (3.123)
Observations	771	771	771	771	771	771	771	771	771	771
Pseudo R squared	0.449	0.449	0.392	0.392	0.461	0.461	0.455	0.455	0.364	0.364

Resource use and costs

B22. Please clarify whether there are any administrative costs associated with the delivery and access of iptacopan to people with the condition (e.g., are delivery costs covered by the company?).

Iptacopan will be provided through homecare, with dispense/delivery and administrative costs all funded by Novartis.

Same as with other complement inhibitors currently used for the treatment of PNH, patients should be vaccinated prior to commencing iptacopan therapy to reduce the risk of serious infections with encapsulated bacteria. The costs of these vaccinations were accounted for in the economic model (see Document B, Section B.3.5.2.1).

Based on feedback from UK clinicians, it is expected that iptacopan can be integrated into the existing National PNH Service without any significant service alterations and additional cost (30).

Section C: Textual clarification and additional points

Literature Searching

C1. Missing Search Strategies: The following search strategies are missing: strategies for conference proceedings; clinical trial registries; health technology agencies; and health authority websites in Appendix D (the clinical evidence searches); strategies for conference proceedings; health technology agencies; and grey literature databases in Appendix G (the cost-effectiveness searches); strategies for conference proceedings; health technology agencies; and grey literature databases in Appendix H (the health-related quality of life searches); strategies for conference proceedings; health technology agencies; and grey literature databases in Appendix I (the cost and healthcare resource identification, measurement and valuation searches); strategies for the systematic literature review conducted for the indirect treatment comparison. Please can the company provide these.

Conference proceedings were planned to be hand-searched for all SLRs, unless already covered by the electronic databases searched. The only conference that was formally hand-searched was the ISPOR 2023 conference, since all other conferences that were listed in the SLR methodology were already indexed in Embase. The only exception to this were the EBMT 2023 congress abstracts, which were not indexed in Embase and unavailable at the time of hand-searching; the abstracts were periodically searched for thereafter, but did not become available prior to the company submission. The ISPOR 2023 conference was hand-searched on 25th May 2023 (source: https://www.ispor.org/conferences-education/conferences/upcoming-conferences/ispor-2023) and the keyword searched was “paroxysmal nocturnal hemoglobinuria”

HTA agency websites were hand-searched for all SLRs on 25th May 2023. Sources and search terms were as follows:

- National Institute for Health and Care Excellence (NICE) – England
    - Source: https://www.nice.org.uk/guidance/published?ndt=Guidance&ndt=Quality%20standard

    - Keyword: “paroxysmal nocturnal haemoglobinuria”
- Scottish Medicines Consortium (SMC) – Scotland
    - Source: https://www.scottishmedicines.org.uk/medicines-advice/
    - Keyword: “paroxysmal nocturnal haemoglobinuria”
- All Wales Medicines Strategy Group (AWMSG) – Wales
    - Source: https://awttc.nhs.wales/
    - Keyword: “paroxysmal nocturnal haemoglobinuria”
- National Centre for Pharmacoeconomics (NCPE) – Ireland
    - Source: https://www.ncpe.ie/
    - Keyword: “PNH”
- Pharmaceutical Benefits Advisory Committee (PBAC) – Australia
    - Source: https://www.pbs.gov.au/medicinestatus/home.html
    - Keyword: “paroxysmal nocturnal haemoglobinuria”
- Canadian Agency for Drugs and Technologies in Health (CADTH) – Canada
    - Source: https://www.cadth.ca/
    - Keyword: “paroxysmal nocturnal hemoglobinuria”
- Haute Autorité de Santé (HAS) – France
    - Source: https://www.has-sante.fr/
    - Keywords: “paroxysmal nocturnal haemoglobinuria” and “PNH”
- German Institute for Quality and Efficiency in Health Care (IQWiG) – Germany
    - Source: https://www.iqwig.de/en/
    - Keyword: “paroxysmal nocturnal hemoglobinuria”
- Gemeinsamer Bundesausschuss (The Federal Joint Committee [G-BA]) – Germany
    - Source: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/ (to find English translations)

    - Keyword: “paroxysmal nocturnal hemoglobinuria”
- Institute for Clinical and Economic Review – United States of America
    - Source: https://icer.org/
    - Keyword: “paroxysmal nocturnal hemoglobinuria”.

Clinical trial registries were hand-searched for the clinical SLR on 22nd May 2023 (sources: [United States National Institutes of Health (NIH) trial registry & results database: https://clinicaltrials.gov/ct2/home] and [World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) registry: https://trialsearch.who.int/]) using the advanced search function without the use of date limits. The keyword searched on both platforms was “paroxysmal nocturnal hemoglobinuria”, using the “condition or disease” search field.

Health authority websites were hand-searched for the clinical SLR on 1st June 2023 (sources: [U.S. Food & Drug Administration (FDA): https://www.fda.gov/] and [European Medicines Agency (EMA): https://www.ema.europa.eu/en]) and the keywords searched were “iptacopan”, “pegcetacoplan”, “eculizumab”, “ravulizumab”, “danicopan”, “crovalimab”, “vemircopan”, “pozelimab”, “cemdisiran”, “NM8074”, “ARO-C3”, “KP104”, and “CAN-106”.

Economic and utility data repositories were hand-searched for the cost-effectiveness, health-related quality of life, and cost and healthcare resource identification, measurement and valuation SLRs on 22nd May 2023. Sources were as follows:

- Cost Effectiveness Analysis (CEA) Registry
    - Source: https://cevr.tuftsmedicalcenter.org/databases/cea-registry
    - Keyword: “paroxysmal nocturnal hemoglobinuria” (for methods, ratios and utilities)
- EconPapers within Research Papers in Economics (RePEc)
    - Source: http://repec.org/

    - Keywords: “paroxysmal nocturnal haemoglobinuria” and “paroxysmal nocturnal hemoglobinuria”

- EQ-5D (health-related quality of life SLR only)
    - Source: www.euroqol.org
    - Keyword: “paroxysmal nocturnal hemoglobinuria” (for EQ-5D documents and EQ-5D in Pubmed)
- University of Sheffield School of Health and Related Research Health Utilities Database (health-related quality of life SLR only)
    - Source: http://www.scharrhud.org/
    - Keyword: “paroxysmal nocturnal hemoglobinuria”
- HTA Database of the International Network Agencies for Health Technology Assessment (INAHTA)
    - Source: http://www.inahta.org/
    - Keywords: “paroxysmal nocturnal hemoglobinuria” and “paroxysmal nocturnal haemoglobinuria”

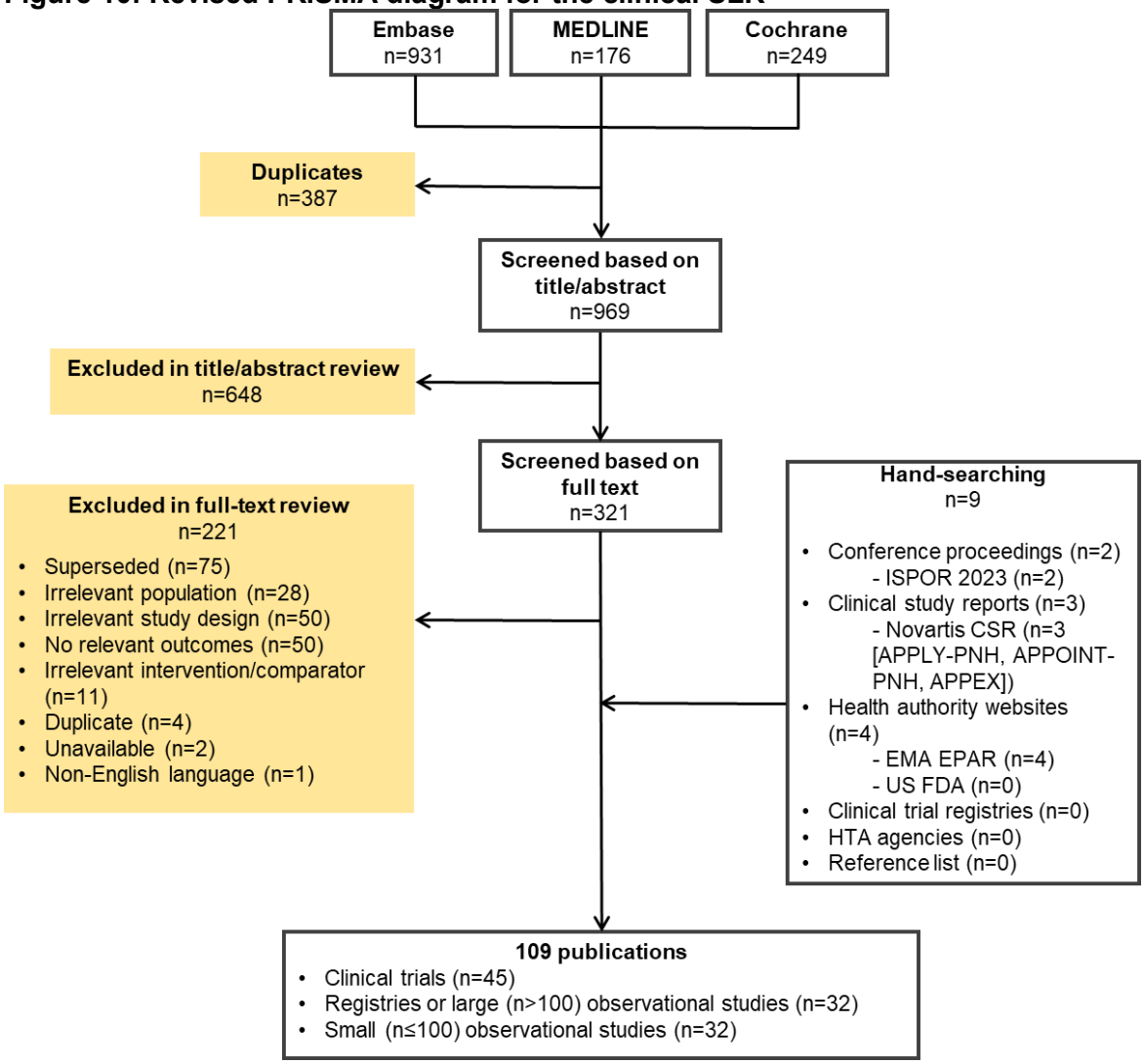
The indirect treatment comparisons (ITCs) included clinical trials identified in the clinical SLR (see Appendix D, sections D.4.1 and D.4.2 for the assessment of studies identified in the clinical SLR with regards to suitability for ITCs in the complement inhibitor-naïve population and the complement inhibitor-experienced population with residual anaemia, respectively).

C2. PRISMA Diagram: The following sources are not listed in PRISMA diagrams: the number of records obtained from: the searches of conference proceedings; clinical trial registries; health technology agencies; or health authority websites in Appendix D (the clinical evidence searches); the number of records obtained from any of the grey literature databases in Appendices G, H, and I (the cost-effectiveness searches,

the health-related quality of life searches, and the cost and healthcare resource identification, measurement and valuation searches).

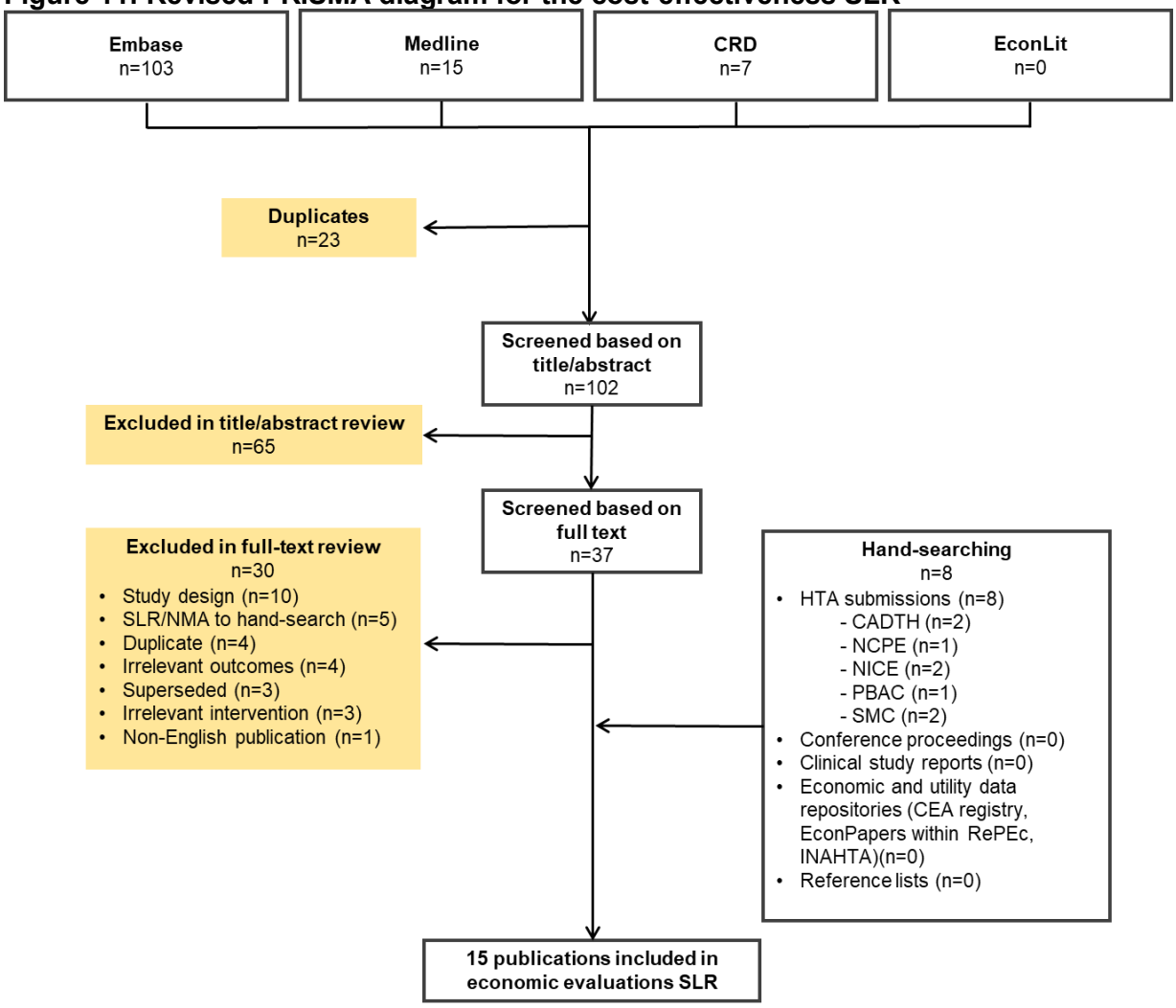
Revised PRISMA diagrams providing further details on the publications identified through hand-searching are shown below.

Figure 10: Revised PRISMA diagram for the clinical SLR



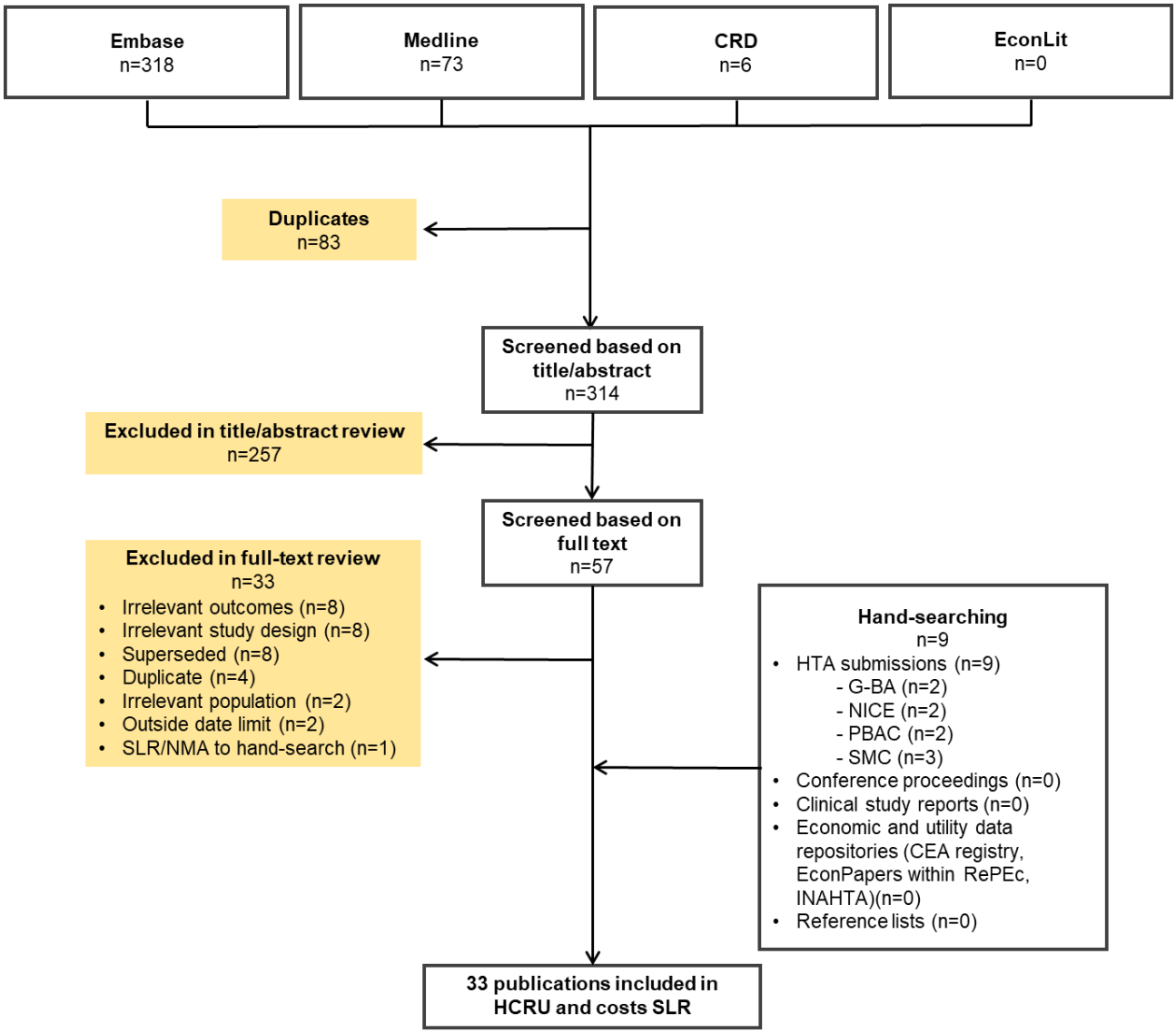
Abbreviations: CSR, clinical study report; EMA, European Medicines Agency; EPAR, European Public Assessment report; FDA, Food and Drug Administration; HTA, health technology assessment; ISPOR, The Professional Society for Health Economics and Outcomes Research; PNH, paroxysmal nocturnal haemoglobinuria; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review; US, United States.

Figure 11: Revised PRISMA diagram for the cost-effectiveness SLR



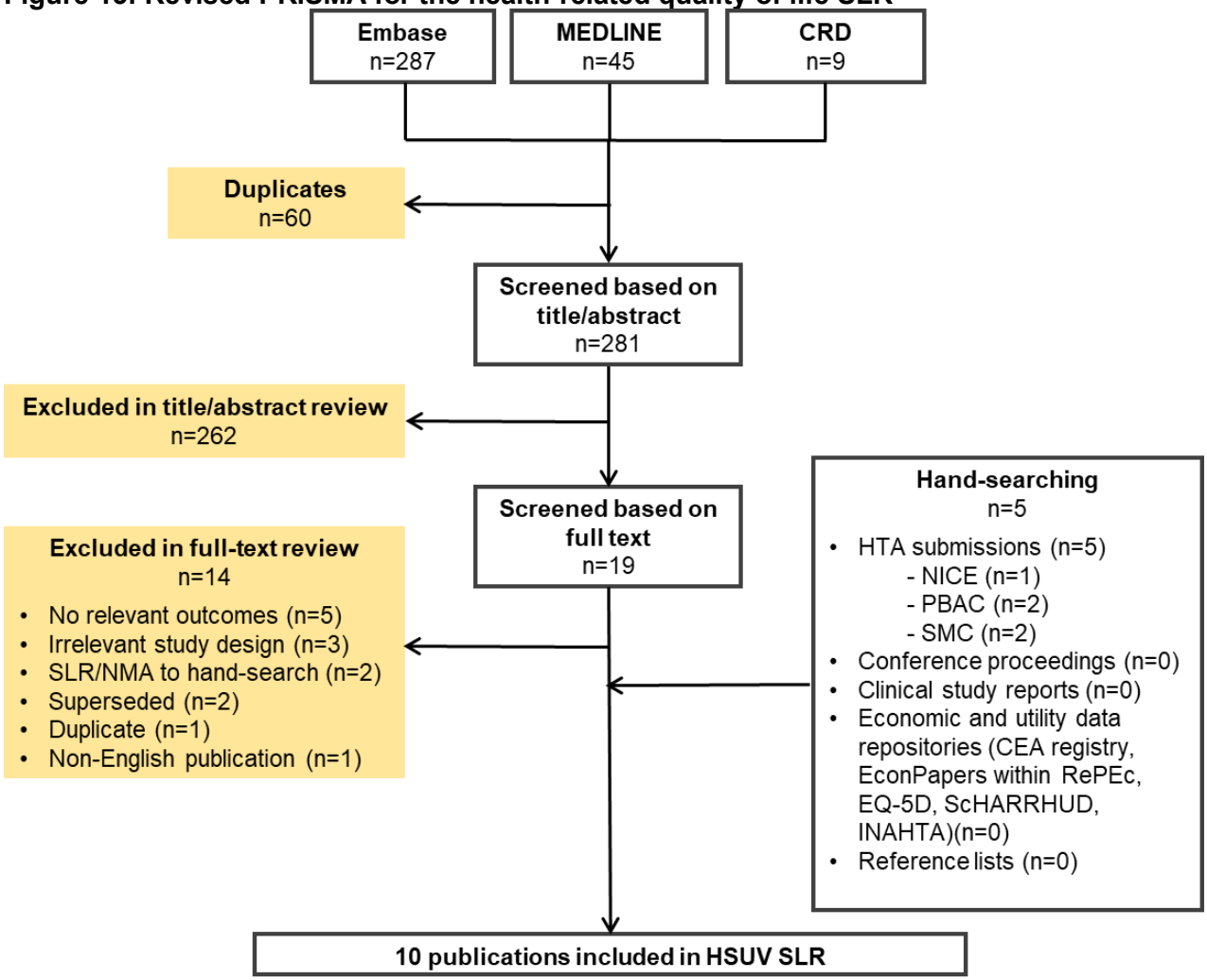
Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; CEA, cost effectiveness analysis; CRD, Centre for Reviews and Dissemination; INAHTA, International Network Agencies for Health Technology Assessment; NCPE, National Centre for Pharmacoeconomics; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; PBAC, Pharmaceutical Benefits Advisory Committee; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RePEc, research papers in economics; SLR, systematic literature review; SMC, Scottish Medicines Consortium.

Figure 12: Revised PRISMA for the cost and healthcare resource identification, measurement and valuation SLR



Abbreviations: CEA, cost effectiveness analysis; CRD, Centre for Reviews and Dissemination; G-BA, Gemeinsamer Bundesausschuss; HCRU, healthcare resource use; INAHTA, International Network Agencies for Health Technology Assessment; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; PBAC, Pharmaceutical Benefits Advisory Committee; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RePEc, research papers in economics; SLR, systematic literature review; SMC, Scottish Medicines Consortium.

Figure 13: Revised PRISMA for the health-related quality of life SLR



Abbreviations: CEA, cost effectiveness analysis; CRD, Centre for Reviews and Dissemination; HSUV, health state utility value; INAHTA, International Network Agencies for Health Technology Assessment; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; PBAC, Pharmaceutical Benefits Advisory Committee; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RePEc, research papers in economics; ScHARRHUD, University of Sheffield School of Health and Related Research Health Utilities Database; SLR, systematic literature review; SMC, Scottish Medicines Consortium.

C3. Error in Population Search Terms: In the Embase strategies for Appendices D and G (the clinical evidence searches and the cost-effectiveness searches), line 2 contains the search term: ‘paroxysmal nocturnal h? emoglobinuria’ with a space after the optional wildcard symbol (?). Repeating the error on Embase yields a similar number of hits, suggesting that this was not an error in formatting. This can also be compared with the correct version of this line in the Embase strategies for Appendices H and I (the health-related quality of life searches, and the cost and healthcare resource identification, measurement and valuation searches) which yields a higher number of hits on the same date. As this is an important search term

in the context of both searches, please can the company clarify if any relevant studies were missed because of this error

We thank the EAG for highlighting this error. The Embase searches for the clinical and cost-effectiveness SLRs were re-run without the space after the wildcard. The corrected searches returned 11 and one additional hits, respectively, none of which were relevant to the SLRs.

C4. Missed Intervention Search Terms: For all strategies in Appendices D and G (the clinical evidence searches and the cost-effectiveness searches), numerous search terms were missed for the interventions and no specific biosimilars were searched for eculizumab. As a single example, the following are some missed terms for eculizumab: abp959, bcd148, bow080, elizaria, isu305, and monoclonal antibody 5G1.1. Please can the company clarify if any relevant studies were missed because of the missed terms.

The searches for the clinical and cost-effectiveness SLRs were amended to include search terms for the eculizumab biosimilars “elizaria”, “bekemv”, “epysqli”, “ABP-959 or ABP 959 or ABP959”, “BCD-148 or BCD 148 or BCD148”, “SB-12 or SB 12 or SB12”, “BOW-080 or BOW 080 or BOW080”, “ISU-305 or ISU 305 or ISU305”, “Alexion”, and “monoclonal antibody 5G1.1 or h5G1.1”, and re-run. These searches returned zero additional hits.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Iptacopan for treating paroxysmal nocturnal haemoglobinuria [ID6176]

Follow-up questions on addendum to company evidence submission

December 2023

File name	Version	Contains confidential information	Date
ID6176_Iptacopan_PNH_NICE_EAG follow-up questions response_[REDACTED]	1	Redacted	14th Dec 2023

Response to EAG follow-up questions on the addendum to the company evidence submission

Q1. Updates to the transition probabilities estimated from APPLY-PNH:
EAG comment: Greater % in transfusion health state for iptacopan and C5 inhibitors. Why have the transition probabilities for C5 inhibitors changed? The missing data was from one patient who received iptacopan: "a transfusion administered to an iptacopan patient… was not included in the Novartis database at the 24-week data cut-off".

In addition to the case where a transfusion administered to an iptacopan patient was not included in the initial analysis due to a data transfer error at a study site, there were further minor updates to APPLY-PNH data. These were due to study sites continuing to enter data in the live database while the treatment extension phase of the trial was ongoing. Please refer to page 4 of the addendum to the company submission, with details provided on page 5.

These additional updates included [redacted], including for [redacted] patients in the C5 inhibitor arm. While these changes did not have an impact on the transfusion avoidance endpoint, they led to changes in the data utilised for generation of transition probabilities. The impact of the data updates on transition probabilities in the C5 inhibitor arm was limited, due to the overall larger number of transfusions than in the iptacopan arm and since [redacted].

Minor changes in the transition probabilities for the C5 inhibitor arm are also related to the joint estimation of transition probabilities for both iptacopan and C5 inhibitors within one multinomial logistic regression model.

Q2. Updates to the utility values estimated from iptacopan trial data:
EAG comment: Why have the standard errors changed significantly in the corrected data, and why have they changed for all health states, when there was only <u>one</u> missed patient (transfusion administered to an iptacopan patient) in the original APPLY-PNH dataset?

The values in Document B, Table 48 labelled as standard errors (SEs) were actually standard deviations (SDs). We apologise for this error. Table 1 reflects the correct SEs for the original utility values; these values were used in the economic model. The correct SEs of the original analysis are very similar to the SEs of the updated analysis (Table 2).

Table 1: Health state utility values: Original analysis (Document B, Table 48)

Health State	Iptacopan			C5 inhibitors		
	Mean	SD*	SE	Mean	SD*	SE
No Transfusion and No Anaemia	0.879	0.098	0.004	0.775	0.126	0.056
No Transfusion and Anaemia	0.819	0.102	0.008	0.743	0.182	0.015
Transfusion	0.800	0.102	0.015	0.695	0.182	0.022

*Erroneously labelled as SE in Document B, Table 48.
Abbreviations: SD, standard deviation. SE, standard error.

Table 2: Health state utility values: Updated analysis (Addendum, Table 15)

Health State	Iptacopan		C5 inhibitors	
	Mean	SE	Mean	SE
No Transfusion and No Anaemia	0.879	0.004	0.775	0.056
No Transfusion and Anaemia	0.822	0.008	0.743	0.015
Transfusion	0.791	0.015	0.695	0.021

Abbreviations: SE, standard error.

Overall, there were minor changes in values in the updated analysis since utilities were derived in a joint model for all health states and treatments.

Q3. Correction of the transition probabilities derived from APPEX data:
EAG comment: Much greater % in transfusion health state for C5 inhibitors, as seen in the Markov trace. What type of error was discovered in how transition

probabilities from APPEX data for C5 inhibitors had been estimated? Why has the error significantly changed the % in transfusion health state?

Due to a programming error, the transition probabilities initially derived from APPEX data only classified patients into the 'Transfusion' health state if they had received a transfusion on the final day of a 4-week cycle (i.e. on Day 28, Day 56, Day 84 etc.). The initial analysis also determined patients' baseline health state as 'Transfusion' if they had received a transfusion at any time in the past. Both of these elements were incorrect, since presence in the transfusion health state was defined by receipt of a blood transfusion at any time within the prior 4 weeks, up to and including the assessment time point (i.e. Day 1–28, Day 29–56, Day 57–84, etc.). This definition was based on methods applied in the estimation of transition probabilities from PEGASUS data, as published in Hakimi et al 2022 (1), and was followed in the estimation of all transition probabilities from APPOINT-PNH and APPLY-PNH data.

Due to above error, a large number of patients who had received transfusions after initiating treatment in the APPEX dataset was therefore not considered in the initial estimation of transition probabilities for C5 inhibitors in the naïve population. As the EAG correctly observes, upon correction of the programming error and consideration of all transfusions as per definition of the health state, the proportion of patients in the transfusion health state is substantially higher than in the initial analysis.

Model predictions generated with the corrected transition probabilities were reviewed by a UK clinician consulted during the preparation of the clarification questions response. Despite the substantial increase in transfusions compared to the initial analysis, the clinician still considered the model outputs conservative in predicting a lower proportion of C5 inhibitor-treated patients in the naïve population receiving transfusions than observed in clinical practice (see response to clarification question B8).

Q4. Changes made to the clinical effectiveness section B.2.9. – Transfusion avoidance endpoint: The introduction of the patient has significantly reduced the uncertainty around the OR in the ITC analysis (Table 10 in addendum compared to previous result in Table 26 in Document B) despite the little or no change in the baseline characteristics of the patients included in the ITC (see

Table 9 of Addendum and Table 25 of Document B).
EAG comment: Why have the APPLY-PNH data changes resulted in such a significant reduction?

It is not unusual for analyses with small numbers of events to be sensitive to small changes in data (2). The number of patients with a transfusion event in the iptacopan arm of APPLY-PNH (per PEGASUS definition) increased from one prior to the data update to two after the data update. (The third patient with a transfusion event included in the calculation of the APPLY-PNH trial endpoint was excluded in the ITC, since this transfusion occurred outside of the PEGASUS assessment period [after Day 140]; see Document B, section B.2.9.3.2.2 and Appendix D, Table 30 on the alignment of timeframes for endpoints in the ITC.)

The increase in the number of patients with a transfusion event from one to two patients resulted in a decrease in the proportion of transfusion-avoidant patients from [redacted]% to [redacted]% (estimate after APPLY-PNH population reweighted to align with the PEGASUS population on key characteristics; see Document B, section B.2.9.3.2.1). Consequently, also the odds of transfusion avoidance for iptacopan decreased from [redacted] in the original analysis to [redacted] in the updated analysis (Table 3). This decrease in the odds of transfusion avoidance for iptacopan accounts for the seemingly large decrease in the odds ratio of being transfusion-avoidant with iptacopan compared to pegcetacoplan from [redacted] to [redacted], after the data update.

The increase in number of events also resulted in a more precise point estimate for the log odds ratio, with the standard error decreasing from [redacted] to [redacted] ([redacted]% reduction) following the data correction. This is in line with an increase in variation in response as shown in Table 3 by the standard deviation of the weighted proportion, which is inversely related to precision.

Overall, the increase in precision of estimates is consistent with an increase in number of events. Furthermore, conclusions regarding the effect size and uncertainty as shown on the scale of estimation (log odds ratio) are not substantially changed by the data update. While the difference in the width of the confidence interval is large between the two analyses, odds ratios are expected to be normally distributed on the log scale, and typically a comparison of values on the log scale is

performed. When this is considered, the difference in the confidence intervals is less marked (Table 3).

Table 3: ITC APPLY-PNH vs PEGASUS: Transfusion avoidance updated calculations

	Prior results	Updated results
Iptacopan: Weighted proportion without transfusion (transfusion avoidant)	[redacted]	[redacted]
Standard deviation of the weighted proportion (transfusion avoidant): $\sqrt{p * (1-p) * N_{match}}$	[redacted]	[redacted]
Odds of transfusion avoidance	**Iptacopan:** $N = 54$† $N_{transfusion\ avoidant} = 53$ $ESS = 15$†† **Pegcetacoplan:** $N = 41$ $N_{transfusion\ avoidant} = 35$ **Odds of transfusion avoidance iptacopan:** [redacted] **Odds of transfusion avoidance pegcetacoplan:** $\frac{0.854}{0.146} = 5.9$	**Iptacopan:** $N = 54$† $N_{transfusion\ avoidant} = 52$ $ESS = 15$†† **Pegcetacoplan:** $N = 41$ $N_{transfusion\ avoidant} = 35$ **Odds of transfusion avoidance iptacopan:** [redacted] **Odds of transfusion avoidance pegcetacoplan:** $\frac{0.854}{0.146} = 5.9$
Iptacopan vs pegcetacoplan: Transfusion avoidance, odds ratio (95% CI)	[redacted]	[redacted]
Iptacopan vs pegcetacoplan: Transfusion avoidance, log odds ratio (95% CI)	[redacted]	[redacted]
Standard error for log odds ratio	[redacted]	[redacted]

†ITC analysis dataset, unweighted. ††ITC analysis dataset, weighted. Details see Document B, section B.2.9.3.3.1 with corrected table in addendum (Table 9).

Conclusions regarding efficacy of iptacopan vs pegcetacoplan based on the ITC of APPLY-PNH vs PEGASUS were unchanged after the data update. Results of the unanchored ITC for the transfusion avoidance endpoint continue to favour iptacopan, and while the point estimate decreased, the result remains statistically significant. In the anchored ITC, which should be interpreted with caution due to large differences in the C5 inhibitor control arms of APPLY-PNH and PEGASUS, the point estimate is also in favour of iptacopan, although not statistically significant (see addendum, Table 10), consistent with the original analysis.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Iptacopan for treating paroxysmal nocturnal haemoglobinuria [ID6176]

Supplementary analyses based on 48-week data

December 2023

File name	Version	Contains confidential information	Date
ID6176_Iptacopan_PNH_NICE_Supplementary analyses (48 wks)_11 Dec 2023_[REDACTED]	1	Redacted	11th Dec 2023

Contents

Tables and figures

1 Background

Economic model inputs in the company evidence submission were based on 24-week data from the iptacopan clinical trials APPOINT-PNH (complement inhibitor-naïve population) and APPLY-PNH (complement inhibitor-experienced population). Both trials continued after the primary efficacy analyses at 24 weeks, up to a total duration of 48 weeks. Results of the full 48-week trial duration (final analysis) are now available, demonstrating maintenance of clinically meaningful benefits of iptacopan treatment (see response to clarification question A3) (1, 2).

In order to allow the NICE committee to consider cost-effectiveness results based on longer-term follow-up data, the model has been updated with an option to conduct analyses utilising 48-week trial data for transition probabilities, and discontinuation and breakthrough haemolysis (BTH) event rates. Results of these analyses are presented in this document, alongside results based on the 24-week trial data.

2 Methodology

Methods for generating transition probabilities from 48-week data of APPOINT-PNH and APPLY-PNH data were consistent with the methods utilised for generating transition probabilities from 24-week data (Document B, section B.3.3.2.1).

For the complement inhibitor-naïve population, transition probabilities for iptacopan were derived from APPOINT-PNH data collected in Week 0–48.

For the complement inhibitor-experienced population, transition probabilities for iptacopan and C5 inhibitors were informed by APPLY-PNH data from the iptacopan arm collected in Week 0–48 and APPLY-PNH data from the C5 inhibitor arm collected in Week 0–24, respectively. While the extension treatment period did not provide additional data for C5 inhibitors, the available data from Week 0–24 was again included in model-fitting to remain consistent with the previously used multinomial logistic regression model including a treatment covariate. Due to joint modelling of iptacopan and C5 inhibitor transition probabilities, the transition probabilities for C5 inhibitors generated with the full 48-week data therefore differ slightly from those generated previously based on 24-week data. A scenario analysis explores the impact of utilising the C5 inhibitor transition probabilities from the 24-

week analysis alongside the iptacopan transition probabilities from the 48-week analysis.

Discontinuation and BTH event rates were derived and implemented in the model following the same approaches as used in the company submission (Document B, sections B.3.3.3 and B.3.3.4).

3 Model inputs

The economic model has been updated with an option to choose between inputs for transition probabilities, discontinuation rates and BTH event rates based either on 24-week or 48-week data from APPOINT-PNH and APPLY-PNH. Model inputs are reflected below. An Excel file containing the 48-week input data and documenting model changes has also been provided.

3.1 Transition probabilities applied in the analysis

3.1.1 Complement inhibitor-naïve population

Transition probabilities for iptacopan in the complement inhibitor-naïve population based on APPOINT-PNH 24-week or 48-week data are summarised in Table 1. Transition probabilities for C5 inhibitors, which were derived from APPEX real-world data, remain unchanged.

Table 1: Health state transition probabilities for the complement inhibitor-naïve population

From	To		
	No Transfusion and No Anaemia	No Transfusion and Anaemia	Transfusion
Based on 24-week data			
Iptacopan			
No Transfusion and No Anaemia	99.1%	0.9%	0.0%
No Transfusion and Anaemia	49.4%	48.2%	2.4%
Transfusion	18.0%	80.1%	1.9%
C5 inhibitors (eculizumab/ravulizumab)			
No Transfusion and No Anaemia	94.1%	4.5%	1.4%
No Transfusion and Anaemia	9.6%	76.1%	14.3%
Transfusion	2.5%	43.3%	54.2%
Based on 48-week data†			
Iptacopan			
No Transfusion and No Anaemia	98.0%	1.8%	0.2%
No Transfusion and Anaemia	37.6%	62.3%	0.1%
Transfusion	5.8%	36.5%	57.7%
C5 inhibitors (eculizumab/ravulizumab)			
No Transfusion and No Anaemia	94.1%	4.5%	1.4%
No Transfusion and Anaemia	9.6%	76.1%	14.3%
Transfusion	2.5%	43.3%	54.2%

†Iptacopan transition probabilities estimated from APPOINT-PNH 48-week data. C5 inhibitor transition probabilities estimated from APPEX data.
Anaemia defined as haemoglobin <10.5 g/dL.

Transition probabilities used in scenario analyses are presented in an updated version of Appendix P.

3.1.2 Complement inhibitor-experienced population

Transition probabilities for the complement inhibitor-experienced population based on APPLY-PNH 24-week or 48-week data are summarised in Table 2. Due to joint estimation of iptacopan and C5 inhibitor transition probabilities in one regression model, slight changes in the C5 inhibitor transition probabilities generated from 48-week data can be observed in comparison to previously used transition probabilities. Transition probabilities for pegcetacoplan are based on PEGASUS data, as published in Hakimi et al 2022 (3).

Table 2: Health state transition probabilities for the complement inhibitor-experienced population

From	To		
	No Transfusion and No Anaemia	No Transfusion and Anaemia	Transfusion
Based on 24-week data			
Iptacopan			
No Transfusion and No Anaemia	97.9%	2.0%	0.0%
No Transfusion and Anaemia	51.0%	44.3%	4.7%
Transfusion	50.7%	32.4%	17.0%
C5 inhibitors (eculizumab/ravulizumab)			
No Transfusion and No Anaemia	45.5%	47.9%	6.6%
No Transfusion and Anaemia	7.7%	65.7%	26.6%
Transfusion	6.2%	33.6%	60.2%
Pegcetacoplan			
No Transfusion and No Anaemia	96.6%	3.1%	0.3%
No Transfusion and Anaemia	49.1%	43.7%	7.2%
Transfusion	61.2%	26.6%	12.2%
Based on 48-week data†			
Iptacopan			
No Transfusion and No Anaemia	93.5%	6.5%	0.0%
No Transfusion and Anaemia	41.1%	56.5%	2.4%
Transfusion	54.6%	39.0%	6.4%
C5 inhibitors (eculizumab/ravulizumab)			
No Transfusion and No Anaemia	43.1%	56.9%	0.0%
No Transfusion and Anaemia	3.9%	69.1%	27.0%
Transfusion	3.2%	30.3%	66.5%
Pegcetacoplan			
No Transfusion and No Anaemia	96.6%	3.1%	0.3%
No Transfusion and Anaemia	49.1%	43.7%	7.2%
Transfusion	61.2%	26.6%	12.2%

†Iptacopan and C5 inhibitor transition probabilities estimated in a joint multinomial logistic regression model utilising APPLY-PNH 48-week data for iptacopan and 24-week data for C5 inhibitors. Pegcetacoplan transition probabilities based on PEGASUS as published in Hakimi et al 2022 (3). Anaemia defined as haemoglobin <10.5 g/dL.

Transition probabilities used in scenario analyses are presented in an updated version of Appendix P.

3.2 Discontinuation

In APPLY-PNH, one patient had discontinued iptacopan due to pregnancy in the 24-week randomised controlled period, and one additional patient discontinued iptacopan during the treatment extension period, also due to pregnancy. Based on the 48-week data of all patients treated with iptacopan in APPLY-PNH, the annual probability of discontinuation for the experienced population was calculated as

2.72% (vs 3.43% based on 24-week data). In APPOINT-PNH, no patient discontinued iptacopan over the full 48-week study duration. The base case for the naïve population conservatively assumes the same iptacopan discontinuation probability as for the experienced population. A new scenario analysis is provided with an iptacopan discontinuation rate pooled across both trials, which gives an annual probability of discontinuation of 1.79%.

All other discontinuation assumptions and model inputs remained unchanged.

Table 3: Treatment discontinuation and subsequent therapy in the base case

Initial therapy	Discontinuation type	Discontinuation probability	Subsequent therapy	Source
Complement inhibitor-naïve population				
Iptacopan	Continuous	• ***24-week data:*** 3.43% per year • ***48-week data:*** 2.72% per year • ***Pooled 48-week data (scenario):*** 1.79% per year	Ravulizumab	Base case: assumed equal to experienced population
Eculizumab	One-time	30% of patients in 'Transfusion' or 'No Transfusion and Anaemia' health states at 6 months	Pegcetacoplan	UK clinical advisory board (4); Expert input in model validation calls (5)
Ravulizumab	One-time	30% of patients in 'Transfusion' or 'No Transfusion and Anaemia' health states at 6 months	Pegcetacoplan	UK clinical advisory board (4); Expert input in model validation calls (5)
Complement inhibitor-experienced population				
Iptacopan	Continuous	• ***24-week data:*** 3.43% per year • ***48-week data:*** 2.72% per year • ***Pooled 48-week data (scenario):*** 1.79% per year	Ravulizumab	APPLY-PNH (2, 6); UK clinical advisory board (4)
Eculizumab	No discontinuation	NA	NA	Expert input in model validation calls (5)
Ravulizumab	No discontinuation	NA	NA	Expert input in model validation calls (5)

Pegcetacoplan	Continuous	16.13% per year	Ravulizumab	PEGASUS (48 weeks) (7), excluding 4 discontinuations due to BTH and one due to death based on UK clinical advisory board input (4); Expert input in model validation calls (5)

Abbreviations: BTH, breakthrough haemolysis; NA, not applicable; UK, United Kingdom.

3.3 Breakthrough haemolysis (BTH) event rate

Updated adjusted annualised BTH rates for iptacopan are available from the 48-week analyses of APPOINT-PNH (0.05, 95% CI: 0.01, 0.17) and APPLY-PNH (0.11, 95% CI: 0.05, 0.23) and have been included in the economic model updated with the 48-week data. Given feedback from a clinician who was consulted in preparation for the response to clarification question B14 that the difference in BTH event rates between APPOINT-PNH and APPLY-PNH may have occurred by chance, a scenario based on the 48-week data explores the impact of an iptacopan BTH event rate pooled across both trials (0.09, 95% CI: 0.05, 0.17).

Table 4: Summary of BTH event rates

Treatment	**Annualised BTH rates**	
	Complement inhibitor-naïve	**Complement inhibitor-experienced**
Iptacopan	***24-week data:*** 0.00 (8) ***48-week data:*** 0.05 (1)	***24-week data:*** 0.07 (6) ***48-week data:*** 0.11 (2)
	Pooled 48-week data (scenario): 0.09	
Eculizumab	0.21 (9)	0.67 (6)
Ravulizumab	0.08 (9)	0.67 (6)
Pegcetacoplan	NA	0.13 (7)

Abbreviations: BTH, breakthrough haemolysis. NA, not applicable (pegcetacoplan is not licensed or used in complement inhibitor-naïve patients).

4 Cost-effectiveness results

4.1 Base-case results

In the complement inhibitor-naïve population (Table 5), iptacopan total costs [redacted] and total QALYs slightly increase based on 48-week data vs 24-week data. Using the iptacopan PAS price and comparator list prices, iptacopan is cost-effective vs eculizumab and ravulizumab ([redacted]). Net health benefit (NHB) of iptacopan vs eculizumab and ravulizumab increases based on 48-week data vs 24-week data (Table 6).

In the complement inhibitor-experienced population with residual anaemia (Table 7), iptacopan total costs [redacted] and total QALYs slightly increase based on 48-week data vs 24-week data. For comparator treatments, there is a [redacted] in total costs and total QALYs slightly decrease. Based on 48-week data and using the iptacopan PAS price and comparator list prices, iptacopan is cost-effective vs all comparators ([redacted]). NHB of iptacopan vs all comparators increases based on 48-week data vs 24-week data (Table 8).

Drivers of changes in cost-effectiveness estimates based on 48-week data vs previous estimates based on 24-week data are discussed in Section 4.3.

Table 5: Base-case results, complement inhibitor-naïve population (iptacopan PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
Based on 24-week data								
Iptacopan (PAS price)	[redacted]	21.05	16.59	–	–	–	–	–
Eculizumab	[redacted]	21.05	15.52	[redacted]	0.00	–1.07	[redacted]	[redacted]
Ravulizumab	[redacted]	21.05	15.53	[redacted]	0.00	–1.06	[redacted]	[redacted]
Based on 48-week data								
Iptacopan (PAS price)	[redacted]	21.05	16.68	–	–	–	–	–
Eculizumab	[redacted]	21.05	15.52	[redacted]	0.00	–1.17	[redacted]	[redacted]
Ravulizumab	[redacted]	21.05	15.53	[redacted]	0.00	–1.16	[redacted]	[redacted]

Analysis uses PAS price for iptacopan and list price for comparators.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 6: Net health benefit, complement inhibitor-naïve population (iptacopan PAS price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Based on 24-week data						
Iptacopan (PAS price)	[redacted]	16.59	–	–	–	–
Eculizumab	[redacted]	15.52	[redacted]	–1.07	[redacted]	[redacted]
Ravulizumab	[redacted]	15.53	[redacted]	–1.06	[redacted]	[redacted]
Based on 48-week data						
Iptacopan (PAS price)	[redacted]	16.68	–	–	–	–
Eculizumab	[redacted]	15.52	[redacted]	–1.17	[redacted]	[redacted]
Ravulizumab	[redacted]	15.53	[redacted]	–1.16	[redacted]	[redacted]

Analysis uses PAS price for iptacopan and list price for comparators.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 7: Base-case results, complement inhibitor-experienced population (iptacopan PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
Based on 24-week data								
Eculizumab	[redacted]	18.89	12.68	–	–	–	–	–
Iptacopan (PAS price)	[redacted]	18.89	14.42	[redacted]	0.00	1.74	[redacted]	[redacted]
Ravulizumab	[redacted]	18.89	12.68	[redacted]	0.00	0.00	[redacted]	[redacted]
Pegcetacoplan	[redacted]	18.89	13.35	[redacted]	0.00	0.67	[redacted]	[redacted]
Based on 48-week data								
Iptacopan (PAS price)	[redacted]	18.89	14.47	–	–	–	–	–
Eculizumab	[redacted]	18.89	12.60	[redacted]	0.00	–1.86	[redacted]	[redacted]
Ravulizumab	[redacted]	18.89	12.60	[redacted]	0.00	–1.86	[redacted]	[redacted]
Pegcetacoplan	[redacted]	18.89	13.29	[redacted]	0.00	–1.18	[redacted]	[redacted]

Analysis uses PAS price for iptacopan and list price for comparators.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 8: Net health benefit, complement inhibitor-experienced population (iptacopan PAS price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Based on 24-week data						
Eculizumab	[redacted]	12.68	–	–	–	–
Iptacopan (PAS price)	[redacted]	14.42	[redacted]	1.74	[redacted]	[redacted]
Ravulizumab	[redacted]	12.68	[redacted]	0.00	[redacted]	[redacted]
Pegcetacoplan	[redacted]	13.35	[redacted]	0.67	[redacted]	[redacted]
Based on 48-week data						
Iptacopan (PAS price)	[redacted]	14.47	–	–	–	–
Eculizumab	[redacted]	12.60	[redacted]	–1.86	[redacted]	[redacted]
Ravulizumab	[redacted]	12.60	[redacted]	–1.86	[redacted]	[redacted]
Pegcetacoplan	[redacted]	13.29	[redacted]	–1.18	[redacted]	[redacted]

Analysis uses PAS price for iptacopan and list price for comparators.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; PAS, patient access scheme; QALY, quality-adjusted life year.

4.2 Exploring uncertainty

4.2.1 Probabilistic sensitivity analysis

Changes in the results of the probabilistic sensitivity analysis (PSA) using the 48-week data vs 24-week data are aligned with the changes in the deterministic analysis. In the complement inhibitor-naïve population, PSA results (Table 9) are congruent with the deterministic results, and iptacopan remains cost-effective ([redacted]) at the iptacopan PAS price and comparator list prices. Figure 1 presents the cost-effectiveness plane. The CEAC (Figure 2) shows that iptacopan [redacted] was cost-effective in [redacted]% of simulations at a willingness-to-pay (WTP) threshold of £20,000 per QALY, and [redacted]% of simulations at a WTP threshold of £30,000 per QALY.

In the complement inhibitor-experienced population, PSA results (Table 10) are congruent with the deterministic results, and iptacopan remains cost-effective vs all comparators ([redacted]). Figure 3 presents the cost-effectiveness plane. The CEAC (Figure 4) shows that iptacopan [redacted] cost-effective at a WTP threshold of £20,000 per QALY in [redacted]% of simulations and at a WTP threshold of £30,000 in [redacted]% of simulations.

Table 9: PSA results, complement inhibitor-naïve population (iptacopan PAS price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
Based on 24-week data						
Iptacopan (PAS price)	[redacted]	16.56	–	–	–	–
Eculizumab	[redacted]	15.51	[redacted]	–1.05	[redacted]	[redacted]
Ravulizumab	[redacted]	15.51	[redacted]	–1.05	[redacted]	[redacted]
Based on 48-week data						
Iptacopan (PAS price)	[redacted]	16.65	–	–	–	–
Eculizumab	[redacted]	15.49	[redacted]	–1.15	[redacted]	[redacted]
Ravulizumab	[redacted]	15.50	[redacted]	–1.15	[redacted]	[redacted]

Analysis uses PAS price for iptacopan and list price for comparators.
Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year

Table 10: PSA results, complement inhibitor-experienced population (iptacopan PAS price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
Based on 24-week data						
Eculizumab	[redacted]	12.68	–	–	–	–
Iptacopan (PAS price)	[redacted]	14.40	[redacted]	1.72	[redacted]	[redacted]
Ravulizumab	[redacted]	12.68	[redacted]	0.00	[redacted]	[redacted]
Pegcetacoplan	[redacted]	13.35	[redacted]	0.67	[redacted]	[redacted]
Based on 48-week data						
Iptacopan (PAS price)	[redacted]	14.44	–	–	–	–
Eculizumab	[redacted]	12.61	[redacted]	–1.84	[redacted]	[redacted]
Ravulizumab	[redacted]	12.61	[redacted]	–1.84	[redacted]	[redacted]
Pegcetacoplan	[redacted]	13.30	[redacted]	–1.15	[redacted]	[redacted]

Analysis uses PAS price for iptacopan and list price for comparators.
Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

Figure 1: Cost-effectiveness plane, complement inhibitor-naïve population – Based on 48-week data

Abbreviation: QALY, quality-adjusted life year.

Figure 2: Cost-effectiveness acceptability curve, complement inhibitor-naïve population – Based on 48-week data

Figure 3: Cost-effectiveness plane, complement inhibitor-experienced population – Based on 48-week data

Abbreviation: QALY, quality-adjusted life year.

Figure 4: Cost-effectiveness acceptability curve, complement inhibitor-experienced population – Based on 48-week data

4.2.2 Scenario analysis

In the complement inhibitor-naïve population (Table 11), at the iptacopan PAS price and comparator list prices, iptacopan is cost-effective vs eculizumab and ravulizumab in all scenarios based on the 48-week data.

In the complement inhibitor-experienced population (Table 12), at the iptacopan PAS price and comparator list prices, iptacopan is cost-effective vs all comparators in all scenarios based on the 48-week data, except for the scenario with no discounting vs eculizumab ([redacted]). In the scenario without discontinuations, iptacopan now generates slightly lower QALYs than pegcetacoplan, but remains cost-effective at the iptacopan PAS price and comparator list prices ([redacted]).

Table 11: Scenario analyses for iptacopan in the complement inhibitor-naïve population (iptacopan PAS price)

Scenario	Iptacopan vs eculizumab			Iptacopan vs ravulizumab		
	Inc. costs	Inc. QALYs	ICER	Inc. costs	Inc. QALYs	ICER
Based on 24-week data						
Base case	[redacted]	**1.07**	[redacted]	[redacted]	**1.06**	[redacted]
Definition of anaemia	[redacted]	1.11	[redacted]	[redacted]	1.10	[redacted]
No imputation for APPEX data	[redacted]	1.23	[redacted]	[redacted]	1.22	[redacted]
Unweighted transition probabilities	[redacted]	1.08	[redacted]	[redacted]	1.07	[redacted]
Comparator dosing	[redacted]	1.07	[redacted]	[redacted]	1.06	[redacted]
No discontinuation for any treatment	[redacted]	2.46	[redacted]	[redacted]	2.44	[redacted]
No discontinuation for iptacopan	[redacted]	1.96	[redacted]	[redacted]	1.95	[redacted]
Treatment independent utilities	[redacted]	0.44	[redacted]	[redacted]	0.43	[redacted]
EORTC QLQ-C30 utilities	[redacted]	1.08	[redacted]	[redacted]	1.07	[redacted]

Scenario	Iptacopan vs eculizumab			Iptacopan vs ravulizumab		
	Inc. costs	Inc. QALYs	ICER	Inc. costs	Inc. QALYs	ICER
No BTH cost	[redacted]	1.07	[redacted]	[redacted]	1.06	[redacted]
No chelation therapy or venesection	[redacted]	1.07	[redacted]	[redacted]	1.06	[redacted]
TA778 resource use	[redacted]	1.07	[redacted]	[redacted]	1.06	[redacted]
No discounting	[redacted]	1.52	[redacted]	[redacted]	1.51	[redacted]
Based on 48-week data						
Base case	[redacted]	**1.17**	[redacted]	[redacted]	**1.16**	[redacted]
Definition of anaemia	[redacted]	1.22	[redacted]	[redacted]	1.21	[redacted]
No imputation for APPEX data	[redacted]	1.35	[redacted]	[redacted]	1.34	[redacted]
Unweighted transition probabilities	[redacted]	1.18	[redacted]	[redacted]	1.17	[redacted]
Comparator dosing	[redacted]	1.17	[redacted]	[redacted]	1.16	[redacted]
No discontinuation for any treatment	[redacted]	2.40	[redacted]	[redacted]	2.39	[redacted]
No discontinuation for iptacopan	[redacted]	1.91	[redacted]	[redacted]	1.90	[redacted]
Treatment independent utilities	[redacted]	0.43	[redacted]	[redacted]	0.42	[redacted]
EORTC QLQ-C30 utilities	[redacted]	1.18	[redacted]	[redacted]	1.17	[redacted]
No BTH cost	[redacted]	1.17	[redacted]	[redacted]	1.16	[redacted]
No chelation therapy or venesection	[redacted]	1.17	[redacted]	[redacted]	1.16	[redacted]
TA778 resource use	[redacted]	1.17	[redacted]	[redacted]	1.16	[redacted]
No discounting	[redacted]	1.76	[redacted]	[redacted]	1.74	[redacted]
New scenario: Pooled discontinuation rate for iptacopan	[redacted]	1.37	[redacted]	[redacted]	1.36	[redacted]

Scenario	Iptacopan vs eculizumab			Iptacopan vs ravulizumab		
	Inc. costs	Inc. QALYs	ICER	Inc. costs	Inc. QALYs	ICER
New scenario: Pooled BTH event rate for iptacopan	[redacted]	1.16	[redacted]	[redacted]	1.15	[redacted]

Analysis uses PAS price for iptacopan and list price for comparators.
Abbreviations: BTH, breakthrough haemolysis; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TA, technology appraisal.

Table 12: Scenario analyses for iptacopan in the complement inhibitor-experienced population (iptacopan PAS price)

Scenario	Iptacopan vs eculizumab			Iptacopan vs ravulizumab			Iptacopan vs pegcetacoplan		
	Inc. costs	Inc. QALYs	ICER	Inc. costs	Inc. QALYs	ICER	Inc. costs	Inc. QALYs	ICER
Based on 24-week data									
Base case	[redacted]	**1.74**	[redacted]	[redacted]	**1.74**	[redacted]	[redacted]	**1.07**	[redacted]
Definition of anaemia	[redacted]	1.58	[redacted]	[redacted]	1.58	[redacted]	[redacted]	0.98	[redacted]
Unweighted transition probabilities	[redacted]	1.78	[redacted]	[redacted]	1.78	[redacted]	[redacted]	1.10	[redacted]
C5 inhibitor efficacy by treatment	[redacted]	1.50	[redacted]	[redacted]	2.12	[redacted]	[redacted]	1.30	[redacted]
C5 inhibitor efficacy from PEGASUS	[redacted]	1.84	[redacted]	[redacted]	1.84	[redacted]	[redacted]	1.13	[redacted]
Comparator dosing	[redacted]	1.74	[redacted]	[redacted]	1.74	[redacted]	[redacted]	1.07	[redacted]
No discontinuation	[redacted]	2.61	[redacted]	[redacted]	2.61	[redacted]	[redacted]	0.03	[redacted]
Treatment independent utilities	[redacted]	1.17	[redacted]	[redacted]	1.17	[redacted]	[redacted]	0.72	[redacted]
EORTC QLQ-C30 utilities	[redacted]	1.63	[redacted]	[redacted]	1.63	[redacted]	[redacted]	1.01	[redacted]
No BTH cost	[redacted]	1.74	[redacted]	[redacted]	1.74	[redacted]	[redacted]	1.07	[redacted]

Scenario	Iptacopan vs eculizumab			Iptacopan vs ravulizumab			Iptacopan vs pegcetacoplan		
	Inc. costs	Inc. QALYs	ICER	Inc. costs	Inc. QALYs	ICER	Inc. costs	Inc. QALYs	ICER
No chelation therapy or venesection	[redacted]	1.74	[redacted]	[redacted]	1.74	[redacted]	[redacted]	1.07	[redacted]
TA778 resource utilisation	[redacted]	1.74	[redacted]	[redacted]	1.74	[redacted]	[redacted]	1.07	[redacted]
No discounting	[redacted]	2.60	[redacted]	[redacted]	2.60	[redacted]	[redacted]	1.81	[redacted]
Based on 48-week data									
Base case	[redacted]	**1.86**	[redacted]	[redacted]	**1.86**	[redacted]	[redacted]	**1.18**	[redacted]
Definition of anaemia	[redacted]	1.82	[redacted]	[redacted]	1.82	[redacted]	[redacted]	1.17	[redacted]
Unweighted transition probabilities	[redacted]	1.89	[redacted]	[redacted]	1.89	[redacted]	[redacted]	1.21	[redacted]
C5 inhibitor efficacy by treatment[§]	[redacted]	1.60	[redacted]	[redacted]	2.22	[redacted]	[redacted]	1.40	[redacted]
C5 inhibitor efficacy from PEGASUS	[redacted]	1.91	[redacted]	[redacted]	1.91	[redacted]	[redacted]	1.21	[redacted]
Comparator dosing	[redacted]	1.86	[redacted]	[redacted]	1.86	[redacted]	[redacted]	1.18	[redacted]
No discontinuation	[redacted]	2.59	[redacted]	[redacted]	2.59	[redacted]	[redacted]	–0.07	[redacted]
Treatment independent utilities	[redacted]	1.24	[redacted]	[redacted]	1.24	[redacted]	[redacted]	0.76	[redacted]
EORTC QLQ-C30 utilities	[redacted]	1.74	[redacted]	[redacted]	1.74	[redacted]	[redacted]	1.10	[redacted]
No BTH cost	[redacted]	1.86	[redacted]	[redacted]	1.86	[redacted]	[redacted]	1.18	[redacted]
No chelation therapy or venesection	[redacted]	1.86	[redacted]	[redacted]	1.86	[redacted]	[redacted]	1.18	[redacted]
TA778 resource utilisation	[redacted]	1.86	[redacted]	[redacted]	1.86	[redacted]	[redacted]	1.18	[redacted]

Scenario	Iptacopan vs eculizumab			Iptacopan vs ravulizumab			Iptacopan vs pegcetacoplan		
	Inc. costs	Inc. QALYs	ICER	Inc. costs	Inc. QALYs	ICER	Inc. costs	Inc. QALYs	ICER
No discounting	[redacted]	2.84	[redacted]	[redacted]	2.84	[redacted]	[redacted]	2.03	[redacted]
New scenario: With C5 inhibitor transition probabilities - 24 weeks†	[redacted]	1.81	[redacted]	[redacted]	1.81	[redacted]	[redacted]	1.14	[redacted]
New scenario: Pooled discontinuation rate for iptacopan	[redacted]	2.07	[redacted]	[redacted]	2.07	[redacted]	[redacted]	1.38	[redacted]
New scenario: Pooled BTH event rate for iptacopan	[redacted]	1.86	[redacted]	[redacted]	1.86	[redacted]	[redacted]	1.18	[redacted]

§Scenario analysis using iptacopan transition probabilities estimated in the multinomial logistic regression model based on APPLY-PNH 48-week data and eculizumab and ravulizumab transition probabilities estimated in the model based on APPLY-PNH 24-week data. Due to insufficient time, no joint regression model could be run. However, given the direction of changes with the 48-week transition probabilities (see Section 4.3), it is expected that the results presented here are conservative.

†Scenario analysis using C5 inhibitor transition probabilities estimated in the multinomial logistic regression model based on APPLY-PNH 24-week data. Analysis uses PAS price for iptacopan and list price for comparators.

Abbreviations: BTH, breakthrough haemolysis; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TA, technology appraisal.

4.3 Interpretation and conclusions of economic evidence

Model updates with longer-term iptacopan data from the 48-week analyses of APPOINT-PNH and APPLY-PNH overall led to improved cost-effectiveness of iptacopan.

The update of transition probabilities based on iptacopan 48-week data only had a minor impact, leading to [redacted] costs and slightly lower QALYs for iptacopan in the complement inhibitor-naïve population (Table 13) and for iptacopan and all comparators in the complement inhibitor-experienced population (Table 14). Update of the BTH event rate of iptacopan also led to a negligible [redacted] of iptacopan costs. The update of the annual probability of iptacopan discontinuation (2.72% based on 48-week data vs 3.43% based on 24-week data) had the largest impact, resulting in [redacted] of iptacopan total costs and an increase in iptacopan total QALYs, and thus constitutes the key driver of changes in cost-effectiveness estimates based on 48-week data vs analyses based on 24-week data.

The results of the analyses indicate that, at its PAS price, iptacopan is expected to be a cost-effective treatment option for PNH, in both complement inhibitor-naïve patients and complement inhibitor-experienced patients with residual anaemia. This conclusion is supported by a wide range of sensitivity analyses, providing reassurance that iptacopan is a cost-effective use of NHS resources.

Table 13: Costs and QALYs in the complement inhibitor-naive population based on 48-week vs 24-week data (iptacopan PAS price)

	Iptacopan		Eculizumab		Ravulizumab	
	Total costs	**Total QALYs**	**Total costs**	**Total QALYs**	**Total costs**	**Total QALYs**
Base case based on 24-week data	[redacted]	**16.59**	[redacted]	**15.52**	[redacted]	**15.53**
48-week transition probabilities	[redacted]	–0.03	+£0	+0.00	+£0	+0.00
+ 48-week discontinuation rate	[redacted]	+0.13	+£0	+0.00	+£0	+0.00
+ 48-week BTH event rate	[redacted]	+0.00	+£0	+0.00	+£0	+0.00
Base case based on 48-week data	[redacted]	**16.68**	[redacted]	**15.52**	[redacted]	**15.53**

Abbreviations: BTH, breakthrough haemolysis; QALY, quality-adjusted life year.

Table 14: Costs and QALYs in the complement inhibitor-experienced population based on 48-week vs 24-week data (iptacopan PAS price)

	Iptacopan		Eculizumab		Ravulizumab		Pegcetacoplan	
	Total costs	**Total QALYs**	**Total costs**	**Total QALYs**	**Total costs**	**Total QALYs**	**Total costs**	**Total QALYs**
Base case based on 24-week data	[redacted]	**14.42**	[redacted]	**12.68**	[redacted]	**12.68**	[redacted]	**13.35**
48-week transition probabilities	[redacted]	–0.09	[redacted]	–0.08	[redacted]	–0.08	[redacted]	–0.06
+ 48-week discontinuation rate	[redacted]	+0.14	+£0	+0.00	+£0	+0.00	+£0	+0.00
+ 48-week BTH event rate	[redacted]	+0.00	+£0	+0.00	+£0	+0.00	+£0	+0.00
Base case based on 48-week data	[redacted]	**14.47**	[redacted]	**12.60**	[redacted]	**12.60**	[redacted]	**13.29**

Abbreviations: BTH, breakthrough haemolysis; QALY, quality-adjusted life year.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Iptacopan for treating paroxysmal nocturnal haemoglobinuria [ID6176]

Addendum to company evidence submission

December 2023

File name	Version	Contains confidential information	Date
ID6176_Iptacopan_PNH_NICE_Addendum_4 Dec 2023_[REDACTED]	1	Redacted	4th Dec 2023

Tables and figures

Background to addendum

The addendum provides corrections to the company submission to account for data changes and errors discovered after the submission of iptacopan for treating paroxysmal nocturnal haemoglobinuria (PNH) [ID6176] to NICE on 26th October 2023.

APPLY-PNH data changes

Following final database lock upon completion of the full 48-week study duration, it was noted that a transfusion administered to an iptacopan patient during the 24-week randomised treatment period had been captured in source data at the study site, but due to an error at the study site, was not included in the Novartis database at the 24-week data cut-off (26th September 2022). Following correction of the affected data, the 24-week efficacy results were re-analysed.

The additional transfusion caused one additional patient in the iptacopan arm to be considered a treatment failure in the transfusion avoidance endpoint (secondary endpoint). Overall, 59/62 patients in the iptacopan arm (vs previously 60/62 patients) were transfusion-avoidant between Day 14 and Day 168, compared with 14/35 patients in the C5 inhibitor arm. Following the data correction, the treatment difference in marginal proportions was estimated as 68.9% (95% CI: 51.4, 83.9) (vs previously 70.3%; 95% CI: 52.6, 84.9). The number of patients considered responders in the two primary haematological responder endpoints, which assessed haemoglobin (Hb) in the absence of transfusions, was unaffected by this change, since the patient whose transfusion was missing in the original dataset was already considered a non-responder due to not meeting the Hb criteria. There were, however, small numerical changes in estimates for all Hb endpoints due to Hb values within 30 days of a transfusion being set to missing and imputed.

In addition, study sites entering data during the treatment extension phase of the study had also made minor updates in patient baseline characteristics as well as data relating to the initial 24-week treatment period (detailed below), which led to small numerical changes in several endpoints.

- Study site updates which altered patients' baseline characteristics:

[redacted]

- Changes affecting 24-week efficacy data:

[redacted]

Revised clinical trial data, where changes occurred, are provided below (Addendum to B.2 Clinical effectiveness). For all endpoints, the impact of the small numerical changes in the efficacy results is negligible and the overall efficacy conclusions for APPLY-PNH showing superiority of iptacopan over C5 inhibitor treatment in treatment-experienced PNH patients with residual anaemia remain unchanged.

Due to changes in trial endpoints included in the indirect treatment comparison (ITC) of APPLY-PNH vs PEGASUS, revised ITC results are also provided (see B.2.9 Indirect and mixed treatment comparisons).

Transition probabilities and utilities were re-estimated from the updated APPLY-PNH individual patient data (IPD). All updated model inputs are provided in section Addendum to B.3 Cost effectiveness.

Correction of error in estimation of transition probabilities from APPEX data

An error was discovered in how transition probabilities for C5 inhibitors in the complement inhibitor-naïve population had been estimated from APPEX data. Corrected transition probabilities are provided in section Addendum to B.3 Cost effectiveness.

Changes made to the economic model & revised cost-effectiveness results

The economic model was updated and all analyses re-run. Please note that the APPLY-PNH data updates affected both the naïve and experienced populations (naïve population due to use of pooled utility values), while the correction of APPEX transition probabilities affected the naïve population only.

Updates of inputs to the economic model were as follows:

- Updating the baseline distribution of patients across health states
- Updates to transition probabilities estimated from APPLY-PNH
- Updates to utility values estimated from iptacopan trial data
- Correction of the transition probabilities derived from APPEX data

In addition, the following change has been made:

- Correction in the calculation of severity multipliers.

A separate Excel file has been provided detailing all of the updated model inputs and where changes have been made in the model.

Revised cost-effectiveness results are presented in section Addendum to B.3 Cost effectiveness, with changes compared to the original submission largely minor in both the naïve and experienced populations.

Addendum to B.2 Clinical effectiveness

B.2.3.6.3 Baseline disease characteristics

Table 1: APPOINT-PNH and APPLY-PNH: Baseline disease characteristics [Update to Document B, Table 7]

	APPOINT-PNH	APPLY-PNH		
	Iptacopan 200 mg BD N=40	Iptacopan 200 mg BD N=62	C5 inhibitor N=35	Overall N=97
Disease duration, years				
Mean (SD)	4.699 (5.5379)	11.88 (9.813)	13.54 (10.947)	12.48 (10.211)
Median (min–max)	3.625 (0.01–23.20)	NR (0.7–40.2)	NR (1.5–42.0)	NR (0.7–42.0)
Length of time since diagnosis, n (%)				
<3 years	18 (45.0)	NR	NR	NR
≥3 years	22 (55.0)	NR	NR	NR
C5 inhibitor medication history – 6 months prior to randomisation -n (%)				
Eculizumab	NA	40 (64.5)	23 (65.7)	63 (64.9)
Ravulizumab	NA	22 (35.5)	12 (34.3)	34 (35.1)
Duration of C5 inhibitor treatment (years)				
Mean (SD)	NA	3.80 (3.567)	4.23 (3.868)	3.96 (3.665)
Median (min–max)	NA	2.56 (0.5–16.6)	2.74 (0.4–16.3)	2.61 (0.4–16.6)
Eculizumab dose administered (mg)				
Median (min–max)	NA	900.0 (900–1,200)	900.0 (900–1,500)	900.0 (900–1,500)
Ravulizumab dose administered (mg)				
Median (min–max)	NA	3,300.0 (3,000–3,600)	3,300.0 (3,000–3,600)	3,300.0 (3,000–3,600)
Baseline Hb, n (%)				
Mean (SD)	8.155 (1.0871)	8.927 (0.7038)	8.850 (0.8949)	8.899 (0.7745)
Baseline LDH level (U/L)				
Mean (SD)	1,698.8 (683.33)	269.1 (70.14)	272.7 (84.80)	270.4 (75.34)
≤1.5 x ULN, n (%)	NR	58 (93.5)	32 (91.4)	90 (92.8)
>1.5 x ULN, n (%)	NR	4 (6.5)	3 (8.6)	7 (7.2)
Transfusion in the last 12 months prior to screening, n (%)				
Yes	27 (67.5)	37 (59.7)	22 (62.9)	59 (60.8)
Transfusion in the last 6 months prior to randomisation, n (%)				
Yes	28 (70.0)	35 (56.5)	21 (60.0)	56 (57.7)
Number of transfusions in the last 6 months prior to study treatment				

	APPOINT-PNH	APPLY-PNH		
	Iptacopan 200 mg BD N=40	Iptacopan 200 mg BD N=62	C5 inhibitor N=35	Overall N=97
<2	19 (47.5)	38 (61.3)	21 (60.0)	59 (60.8)
≥2	21 (52.5)	24 (38.7)	14 (40.0)	38 (39.2)
Number of transfusions in the last 6 months prior to study treatment among patients who had a transfusion				
N	28	35	21	56
Mean (SD)	3.1 (2.09)	3.1 (2.58)	4.0 (4.34)	3.4 (3.34)
Median (min–max)	2.0 (1–8)	2.0 (1–13)	2.0 (1–19)	2.0 (1–19)
Platelets (10^9/L)				
Mean (SD)	159.4 (61.09)	160.2 (63.83)	147.3 (77.01)	155.6 (68.77)
Absolute reticulocyte counts (10^9/L)				
Mean (SD)	154.33 (63.666)	193.22 (83.637)	190.59 (80.922)	192.27 (82.254)
Baseline FACIT-Fatigue total score				
Mean (SD)	32.78 (10.170)	34.7 (9.82)	30.8 (11.45)	33.4 (10.52)
Median (min–max)	34.25 (13.0–50.5)	34.8 (11–52)	31.5 (10–50)	33.0 (10–52)
Total PNH RBC clone size (%)†				
Mean (SD)	42.706 (21.2276)	64.645 (27.4543)	57.391 (29.7258)	62.028 (28.3576)
History of MAVE				
Yes	5 (12.5)	12 (19.4)	10 (28.6)	22 (22.7)
History of aplastic anaemia				
Yes	16 (40.0)	9 (14.5)	5 (14.3)	14 (14.4)

Source: Novartis, Data on file, APPOINT-PNH CSR, Table 10.6, Table 14.1-3.2 (1); Novartis, Data on file, APPLY-PNH Supplementary Report, Table 3-1, Table 3-2 (2)
Updated values to original company evidence submission underlined and in red font.
†Total PNH clone size is calculated as sum of percentages of positive RBC of Type II and Type III.
Abbreviations: BD, twice daily; CSR, clinical study report; FACIT, Functional Assessment of Chronic Illness Therapy; Hb, haemoglobin; LDH, lactate dehydrogenase; NA, not applicable; NR, not reported; SD, standard deviation.

B.2.6 Clinical effectiveness results of the relevant studies – APPLY-PNH

Table 2: APPLY-PNH: Summary of changes in primary and secondary endpoints (24-week analysis) due to APPLY-PNH data changes

Endpoint		Iptacopan (N=62)	C5 inhibitor (N=35)	Iptacopan vs C5 inhibitor treatment effect (95% CI) adjusted for covariates	Unadjusted two–sided p–value
Primary endpoints					
		Number of patients meeting criterion[#] Marginal proportion		**Difference between % responding[†]**	
≥2 g/dL increase in Hb from baseline[‡] in the absence of RBC transfusions[¶]	Original values	51/60 82.3%	0/35 2.0%	80.3 (71.3, 87.6)	<0.0001
	Updated values	51/60 82.3%	0/35 2.0%	80.2 (71.2, 87.6)	<0.0001
Hb ≥12 g/dL[‡] in the absence of RBC transfusions[¶]	Original values	42/60 68.8%	0/35 1.8%	67.0 (56.3, 76.9)	<0.0001
	Updated values	42/60 68.8%	0/35 1.8%	67.0 (56.4, 76.9)	<0.0001
Secondary endpoints					
Transfusion avoidance[¶]	Original values	60/62 96.4%	14/35 26.1%	70.3 (52.6, 84.9)	<0.0001
	Updated values	59/62 94.8%	14/35 25.9%	68.9 (51.4, 83.9)	<0.0001
		Mean	**Mean**	**Difference between means**	
Change from baseline in Hb (g/dL)[‡]	Original values	3.59	–0.04	3.63 (3.18, 4.08)	<0.0001
	Updated values	3.60	–0.06	3.66 (3.20, 4.12)	<0.0001
Change from baseline in FACIT–Fatigue scores[‡]	Original values	8.6	0.3	8.3 (5.3, 11.3)	<0.0001
	Updated values	No change			
Change from baseline in absolute reticulocyte counts (10^9/L)[‡]	Original values	–115.9	0.37	–116.3 (–132.2, –100.4)	<0.0001
	Updated values	–115.8	0.34	–116.2 (–132.0, –100.3)	<0.0001

Endpoint		Iptacopan (N=62)	C5 inhibitor (N=35)	Iptacopan vs C5 inhibitor treatment effect (95% CI) adjusted for covariates	Unadjusted two–sided p–value
		Geometric mean	**Geometric mean**	**Ratio of geometric means**	
Ratio to baseline in LDH (U/L)‡	Original values	0.96	0.98	0.99 (0.89, 1.10)	0.8345
	Updated values	0.96	0.98	0.99 (0.89, 1.10)	0.8361
		Number of patients with an event	**Number of patients with an event**	**Annualised rate ratio**	
Clinical BTH§	Original values	2	6	0.10 (0.02, 0.61)	0.0118
	Updated values	No change			
MAVEs§	Original values	1	0	Not estimable	0.3173
	Updated values	No change			

Source: Novartis, Data on file, APPLY-PNH Supplementary Report, Table 3-3, Table 3-4, Table 3-6, Table 3-8 (2)
Updated values to original company evidence submission underlined and in red font.
†Model-based estimate; ‡assessed between Day 126–168; ¶ between Day 14–168; § between Day 1–168; # among patients with evaluable/non-missing data.
Abbreviations: BTH, breakthrough haemolysis; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy – Fatigue; FAS, full analysis set; N, number of patients in the FAS; Hb, haemoglobin; LDH, lactate dehydrogenase; MAVE, major adverse vascular event; RBC, red blood cells.

Primary endpoints: Haematological response

Table 3: APPLY-PNH: Responder analysis of Hb between Day 126 and Day 168 in the absence of RBC transfusions between Day 14 and Day 168 (FAS) [Update to Document B, Table 13]

Responder criterion	n/M	Marginal proportion (95% CI)†	Diff. in marginal proportion (95% CI)†	Ratio of marginal proportion (95% CI)†	Unadjusted for multiplicity Two-sided p-value‡
Increase in Hb levels ≥2g/dL¶ from baseline without requiring RBC transfusions§					
Iptacopan 200 mg BD N=62	51/60	82.3 (73.4, 90.2)	80.2 (71.2, 87.6)	40.20 (20.73, 74.82)	<0.0001
C5 inhibitor N=35	0/35	2.0 (1.1, 4.0)	–	–	–
Hb levels ≥12 g/dL¶ without requiring RBC transfusions§					
Iptacopan 200 mg BD N=62	42/60	68.8 (58.4, 78.9)	67.0 (56.4, 76.9)	38.22 (16.87, 78.63)	<0.0001
C5 inhibitor N=35	0/35	1.8 (0.9, 4.0)	–	–	–

Source: Novartis, Data on file, APPLY-PNH Supplementary Report, Table 3-4 (2)
Updated values to original company evidence submission underlined and in red font.
†Logistic regression model using Firth correction with common intercept and randomization strata, sex, indicator variable of age ≥45 years, indicator variable of baseline Hb ≥9 g/dL as factors. The 95% CI is computed using bootstrap. ‡Logistic regression model using Firth correction with randomisation strata, sex, indicator variable of age ≥45 years, indicator variable of baseline Hb ≥9 g/dL as factors. ¶Between Day 126 and 168 (≥ 3 out of 4 scheduled measurements); §Between Day 14 and Day 168. Requiring RBC transfusions refers to any patient receiving transfusions or meeting protocol defined criteria for transfusion.
Abbreviations: BD, twice daily; CI, confidence interval; FAS, full analysis set; Hb, haemoglobin; M, evaluable patients; n, the number of patients who responded based on non-missing data; RBC, red blood cell.

Table 4: APPLY-PNH: Summary of primary and sensitivity analyses for the primary endpoints – analysis of Hb between Day 126 and Day 168 in the absence of RBC transfusions between Day 14 and Day 168 (FAS) [Update to Document B, Table 14]

Analysis description	Iptacopan 200 mg BD vs C5 inhibitor Difference between % achieving endpoint (95% CI)	Unadjusted two-sided p-value
Increase in Hb levels ≥2g/dL† from baseline without requiring RBC transfusions‡		
Primary analysis	80.2 (71.2, 87.6)	<0.0001
Tipping point analysis • Imputed Hb values were lowered by a value delta (2 g/dL in the iptacopan group)¶	76.8 (66.9, 85.4)	NR
Analysis including local lab data • If central lab data missing, local laboratory data was included	80.3 (71.2, 87.6)	<0.0001
Cochran-Mantel-Haenszel • Hypothesis testing using a CMH test	NA	<0.0001
Post-hoc sensitivity analysis • With MI Hb between >7 and ≤9 g/dL were considered by default as not having signs and/or symptoms and therefore not meeting the criteria for transfusion	80.3 (71.3, 87.6)	<0.0001
Post-hoc sensitivity analysis • Determining transfusion avoidance without imputation	80.3 (71.3, 87.6)	<0.0001
Hb levels ≥12 g/dL† without requiring RBC transfusions‡		
Primary analysis	67.0 (56.4, 76.9)	<0.0001
Tipping point analysis • Imputed Hb values were lowered by a value delta (2 g/dL in the iptacopan group)¶	64.1 (52.9, 74.0)	NR
Analysis including local labs • If central lab data missing, local laboratory data was included	67.0 (56.4, 76.8)	<0.0001
Cochran-Mantel-Haenszel • Hypothesis testing using a CMH test	NA	<0.0001
Post-hoc sensitivity analysis • With MI Hb between >7 and ≤9 g/dL were considered by default as not having signs and/or symptoms and therefore not meeting the criteria for transfusion	67.0 (56.4, 76.9)	<0.0001
Post-hoc sensitivity analysis • Determining transfusion avoidance without imputation	67.0 (56.4, 76.9)	<0.0001

Source: Novartis, Data on file, APPLY-PNH Supplementary Report, Table 3-5 (2)
Updated values to original company evidence submission underlined and in red font.
†Between Day 126 and 168 (≥3 out of 4 scheduled measurements); ‡Between Day 14 and Day 168. Requiring RBC transfusion refers to any patient receiving transfusions or meeting protocol defined criteria for transfusion; ¶Missing Hb values in each treatment group were imputed as for the primary analysis but an adjustment for the iptacopan group was applied to the imputed values. Missing haemoglobin values were imputed and missing values in the iptacopan arm were decreased by a value delta. Delta ranged from 0 g/dL (primary analysis) to 2 g/dL (considered clinically meaningful change).

Abbreviations: CI, confidence interval; CMH, Cochran Mantel Haenszel; CSR, clinical study report; Hb, haemoglobin; FAS, full analysis set; MI, multiple imputation; NA, not applicable; NR, not reported; RBC, red blood cell.

Revised subgroup analyses of the primary endpoints of APPLY-PNH are presented in an updated Appendix E provided with this addendum.

Secondary endpoints

Transfusion avoidance

Table 5: APPLY-PNH: Transfusion avoidance between Day 14 and Day 168 (FAS) [Update to Document B, Table 15]

	Iptacopan 200 mg BD N=62	C5 inhibitor N=35
n/M	59/62	14/35
Marginal proportion (95% CI)†	94.8 (88.1, 100.0)	25.9 (11.6, 42.4)
Difference in marginal proportion (95% CI)†	68.9 (51.4, 83.9)	–
Ratio of marginal proportion (95% CI)†	3.70 (2.23, 8.17)	–
Unadjusted for multiplicity OR (95% CI)‡	108.41 (17.25, 681.24)	–
Unadjusted for multiplicity p-value‡	<0.0001	–

Source: Novartis, Data on file, APPLY-PNH Supplementary Report, Table 3-6 (2)
Updated values to original company evidence submission underlined and in red font.
†Logistic regression model with common intercept and randomisation strata, sex, indicator variable of age ≥45 years, indicator variable of baseline Hb ≥9 g/dL as factors. The 95% CI is computed using bootstrap. ‡Conditional logistic regression model with randomisation strata, sex, indicator variable of age ≥45 years, indicator variable of baseline Hb ≥9 g/dL as factors.
Abbreviations: BD, twice daily; CI, confidence interval; CSR, clinical study report; FAS, full analysis set; Hb, haemoglobin; M, The number of patients in the treatment group with response variable defined based on non-missing data (evaluable patients); n, the number of patients who did not receive transfusions nor meet protocol defined criteria between Day 14 and Day 168; OR, odds ratio.

Change from baseline in Hb levels (g/dL)

Table 6: APPLY-PNH: Change from baseline in Hb levels (g/dL) (assessed between Day 126 and Day 168) (FAS) [Update for Document B, Section B.2.6.2.2.2 text on p. 60]

	Iptacopan 200 mg BD N=62	C5 inhibitor N=35
n	62	29
Adjusted mean (95% CI)	3.60 (3.33, 3.88)	–0.06 (–0.45, 0.34)
Adjusted mean difference (95% CI)	3.66 (3.20, 4.12)	–
Unadjusted for multiplicity p-value‡	p<0.0001	–

Source: Novartis, Data on file, APPLY-PNH Supplementary Report, Table 3-8 (2)
Updated values to original company evidence submission underlined and in red font.
Change from baseline is analysed using a MMRM which includes randomisation strata, age indicator variable of age ≥45 years, sex, treatment, visit, baseline Hb, timepoint as fixed effects, treatment*timepoint and timepoint*baseline Hb as interaction terms. The correlations between visits within patients were modelled using an unstructured covariance matrix.
Abbreviations: BD, twice daily; CI, confidence interval; FAS, full analysis set; Hb, haemoglobin; MMRM, mixed model of repeated measures; n, number of patients with values non-missing/ not imputed as per the intercurrent event handling strategy.

Change from baseline in absolute reticulocyte counts (10^9/L)

Table 7: APPLY-PNH: Change from baseline in absolute reticulocyte counts (10^9/L) (assessed between Day 126 and Day 168) (FAS) [Update for Document B, Section B.2.6.2.2.4 text on p. 61]

	Iptacopan 200 mg BD N=62	C5 inhibitor N=35
n	62	35
Adjusted mean (95% CI)	–115.81 (–126.40, –105.23)	0.34 (–13.04, 13.72)
Adjusted mean difference (95% CI)	–116.15 (–132.04, –100.26)	–
Unadjusted for multiplicity p-value‡	p<0.0001	–

Source: Novartis, Data on file, APPLY-PNH Supplementary Report, Table 3-11 (2)
Updated values to original company evidence submission underlined and in red font.
Change from baseline is analysed using a MMRM which includes randomisation strata, age indicator variable of age ≥45 years, sex, treatment, visit, baseline reticulocyte counts, timepoint as fixed effects, treatment*timepoint and timepoint*baseline reticulocyte counts as interaction terms. The correlations between visits within patients were modelled using an unstructured covariance matrix.
Abbreviations: BD, twice daily; CI, confidence interval; FAS, full analysis set; MMRM, mixed model of repeated measures.

Change from baseline in LDH levels (U/L)

Table 8: APPLY-PNH: Log-transformed LDH (U/L) ratio to baseline (assessed between Day 126 and Day 168)† (FAS) [Update to Document B, Table 17]

	Iptacopan 200 mg BD N=62	C5 inhibitor N=35
n	62	35
Geometric adjusted mean (95%CI)	0.96 (0.90, 1.03)	0.98 (0.89, 1.07)
Geometric mean ratio (95% CI)	0.99 (0.89, 1.10)	–
% Reduction (95% CI)	1.14 (–10.19, 11.31)	
Two-sided p-value	0.8361	

Source: Novartis, Data on file, APPLY-PNH Supplementary Report, Table 3-13 (2)
Updated values to original company evidence submission underlined and in red font.
†Log transformed ratio to baseline is analysed using a mixed model of repeated measures which was stratified by randomisation strata, and includes age indicator variable of age >=45 years, sex, treatment, visit, log-transformed baseline LDH level, timepoint as fixed effects, treatment*timepoint and timepoint*log- transformed baseline LDH level as interaction terms. The correlations between visits within patients were modelled using an unstructured covariance matrix. The log transformation used refers to the natural log (base of e). Results are back-transformed and expressed as geometric means.
Abbreviations: BD, twice daily; CI, confidence interval; CSR, clinical study report; FAS, full analysis set; LDH, lactate dehydrogenase.

B.2.9 Indirect and mixed treatment comparisons

Complement inhibitor-experienced population

Results

Table 9: Comparison of baseline characteristic between iptacopan (APPLY-PNH) and pegcetacoplan (PEGASUS): ITT population (N= 62), and analysis set (N = 54) before and after weighting [Update to Document B, Table 25]

Characteristics	Pegcetacoplan (PEGASUS)	Iptacopan (APPLY-PNH)					
		ITT		ITC analysis dataset† Unweighted		ITC analysis dataset† Weighted‡	
	N=41	N=62	SMDs	N=54	SMDs	ESS=15	SMDs
Hb, g/dL: mean (SD)¶	8.7 (1.1)	8.9 (0.7)	0.186	8.8 (0.7)	0.146	8.7 (1.1)	0.000
LDH (U/L): mean (SD)	257.5 (97.6)	269.1 (70.1)	0.137	263.5 (71.5)	0.070	257.5 (73.5)	0.000
Age, years: mean (SD)	50.2 (16.3)	51.7 (16.9)	0.091	51.7 (16.6)	0.092	50.2 (16.5)	0.001
Screening reticulocytes (10^9/L): mean (SD)	217.5 (75.0)	204.0 (84.1)	0.169	210.7 (84.1)	0.086	217.6 (76.3)	0.002
Sex female: n (%)	27 (65.9)	43 (69.4)	0.075	37 (68.5)	0.057	66%	0.003
Transfusion free, 12 months prior: n (%)	10 (24.4)	25 (40.3)	0.346	22 (40.7)	0.354	24%	0.008
Duration of C5 inhibitor, years: mean (SD)	5.5 (3.9)	3.8 (3.6)	0.454	3.9 (3.7)	0.430	5.4 (4.0)	0.018
Screening platelet count (10^9/L): mean (SD)	166.6 (98.3)	160.9 (55.9)	0.071	167.4 (55.1)	0.010	152.2 (66.2)	0.172
FACIT-F score: mean (SD)	32.2 (11.4)	34.7 (9.8)	0.234	35.1 (10.1)	0.274	35.1 (10.8)	0.257
Time since diagnosis, years: mean (SD)	8.7 (7.4)	11.9 (9.8)	0.362	11.9 (9.6)	0.372	10.9 (6.9)	0.309
BMI (kg/m^2): mean (SD)	26.7 (4.3)	24.9 (5.0)	0.385	24.5 (4.3)	0.523	25.2 (4.4)	0.344
History of aplastic anaemia: n (%)	11 (26.8)	9 (14.5)	0.308	8 (14.8)	0.299	12.5%	0.368
Race, white: n (%)	24 (58.5)	48 (77.4)	0.413	42 (77.8)	0.422	34.8 (84.5)	0.602
≥4 transfusions of pRBCs, 12 months prior: n (%)	21 (51.2)	16 (25.8)	0.541	15 (27.8)	0.494	20.2%	0.684
History of MAVE: n (%)	NR	12 (19.4)	NA	11 (20.4)	NA	14.6%	NA

Updated values to original company evidence submission underlined and in red font.
Green = SMD ≤0.1 (small difference); Yellow = 0.1 > SMD ≤ 0.2 (moderate difference); Red = SMD > 0.2 (substantial difference). These conservative thresholds were informed by Austin 2009 and 2011 (104, 105).
†8 patients removed from the APPLY-PNH iptacopan dataset, who were not eligible for PEGASUS based on criteria for reticulocyte count, platelet count and BMI; ‡Reweights APPLY-PNH data to balance with PEGASUS on baseline Hb per PEGASUS definition, sex, proportion transfusion-free within 12 months prior to baseline, reticulocyte count at screening, baseline LDH, and age; ¶Baseline Hb was calculated as per PEGASUS definition, as an average of values recorded prior to run-in dosing including local and central laboratory values.
Abbreviations: BMI, body mass index; ESS, effective sample size; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; ITT, intent-to-treat; LDH, lactate dehydrogenase; MAVE, major adverse vascular event; NA, not applicable; NR, not reported; pRBC packed red blood cell; SD, standard deviation; SMD, standardised mean difference.

Table 10: Overview of results for iptacopan vs pegcetacoplan in the complement inhibitor-experienced population: ITC using APPLY-PNH vs PEGASUS [Update to Document B, Table 26]

	CFB in Hb, excluding post-transfusion data (95% CI)	CFB in Hb, including post-transfusion data (95% CI)	Transfusion avoidance
Iptacopan (ESS=15†)	3.38 (2.99, 3.77)	3.42 (3.02, 3.82)	98.7%
Pegcetacoplan (N=41)	2.37 (1.66, 3.08)	2.66 (2.17, 3.15)	85.4%
Eculizumab/ ravulizumab APPLY-PNH (ESS=7†)	[redacted]	[redacted]	[redacted]
Eculizumab PEGASUS (N=39)	*–1.47 (–2.78, –0.16)*	*–0.03 (–0.54, 0.48)*	*15.4%*
Unanchored ITC results			
Iptacopan vs pegcetacoplan	**MD 1.01 (95% CI 0.21, 1.82) p=0.014**	**MD 0.76 (95% CI 0.13, 1.39) p=0.018**	**OR 12.71 (95% CI 1.87, 86.22) p=0.009**
Anchored ITC results			
Iptacopan vs pegcetacoplan	MD – [redacted] (95% CI – [redacted]) p=0.873	MD [redacted] (95% CI – [redacted]) p=0.141	OR [redacted] (95% CI [redacted]) p=0.392

Updated values to original company evidence submission underlined and in red font.
MD >0 implies higher value for iptacopan vs pegcetacoplan; OR >1 implies higher odds for iptacopan vs pegcetacoplan; **Bold** values indicate statistical significance and corresponds to a two-tailed p-value <0.05.
†APPLY-PNH results using PEGASUS endpoint definitions and population adjusted, reweighted to balance with PEGASUS on baseline Hb (mean and SD), proportion of females, proportion transfusion-free within 12 months prior, screening reticulocyte (mean and SD), baseline LDH (mean and SD), and age (mean and SD).
Abbreviations: CFB, change from baseline; CI, confidence interval; ESS, effective sample size; Hb, haemoglobin; ITC, indirect treatment comparison; LDH, lactate dehydrogenase; MD, mean difference (in CFB); OR, odds ratio.

Addendum to B.3 Cost effectiveness

B.3.3 Clinical parameters and variables

Patient characteristics

Table 11: Distribution of patients at baseline [Update to Document B, Table 41]

Health state	Complement inhibitor-naïve patients	Complement inhibitor-experienced patients
No Transfusion and No Anaemia	0%	0%
No Transfusion and Anaemia	75.0%	74.2%
Transfusion	25.0%	25.8%

Updated values to original company evidence submission underlined and in red font.

Transition probabilities applied in the analysis

Complement inhibitor-naïve population

Table 12: Health state transition probabilities for the complement inhibitor-naïve population [Update to Document B, Table 42]

From	To		
	No Transfusion and No Anaemia	No Transfusion and Anaemia	Transfusion
Iptacopan			
No Transfusion and No Anaemia	99.1%	0.9%	0.0%
No Transfusion and Anaemia	49.4%	48.2%	2.4%
Transfusion	18.0%	80.1%	1.9%
C5 inhibitors (eculizumab/ravulizumab)			
No Transfusion and No Anaemia	94.1%	4.5%	1.4%
No Transfusion and Anaemia	9.6%	76.1%	14.3%
Transfusion	2.5%	43.3%	54.2%

Updated values to original company evidence submission underlined and in red font.
Anaemia defined as Hb <10.5 g/dL.
Abbreviations: Hb, haemoglobin.

Transition probabilities used in scenario analyses are presented in an updated version of Appendix P.

Complement inhibitor-experienced population

Table 13: Health state transition probabilities for the complement inhibitor-experienced population [Update to Document B, Table 43]

From	To		
	No Transfusion and No Anaemia	No Transfusion and Anaemia	Transfusion
Iptacopan			
No Transfusion and No Anaemia	97.9%	2.0%	0.0%
No Transfusion and Anaemia	51.0%	44.3%	4.7%
Transfusion	50.7%	32.4%	17.0%
C5 inhibitors (eculizumab/ravulizumab)			
No Transfusion and No Anaemia	45.5%	47.9%	6.6%
No Transfusion and Anaemia	7.7%	65.7%	26.6%
Transfusion	6.2%	33.6%	60.2%
Pegcetacoplan			
No Transfusion and No Anaemia	96.6%	3.1%	0.3%
No Transfusion and Anaemia	49.1%	43.7%	7.2%
Transfusion	61.2%	26.6%	12.2%

Updated values to original company evidence submission underlined and in red font.
Anaemia defined as Hb <10.5 g/dL.
Abbreviations: Hb, haemoglobin.

Transition probabilities used in scenario analyses are presented in an updated version of Appendix P.

B.3.4 Measurement and valuation of health effects

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

Table 14: Multivariable regression results for selected utility model [Update to Document B, Table 47]

Covariate	Point Estimate	SE	Lower 95% CI	Upper 95% CI
Intercept	0.790	0.028	0.735	0.845
Health state (reference: Transfusion)				
No transfusion and Anaemia	0.007	0.014	–0.021	0.035
No transfusion and No Anaemia	0.029	0.016	–0.003	0.061
Treatment (iptacopan vs C5 inhibitors)	0.071	0.022	0.027	0.114
Baseline utility	0.487	0.038	0.412	0.562
Study (APPLY–PNH vs APPOINT-PNH)	–0.019	0.018	–0.055	0.017
Follow–up visit				
Baseline	–0.076	0.016	–0.107	–0.045
Day 14	–0.026	0.014	–0.054	0.002
Day 42	–0.013	0.013	–0.039	0.013
Day 84	–0.003	0.013	–0.029	0.023
Day 126	–0.013	0.013	–0.039	0.014
Day 140	–0.019	0.013	–0.045	0.007
Day 154	–0.010	0.013	–0.036	0.016

Updated values to original company evidence submission underlined and in red font.
Anaemia defined as Hb <10.5 g/dL.
Abbreviations: CI, confidence interval; Hb, haemoglobin; SE, standard error.

Table 15: Health state utility values [Update to Document B, Table 48]

Health State	Iptacopan		C5 inhibitors	
	Mean	SE	Mean	SE
No Transfusion and No Anaemia	0.879	0.004	0.775	0.056
No Transfusion and Anaemia	0.822	0.008	0.743	0.015
Transfusion	0.791	0.015	0.695	0.021

Updated values to original company evidence submission underlined and in red font.
Note: Iptacopan health state utility values were also applied to pegcetacoplan. Anaemia defined as Hb <10.5 g/dL.
Abbreviations: Hb, haemoglobin; SE, standard error.

The utility values used in scenario analyses are presented in an updated version of Appendix P.

Table 16: Summary of utility values for cost-effectiveness analysis [Update to Document B, Table 50]

State	Utility value, mean (SE)	95% CI	Reference in submission (section and page number)	Justification
Health state utility values for iptacopan and pegcetacoplan				
No Transfusion and No Anaemia	0.879	0.871, 0.887	Section B.3.4.5, page 122	Based on trial data from APPOINT-PNH and APPLY-PNH. Pegcetacoplan has been assumed equivalent to iptacopan.
No Transfusion and Anaemia	0.822	0.807, 0.838		
Transfusion	0.791	0.761, 0.821		
Health state utility values for C5 inhibitors				
No Transfusion and No Anaemia	0.775	0.665, 0.885	Section B.3.4.5, page 122	Based on trial data from APPOINT-PNH and APPLY-PNH.
No Transfusion and Anaemia	0.743	0.714, 0.773		
Transfusion	0.695	0.654, 0.736		
Disutility for eculizumab administration (scenario analysis)				
Disutility	–0.025	NA	Section B.3.4.5.1, page 124	In line with previous appraisals (19, 20)
BTH disutility				
BTH	–0.11	–0.188, –0.041	Section B.3.4.5.2, page 125	In line with TA698 (19)

Updated values to original company evidence submission underlined and in red font.
Abbreviations: AE, adverse effect; BTH, breakthrough haemolysis; CI, confidence interval; NA, not applicable; SE, standard error.

B.3.6 Severity

Table 17: QALY shortfall in the complement inhibitor-naïve population [Update to Document B, Table 62]

Treatment	Expected general population QALYs	Total QALYs in the model	Absolute shortfall	Proportional shortfall
Eculizumab	17.50	15.52	1.98	0.11
Ravulizumab		15.53	1.97	0.11

Updated values to original company evidence submission underlined and in red font.
Abbreviations: QALY, quality-adjusted life year.

Table 18: QALY shortfall in the complement inhibitor-experienced population [Update to Document B, Table 63]

Treatment	Expected general population QALYs	Total QALYs in the model	Absolute shortfall	Proportional shortfall
Eculizumab	14.81	12.68	2.13	0.14
Ravulizumab		12.68	2.13	0.14
Pegcetacoplan		13.35	1.46	0.10

Updated values to original company evidence submission underlined and in red font.
Abbreviations: QALY, quality-adjusted life year.

B.3.8 Summary of base-case analysis inputs and assumptions

Table 19: Summary of variables applied in the economic model [Update to Document B, Table 64]

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
General parameters			
Discount rate, costs	3.5%	Fixed	B.3.2.3
Discount rate, outcomes	3.5%	Fixed	
Time horizon	Lifetime	Fixed	
Baseline age, complement inhibitor-naïve	42.1	Fixed	B.3.3.1
% male, complement inhibitor-naïve	57.5%	Fixed	
Body weight, complement inhibitor-naïve	70.1	Fixed	
Baseline age, complement inhibitor-experienced	51.0	Fixed	
% male, complement inhibitor-experienced	30.9%	Fixed	
Body weight, complement inhibitor-experienced	71.6	Fixed	
Transition probabilities			
Iptacopan, complement inhibitor-naïve	Multinomial logistic regression using APPOINT-PNH data	Dirichlet	Appendix P
Eculizumab, complement inhibitor-naïve	Multinomial logistic regression using APPEX data		
Ravulizumab, complement inhibitor-naïve			

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
	matched to APPOINT-PNH		
Iptacopan, complement inhibitor-experienced	Multinomial logistic regression using APPLY-PNH data matched to PEGASUS	Dirichlet	Table 16
Eculizumab, complement inhibitor-experienced			
Ravulizumab, complement inhibitor-experienced			
Pegcetacoplan, complement inhibitor-experienced	Multinomial logistic regression using PEGASUS data as reported in Hakimi et al (114)		
Discontinuation			
Iptacopan, complement inhibitor-naïve	3.43%	Beta distribution	B.3.3.3
Eculizumab, complement inhibitor-naïve	30%		
Ravulizumab, complement inhibitor-naïve	30%		
Iptacopan, complement inhibitor-experienced	3.43%		
Pegcetacoplan, complement inhibitor-experienced	16.13%		
BTH, annual rate			
Iptacopan, complement inhibitor-naïve	0.00	Log-normal distribution	B.3.3.4
Eculizumab, complement inhibitor-naïve	0.21		
Ravulizumab, complement inhibitor-naïve	0.08		
Iptacopan, complement inhibitor-experienced	0.07		
Eculizumab, complement inhibitor-experienced	0.67		
Ravulizumab, complement inhibitor-experienced	0.67		
Pegcetacoplan, complement inhibitor-experienced	0.13		
Mortality			
Mortality	England and Wales lifetables	Fixed	B.3.3.5
Utility values			

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
No transfusion, no anaemia, iptacopan and pegcetacoplan	0.879	Beta distribution	B.3.4.5
No transfusion, anaemia, iptacopan and pegcetacoplan	0.822		
Transfusion, iptacopan and pegcetacoplan	0.791		
No transfusion, no anaemia, C5 inhibitors	0.775		
No transfusion, anaemia, C5 inhibitors	0.743		
Transfusion, C5 inhibitors	0.695		
Disutility for BTH	–0.11	Normal distribution	
Treatment costs			
Iptacopan (PAS price)	£[redacted]	Fixed	B.3.5.1.1
Eculizumab	£3,150.00		
Ravulizumab	£4,533.00		
Pegcetacoplan	£3,100.00		
Administration costs			
Eculizumab	£99.92	Fixed	B.3.5.1.2
Ravulizumab	£99.92		
Pegcetacoplan	£74.67		
Other costs			
Treatment-related resource use	Table 29, Table 30, Table 31	Fixed	B.3.5.2.1
Health state resource use	Table 32, Table 33, Table 34	Fixed	B.3.5.2.2
Cost of BTH treatment	£9,450	Fixed	B.3.5.3
Proportion of BTH events treated	10%	Fixed	

Updated values to original company evidence submission underlined and in red font.
Abbreviations: BTH, breakthrough haemolysis; C5, complement component 5; CI, confidence interval; PAS, patient access scheme; SC, subcutaneous.

B.3.9 Base-case results

Table 20: Base-case results, complement inhibitor-naïve population (iptacopan PAS price) [Update to Document B, Table 66]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
Original submission								
Iptacopan (PAS price)	[redacted]	21.05	16.60	–	–	–	–	–
Eculizumab	[redacted]	21.05	15.54	[redacted]	0.00	–1.06	[redacted]	[redacted]
Ravulizumab	[redacted]	21.05	15.55	[redacted]	0.00	–1.05	[redacted]	[redacted]
With corrected data								
Iptacopan (PAS price)	[redacted]	21.05	16.59	–	–	–	–	–
Eculizumab	[redacted]	21.05	15.52	[redacted]	0.00	-1.07	[redacted]	[redacted]
Ravulizumab	[redacted]	21.05	15.53	[redacted]	0.00	-1.06	[redacted]	[redacted]

Updated values to original company evidence submission underlined and in red font.
Analysis uses PAS price for iptacopan and list price for comparators.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 21: Net health benefit, complement inhibitor-naïve population (iptacopan PAS price) [Update to Document B, Table 67]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Original submission						
Iptacopan (PAS price)	[redacted]	16.60	–	–	–	–
Eculizumab	[redacted]	15.54	[redacted]	–1.06	[redacted]	[redacted]
Ravulizumab	[redacted]	15.55	[redacted]	–1.05	[redacted]	[redacted]
With corrected data						
Iptacopan (PAS price)	[redacted]	16.59	–	–	–	–
Eculizumab	[redacted]	15.52	[redacted]	-1.07	[redacted]	[redacted]
Ravulizumab	[redacted]	15.53	[redacted]	-1.06	[redacted]	[redacted]

Updated values to original company evidence submission underlined and in red font.
Analysis uses PAS price for iptacopan and list price for comparators.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 22: Base-case results, complement inhibitor-experienced population (iptacopan PAS price) [Update to Document B, Table 68]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
Original submission								
Eculizumab	[redacted]	18.89	12.69	–	–	–	–	–
Iptacopan (PAS price)	[redacted]	18.89	14.42	[redacted]	0.00	1.73	[redacted]	[redacted]
Ravulizumab	[redacted]	18.89	12.69	[redacted]	0.00	0.00	[redacted]	[redacted]
Pegcetacoplan	[redacted]	18.89	13.35	[redacted]	0.00	0.67	[redacted]	[redacted]
With corrected data								
Eculizumab	[redacted]	18.89	12.68	–	–	–	–	–
Iptacopan (PAS price)	[redacted]	18.89	14.42	[redacted]	0.00	1.74	[redacted]	[redacted]
Ravulizumab	[redacted]	18.89	12.68	[redacted]	0.00	0.00	[redacted]	[redacted]
Pegcetacoplan	[redacted]	18.89	13.35	[redacted]	0.00	0.67	[redacted]	[redacted]

Updated values to original company evidence submission underlined and in red font.
Analysis uses PAS price for iptacopan and list price for comparators.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 23: Net health benefit, complement inhibitor-experienced population (iptacopan PAS price) [Update to Document B, Table 69]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Original submission						
Eculizumab	[redacted]	12.69	–	–	–	–
Iptacopan (PAS price)	[redacted]	14.42	[redacted]	1.73	[redacted]	[redacted]
Ravulizumab	[redacted]	12.69	[redacted]	0.00	[redacted]	[redacted]
Pegcetacoplan	[redacted]	13.35	[redacted]	0.67	[redacted]	[redacted]
With corrected data						
Eculizumab	[redacted]	12.68	–	–	–	–
Iptacopan (PAS price)	[redacted]	14.42	[redacted]	1.74	[redacted]	[redacted]
Ravulizumab	[redacted]	12.68	[redacted]	0.00	[redacted]	[redacted]
Pegcetacoplan	[redacted]	13.35	[redacted]	0.67	[redacted]	[redacted]

Updated values to original company evidence submission underlined and in red font.
Analysis uses PAS price for iptacopan and list price for comparators.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; PAS, patient access scheme; QALY, quality-adjusted life year.

B.3.10 Exploring uncertainty

Probabilistic sensitivity analysis

Table 24: PSA results, complement inhibitor-naïve population (iptacopan PAS price) [Update to Document B, Table 70]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
Original submission						
Iptacopan (PAS price)	[redacted]	16.58	–	–	–	–
Eculizumab	[redacted]	15.54	[redacted]	-1.05	[redacted]	[redacted]
Ravulizumab	[redacted]	15.54	[redacted]	-1.04	[redacted]	[redacted]
With corrected data						
Iptacopan (PAS price)	[redacted]	16.56	–	–	–	–
Eculizumab	[redacted]	15.51	[redacted]	-1.05	[redacted]	[redacted]
Ravulizumab	[redacted]	15.51	[redacted]	-1.05	[redacted]	[redacted]

Updated values to original company evidence submission underlined and in red font.
Analysis uses PAS price for iptacopan and list price for comparators.
Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year

Table 25: PSA results, complement inhibitor-experienced population (iptacopan PAS price) [Update to Document B, Table 71]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
Original submission						
Eculizumab	[redacted]	12.69	–	–	–	–
Iptacopan (PAS price)	[redacted]	14.40	[redacted]	1.71	[redacted]	[redacted]
Ravulizumab	[redacted]	12.69	[redacted]	0.00	[redacted]	[redacted]
Pegcetacoplan	[redacted]	13.36	[redacted]	0.67	[redacted]	[redacted]
With corrected data						
Eculizumab	[redacted]	12.68	–	–	–	–
Iptacopan (PAS price)	[redacted]	14.40	[redacted]	1.72	[redacted]	[redacted]
Ravulizumab	[redacted]	12.68	[redacted]	0.00	[redacted]	[redacted]
Pegcetacoplan	[redacted]	13.35	[redacted]	0.67	[redacted]	[redacted]

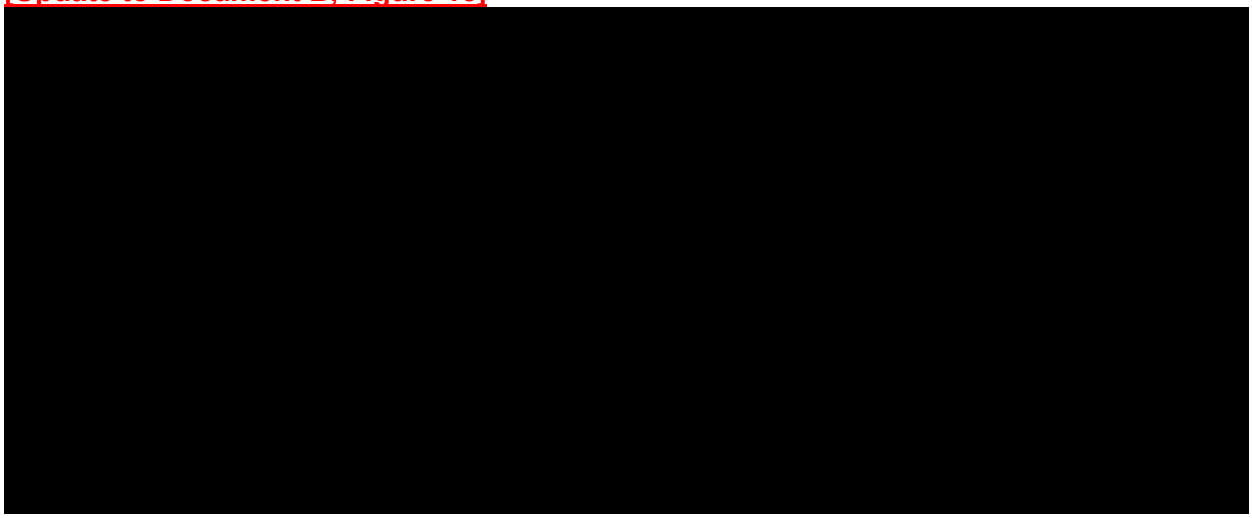
Updated values to original company evidence submission underlined and in red font.
Analysis uses PAS price for iptacopan and list price for comparators.
Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

Figure 1: Cost-effectiveness plane, complement inhibitor-naïve population [Update to Document B, Figure 13]

Abbreviation: QALY, quality-adjusted life year.

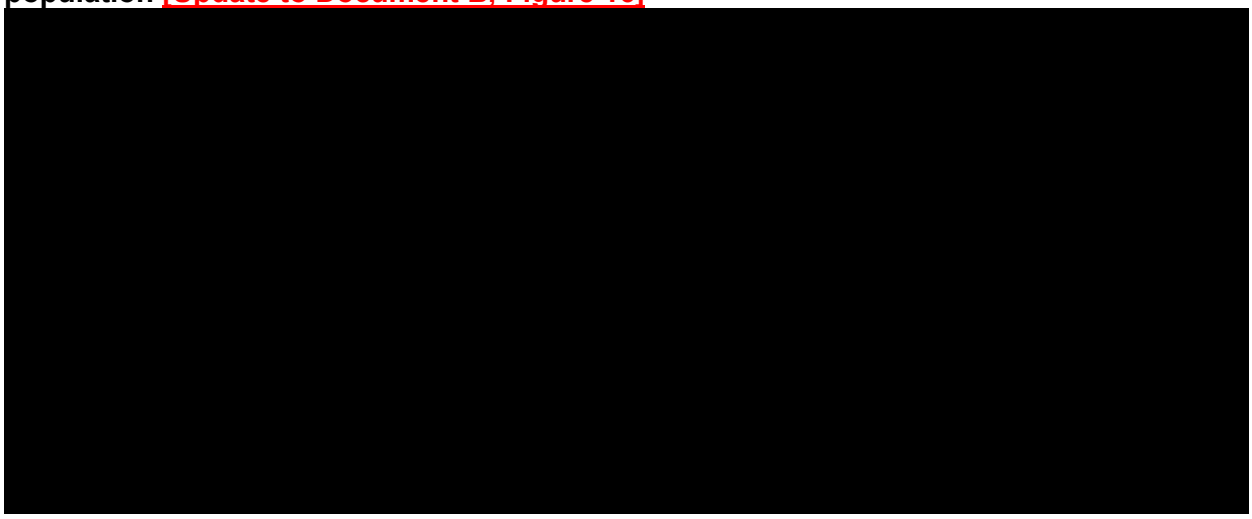
Figure 2: Cost-effectiveness acceptability curve, complement inhibitor-naïve population [Update to Document B, Figure 14]

Figure 3: Cost-effectiveness plane, complement inhibitor-experienced population [Update to Document B, Figure 15]



Abbreviation: QALY, quality-adjusted life year.

Figure 4: Cost-effectiveness acceptability curve, complement inhibitor-experienced population [Update to Document B, Figure 16]



Scenario analysis

Table 26: Scenario analyses for iptacopan in the complement inhibitor-naïve population (iptacopan PAS price) [Update to Document B, Table 73]

Scenario	Iptacopan vs eculizumab			Iptacopan vs ravulizumab		
	Inc. costs	Inc. QALYs	ICER	Inc. costs	Inc. QALYs	ICER
Original submission						
Base case	[redacted]	**1.06**	[redacted]	[redacted]	**1.05**	[redacted]
Definition of anaemia	[redacted]	1.07	[redacted]	[redacted]	1.06	[redacted]
No imputation for APPEX data	[redacted]	1.16	[redacted]	[redacted]	1.15	[redacted]
Unweighted transition probabilities	[redacted]	1.06	[redacted]	[redacted]	1.05	[redacted]
Comparator dosing	[redacted]	1.06	[redacted]	[redacted]	1.05	[redacted]
No discontinuation for any treatment	[redacted]	2.40	[redacted]	[redacted]	2.38	[redacted]
No discontinuation for iptacopan	[redacted]	1.93	[redacted]	[redacted]	1.92	[redacted]
Treatment independent utilities	[redacted]	0.48	[redacted]	[redacted]	0.44	[redacted]
EORTC QLQ-C30 utilities	[redacted]	1.06	[redacted]	[redacted]	1.05	[redacted]
No BTH cost	[redacted]	1.06	[redacted]	[redacted]	1.05	[redacted]
No chelation therapy or venesection	[redacted]	1.06	[redacted]	[redacted]	1.05	[redacted]
TA778 resource use	[redacted]	1.06	[redacted]	[redacted]	1.05	[redacted]
No discounting	[redacted]	1.52	[redacted]	[redacted]	1.50	[redacted]
With corrected data						
Base case	[redacted]	**1.07**	[redacted]	[redacted]	**1.06**	[redacted]
Definition of anaemia	[redacted]	1.11	[redacted]	[redacted]	1.10	[redacted]
No imputation for APPEX data	[redacted]	1.23	[redacted]	[redacted]	1.22	[redacted]

Unweighted transition probabilities	[redacted]	1.08	[redacted]	[redacted]	1.07	[redacted]
Comparator dosing	[redacted]	1.07	[redacted]	[redacted]	1.06	[redacted]
No discontinuation for any treatment	[redacted]	2.46	[redacted]	[redacted]	2.44	[redacted]
No discontinuation for iptacopan	[redacted]	1.96	[redacted]	[redacted]	1.95	[redacted]
Treatment independent utilities	[redacted]	0.44	[redacted]	[redacted]	0.43	[redacted]
EORTC QLQ-C30 utilities	[redacted]	1.08	[redacted]	[redacted]	1.07	[redacted]
No BTH cost	[redacted]	1.07	[redacted]	[redacted]	1.06	[redacted]
No chelation therapy or venesection	[redacted]	1.07	[redacted]	[redacted]	1.06	[redacted]
TA778 resource use	[redacted]	1.07	[redacted]	[redacted]	1.06	[redacted]
No discounting	[redacted]	1.52	[redacted]	[redacted]	1.51	[redacted]

Updated values to original company evidence submission underlined and in red font.
Analysis uses PAS price for iptacopan and list price for comparators.
Abbreviations: BTH, breakthrough haemolysis; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TA, technology appraisal.

Table 27: Scenario analyses for iptacopan in the complement inhibitor-experienced population (iptacopan PAS price) [Update to Document B, Table 74]

Scenario	Iptacopan vs eculizumab			Iptacopan vs ravulizumab			Iptacopan vs pegcetacoplan		
	Inc. costs	Inc. QALYs	ICER	Inc. costs	Inc. QALYs	ICER	Inc. costs	Inc. QALYs	ICER
Original submission									
Base case	[redacted]	**1.73**	[redacted]	[redacted]	**1.73**	[redacted]	[redacted]	**1.07**	[redacted]
Definition of anaemia	[redacted]	1.58	[redacted]	[redacted]	1.58	[redacted]	[redacted]	0.98	[redacted]
Unweighted transition probabilities	[redacted]	1.65	[redacted]	[redacted]	1.65	[redacted]	[redacted]	1.02	[redacted]
C5 inhibitor efficacy by treatment	[redacted]	1.50	[redacted]	[redacted]	2.11	[redacted]	[redacted]	1.30	[redacted]
C5 inhibitor efficacy from PEGASUS	[redacted]	1.84	[redacted]	[redacted]	1.84	[redacted]	[redacted]	1.13	[redacted]
Comparator dosing	[redacted]	1.73	[redacted]	[redacted]	1.73	[redacted]	[redacted]	1.07	[redacted]
No discontinuation	[redacted]	2.60	[redacted]	[redacted]	2.60	[redacted]	[redacted]	0.03	[redacted]
Treatment independent utilities	[redacted]	1.19	[redacted]	[redacted]	1.15	[redacted]	[redacted]	0.71	[redacted]
EORTC QLQ-C30 utilities	[redacted]	1.62	[redacted]	[redacted]	1.62	[redacted]	[redacted]	1.00	[redacted]
No BTH cost	[redacted]	1.73	[redacted]	[redacted]	1.73	[redacted]	[redacted]	1.07	[redacted]
No chelation therapy or venesection	[redacted]	1.73	[redacted]	[redacted]	1.73	[redacted]	[redacted]	1.07	[redacted]
TA778 resource utilisation	[redacted]	1.73	[redacted]	[redacted]	1.73	[redacted]	[redacted]	1.07	[redacted]
No discounting	[redacted]	2.59	[redacted]	[redacted]	2.59	[redacted]	[redacted]	1.80	[redacted]

With corrected data									
Base case	[redacted]	**1.74**	[redacted]	[redacted]	**1.74**	[redacted]	[redacted]	**1.07**	[redacted]
Definition of anaemia	[redacted]	1.58	[redacted]	[redacted]	1.58	[redacted]	[redacted]	0.98	[redacted]
Unweighted transition probabilities*	[redacted]	1.78	[redacted]	[redacted]	1.78	[redacted]	[redacted]	1.10	[redacted]
C5 inhibitor efficacy by treatment	[redacted]	1.50	[redacted]	[redacted]	2.12	[redacted]	[redacted]	1.30	[redacted]
C5 inhibitor efficacy from PEGASUS	[redacted]	1.84	[redacted]	[redacted]	1.84	[redacted]	[redacted]	1.13	[redacted]
Comparator dosing	[redacted]	1.74	[redacted]	[redacted]	1.74	[redacted]	[redacted]	1.07	[redacted]
No discontinuation	[redacted]	2.61	[redacted]	[redacted]	2.61	[redacted]	[redacted]	0.03	[redacted]
Treatment independent utilities	[redacted]	1.17	[redacted]	[redacted]	1.17	[redacted]	[redacted]	0.72	[redacted]
EORTC QLQ-C30 utilities	[redacted]	1.63	[redacted]	[redacted]	1.63	[redacted]	[redacted]	1.01	[redacted]
No BTH cost	[redacted]	1.74	[redacted]	[redacted]	1.74	[redacted]	[redacted]	1.07	[redacted]
No chelation therapy or venesection	[redacted]	1.74	[redacted]	[redacted]	1.74	[redacted]	[redacted]	1.07	[redacted]
TA778 resource utilisation	[redacted]	1.74	[redacted]	[redacted]	1.74	[redacted]	[redacted]	1.07	[redacted]
No discounting	[redacted]	2.60	[redacted]	[redacted]	2.60	[redacted]	[redacted]	1.81	[redacted]

Updated values to original company evidence submission underlined and in red font.
*Please note that larger changes in this scenario are due to the original analysis erroneously including iptacopan transition probabilities for C5 inhibitors in one column of the transition probability matrix.
Analysis uses PAS price for iptacopan and list price for comparators.
Abbreviations: BTH, breakthrough haemolysis; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TA, technology appraisal.

B.3.13 Validation

External model validation

Table 28: Comparison of model outcomes with Hakimi et al [Update to Document B, Table 75]

Outcome	Ravulizumab		Pegcetacoplan	
	Modelled outcome	Hakimi et al (114)	Modelled outcome	Hakimi et al (114)
Total costs	[redacted]	£6,660,676	[redacted]	£6,409,166
Total QALYs	12.679	12.942	13.346	14.694

Updated values to original company evidence submission underlined and in red font.
Abbreviations: QALY, quality-adjusted life-year.

Table 29: Comparison of model outcomes with Hakimi et al when matching inputs [Update to Document B, Table 76]

Outcome	Ravulizumab		Pegcetacoplan	
	Modelled outcome	Hakimi et al (114)	Modelled outcome	Hakimi et al (114)
Total costs	[redacted]	£6,660,676	[redacted]	£6,409,166
Total QALYs	13.077	12.942	14.663	14.694

Updated values to original company evidence submission underlined and in red font.
Abbreviations: QALY, quality-adjusted life-year.

References

1. Novartis. Data on file. CONFIDENTIAL. APPOINT-PNH CSR. 2023.
2. Novartis. Data on file. CONFIDENTIAL. APPLY-PNH CSR. Supplementary Report. Updated results for the 24-week primary and secondary efficacy analyses. 2023.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal
Iptacopan for treating paroxysmal nocturnal haemoglobinuria [ID6176]
Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	PNH Support
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	PNH Support (www.pnhuk.org) is a Charitable Incorporated Organisation registered with the Charities Commission of England and Wales (no.1161518). The 4 patient trustees operate within PNH Support's constitution dated 30 April 2015 amended on 16 May 2021. The Constitution is an 'Association' model and has 152 voting members. The objects of PNH Support (as set out in its Constitution) are as follows: 1) To promote, protect and preserve the physical and mental health of those diagnosed with PNH who reside in England, Wales and Northern Ireland (either permanently or temporarily) through the provision of support, education, advocacy and practical advice; 2) To advance the education of patients with PNH who reside in England, Wales and Northern Ireland, in particular but not exclusively, by the provision of advice and a point of contact for newly diagnosed PNH patients, in England, Wales and Northern Ireland. We moderate a closed Facebook group, send email updates to members, hold regional face-to-face and online patient and family meetings and a biennial patient and family conference. PNH Support is funded by donations, honoraria and consultancy fees for the provision of advice relating to the lived experience of PNH. PNH Support has received small grants from pharmaceutical companies in the past.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	**Novartis** 15.08.23 - £619.50 - providing a patient advocate perspective as part of the Novartis Global Oncology Patient Involvement Panel (GOPIP) on awareness raising campaign, a patient advisory board and working together generally 06.06.23 - £737.50 - providing a patient advocate perspective re awareness raising campaign; proposed patient engagement plans 30.06.23 - £236.00 - providing a patient advocate perspective re sharing trial results and patient engagement strategy 15.11.22 - £649.00 - providing a patient advocate perspective re informed consent form and future GOPIP involvement 01.09.22 - £383.50 - providing a patient advocate perspective on switch study **Alexion Pharmaceuticals (danicopan eculizumab, ravulizumab)** 01.09.23 - £190 - providing a patient advocate perspective on trial design **Roche Products (crovalimab)** 25.05.23 - £1,125.00 - preparation, attendance and follow up for 2 day patient advisory board **Swedish Orphan Biovitrum (pegcetacoplan)** 30.09.22 - £948.75 - providing a patient advocate perspective on: developing an app; ethnographic research into PNH burden of illness; and patient survey

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We undertook an online survey (comprising primarily multi-choice questions) of PNH patients and carers across England and Wales. The survey was disseminated via: email to PNH Support members; posts on our closed Facebook group; email by the PNH National Service (Kings College Hospital, London) to patients for which they held email addresses; and email by the PNH National Service (St James's Hospital, Leeds) to patients treated with iptacopan. Altogether 94 patients and carers provided completed survey responses. 90 responses were received from England: and 4 from Wales. 75 patients and 19 carers responded. **Ethnicity:** 80% (n=60/75) of **patients** identified as **"**English / Welsh / Scottish / Northern Irish / British" with the remainder identifying as set out in **Figure 1 i**n the Appendix. 84% (n=16/19) of **carer**s identified as **"**English / Welsh / Scottish / Northern Irish / British". One carer identified as Carribean and 2 preferred not to say. See **Figure 2**. in the Appendix **Gender:** Of the 75 **patients** who responded, 57% (n=43/75) identified as **female** and 42% (n=32/75) identified as **male**. Of the 19 **carers** who responded, 68% (n=13/19) identified as **female** and 32% (n=6/19) identified as **male.** **Age:** The average age of **patients** who completed the survey was 60. The average age of **carers** who completed the survey was 52. See F**igure 3** in the Appendix for details of patient ages and **see Figure 4** in the Appendix for details of carer ages. **Treatment:** Of the respondents, 6 patients are being treated with iptacopan with one carer of an iptacopan patient responding. The remaining respondents are being treated (or are carers of those being treated) with various other treatments or no treatment at all (see **Figures 5 and 6** in the Appendix).

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Respondents were asked to describe what life is like for them to currently live with PNH where they could choose more than one multi-choice answer.
	Patients
	• 72% (n= 54/75) chose "My (or the person I care for's) PNH is managed well";
	• 55% (n = 41/75) chose "I need to restrict my everyday activities because of PNH";
	• 43% (n = 32/75) chose "I have a fear of getting infections (or the person I care for getting them) which will make PNH worse";
	• 49% (n = 37/75) chose "I consider myself to have a normal quality of life";
	• 39% (n = 29/75) chose "PNH symptoms are unpredictable";
	• 35% (n= 26/75) chose "There is a lack of understanding of PNH by non-PNH specialists which impacts me negatively";
	• 33% (n = 25/75 chose "PNH has a negative impact on my family and social life";
	• 29% (n= 22/75) chose "Living with (or caring for someone with) PNH has a minimal impact on my life";
	• 25% (n= 19/75) chose "My (or their) veins are damaged because of repeated cannulation from infusions";
	• 23% (n=17/75) chose PNH has a negative impact on my mental health
	• 16% (n =12/75) chose "Travelling is difficult due to treatment restrictions";
	• 15% (n = 11/75) chose "Taking daily prophylactic antibiotics has a negative impact on me";
	• 6% (5/75) chose "I (or they) experience side effects from treatment which have a negative impact on me";
	
	In terms of symptoms, patients were asked if they experienced any PNH symptoms and to select as many listed as they wished and/or to provide their own.
	• 83% (n=62/75) experience "fatigue (e.g. exhaustion, limited energy, heaviness in limbs)". All patients were then asked to rate their fatigue with 1 being not fatigued at all and 10 being severely fatigued (to which 66/75 patients rather than 62/75 provided ratings) and the average rating was 6.
	• 52% (n =39/75) experience "shortness of breath (difficulty breathing or breathlessness)"
	• 45% (n=34/75) experience "cognitive problems (e.g. memory problems, brain fog, problems concentrating, difficulty focusing on tasks)". All patients were then asked what cognitive problems they experience or to provide their own to which 45/75 (rather than 35/75) responded as follows:
	  • 67% (n=30/45) experience "brain fog";
	  • 51% (n=23/45) experience "memory problems (long term or short term)";
	  • 51% (n=23/45) experience "problems concentrating;"
	  • 44% (n=20/45) experience "word finding difficulties";
	  • 38% (n=17/45) experience "difficulty focusing on tasks";
	  • 4% (n = 2/45) preferred not to say;
	  • 2% (n= 1/45) said "*inability to complete mental tasks and explain things to other that I would easily have done prior to become ill*";
	  • 2% (n =1/45) said "*mental fatigue*";

	• 2% (n=1/45) said "*problems understanding conversation"*.; • 2% (n=1/45) said "*all of these when I am more tired"*; • 39% (n=29/75) experience "digestive problems e.g. gas, bloating, slow digestion;" • 32% (n=24/75) experience "joint pain"; • 29% (n=22/75) experience "back pain"; • 28% (n=21/75) experience "yellow pigmenting in eyes due to jaundice"; • 27% (n=20/75) experience "difficulty with swallowing (dysphagia)"; • 25% (n=19/75) experience "abdominal pain"; • 20% (n=15/75) experience "breakthrough haemolysis (return of dark urine/return of my symptoms/anaemia)"; • 20% (n=15/75) experience "leg pain"; • 19% (n=14/75) experience "dark urine (haemoglobinuria)"; • 19% (n=14/75) experience "headaches (on a regular basis)"; • 16% (n=12/75) experience "anaemia requiring blood red blood cell transfusions"; • 15% (n=11/75) experience "erectile dysfunction"; • 12% (n= 9/75) experience "chest pain;" • 11% (n= 8/75) don't experience any PNH symptoms; • 9% (n =7/75) experience "hair loss"; • 6% (n= 5/75) experience "blood clot/s"; • 1% (n= 1/75) experience "high sensitivity to low temperature which intensifies many symptoms of PNH, including joint and muscle pain, inflammation, and high fever)"; • 1% (n=1/75) experience "itchy skin" **Carers** In response to being asked to describe what life is like to care for someone with PNH where they could choose more than one multi-choice answer: • 63% (n=12/19) chose "I have a fear of getting infections (or the person I care for getting them) which will make PNH worse"; • 58% (n=11/19) chose "PNH has a negative impact on my mental health"; • 47% (n=9/19) chose "My (or the person I care for's) PNH is managed well"; • 47% (n=9/19) chose "I (or they) experience side effects from treatment which have a negative impact on me"; • 42% (n= 8/19) chose "PNH has a negative impact on my family and social life"; • 42% (n= 8/19) chose "PNH symptoms are unpredictable"; • 42% (n= 8/19) chose "There is a lack of understanding of PNH by non-PNH specialists which impacts me negatively"; • 32% (n=6/19) chose "Travelling is difficult due to treatment restrictions"; • 26% (n= 5/19) chose "Living with (or caring for someone with) PNH has a minimal impact on my life"; • 21% (n= 4/19) chose "My (or their) veins are damaged because of repeated cannulation from infusions"; • 16% (n= 3/19) chose "I consider myself to have a normal quality of life";

	• 11% (n= 2/19) chose “Taking daily prophylactic antibiotics has a negative impact on me”; • 11% (n= 2/19) chose “I need to restrict my everyday activities because of PNH”;

7. What do patients or carers think of current treatments and care available on the NHS?	**Current Treatments – Patients** When patients were asked what they thought of the **current PNH treatments available on the NHS** (where they could choose more than one answer and/or provide their own): • 68% (n= 51/75) patients chose "I am satisfied with the currently available treatments. Although 24/51 chose that they were satisfied with the currently available treatments, they also chose another response relating to either wanting treatment options with different delivery methods or treatment options which provided a better quality of life. • 61% (n = 46/75) chose they would like there to be more treatment options with different delivery methods e.g. injections, tablets etc. One patient commented "*Tablet form if effective would be brilliant. Saving cannulation*"; • 52% (n= 39/75) chose "The opportunity to take part in clinical trials is an advantage"; • 45% (n=34/75) chose "I would like there to be more treatment options which provide me with better quality of life (less symptoms etc)"; • 17% (n =13/75) chose "I am neither satisfied nor dissatisfied with the current treatment options"; • 9% (n = 7/75) chose "I don't require treatment so I am not aware of treatment options"; • 4% (n= 3/75) chose "I am dissatisfied with the currently available treatments"; • 4% (n= 3/75) chose "I don't know/Prefer not to say"; **Current Treatments – Carers** • When carers were asked what they thought of the **current PNH treatments available on the NHS** (where they could choose more than one answer and/or provide their own): • 63% (n=12/19) chose that they would like there to be more treatment options with different delivery methods e.g. injections, tablets etc.; • 47% (n= 9/19) chose "I would like there to be more treatment options which provide me with better quality of life (less symptoms etc); • 37% (n=7/19) chose "The opportunity to take part in clinical trials is an advantage"; • 32% (n= 6/19) chose "I am satisfied with the currently available treatments", however 5/6 also selected "I would like there to be more treatment options with different delivery methods e.g. injections, tablets etc " and/or "I would like there to be more treatment options which provide me with better quality of life (less symptoms etc)"; • 16% (n= 3/19) chose "I am neither satisfied nor dissatisfied with the current treatment options"; • 5% (n= 1/19) chose "I don't require treatment so I am not aware of treatment options"; • 5% (n= 1/19) chose "I am dissatisfied with the currently available treatments"; **Current Care - Patients** Care provided by the PNH National Service and care provided by the NHS (outside the PNH National Service) was asked about separately. When patients were asked to choose what they thought of the **current care available for PNH from the PNH National Service:** • 69% (n=52/75) chose "Very satisfactory"; • 21% (n=16/75) chose "Somewhat Satisfactory"; • 5% (n=4/75) chose "I don't know/Prefer not to say";

	• 3% (n=2/75) chose "Neither satisfactory nor unsatisfactory" • One patient commented "*PNH has many forms, and patients have very individual treatment needs. Currently, NHS covers only a small part of these needs, offering a service addressed mainly to the patients struggling with intra-vascular haemolysis, leaving out patients with extra-vascular haemolysis and Aplastic Anaemia, which often occurs concurrently with PNH*." When patients were asked to choose what they thought of the **current care available from the NHS for PNH outside the PNH National Service e.g. GPs, local haematologists (not part of the PNH National Service), other healthcare professionals:** • 21% (n=16/75) chose "Very Satisfactory"; • 17% (n= 13/75) chose "Somewhat Satisfactory"; • 13% (n=10/75) chose "Neither satisfactory nor unsatisfactory"; • 13% (n=10/75) chose "Unsatisfactory"; • 1% (n=1/75) chose "I don't know/Prefer not to say"; • One patient commented "*I've never required pnh treatment on a local le*vel". • One patient only commented "*Most medical professionals outside of the PNH service have not heard of PNH which can be frustrating*" **Current Care - Carers** When carers were asked to choose what they thought of the **current care available for PNH from the PNH National Service:** • 53% (n=10/19) chose "Very Satisfactory"; • 26% (n=5/19) chose "Somewhat Satisfactory"; • 11% (n=2/19) chose "Neither satisfactory nor unsatisfactory"; • 5% (n=1/19) chose "Somewhat unsatisfactory"; • 5% (n=1/19) chose "Very unsatisfactory"; When carers were asked to choose what they thought of the **current care available from the NHS for PNH outside the PNH National Service e.g. GPs, local haematologists (not part of the PNH National Service), other healthcare professionals:** • 42% (n=8/19) chose "Unsatisfactory"; • 26% (n=5/19) chose "Somewhat Satisfactory"; • 16% (n=3/19) chose "Very satisfactory"; • 5% (n=1/19) chose "Neither satisfactory nor unsatisfactory"; • 5% (n=1/19) chose "Very unsatisfactory"; • 5% (n=1/19) chose "I don't know/Prefer not to say";

8. Is there an unmet need for patients with this condition?	When patients were asked if they had any unmet needs with unmet need defined as "something that is not addressed by current NHS care or available treatments": • 65% (n=49/75) chose they did not have any **unmet need**; • 21% (n=16/75) chose they didn't know; • 11% (n=8/75) chose they did have unmet needs; • 3% (n=2/75) chose "Other" and listed their unmet need as: "*Mentoring when first diagnosed*" and "*To date, the greatest unmet need has been the treatment of extra-vascular haemolysis, which has caused critical damage to my health condition on a daily basis*." Those who said they had an unmet need were asked to choose all of the following that were relevant: • 50% (n=4/8) chose "Lack of education of healthcare professionals about PNH"; • 50% (n=4/8) chose "Lack of psychological support"; • 37% (n=3/8) chose "I still have PNH symptoms"; • 37% (n=3/8) chose "Lack of available information about PNH for patients and carers"; • 37% (n=3/8) chose "The impact of repeated cannulation (vein access) for treatment with infusions"; • 25% (n=2/8) chose "There is a need for more treatment choices"; • 25% (n=2/8) chose "The burden of treatments with infusions"; • 25% (n=2/8) chose "Negative side effects from treatment"; Although only 11% of patients said they had unmet needs, when asked at the end of the survey to "Please tell us what support you would like to better live well with PNH", 32% (n=24/75) patients made comments indicating they did have an unmet need. The main themes of these comments were: • Access to psychological support • Treatments which address their symptom burden including extra-vascular haemolysis and are less burdensome • Concern about risks of contracting infections • More awareness by general medical staff about PNH • Increased funding for clinical nurse specialists to support patients • Nutritional support

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	The 6 patients treated with iptacopan were asked what they thought the **advantages of the treatment** were (where they could choose more than one answer and/or provide their own: • 100% (n=6/6) chose the delivery method of this treatment (i.e. tablet) was an advantage • 83% (n=5/6) chose it had improved their PNH symptoms, (*"Normalised haemoglobin which had an extraordinary improvement in my health - no longer being anaemic made me feel full of energy*"), had a positive impact on their ability to work or undertake education, had a positive impact on their family and social life and had a positive impact on their mental health ("*It has had a very positive impact on both my physical and mental health. I no longer live in fear of haemolysis episodes and so my anxiety has greatly improved. I am also much more physically robust. I also have a long-term needle phobia and so daily tablets are a great improvement for me"*) • 66% (n=4/6) chose the ability to travel with the medication was an advantage • 33% (n=2/6) chose the frequency of the treatment was an advantage (i.e. twice per day) One patient commented "*Participation in the trial brought my haemoglobin to the norm level for the very first time in 30 years. Not only has the colour of my entire body changed (previously it was yellow due to a constant jaundice crisis caused by hemolytic conditions that lasted for months and years), but I am also much more independent, focused, active, dynamic, energetic, able to work, climb stairs, travelling longer distances, take longer walks. I can handle stress better. I do not have insomnia. My immunity has hugely improved."* Another patient said "*Having had the experience of 30 years of living at 40-60% of my body's capacity, being dependent on blood transfusions and infusions for years, now, while taking part in the trial for the first time, I am experiencing a different quality of life. A quality that I did not know before. Not only has my life changed, but so has my family's life, as they can be at least partially relieved of the pressure of constant care for me. This treatment is an investment in the lives of many members of society - first and foremost, the PNH patients, but also their close ones.*" The one **carer** of a patient who had only been on this treatment for 2 weeks said "*There are no advantages to me; Have to travel 80 miles to collect tablets as there not funded by NHS"*

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The 6 patients treated with iptacopan were asked what they thought the **disadvantages of the treatment** were (where they could choose more than one answer and/or provide their own: • 50% (n=3/6) chose "there are no disadvantages"; • 33% (n=2/6) chose "concern about long term side effects is a disadvantage"; • 16% (n=1/6) chose "the number of times the iptacopan tablets need to be taken per day is a disadvantage" • 16% (n=1/6) chose "current side effects are a disadvantage" • 16% (n= 1/6) stated "*Currently the tablets need to be stored in the fridge. This is restrictive to some forms of travel (long distance).*" In addition one patient said "*My experience with Iptacopan has been extremely positive along with the care and support I have received from the Clinical Research team at Kings College. The only negative is that it has not eased my erectile dysfunction symptoms"*. **Carer -** The one carer respondent said that the patient they care for had only been on the treatment a few weeks.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	From the available data, patients who experience extravascular haemolysis and associated symptoms including anaemia requiring blood transfusions whilst being treated with a C5 inhibitor will benefit in particular from this therapy. The following groups of patients will also benefit from this treatment: • those whose veins are damaged from repeated cannulation; • those whose work, education or caregiving responsibilities are currently disrupted by infusions and who will be able to self-manage their treatment; • those who need, or wish, to travel more freely without being bound by infusion schedules (subject to cold chain requirements)

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	We are not aware of any equality issues.

Other issues

13. Are there any other issues that you would like the committee to consider?	21% (16/75) patients said their **employment status** was affected by PNH. 50% (n=8/16) work part time (one of which is also a stay-at-home parent): "*I work part-time because I get tired from the PNH, and could not work full-time hours*".; "*I cannot manage to commute for more than two days a week*"; " 31% n=5/16) work full time: "*I had to retire from my teaching career due to ill health (PNH) and take a lesser paid/less demanding job";* 12% (n=2/16) are unemployed with one stating they are unable to work due to PNH; 6% (n=1/16) preferred not to say and stated "*not been well enough to work since recent diagnoses*" 6% (n=1/16) is retired and stopped working due to severe symptoms **Carers** 32% (n=6/19) carers said their employment status was affected by caring for someone with PNH where one person was a full time carer for a PNH patient. 33% (n=2/6) work full time with one saying "*I have more responsibility in the home which can affect work time. I also feel that I have to work full time because my partner can no longer work as he has pnh*". 16% (n=1/6) took early retirement to help care for their partner with PNH. 16% (n=1/6) works part time and has a 14 year with PNH 16% (n=1/6) preferred not to say and that "*Care is required at certain times of the day*"; **Of those patients treated with iptacopan:** 50% (n=3/6) can now work full time and of these 33% (n=1/3) can also now study part time and care for dependants, 16% (n=1/6) can now work part time, 16% (n=1/6) can now care for dependants. The EQ 5D-5L questionnaire asks patients about their ability to undertake "usual activities (e.g. work, study, housework, family or leisure activities)". The way this question is worded won't necessarily capture patients who have not been working or studying or caring for dependants as these activities would not be considered usual for them. This therapy presents a cost saving to the: • public purse for patients who (as a result of the impact of this treatment, including addressing extravascular and well as intravascular haemolysis) are now able to work, work more, study or care for dependants. It also means that work, study, or caregiving is not interrupted by having infusions. • NHS by reducing the time and costs needed to manage, care for and treat patients whose symptoms resulting from extravascular haemolysis have improved (including anaemia and therefore don't need blood transfusions) as a result of this therapy

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• All patients treated with iptacopan (n=6) identified its main advantage to be the delivery method, 83% (n=5/6) said iptacopan: had improved PNH symptoms; had a positive impact on their family and social life; and had a postive impact on their mental health. • All patients treated with iptacopan are now able to either work part time or full time or provide caregiving as a result of this treatment. Employment means patients can contribute more fully to society and can rely less on the State and their families leading to increased independence and quality of life. • 61% of patients and 63% of carers said they would like more treatment options with different delivery methods and 45% patients and 47% carers said they would like there to be more treatment options which provide patients with better quality of life (less symptoms etc). • Only 11% of patients said they had an unmet need (with 50% of those stating that both lack of education of healthcare professionals about PNH and lack of psychological support were their unmet needs). However it is clear that this does not reflect reality or that patients don't understand the concept of an "unmet need" as 32% made comments at the end of the survey setting out what their unmet need was in terms of care and treatment summarised above. In addition 83% of patients said they experienced fatigue which is clearly also an unmet need. • Although the burden of PNH has been mitigated significantly in many patients by intravenous treatments with C5 inhibitors, and a sub-cutaneous C3 inhibitor, patients affected by both intra and extravascular haemloysis (and their families) would like the freedom to have as normal a life as possible with a treatment with the least invasive delivery method; which this treatment allows.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Appendix – PNH Support's submission for Iptacopan appraisal ID6176]

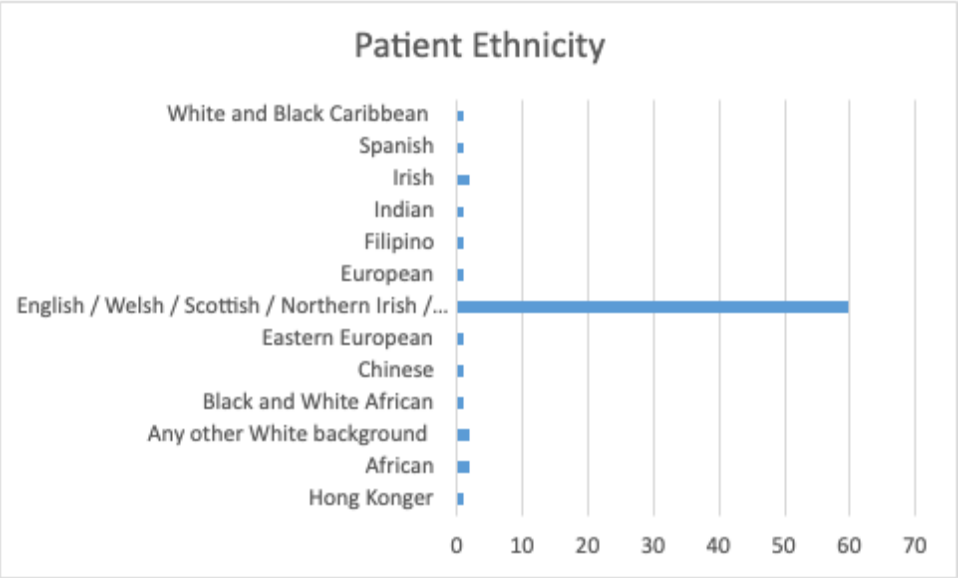

Figure 1 – Patient Ethnicity

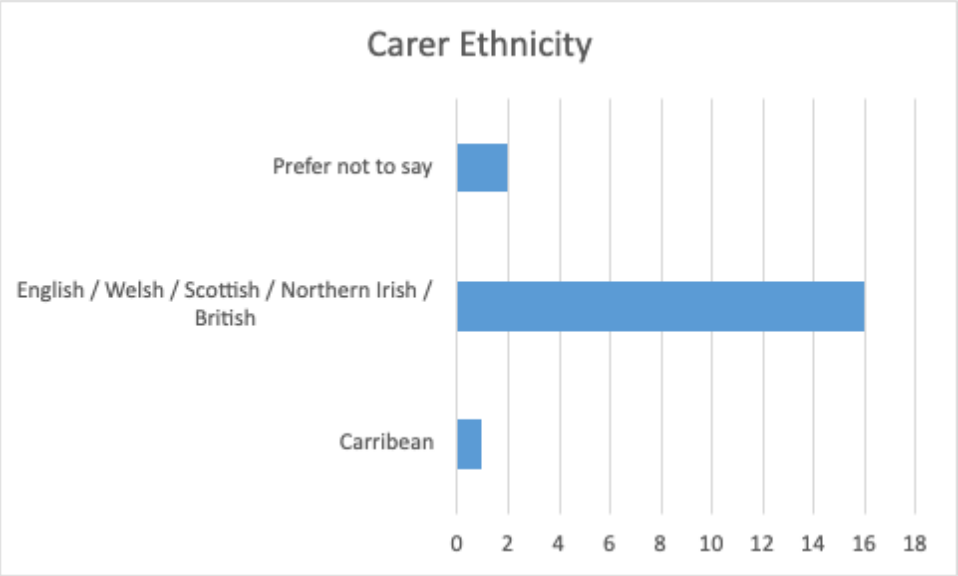

Figure 2 – Carer Ethnicity

Age group in years (Patients)	n	%
17 - 25	2	3
26-35	6	8
36-45	4	5
46-56	15	20
57-65	19	25
66 -75	17	23
76 plus	12	16
Total	75	

Figure 3 – Patient- Age in years

Age group in years (Carers)	n	%
17 - 25	1	5
26-35	3	16
36-45	2	10
46-56	3	16
57-65	7	37
66 -75	3	16
76 plus	0	0
Total	19	

Figure 4 – Carer – Age in years

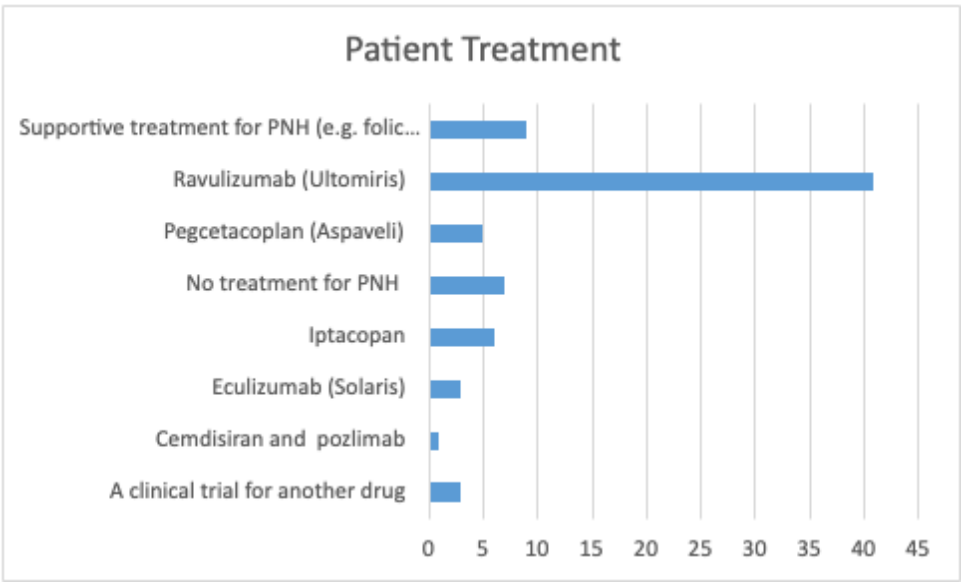

Figure 5 – Patient respondents' treatment

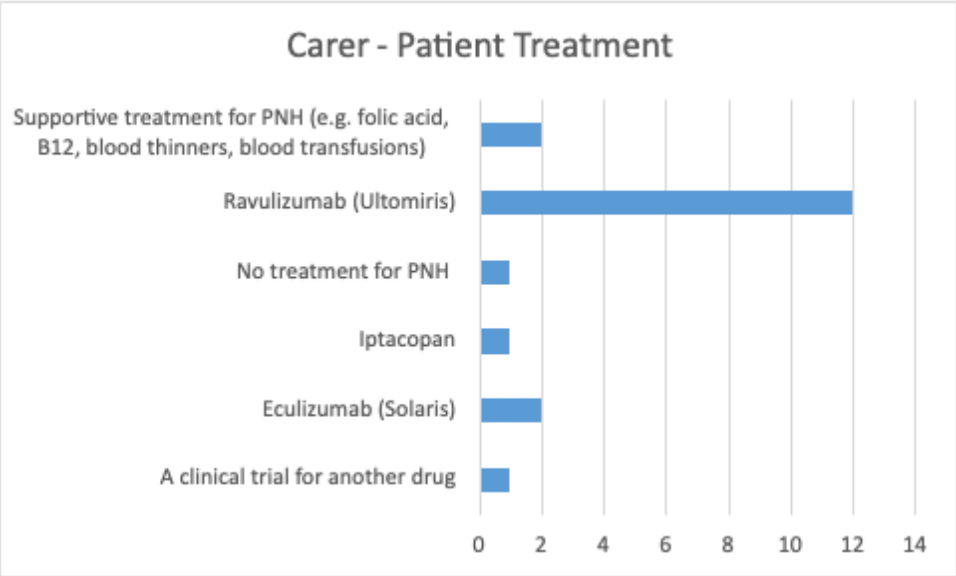

Figure 6 – Carer respondents stating which treatment the patient for whom they care is on

NICE National Institute for Health and Care Excellence

Single Technology Appraisal
Iptacopan for treating paroxysmal nocturnal haemoglobinuria [ID6176]
NHS organisation submission

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

The Department of Health and Social Care and the Welsh Government provide a unique perspective on the technology, which is not typically available from the published literature. NICE believes it is important to involve NHS organisations that are responsible for commissioning and delivering care in the NHS in the process of making decisions about how technologies should be used in the NHS.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Short, focused answers, giving a Department of Health and Social Care and Welsh Government perspective on the issues you think the committee needs to consider, are what we need.

NICE National Institute for Health and Care Excellence

About you

Your name	[redacted]
Name of your organisation	The Royal College of Pathologists and PNH UK national service
Please indicate your position in the organisation	Department of Health and Social Care or Welsh Government in general? • A specialist in the treatment of people with the condition for which NICE is considering this technology? • A specialist in the clinical evidence base that is to support the technology (e.g. participation in clinical trials for the technology)?
Do you have any links with, or funding from, the tobacco industry? Please declare any direct or indirect links to, and receipt of funding from the tobacco industry	No

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences in opinion between professionals as to what current practice should be? What are the	PNH is a rare haemolytic and thrombotic condition. We have approximately 1000 patients within our service, with 406 patients on complement inhibition: 342 Ravulizumab, eculizumab or Pegcetacoplan (NHS funded) and 64 within clinical trials. Indications for treatment include haemolytic PNH with anaemia, and a high LDH, PNH related complications such as renal failure, PNH related thrombosis, pregnancy (eculizumab only) and exceptional circumstances. There is no geographical variation across the UK. No difference of opinion between clinicians within the PNH service as to indications for Iptacopan use: patients experiencing anaemia on a C5 inhibitor

current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?	Ipactopan is an oral proximal complement inhibitor targeting factor B. Taken twice a day. Currently within clinical trials and a managed access programme for patients with PNH on a C5 inhibitor who are experiencing ongoing anaemia due to extravascular haemolysis. Initial trial data reports marked haemoglobin increase with 82% of patients achieving a >2g/dl rise in haemoglobin, improved quality of life and continued control of intravascular haemolysis. Current alternatives: Pegcetacoplan: subcutaneous infusion twice a week, inhibition at C3 in the complement cascade. Advantages: Currently approved by NICE for patients with anaemia on a C5 inhibitor as a replacement treatment, it managed and control the extravascular haemolysis as well as intravascular haemolysis. Mean Hb difference within trials was 3.84g/dl, marked improvement in quality of life, with ongoing control of PNH Disadvantages: subcutaneous infusion treatment twice a week – not all patients want to self administer an injection, and not all patients are able to manage the equipment. Added difficulty for travelling with carrying equipment, cool bags etc. Other comparator products are currently within clinical trials: Danicopan which is used in combination with current C5 inhibitors (ravulizumab or eculizumab).

To what extent and in which population(s) is the technology being used in your local health economy?	Patients with PNH on Ravulizumab or eculizumab who are anaemic due to extravascular haemolysis New patients with haemolytic PNH (as an alternative to Eculizumab and Ravulizumab)
Is there variation in how it is being used in your local health economy?	No
Is it always used within its licensed indications? If not, under what circumstances does this occur?	Currently not licenced
What is the impact of the current use of the technology on resources?	Iptacopan is an oral treatment, which would reduce healthcare resource as current treatments (ravulizumab and eculizumab) require the first dose in a hospital, then homecare nurse administration. Pegcetacoplan requires training for the patient with equipment, first dose in hospital, and a homecare nursing service for troubleshooting
What is the outcome of any evaluations or audits of the use of the technology?	
What is your opinion on the appropriate use of the technology?	The PNH National Service welcomes the option for patients to have an oral treatment option for PNH. The clinical trial data and those on the managed access scheme have shown Iptacopan to be an effective treatment for managing PNH and improving quality of life. It will expand treatment options available for patients.

Potential impact on the NHS if NICE recommends the technology

What impact would the guidance have on the delivery of care for patients with this condition?	Iptacopan is an oral treatment. The PNH service would continue to provide the same service with appointments, advice and emergency out of hours care. An oral treatment will reduce homecare nursing

	requirements significantly, and will reduce space on day units for patients who require a change of treatment or training for pegcetacoplan.
In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional resources (for example, staff, support services, facilities or equipment)?	Specialist care: PNH is an ultrarare condition, all patients should continue to be managed by the National PNH service, who have the expertise and experience in treating patients, advising about medication, and managing complications/infections if they arise. No additional resource will be needed
Can you estimate the likely budget impact? If this is not possible, please comment on what factors should be considered (for example, costs, and epidemiological and clinical assumptions).	It is likely to have no direct impact on budget from a PNH service point of view, however homecare services/nursing provision within homecare would be reduced (this is currently outsourced)
Would implementing this technology have resource implications for other services (for example, the trade-off between using funds to buy more diabetes nurses versus more insulin pumps, or the loss of funds to other programmes)?	No

Would there be any need for education and training of NHS staff?	The PNH service are familiar with the use of Iptacopan. Education would focus on webinars to highlight change in treatment provision to shared care colleagues around the UK and how Iptacopan is different from other complement inhibition, as if approved, this would be the first oral therapy in PNH.

Equality

Please let us know if you think that this appraisal: **Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licenced** **Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology** **Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.**	No No No
Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.	

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Other issues

Please include here any other issues you would like the appraisal committee to consider when appraising this technology	

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Iptacopan for treating paroxysmal nocturnal haemoglobinuria [ID6176]

NHS organisation submission (ICBs and NHS England)

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	[redacted]
2. Name of organisation	NHS England
3. Job title or position	[redacted]

4. Are you (please select Yes or No):	Commissioning services for an ICB or NHS England in general? Yes Commissioning services for an ICB or NHS England for the condition for which NICE is considering this technology? Yes Responsible for quality of service delivery in an ICB (for example, medical director, public health director, director of nursing)? No An expert in treating the condition for which NICE is considering this technology? No An expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? No Other (please specify):
5a. Brief description of the organisation (including who funds it).	NHS England is funded by the DHSC
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

Current treatment of the condition in the NHS

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There is existing NICE Guidance for the use of ravulizumab and pegcetacoplan. Eculizumab is commissioned by NHS England to treat PNH. Crovalimab and Danicopan with a C5 inhibitor are both subject to NICE ongoing appraisal.
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is well defined. There are two centres commissioned to provide treatment for this cohort of patients who work collaboratively. There are no differences of opinion relating to the care pathway.
8. What impact would the technology have on the current pathway of care?	It would provide an alternative for eculizumab and ravulizumab, for both existing and new patients. As this technology is an oral therapy and the other treatments are infusions, this technology would be a major improvement in the patient experience.

The use of the technology

9. To what extent and in which population(s) is the technology being used in your local health economy?	There are some patients who have been in a clinical trial relating to this intervention, but it is not currently commissioned by NHS England
10. Will the technology be used (or is it already used) in the same way	The technology would be used in the treatment pathway for PNH as a first line treatment.

as current care in NHS clinical practice?	
10a. How does healthcare resource use differ between the technology and current care?	The technology is an oral treatment so uses less health care resources to administer than the current infusion pathway.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This technology would only be available through the two commissioned tertiary services.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No new investment is required.
10d. If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	Patients would need to meet the service treatment thresholds and treatment commencement is confirmed by the MDT. No additional testing is required. The clinicians are best placed to provide the detail.
11. What is the outcome of any evaluations or audits of the use of the technology?	This drug is not routinely commissioned, there are no NHS audits as far as the commissioners are aware.

Equality

12a. Are there any potential equality issues that should be taken into account when considering this treatment?	This is an oral therapy which means it would be easier for patients with needle phobias and who have compromised venous access to comply with treatment.
12b. Consider whether these issues are different from issues with current care and why.	The current treatment options are infusions which are invasive and time consuming for patients.

Thank you for your time.

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External Assessment Group Report
Iptacopan for treating paroxysmal nocturnal haemoglobinuria

Produced by CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD

Authors Mark Rodgers, Research Fellow, Centre for Reviews and Dissemination, University of York

Natalia Kunst, Senior Research Fellow, Centre for Health Economics, University of York

Chinyereugo Umemneku-Chikere, Research Fellow, Centre for Reviews and Dissemination, University of York

Anqian Zhou, Research Fellow, Centre for Health Economics, University of York

Minyue Gao, Research Fellow, Centre for Health Economics, University of York

Helen Fulbright, Information Specialist / Research Fellow, Centre for Reviews and Dissemination, University of York

Alison Eastwood, Professor (Research), Centre for Reviews and Dissemination, University of York

Claire Rothery, Professor of Health Economics, Centre for Health Economics, University of York

Correspondence to Claire Rothery, Professor of Health Economics, Centre for Health Economics, University of York

Date completed 26/01/2024

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Declared competing interests of the authors

None

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Dr Richard Kelly, Consultant Haematologist and Joint PNH Service Lead, Leeds Teaching Hospitals NHS Trust, provided expert clinical advice and commented on a draft of the report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

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Contributions of authors

Mark Rodgers performed the critical review of the clinical evidence and contributed to drafting sections 1, 2 and 3 of the report

Natalia Kunst performed the critical review of the economic analyses, conducted the EAG additional analyses and contributed to drafting Sections 4 and 6 of the report.

Chinyereugo Umemneku-Chikere performed the critical appraisal of the indirect treatment comparisons contributed to sections 2 and 3 of the report

Anqian Zhou performed the critical review of the economic analyses, conducted the EAG additional analyses and contributed to drafting Sections 4 and 5 of the report.

Minyue Gao performed the critical review of the economic analyses, conducted the EAG additional analyses and contributed to drafting Sections 4 and 5 of the report.

Helen Fulbright performed the critical review of the search strategies and drafted Appendix 1 of the report

Alison Eastwood contributed to sections 2 and 3 of the report, and took overall responsibility for the clinical sections of the report and joint responsibility for the report as a whole.

Claire Rothery performed the critical review of the economic analyses, conducted the EAG additional analyses, contributed to drafting Sections 4, 5 and 6 of the report, led the overall economic analyses and takes joint responsibility for the report as a whole.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all depersonalised data (DPD) are highlighted in pink and underlined.

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List of abbreviations

AEs	Adverse events
AESI	Adverse event of special interest
AIC	Akaike information criterion
AIPW	Augmented inverse probability weight
Bas	Baseline
BD	Twice daily
BIC	Bayesian information criterion
BNF	British national Formulary
BTH	Breakthrough haemolysis
C5	Complement 5
CAC BTH	Complement-amplifying condition breakthrough haemolysis
CASP	Critical Appraisal Skills Programme
CFB	Change from baseline
CI	Confidence interval
CMH	Cochran Mantel Haenszel
CMU	Commercial medicine unit
cPAS	Confidential patient access scheme
CS	Company submission
CSR	Clinical study report
EAG	External Assessment Group
ECU	Eculizumab
eGFR	estimated glomerular filtration rate
EMIT	Electronic market information tool
EVBTH	Extravascular BTH
EVH	Extravascular haemolysis
FACT-IT	Fatigue, Functional Assessment of Chronic Illness Therapy
FAS	Full analysis set
FB	Factor B
Hb	Haemoglobin
HRQoL	Health related quality of life
HSCT	Hematopoietic stem cell transplantation
ICER	Incremental cost-effectiveness ratios
ITC	Indirect comparison
IV	Intravenous
IVBTH	Intravascular BTH
IVH	Intravascular haemolysis
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
LYG	Life years gained
MAIC	Match indirect adjusted comparison
MAVE	Major adverse vascular event
NHB	Net health benefit
NHS	National Health Services
NICE	National Institute for Care and Excellence
PAS	Patient access scheme
PEG	Pegcetacoplan
PfC	Point of clarification
PNH	Paroxysmal Nocturnal Haemoglobinuria
pRBC	Packed red blood cell

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSS	Personal social service
PSSRU	Personal social service research unit
Q8W	Once every eight weeks
QALY	Quality-adjusted life year
QW	Once weekly
RAV	Ravulizumab
RBC	Red blood cell
RCT	Randomised control trial
RWE	Real World Evidence
SAEs	Serious adverse events
SAS	Safety analysis set
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SMD	Standardized mean difference
SmPC	Summary of product characteristics
TA	Technology Appraisal
TSD	Technical support document
UK	United Kingdom
ULN	Upper limit of normal
WTP	Willingness to pay

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1 Summary of key issues

ID6176	Summary of issue	Report sections
1	No direct comparative evidence for the complement inhibitor-naïve population	3.2.1.3 and 3.4 and 3.5.1
2	Highly uncertain treatment effect of iptacopan relative to pegcetacoplan in the complement inhibitor-experienced population with residual anaemia	3.4 and 3.5.2
3	Lack of evidence on rare events and longer-term effects of iptacopan	3.2.1.3, 3.2.2.3 and 3.2.3
4	No direct link between the iptacopan trial endpoints and the transition probabilities used in the model	4.2.6.1
5	Modelled treatment sequence in the complement inhibitor-naïve population	4.2.4.1
6	Transition probabilities based on a lack of direct or indirect comparison of treatments	4.2.6.1
7	Assessment time period from the iptacopan trials	4.2.6.1
8	Annual discontinuation rates for iptacopan and pegcetacoplan	4.2.6.4
9	Treatment-specific health state utility values	4.2.8.3
10	Concomitant eculizumab acquisition costs for patients initiating pegcetacoplan	4.2.9.2

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are: (i) the modelled treatment sequence in the complement inhibitor naïve population, where the EAG considers it more appropriate to compare the sequence iptacopan to C5 inhibitors vs. C5 inhibitors, rather than the comparison iptacopan to ravulizumab vs. C5 inhibitors to pegcetacoplan

as used in the company's base case; (ii) a lower discontinuation rate for pegcetacoplan of 10% per annum in the complement inhibitor-experienced population with residual anaemia compared to the rate of 16.13% per annum used in the company's base case; (iii) treatment-independent utility values for the modelled health states rather than treatment-specific health state utility values used in the company's base case; and (iv) exclusion of concomitant eculizumab acquisition costs for patients initiating pegcetacoplan.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing the proportion of patients who are not receiving transfusions and do not have anaemia, which is associated with improved health-related quality of life compared to the comparator complement inhibitors.
- Reducing the proportion of patients requiring transfusions, which is associated with lower health-related quality of life compared to the comparator complement inhibitors.
- Treatment-specific health state utility values are included in the company's base case, with iptacopan modelled to have better health-related quality of life compared to treatment with C5 inhibitors.

Overall, the technology is modelled to affect costs by:

- No administration costs for iptacopan because the treatment is given as an oral tablet.
- Lower healthcare resource use associated with occupancy of improved health states, e.g., reduced proportion of patients requiring transfusions on iptacopan.
- Reducing the incidence rate of breakthrough haemolysis (BTH) events.

The largest component of cost associated with treatment for PNH relates to drug acquisition costs, with a much smaller relative proportion associated with health state resource use (including blood transfusions), adverse event costs (including BTH events) and drug administration costs.

The modelling assumptions that have the greatest effect on the ICER are:

- The subsequent line of treatment after complement inhibitor initiation in the complement inhibitor-naïve population, i.e., the modelled treatment sequence in this population.

- Transition probabilities for iptacopan based on 48-week data (treatment extension period of iptacopan clinical trials) vs. 24-week data (core treatment period of iptacopan clinical trials) in the complement inhibitor-experienced population with residual anaemia.
- Transition probabilities for C5 inhibitors in the complement inhibitor-experienced population with residual anaemia.
- Annual rate of treatment discontinuation for pegcetacoplan compared to iptacopan in the complement inhibitor-experienced population with residual anaemia.
- Treatment-independent health state utility values.

1.3 The decision problem: summary of the EAG's key issues

There are no key issues relating specifically to the decision problem.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 1 No direct comparative evidence for the complement inhibitor-naïve population

Report section	3.2.1.3 and 3.4 and 3.5.1
Description of issue and why the EAG has identified it as important	A small single-armed study (APPOINT-PNH) provided direct evidence on the treatment effects of iptacopan in the complement inhibitor-naïve population. In the absence of direct evidence, two unanchored indirect treatment comparisons (ITCs) were conducted to estimate the treatment effects of iptacopan relative to C5 complement inhibitors. However, one ITC could not adequately adjust for baseline differences between studies, and the second could only estimate effect relative to eculizumab, due to a lack of patients receiving the preferred C5 inhibitor for most patients in current NHS practice (ravulizumab)
What alternative approach has the EAG suggested?	None available due to absence of evidence.
What is the expected effect on the cost-effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	A randomised controlled trial (RCT) comparing iptacopan to C5 complement inhibitor treatment in the complement inhibitor-naive population (similar to the APPLY-PNH trial in the complement inhibitor-experienced population) would be the preferred source of evidence.

Issue 2 Highly uncertain treatment effect of iptacopan relative to pegcetacoplan in the complement inhibitor-experienced population with residual anaemia

Report section	3.4 and 3.5.2

Description of issue and why the EAG has identified it as important	Anchored and unanchored ITCs comparing iptacopan to pegcetacoplan were inconsistent in their estimates of relative treatment effect on haemoglobin and transfusion avoidance outcomes. These ITC results were also highly uncertain due to a very small effective sample size for iptacopan, and discrepancies in C5 inhibitor comparator arms. The pegcetacoplan study used for the ITC (PEGASUS) incorporated a pegcetacoplan-plus-eculizumab run-in period.
What alternative approach has the EAG suggested?	None available due to absence of evidence.
What is the expected effect on the cost-effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Studies directly comparing iptacopan with pegcetacoplan in the complement inhibitor-experienced population with residual anaemia, or pegcetacoplan studies that could inform a more robust ITC.

Issue 3 Lack of evidence on rare events and longer-term effects of iptacopan

Report section	3.2.1.3 and 3.2.2.3 and 3.2.3
Description of issue and why the EAG has identified it as important	The evidence on iptacopan is currently limited to two small studies powered to detect changes in haematological response but not uncommon events. At the latest data-cut, data are available for 48 weeks of treatment.
What alternative approach has the EAG suggested?	Data should continue to be collected from patients receiving iptacopan to establish its longer-term safety and effectiveness.
What is the expected effect on the cost-effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	NCT04747613 is a single-arm, open-label, multicentre, roll-over extension study to characterise long-term safety, tolerability and efficacy of iptacopan in PNH, and to provide access to iptacopan to patients who have completed Novartis-sponsored Phase 2 or 3 studies with iptacopan in PNH.The estimated study completion date of NCT04747613 is June 2026.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

Issue 4 No direct link between the iptacopan trial endpoints and the transition probabilities used in the model

Report section	4.2.6.1

Description of issue and why the EAG has identified it as important	There is no direct link between the iptacopan trial endpoints and the health state transition probabilities used in the model, which makes a comparison and validation of the transition probabilities informing the cost-effectiveness of iptacopan challenging as it is not clear if the model findings are in line with the primary and secondary outcomes of the trials. The model includes the same health states as used in TA778 for the pegcetacoplan model in order to allow a comparison of the cost-effectiveness of iptacopan with pegcetacoplan, using published transition probabilities for pegcetacoplan. The EAG acknowledges the reasons for the approach taken by the company but considers there to be uncertainty in the treatment effectiveness evidence informing the model without a direct comparison of trial endpoints and modelled health state transitions.
What alternative approach has the EAG suggested?	An alternative model structure, or definition of health states, that more closely align with the trial endpoints could be considered for the comparison of iptacopan with C5 inhibitors, noting that pegcetacoplan is only a relevant comparator in the complement inhibitor-experienced population with residual anaemia.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Exploration of alternative model structures or health states that align with the iptacopan clinical trial endpoints.

Issue 5 Modelled treatment sequence in the complement inhibitor-naïve population

Report section	4.2.4.1
Description of issue and why the EAG has identified it as important	In the complement inhibitor-naïve population, the company modelled the treatment sequence: iptacopan to ravulizumab vs. C5 inhibitors to pegcetacoplan, and used the transition probabilities from the complement inhibitor-experienced population with residual anemia for pegcetacoplan when used as a second-line treatment after C5 inhibitors, while the transition probabilities from the complement inhibitor-naïve population was used for second-line ravulizumab after iptacopan.. This creates an inconsistency in approach for second-line pegcetacoplan and ravulizumab in the complement inhibitor-naïve population, and makes it less clear whether it is appropriate to model a subsequent line of therapy in the naïve population if these patients are now classified as complement inhibitor-experienced with residual anaemia, after discontinuation from their initial treatment.

What alternative approach has the EAG suggested?	The EAG considers it more appropriate to model the sequence: iptacopan to ravulizumab vs. C5 inhibitors (no discontinuation) in the complement inhibitor-naïve population, where C5 inhibitors is considered the current standard of care in the NHS in the treatment naïve population, and use the transition probabilities from the naïve population for C5 inhibitors at first and second-line, in order to avoid the inconsistency in approach used by the company. Furthermore, the EAG's proposed modelled sequence in the naïve population is in line with the approach used by the company in the complement inhibitor-experienced population, where a subsequent line of treatment is not considered for C5 inhibitors.
What is the expected effect on the cost-effectiveness estimates?	EAG Scenario 4 shows that [redacted] (same as company's base case), while the ICER for iptacopan compared to eculizumab is [redacted] using 24-week data and [redacted] using 48-week data, which is driven by lower QALYs associated with eculizumab treatment (a greater proportion in the anaemia and transfusion health states compared to iptacopan) but [redacted] that is used as the subsequent treatment following discontinuation from eculizumab in the company's base case.
What additional evidence or analyses might help to resolve this key issue?	No further additional analyses required.

Issue 6 Transition probabilities based on a lack of direct or indirect comparison of treatments

Report section	4.2.6.1
Description of issue and why the EAG has identified it as important	The transition probabilities used in the model are based on a lack of direct or indirect comparison of iptacopan with C5 inhibitors in the complement inhibitor-naïve population, and iptacopan with pegcetacoplan in the complement inhibitor-experienced population with residual anaemia.
What alternative approach has the EAG suggested?	The EAG acknowledges that the validity of any indirect comparison of transition probabilities for iptacopan and pegcetacoplan from APPLY-PNH and PEGASUS is likely to be severely limited due to large differences observed in outcomes of the C5 inhibitor arms across the two trials. Therefore this issue is unlikely to be resolved without direct (head-to-head) evidence on the effectiveness of the treatments.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Studies directly comparing iptacopan with pegcetacoplan in the complement inhibitor-experienced population with residual

	anaemia, and iptacopan with C5 inhibitors in the complement inhibitor-naive population.

Issue 7 Assessment time period from the iptacopan trials

Report section	4.2.6.1
Description of issue and why the EAG has identified it as important	Treatment effectiveness in the company submission Document B is based on data up to Day 168 from the iptacopan trials, which marks the end of the randomised treatment period of APPLY-PNH and core treatment period of APPOINT-PNH (the 24-week data analysis). Supplementary analyses based on the full 48-week trial duration of APPLY-PNH and APPOINT-PNH (the 48-week data analysis) is provided for transition probabilities, discontinuation and BTH event rates for iptacopan only. The available data up to week 24 from APPLY-PNH is used for C5 inhibitors in the 48-week data analysis, while the same transition probabilities for C5 inhibitors and pegcetacoplan are used in the 24-week and 48-week data analysis. This means that different assessment time periods are used to inform the transition probabilities, discontinuation and BTH event rates for iptacopan and the comparator complement inhibitors, while the 24-week data for utility values from the APPOINT-PNH and APPLY-PNH trials is used for iptacopan in the 48-week data analysis While the EAG considers the use of longer follow-up data to be best practice, in general, the EAG is concerned that the 48-week data analysis is not making a fair comparison of iptacopan and the comparator complement inhibitors because of the variation in length of assessment time period used for the comparators and inconsistencies in data cut used across modelled parameters.
What alternative approach has the EAG suggested?	Use of the 24-week data for iptacopan avoids all inconsistencies in the 48-week analysis.
What is the expected effect on the cost-effectiveness estimates?	For completeness, all scenarios and cost-effectiveness results are presented for both the 24-week data and 48-week data.
What additional evidence or analyses might help to resolve this key issue?	No further additional analyses required.

Issue 8 Annual discontinuation rates for iptacopan and pegcetacoplan

Report section	4.2.6.4
Description of issue and why the EAG has identified it as important	An annual probability of discontinuation for iptacopan (3.43% in the 24-week data and 2.72% in the 48-week data) and pegcetacoplan (16.13%) was informed by treatment-specific all-

	cause discontinuation rates from APPLY-PNH and PEGASUS, respectively. The EAG's clinical advisor considered it unlikely that a large difference in the annual discontinuation rates for iptacopan and pegcetacoplan would be observed in clinical practice. Participants that discontinued pegcetacoplan in the PEGASUS trial are likely to be managed differently in the UK and likely to remain on pegcetacoplan for longer; in addition, some of the observed events in the PEGASUS trial that resulted in discontinuation of pegcetacoplan (e.g., diffuse large B cell lymphoma and acute leukaemia) are not treatment-specific. The cost-effectiveness of iptacopan and pegcetacoplan is largely determined by the differential discontinuation rates between the two treatments because after discontinuation from either iptacopan or pegcetacoplan the model assumes that patients switch to ravulizumab, which is associated with a higher percentage of patients with uncontrolled anaemia and a higher percentage of patients' transfusion dependent. The EAG is concerned that the use of treatment-specific annual discontinuation rates from the short-term clinical trials may not reflect long-term treatment persistence, or how patients are managed in the NHS.
What alternative approach has the EAG suggested?	The EAG considered alternative assumptions for the annual discontinuation rate of pegcetacoplan compared to iptacopan in the complement inhibitor-experienced population with residual anaemia: • EAG Scenario 5a considers the same annual discontinuation rate for pegcetacoplan and iptacopan of 3.43% per year (24-week data, or 2.72% per year for 48-week data); • EAG Scenario 5b considers a slightly higher discontinuation rate for pegcetacoplan of 5% per year compared to iptacopan of 3.43% per year (24-week data, or 2.72% per year for 48-week data); • EAG Scenario 5c considers a higher discontinuation rate for pegcetacoplan of 10% per year compared to iptacopan of 3.43% per year (24-week data, or 2.72% per year for 48-week data).
What is the expected effect on the cost-effectiveness estimates?	EAG scenario 5a shows that the QALY gains for iptacopan compared to pegcetacoplan are substantially reduced to near zero (because the company assumes the same treatment-specific health state utility values for pegcetacoplan and iptacopan). EAG scenario 5b shows that the QALY gains for iptacopan compared to pegcetacoplan are reduced by 75%. EAG scenario 5c shows that the QALY gains for iptacopan compared to pegcetacoplan are reduced by 29%.

	However, across all scenarios, [redacted].
What additional evidence or analyses might help to resolve this key issue?	Long-term data on treatment continuation rates in the NHS.

Issue 9 Treatment-specific health state utility values

Report section	4.2.8.3
Description of issue and why the EAG has identified it as important	The model uses treatment-specific health state utility values and the difference in utility between iptacopan and C5 inhibitors is substantial despite being in the same health state. The EAG considers that the only plausible explanation for a difference in health state utility by treatment is due to the disutility associated with mode of treatment administration; however, the EAG does not consider the magnitude of the difference in treatment-dependent utility values between iptacopan and C5 inhibitors to be realistic. The underlying evidence for this difference is weak and the baseline utility value (utility value at Day 1) differed substantially between patients treated with iptacopan and C5 inhibitors in APPLY-PNH indicating that the difference in the utility values could be due to small sample sizes and baseline characteristics between patients treated with iptacopan and C5 inhibitors. The EAG considers that the health benefits of treatment are already captured in the transitions between health states and the application of treatment-specific utility values leads to double-counting of the treatment effect.
What alternative approach has the EAG suggested?	The EAG considers it more appropriate to use treatment-independent health state utility values, which is in line with the approach used in TA778 and TA698. EAG Scenario 6 considers the cost-effectiveness of iptacopan relative to the comparator complement inhibitors when treatment-independent health state utility values are used in the model.
What is the expected effect on the cost-effectiveness estimates?	In the complement inhibitor-naïve population, EAG Scenario 6 does not change the company's base case conclusion [redacted], but the QALY gain from iptacopan compared to C5 inhibitors is substantially reduced (over 50% reduction) relative to the company's base case. In the complement inhibitor-experienced population with residual anaemia, the QALY gains for iptacopan vs. the comparator complement inhibitors are reduced by 30% in EAG Scenario 6 [redacted]

	[redacted].
What additional evidence or analyses might help to resolve this key issue?	No further additional analyses required.

Issue 10 Concomitant eculizumab acquisition costs for patients initiating pegcetacoplan.

Report section	4.2.9.2
Description of issue and why the EAG has identified it as important	The model includes 4-week concomitant eculizumab acquisition costs for 12% of patients initiating pegcetacoplan in order to reflect the PEGASUS trial. The EAG considers the inclusion of these costs to be inappropriate because the transition probabilities used in the model for pegcetacoplan are based on the randomised controlled period of the PEGASUS trial from weeks 4-16, in which patients had either pegcetacoplan or eculizumab, and not the 4-week run-in period in which both treatments were given, i.e., the transition probabilities are based only on weeks 4-16 after the 4-week washout period in order to mitigate any 'hangover' effect of the run-in period in PEGASUS.
What alternative approach has the EAG suggested?	The EAG considers it more appropriate to exclude concomitant eculizumab acquisition costs for patients initiating pegcetacoplan. EAG Scenario 7 considers the cost-effectiveness of iptacopan relative to the comparator complement inhibitors when concomitant eculizumab acquisition costs for patients initiating pegcetacoplan are excluded in the complement inhibitor-experienced population with residual anaemia.
What is the expected effect on the cost-effectiveness estimates?	EAG Scenario 7 had only a small impact on the cost-effectiveness results and did not change the company's base case ICER results.
What additional evidence or analyses might help to resolve this key issue?	No further additional analyses required.

1.6 Other key issues: summary of the EAG's view

No other key issues identified.

1.7 Summary of EAG's preferred assumptions and resulting ICER

Section 6.3 and Table 2 summarises the EAG's preferred assumptions and resulting ICER in the complement inhibitor-naïve population using 24-week data and 48-week data, respectively. Table 3 and Table 4 summarises the EAG's preferred assumptions and resulting ICER in the complement

inhibitor-experienced population with residual anaemia using 24-week data and 48-week data, respectively.

Table 2 Summary of EAG's preferred assumptions and resulting ICER in the complement inhibitor-naïve population using 24-week data.

Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER
company base-case	Iptacopan	[redacted]	16.59	-	-	-
	Eculizumab	[redacted]	15.52	[redacted]	-1.07	[redacted]
	Ravulizumab	[redacted]	15.53	[redacted]	-1.06	[redacted]
Scenario 4: Modelled treatment sequence	Eculizumab	[redacted]	15.02	-	-	-
	Iptacopan	[redacted]	16.59	[redacted]	1.57	[redacted]
	Ravulizumab	[redacted]	15.03	[redacted]	-1.55	[redacted]
Scenario 6: Treatment-independent health state utility values	Iptacopan	[redacted]	17.12	-	-	-
	Eculizumab	[redacted]	16.68	[redacted]	-0.44	[redacted]
	Ravulizumab	[redacted]	16.69	[redacted]	-0.43	[redacted]
EAG's preferred base case EAG Scenarios 4+6	Eculizumab	[redacted]	16.51	-	-	-
	Iptacopan	[redacted]	17.12	[redacted]	0.61	[redacted]
	Ravulizumab	[redacted]	16.52	[redacted]	-0.60	[redacted]

Table 3 Summary of EAG's preferred assumptions and resulting ICER in complement inhibitor-naïve population using 48-week data.

Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER
company base-case	Iptacopan	[redacted]	16.68	-	-	-
	Eculizumab	[redacted]	15.52	[redacted]	-1.17	[redacted]
	Ravulizumab	[redacted]	15.53	[redacted]	-1.16	[redacted]
Scenario 4: Modelled treatment sequence	Eculizumab	[redacted]	15.02	-	-	-
	Iptacopan	[redacted]	16.68	[redacted]	1.66	[redacted]
	Ravulizumab	[redacted]	15.03	[redacted]	-1.65	[redacted]
Scenario 6: Treatment-independent health state utility values	Iptacopan	[redacted]	17.11	-	-	-
	Eculizumab	[redacted]	16.68	[redacted]	-0.43	[redacted]
	Ravulizumab	[redacted]	16.69	[redacted]	-0.42	[redacted]
EAG's preferred base case EAG Scenarios 4+6	Eculizumab	[redacted]	16.51	-	-	-
	Iptacopan	[redacted]	17.11	[redacted]	0.60	[redacted]
	Ravulizumab	[redacted]	16.52	[redacted]	-0.59	[redacted]

Table 4 Summary of EAG's preferred assumptions and resulting ICER in the complement inhibitor-experienced population with residual anaemia using 24-week data.

Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER
company base-case	Eculizumab	[redacted]	12.68	-	-	-
	Iptacopan	[redacted]	14.42	[redacted]	1.74	[redacted]
	Ravulizumab	[redacted]	12.68	[redacted]	-1.74	[redacted]
	Pegcetacoplan	[redacted]	13.35	[redacted]	-1.07	[redacted]
Scenario 5c: Discontinuation rate for pegcetacoplan of 10% per year	Eculizumab	[redacted]	12.68	-	-	-
	Iptacopan	[redacted]	14.42	[redacted]	1.74	[redacted]
	Ravulizumab	[redacted]	12.68	[redacted]	-1.74	[redacted]
	Pegcetacoplan	[redacted]	13.65	[redacted]	-0.77	[redacted]
Scenario 6: Treatment-independent health state utility values	Eculizumab	[redacted]	13.51	-	-	-
	Iptacopan	[redacted]	14.68	[redacted]	1.17	[redacted]
	Ravulizumab	[redacted]	13.51	[redacted]	-1.17	[redacted]
	Pegcetacoplan	[redacted]	13.95	[redacted]	-0.72	[redacted]
Scenario 7: Exclusion of concomitant eculizumab acquisition costs for patients initiating pegcetacoplan	Eculizumab	[redacted]	12.68	-	-	-
	Iptacopan	[redacted]	14.42	[redacted]	1.74	[redacted]
	Ravulizumab	[redacted]	12.68	[redacted]	-1.74	[redacted]
	Pegcetacoplan	[redacted]	13.35	[redacted]	-1.07	[redacted]
EAG's preferred base case EAG Scenarios 5c+6+7	Eculizumab	[redacted]	13.51	-	-	-
	Iptacopan	[redacted]	14.68	[redacted]	1.17	[redacted]
	Ravulizumab	[redacted]	13.51	[redacted]	-1.17	[redacted]
	Pegcetacoplan	[redacted]	14.16	[redacted]	-0.52	[redacted]

Table 5 Summary of EAG's preferred assumptions and resulting ICER in the complement inhibitor-experienced population with residual anaemia using 48-week data.

Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER
company base-case	Iptacopan	[redacted]	14.47	-	-	-
	Eculizumab	[redacted]	12.60	[redacted]	-1.86	[redacted]
	Ravulizumab	[redacted]	12.60	[redacted]	-1.86	[redacted]
	Pegcetacoplan	[redacted]	13.29	[redacted]	-1.18	[redacted]
Scenario 5c: Discontinuation rate for pegcetacoplan of 10% per year	Iptacopan	[redacted]	14.47	-	-	-
	Eculizumab	[redacted]	12.60	[redacted]	-1.86	[redacted]
	Ravulizumab	[redacted]	12.60	[redacted]	-1.86	[redacted]
	Pegcetacoplan	[redacted]	13.61	[redacted]	-0.86	[redacted]
Scenario 6: Treatment-independent health state utility values	Iptacopan	[redacted]	14.62	-	-	-
	Eculizumab	[redacted]	13.37	[redacted]	-1.24	[redacted]
	Ravulizumab	[redacted]	13.37	[redacted]	-1.24	[redacted]
	Pegcetacoplan	[redacted]	13.85	[redacted]	-0.76	[redacted]

Scenario 7: Exclusion of concomitant eculizumab acquisition costs for patients initiating pegcetacoplan	Iptacopan	[redacted]	14.47	-	-	-
	Eculizumab	[redacted]	12.60	[redacted]	-1.86	[redacted]
	Ravulizumab	[redacted]	12.60	[redacted]	-1.86	[redacted]
	Pegcetacoplan	[redacted]	13.29	[redacted]	-1.18	[redacted]
EAG's preferred base case EAG Scenarios 5c+6+7	Iptacopan	[redacted]	14.62	-	-	-
	Eculizumab	[redacted]	13.37	[redacted]	-1.24	[redacted]
	Ravulizumab	[redacted]	13.37	[redacted]	-1.24	[redacted]
	Pegcetacoplan	[redacted]	14.07	[redacted]	-0.55	[redacted]

EXTERNAL ASSESSMENT GROUP REPORT

2 INTRODUCTION AND BACKGROUND

Important note: During the appraisal process the EAG received additional data from the company, including corrections to data that were presented in the original company submission (CS). This EAG report incorporates and/or refers to the most accurate and up-to-date available evidence throughout. Some tables from the submitted company documents have been reproduced here for clarity and ease of reference.

2.1 Introduction

In this report, the EAG has reviewed the clinical and cost-effectiveness evidence in the Company Submission (CS) and additional materials in support of iptacopan for treating paroxysmal nocturnal haemoglobinuria (PNH). GB marketing authorisation is anticipated in [redacted]

In this section, the EAG critiques the company's proposed treatment pathway, positioning of iptacopan, and its definition of the decision problem when compared with the NICE scope.

2.2 Background

Iptacopan is a proximal complement inhibitor targeting Factor B (FB) administered orally twice-daily at 200mg per dose. Its mechanism of action is defined in table 2 of the CS. Briefly, iptacopan acts proximally to control both C3b-mediated extravascular haemolysis (EVH) and terminal complement-mediated intravascular haemolysis (IVH).

Section B.1.3 of the CS provides a brief and accurate overview of PNH, its aetiology, epidemiology, and prognosis.

2.2.1 Treatment pathway

The treatment pathway described in section B.1.3.3 of the CS broadly reflects current UK practice for the management of PNH.

In relation to clinical subtypes, the EAG's clinical advisor noted that subclinical PNH is largely irrelevant, as only symptomatic PNH is treated.

Across the UK, around 35-40% of patients seen in the National PNH Service are treated with anti-complement therapy, with the majority of patients receiving ravulizumab as initial treatment. Eculizumab is also considered a useful option, particularly in an emergency setting to avoid thrombosis in newly diagnosed patients. For patients who remain anaemic on ravulizumab or

eculizumab, switching to pegcetacoplan will be attempted after around 6 months. Currently around 15% of patients receive pegcetacoplan, though this proportion is increasing. Patients with renal failure or pregnancy will typically continue to receive eculizumab, given the relative shortage of safety data for ravulizumab or pegcetacoplan.

Section B.1.3.3.2 of the CS describes supportive care. The EAG's clinical advisor noted that due to tolerability issues associated with chelation treatment, iron levels are usually monitored but not always treated if slightly elevated. Consequently, real-world levels of iron chelation are likely to be lower than those observed in clinical trials (estimated to be around 3-5%).

Section B.1.3.3.2 of the CS describes allogeneic bone marrow transplant as a rarely available curative option. The EAG's clinical advisor clarified that, due to poor outcomes, essentially no NHS patients receive a bone marrow transplant for PNH – the procedure is only undertaken if indicated for concomitant bone marrow failure.

Section B.1.3.4.4.2 of the CS discusses the limitations of the modes of administration of currently available complement inhibitors, which are delivered via intravenous (eculizumab/ravulizumab) or subcutaneous infusion (pegcetacoplan). The EAG's clinical advisor agreed with the difficulties associated with infusion, but also raised the possibility of patient-specific compliance issues among some younger and older patients with a twice daily oral treatment such as iptacopan. The mode of administration means that compliance can be directly monitored for eculizumab and ravulizumab, but not for pegcetacoplan or iptacopan.

2.2.2 Company's proposed positioning

The ERG agrees with the company's proposed positioning of iptacopan in adult patients with PNH who are either complement inhibitor-naïve or complement inhibitor-experienced with residual anaemia (Figure 2 of CS). This is in line with the anticipated marketing authorisation and the respective APPOINT-PNH and APPLY-PNH study populations.

2.2.3 Equality considerations

As noted in section B.1.4 of the CS, the existing treatment options that are administered by SC or IV infusion, may disadvantage patients with needle phobia and/or dexterity, visual or cognitive issues (where treatment is self-administered). The company suggests that, as the first oral complement inhibitor monotherapy for PNH, iptacopan may provide an alternative treatment for such patients. The EAG's clinical advisor agreed with these concerns, but also highlighted that self-administered twice-daily oral treatment with iptacopan could potentially disadvantage patients with memory issues, compared with a relatively infrequent infusion delivered by a health-professional, such as

ravulizumab. Clinician preference would be for a range of administration options to be available, thereby permitting patient-specific decisions.

2.3 Critique of company's definition of decision problem

Table 6 summarises the decision problem as defined in the NICE scope and the CS.

The CS appropriately presents the results for (1) complement inhibitor-naïve patients who have haemolysis with clinical symptoms and (2) complement inhibitor-experienced patients with residual anaemia. This reflects the anticipated licence for iptacopan.

The APPOINT-PNH trial includes a substantially larger proportion of East Asian patients (67.5%) than would be seen in the UK complement-inhibitor naïve treatment population. The EAG's clinical advisor noted that patients in Southeast Asia, Japan and South Korea are likely to have more bone marrow failure and less thrombosis than UK patients, but the populations are broadly comparable i.e. all are symptomatic patients with PNH, high LDH levels and anaemia. The EAG's clinical advisor also noted that patients with current aplastic anaemic are typically excluded from trials, so mortality in real world settings is likely to be higher due to aplasia.

As stated by the company, the CS highlights difficulties in self-administering pegcetacoplan as a subcutaneous infusion for patients with dexterity, visual or cognitive disabilities. However, the CS does not present any subgroup evidence specific to such patients. The CS also does not provide evidence on compliance with daily oral iptacopan treatment. Given the relatively short half-life of iptacopan, it may be worth considering whether there are also subgroups at risk of missing doses and subsequent breakthrough haemolysis e.g. patients with age-related cognitive decline. While not reported in the CS, clinical study report data suggest high compliance with oral iptacopan in the short term, though longer-term data are not yet available (see section 3.2).

Table 6 Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with PNH	Adults with PNH: Complement inhibitor-naïve patients who have haemolysis with clinical symptom(s) Complement inhibitor-experienced patients with anaemia despite treatment with a complement inhibitor	The submission covers two subpopulations of adult patients with PNH, in line with the evidence available from iptacopan Phase 3 clinical trials (APPOINT-PNH and APPLY-PNH) and the expected licence wording. This also allows consideration of differences in relevant comparators for the two subpopulations.	As stated by the company, the two stated subpopulations reflect the APPOINT-PNH and APPLY-PNH studies and match the draft Summary of product characteristics (SmPC) for iptacopan. APPOINT-PNH population includes a substantially larger proportion of East Asian patients (67.5%) than would be seen in UK practice. However, the clinical differences between populations recruited in Asia and the UK are not likely to be important for this evaluation (see section 3.2.1). Patients with current aplastic anaemic are typically excluded from trials, so mortality in real world settings is likely to be higher.[1]
Intervention	Iptacopan	Iptacopan	–	The intervention is consistent with the NICE scope.
Comparator(s)	• Eculizumab • Ravulizumab • Pegcetacoplan • Danicopan with a C5 inhibitor (subject to NICE ongoing appraisal)	Complement inhibitor-naïve patients: • Eculizumab • Ravulizumab Complement inhibitor-experienced patients with anaemia: • Eculizumab • Ravulizumab • Pegcetacoplan	Pegcetacoplan is not a relevant comparator for the naïve population since its licence and NICE recommendation are restricted to patients who have anaemia after ≥3 months of treatment with a C5 inhibitor Danicopan with a C5 inhibitor has not been considered since it does not currently have a licence and is not expected to become established NHS	The EAG agrees with the company's rationales for excluding danicoplan and pegcetacoplan (for the naïve population) as comparators for this appraisal

			clinical practice prior to the appraisal of iptacopan by committee.	
Outcomes	The outcome measures to be considered include: • overall survival • intravascular haemolysis • extravascular haemolysis • breakthrough haemolysis • transfusion avoidance • haemoglobin • thrombotic events • adverse effects of treatment • health-related quality of life.	The outcome measures assessed in the submission include: • overall survival • intravascular haemolysis (as measured by lactate dehydrogenase) • extravascular haemolysis (as measured by reticulocyte count) • breakthrough haemolysis • transfusion avoidance • haemoglobin • thrombotic events • adverse effects of treatment • health-related quality of life.	Consistent with final scope	The outcomes are consistent with the NICE scope.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	The reference case has been adhered to.	Not applicable – in line with final NICE scope	In line with NICE scope.
Subgroups	If the evidence allows the subgroups based on previous treatment with complement inhibitors will be considered: • treatment naïve • treatment experienced	Complement inhibitor-naïve patients Complement inhibitor-experienced patients with anaemia despite treatment with a complement inhibitor	The submission covers all patient populations for whom evidence from iptacopan Phase 3 trials is available. The APPOINT-PNH study included complement inhibitor-naïve	As stated by the company, the anticipated licence applies to just two of the subgroups listed in the NICE scope: (1) treatment naïve

	• treatment experienced with anaemia despite previous treatment		patients, while the APPLY-PNH study included complement inhibitor-experienced patients with anaemia. No evidence is available for treatment-experienced patients without anaemia, and the licence is not expected to cover this patient subgroup.	(2) treatment experienced with anaemia despite previous treatment
Special considerations including issues related to equity or equality	The NICE equality impact assessment – Scoping, preliminary view noted that: All protected characteristics will be considered by committee when making its recommendations. However, the committee can only make recommendations within a technology's marketing authorisation. The committee will consider the potential implications of pegcetacoplan being a self-administered subcutaneous injection† and iptacopan offering a potentially easier route of administration for people who find it difficult, or might not be able to self-administer pegcetacoplan.	The submission highlights the limitations of pegcetacoplan as a subcutaneous infusion† for patients with dexterity, visual or cognitive disabilities. These groups may find difficulty or not be able to self-administer the treatment. Iptacopan – as an oral treatment – would offer an advantage to these patients.	–	The EAG note that there is no specific subgroup evidence for patients with dexterity, visual or cognitive disabilities. The CS also did not provide evidence on compliance with daily oral treatment, though compliance data from from clinical study reports and the company's response to points for clarification are presented in section 3.2

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company conducted a systematic literature review (SLR) to identify evidence on the clinical effectiveness and safety of complement inhibitors for the treatment of PNH that are currently available or in development; the list of included comparators was thus broader than specified in the NICE decision problem. The SLR also aimed to identify real-world evidence to provide supplementary information. Full details of the review are reported in Appendix D of the CS.

Searches

The CS included searches to identify evidence on the clinical effectiveness and safety of currently available complement inhibitors, as well as complement inhibitors currently in development, for PNH. A detailed description of the searches and most of the search strategies were included in Appendix D.1.2 of the CS.

In response to the EAG's PfCs (C1-C4), the company provided additional search strategies, PRISMA diagrams, and revised/corrected searches. No additional studies were identified from these revised searches.

An appraisal of the literature searches is presented in Appendix 1

Inclusion criteria

The eligibility criteria used to select studies for inclusion in the systematic review were presented in Table 5 of CS Appendix D. The EAG considers these criteria to be appropriate to the decision problem. Two independent reviewers evaluated all titles and abstracts, and full-texts (with arbitration by a third reviewer where necessary), which reduces the possibility of reviewer errors or bias affecting the selection process.

Critique of data extraction

The CS appendix stated that data were extracted by one reviewer and checked for accuracy by a second, which reduces the possibility of errors or bias affecting data extraction.

Data were only extracted for clinical trials, registry studies and large observational studies (n >100). Smaller observational studies (n≤100) were listed in Appendix D.

Quality assessment

Studies included in the systematic review were evaluated for risk of bias by one reviewer and checked by a second, using version 2 of the Cochrane risk of bias tool (applied to APPLY-PNH, Study 301, PEGASUS, and TRIUMPH), an adaptation of the Critical Appraisal Skills Programme (CASP)

checklist (applied to APPOINT-PNH), or the NICE Real World Evidence (RWE) framework (applied to APPEX).

The results were reported in table 10 and 11 Appendix D3; only domain-level judgements were reported, so the ERG therefore checked the risk of bias assessments in the two key iptacopan studies (APPOINT-PNH and APPLY-PNH) and comparator studies used in the indirect treatment comparisons (Study 310, TRIUMPH, APPEX and PEGASUS).

Table 7, Table 8, and Table 9 below show the company's and, where appropriate, the EAG's risk of bias assessments. The company and EAG agreed, on the basis of the study-specific tools that most studies included in the CS had an overall low risk of bias for their particular design (RCT, single arm observational study, real world data). However, concerns other than risk of bias are described in section 3.3 of this report and concerns specific to the indirect treatment comparisons are described in section 3.4.

The EAG noted some concerns about baseline differences between arms in the TRIUMPH study. However, this study was not used for the analyses presented in main CS report (see section 3.4 on indirect treatment comparisons).

Table 7 Quality assessment of RCTs using Cochrane RoB 2.0

		Domain 1: Randomisation process	Domain 2: Deviations from intended interventions	Domain 3: Risk of bias due to missing outcome data	Domain 4: Risk of bias in measurement of the outcome	Domain 5: Risk of bias in selection of the reported result	Algorithm's overall risk of bias judgement (low risk/high risk/some concerns)	Assessor's overall judgement (low risk/high risk/some concerns)
		Risk-of bias judgement (low/high/some concerns)	Risk-of bias judgement (low/high/some concerns)	Risk-of-bias judgement (low risk/high risk/some concerns)	Risk of bias judgement (low risk/high risk/some concerns)	Risk of bias judgement (low risk/high risk/some concerns)		
TRIUMPH[2]	Company assessment	Some concerns	Low	Low	Low	Low	Some concerns	Some concerns
	EAG Assessment	Some concerns*	Low	Low	Low	Low	Some concerns	Some concerns
Study 301[3]	Company assessment	Some concerns	Low	Low	Low	Low	Some concerns	Low
	EAG Assessment	Some concerns**	Low	Low	Low	Low	Some concerns	Low
APPLY-PNH [4]	Company assessment	Low	Low	Low	Low	Low	Low	Low
	EAG Assessment	Low	Low	Low	Low	Low	Low	Low
PEGASUS[5]	Company assessment	Low	Low	Low	Low	Low	Low	Low
	EAG Assessment	Low	Low	Low	Low	Low	Low	Low†

* Baseline differences in history of aplastic anaemia; use of anticoagulants
** Stratified randomisation. Method of allocation concealment not described. However, likely to have been concealed
†After the combination (pegcetacoplan + eculizumab) run-in period, eculizumab-arm patients reverted to baseline haemoglobin levels by 4 weeks, while study endpoint was 16 weeks. However, the trial design has implications for indirect treatment comparisons (see section 3.4)

Table 8: Quality assessment of APPOINT-PNH adapted from the CASP checklist

		APPOINT-PNH4	
No	**Items**	**Company assessment**	**EAG assessment**
1	Was the cohort recruited in an acceptable way?	Yes	Yes
2	Was the exposure accurately measured to minimise bias?	Yes	Yes
3	Was the outcome accurately measured to minimise bias?	Yes	Yes
4	Have the authors identified all important confounding factors?	Yes	Yes
5	Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Yes
6	Was the follow-up‡ of patients complete?	Yes	Yes
7	How precise (for example, in terms of confidence interval and p values) are the results?	Yes	Yes

‡Defined as the follow-up by the end of study duration

Table 9: APPEX: Risk of bias assessment

Type of bias	How bias was addressed or assessed
Selection bias at study entry	Risk of selection bias at study entry was reduced by using a target trial framework defining inclusion and exclusion criteria for the population. All patients from the centre in France who met the eligibility criteria and had baseline and post-baseline measurements were included in the APPEX cohort. In the UK centre, patients were randomly selected among those meeting the eligibility criteria, using random number assignment.
Selection bias at study exit	Risk of selection bias at study exit is considered small; while patients who were lost to follow-up prior to completing 6 months of C5 inhibitor treatment were not included in the study, there are only two centres in the UK treating PNH patients and the risk of loss to follow-up is low.
Addressing confounding	Confounding bias due to potential differences between the APPEX real-world cohort and APPOINT-PNH trial population on prognostic or predictive factors of the outcomes was identified as a risk for the comparative effectiveness assessment. A target trial framework was employed to reduce the risk of bias. Potential confounders and prognostics factors were identified through systematic literature review and expert assessment. The corresponding variables collected from the clinical record sources were as follows: • Transfusion needs (implemented as total number of packed RBC transfused 24 weeks prior to index date), • Baseline haemoglobin, • Baseline reticulocyte count, • Ongoing bone marrow failure including aplastic anaemia and neutropenia, and • History of MAVE. Renal disease/eGFR could not be included in the propensity score because no information was available from the data sources. To protect against unmeasured confounding, age and sex were included as a perturbation variable, for being weakly correlated with eGFR. To reduce the risk of bias introduced from the propensity score model and outcome model in the estimation of comparative effectiveness, a debiased/double machine learning algorithm was implemented using 4-fold cross fitting of orthogonalized scores from efficient influence function.
Detection bias	PNH patients in the UK are centrally managed by the National PNH Service, and healthcare practices for PNH patients are assumed to be consistent across the UK and in France. However, irregular or infrequent Hb outcome assessment in clinical practice presents a limitation for the comparison vs APPOINT-PNH clinical trial data. Patients included in the APPEX cohort were incident users of C5 inhibitors and had sufficient length of follow up as defined in the analysis plan (duration of treatment exposure to eculizumab (84 patients), mean (SD): 199.8 days (1.14); to ravulizumab (1 patient): 200 days), to enable a comparison to APPOINT-PNH data collected up to Week 24.
Measurement error and misclassification	The risk of measurement error and misclassification is considered low. In the assessments of data quality, measurements seemed to correspond adequately to known clinical status. Errors identified by values outside standard normal ranges were few.
Missing data	Missing outcomes data and less frequent assessments in a real-world cohort compared to a clinical trial were recognised as a potential source of bias. In the French data source, measurements of Hb in particular were taken more frequently than in the UK data source. Data on LDH and reticulocyte counts was sparser in both data sources. The extent of mismatch in available values and conduct was assessed, and a sensitivity analysis using alternative assessment time windows for the APPEX cohort was conducted. Endpoints in the APPEX cohort were derived based on the mean of observations falling within assessment windows, which was intended to protect against informative missingness of measurements.

Type of bias	How bias was addressed or assessed
Reverse causation	The risk of reverse causation bias is considered low. Patients included in the APPEX cohort were incident users of C5 inhibitors, with the index date defined as the day of first exposure to C5 inhibitor treatment. Since C5 inhibitors are administered intravenously, the risk of misclassification of exposure is low. Patients with PNH receiving complement inhibitor treatment are closely followed up in clinical practice and the included secondary care centres are assumed to record all data relevant to the registry in a timely manner. The analyses used longitudinal outcomes data.

Evidence synthesis

In Appendix D.1.5, the company state that they included 16 unique clinical trials, 32 registries or large (n>100) observational studies, and 32 small (n≤100) observational studies.

Of these studies, the APPOINT-PNH and APPLY-PNH studies provided the only evidence for iptacopan in the CS. Details of these studies were presented in sections B.2.1 to B.2.7 of the CS and are discussed in section 3.2 of this EAG report.

Additional studies providing evidence for comparators in the indirect treatment comparisons (ITCs) were: Study 301 (RCT comparing ravulizumab vs. eculizumab in complement inhibitor-naïve patients), TRIUMPH (placebo-controlled RCT of eculizumab in complement inhibitor-naïve patients), APPEX (real world individual participant data on C5 inhibitor treatment in previously complement inhibitor-naïve patients), and PEGASUS (RCT comparing pegcetacoplan vs eculizumab in patients with PNH with residual anaemia despite eculizumab therapy for ≥3 months); see Table 10. Details of these studies and the ITCs were presented in section B.2.9 and Appendix D.4 of the CS.

Other studies identified in the SLR were excluded from the CS on the basis of non-relevant comparators, non-licensed dosage regimens, substantially different analysis timepoints to the iptacopan studies, unlicenced use of iptacopan (as an add-on to eculizumab), or currently unlicenced comparator (danicopan). A full list of reasons for exclusion was presenting in tables 12 and 13 of Appendix D.4.2.

Table 10 Evidence included in the company submission

	Complement inhibitor-naïve patients who have haemolysis with clinical symptom(s)	**Complement inhibitor-experienced patients with anaemia despite treatment with a complement inhibitor**
Direct evidence	***APPOINT-PNH*** (iptacopan single arm study)	***APPLY-PNH*** (iptacopan vs ecu/rav)
Indirect treatment comparison(s)	1. ***APPOINT-PNH*** (iptacopan) vs ***Study 301*** (eculizumab vs ravulizumab)* 2. ***APPOINT-PNH*** (iptacopan) vs ***APPEX*** (eculizumab or ravulizumab)* 3. ***APPOINT-PNH*** (iptacopan) vs ***TRIUMPH*** (eculizumab vs placebo)*†	***APPLY-PNH*** (iptacopan vs ecu/rav) vs ***PEGASUS*** (pegcetacoplan vs ecu)**

*Unanchored **Both anchored and unanchored are presented †Only presented in appendix D

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

Sections B.2.1 to B.2.7 of the CS summarised two phase three clinical studies of iptacopan: APPOINT-PNH (complement inhibitor naïve population) and APPLY-PNH (complement inhibitor experienced population with residual anaemia).

Note that the original CS included only 24-week follow-up data for these two studies. Following a clarification request from the EAG (PfC A3), the company also provided 48-week follow-up data from a more recent data cut. This EAG report will address both the 24- and 48-week data.

3.2.1 Complement inhibitor-naïve population: APPOINT-PNH

3.2.1.1 Trial design and methods

Table 5 (p.33) and section B.2.3.1 of the CS summarises the design and methodology of the APPOINT-PNH study. Briefly, this was a multicentre, open-label, single-arm study.

The study included 40 adults with a confirmed diagnosis of PNH with haemolysis, as defined by a clone size ≥ 10%, mean haemoglobin level <10 g/dL, LDH >1.5 times the upper limit of normal, and no prior treatment with a complement inhibitor. Participants with a history of bone marrow failure, hematopoietic stem cell transplantation (HSCT), or known or suspected hereditary complement deficiency were excluded.

After an 8-week screening period, all participants received 200 mg twice-daily oral iptacopan for 24 weeks, followed by a 24-week treatment extension period (CS figure 3, p.36)

The primary endpoint was haematological response, defined as an increase in haemoglobin of ≥2 g/dL from baseline in the absence of packed red blood cell (pRBC) transfusions.

Points for critique

Single-arm open-label design

APPOINT-PNH was a single arm study, so could only provide evidence of change from baseline for its specified endpoints. The absence of a comparator precludes within-study estimates of relative treatment effect, as well as increasing the risks of selection bias, attrition bias and confounding. However, patients included in APPOINT-PNH were broadly similar to those treated in UK practice (see section 3.2.1.2), and there appeared to be no attrition at 24 or 48 weeks,[4] Table 8 (p.42) of the CS suggests differences in concomitant medications (e.g. unspecified herbal and traditional medicines) between the trial and UK populations, but these are not considered an important confounder in the direct or indirect comparisons.

APPOINT-PNH was an open-label study, so subjective outcomes may have been influenced by knowledge of the intervention being received. However, with the exception of fatigue and health-related quality of life, all study endpoints (including the primary endpoint of increase from baseline Hb levels in the absence of transfusions) used objective measures.

3.2.1.2 Population

Table 6 and 7 of the CS (p.39) summarised patient baseline participant and disease characteristics for APPOINT-PNH.

Points for critique

The most notable difference between the study and NHS populations is the high proportion of East Asian patients (67%) in APPOINT-PNH. The EAG's clinical advisor indicated that patients recruited in Asia, Japan and South Korea may be somewhat more likely to have bone marrow failure and less likely to experience thrombosis. However, the study population appears comparable to NHS treatment population, in that all symptomatic patients with PNH have high LDH levels and anaemia.

3.2.1.3 Effectiveness

The CS reported only 24-week timepoint efficacy results for APPOINT-PNH (section B.2.6.1). In response to an EAG point for clarification (PfC A3), the company provided 48-week data from a more recent analysis of the APPOINT-PNH data. For ease of reference, the EAG have presented these data together in Table 11.

Table 11: APPOINT-PNH: Summary of 24 and 48-week efficacy results

	Summary measure	24-weeks*	48 weeks
Primary endpoint			
≥2 g/dL increase from baseline in Hb[α]	n/M (%)	31/33 patients 92.2%	38/39 patients 97.4%
Secondary endpoints			
Hb ≥12 g/dL[α]	n/M (%)	19/33 patients (62.8%)	31/39 patients (79.5%)
Transfusion avoidance[†]	Marginal proportion (95% CI)	97.6% (95% CI: 92.5, 100.0)	97.5% (95% CI: 92.5%, 100.0%)
Change from baseline in Hb levels, factoring out the effect of transfusion (g/dL)[‡]	Mean (SD)	+4.28 g/dL (95% CI: 3.87, 4.70)	+5.09 g/dL (SD: 2.010 g/dL)
Change from baseline in LDH levels (U/L)[‡]	Mean % reduction (95% CI) Mean (SD)	-83.6% (95% CI: -84.9%, -82.1%)	−1393.3 U/L (SD: 652.15 U/L)
Clinical BTH	Adjusted annualised rate (95% CI)[¶]	0.00 (95% CI: 0.00, 0.17)	0.05 (95% CI: 0.01, 0.17)
Change from baseline in absolute reticulocyte counts (10^9/L)[‡]	Mean % reduction (95% CI) Mean (SD)	-82.48 x 10^9/L (95% CI: -89.33, -75.62)	−76.55 10^9/L (SD: 50.149 10^9/L)
Change from baseline in FACIT-Fatigue scores[‡]	Mean (SD)	+10.75 points (95% CI: 8.66, 12.84)	+10.4 points (SD: 10.14 points)
MAVEs	Adjusted annualised rate (95% CI)[¶]	0.00 (95% CI: 0.00, 0.17)	0.00 (95% CI: 0.00, 0.09)

Source: Novartis data on file, 48-week APPOINT-PNH CSR (2023)
*data reported in section B.2.6.1 of the CS
[α]haematological response endpoints in the 48-week analysis included all Hb values irrespective of red blood cell (RBC) transfusions, whereas the primary analysis at 24 weeks required the absence of transfusions as an integral part of the endpoints.
†Marginal proportion of patients not receiving or not requiring transfusions between Day 14 and Day 336. The marginal proportion of responders was computed using simple proportion, based on observed data. The 95% CI was obtained using the bootstrap method; ‡Summary statistics for change from baseline to mean of visits between Day 126 and Day 168 (24 week timepoint) or up to Day 336 (48-week timepoint);
¶Adjusted mean CFB between Day 126 and Day 168 (24-week timepoint); between Day 1 and Day 336 (48-week timepoint).
Abbreviations: BTH, breakthrough haemolysis; CI, confidence interval; FACIT-Fatigue, Functional Assessment Of Chronic Illness Therapy – Fatigue; Hb, haemoglobin; LDH, lactate dehydrogenase; M, number of patients with evaluable/non-missing data; MAVE, major adverse vascular event; n, number of patients meeting the specified criterion; SD, standard deviation.

Briefly, the primary endpoint of haematological response based on a sustained increase in Hb levels from baseline of ≥2 g/dL in the absence of RBC transfusions was met. A marginal proportion of 92.2% of patients (95% CI: 82.5, 100.0) met this endpoint at 24 weeks, and this level of response was sustained at 48 weeks (97.4%). In the absence of a comparator, an *a priori* threshold of 15% was pre-specified in the study protocol. The lower bound of the confidence intervals at both 24 and 48 weeks substantially exceeded this threshold.

Table 10 also shows secondary endpoint data reported in the CS and PfC response. Transfusion avoidance was high from day 14 of iptacopan treatment to both 24 and 48-week assessment timepoints (97.6% and 97.5% respectively), compared with 28/40 patients (70.0%) receiving at least one transfusion in the six months prior to start of study treatment. All six patients meeting the transfusion criteria did so prior to Day 14 of treatment (CS section B.2.6.1.3.1). This finding appears consistent with the haemoglobin response endpoints.

No patients had experienced clinical breakthrough haemolysis (BTH) during the core 24-week treatment period and 2/40 patients (5.0%) each had one clinical BTH event in the extension treatment period. Over the total 48-week study duration, this resulted in an adjusted annualised clinical BTH rate of 0.05 (95% CI: 0.01, 0.17).

No patients experienced a major adverse vascular event (MAVE) over the 48-week study duration.

The CS reported exploratory endpoints (section B.2.6.1.3.3 and Appendix N). This includes PNH-related signs and symptoms.

Points for critique

Missing primary outcome data

17.5% (7/40) APPOINT-PNH patients had non-evaluable or missing haemoglobin outcome data. However, sensitivity analyses of 24-week data suggested that this finding was robust to different assumptions regarding the handling of missing data (CS table 10, p.49). In addition, all 40 participants avoided blood transfusions during the study period, suggesting adequate haematologic response.

Study duration and sample size

Although iptacopan appeared to be well tolerated (see section 3.2.3), there is little long-term evidence available for proximal inhibitors (including both iptacopan and pegcetacoplan), so concerns remain about the unknown longer-term risks of BTH and thrombosis. Though no BTH events were observed in the 24-week APPOINT-PNH data (CS section B.2.6.1.2.5, p.52), the EAG's clinical advisor considered it inappropriate to assume zero long-term BTH events over the longer term.

Additional 48-week data reported in the Addendum reports adjusted annualised rates of BTH and MAVEs of 0.05 (95% CI: 0.01, 0.17) and 0.00 (95% CI: 0.00, 0.09) respectively. The EAG's clinical advisor believes that while there may be fewer breakthrough events on iptacopan, the true value is unlikely to be 0. If there are compliance issues (which are more likely in a real world setting than a trial), BTH would be more likely.

Regarding thromboses on iptacopan, again with the limited data we have this can only be confirmed with long-term real world data. It is difficult to know the actual rate of thrombosis in this group.

In addition to the relatively short observation period, the small number of patients (n=40) in APPOINT-PNH precludes the detection of rare but clinically significant events.

Treatment compliance and missed doses

The draft SmPC for iptacopan recommends 200 mg iptacopan taken orally twice daily (i.e. 400mg total daily dose) and discourages discontinuation. The CS did not present any information on treatment compliance or missed doses. However, the EAG have extracted this information from the APPOINT-PNH clinical study report[4] in Table 12 below. The company also provided compliance data in response to points for clarification (PfC B13).

These data suggest that around a third of patients missed at least one daily dose of oral iptacopan, though 5% or fewer patients missed at least one full day of treatment. No AEs or evidence of haemolysis was reported among patients who missed treatment doses.

There is no evidence on longer-term iptacopan dose modifications or treatment compliance outside the APPOINT-PNH and APPLY-PNH studies.

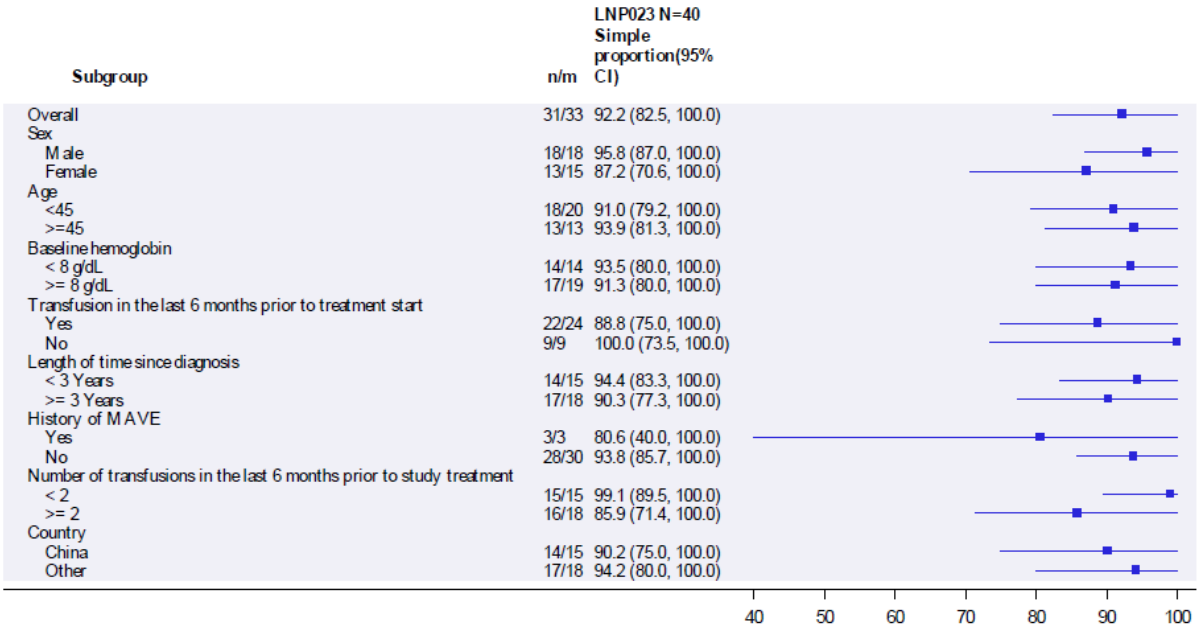
Table 12 Treatment compliance and missed doses reported in APPOINT-PNH clinical study report[4]

	Core treatment period (24 weeks)	Extension treatment period (24-48 weeks)	Clinical consequences
Completed treatment period, n/N (%)	[redacted]	[redacted]	-
Treatment ongoing, n/N (%)	[redacted]	[redacted]	-
Mean (SD) relative dose intensity, %	[redacted]	[redacted]	-
Dose interruptions At least one full day with no dose, n/N (%)	[redacted]	[redacted]	"No associated AEs nor changes in hematological parameters suggestive of hemolysis were reported in these two patients"
Missing doses At least one missing capsule of iptacopan 200mg/day), n/N(%) Mean (SD) cumulative duration of missed dose, days	[redacted] [redacted]	[redacted] [redacted]	"No associated AEs nor changes in hematological parameters suggestive of hemolysis were reported due to these unintentional missed doses"

3.2.1.4 Subgroup data

Appendix E of the CS presented subgroup analyses for the primary endpoint of increase from baseline Hb levels ≥2 g/dL assessed between Day 126 and Day 168, which for ease of reference are presented in Figure 1 below.

Figure 1 Forest plot of subgroup analysis of response based on increase in Hb (≥2 g/dL) between Day 126 and Day 168 in the absence of requirement of pRBC transfusions between Day 14 and Day 168 (FAS)



Source: Novartis, Data on file, APPOINT-PNH CSR, Figure 11.1. Abbreviations: CFB, change from baseline; CI, confidence interval; FAS, full analysis set; Hb, haemoglobin; LNP023, iptacopan; MAVE, major adverse vascular event; pRBC, packed red blood cell.

Points for critique

24-week APPOINT-PNH subgroup data appear broadly consistent with the primary endpoint result. Small patient numbers resulted in high uncertainty for some subgroup estimates, though the lower confidence interval of all subgroups exceeded the *a priori* response threshold of 15%.

The company's response to the EAG request for updated data did not include any 48-week subgroup analyses for APPOINT-PNH. Subgroup analyses were not conducted for secondary endpoints.

3.2.2 Complement inhibitor-experienced population with residual anaemia: APPLY-PNH

3.2.2.1 Trial design and methods

Section B.2.3.1 of the CS described the design and methods of the APPLY-PNH trial.[6]

Briefly, this was a multicentre, open-label, randomized controlled trial comparing iptacopan versus ongoing C5 inhibitor monotherapy (eculizumab or ravulizumab) in PNH patients previously treated with C5 inhibitors who had clinically significant EVH.

Patients were included if they had clone size ≥10%, mean haemoglobin <10g/dL, a reticulocyte count of ≥100 × 10^9 cells/L, and were on a stable regimen of eculizumab or ravulizumab for ≥6 months prior to randomization.

After an 8-week screening period, patients were randomised to 200mg twice-daily oral iptacopan or intravenous C5 inhibitor (stratified by prior C5 inhibitor treatment and RBC transfusions in the preceding 6 months) for 24 weeks. The randomised period was followed by a 24-week extension period in which all patients received oral iptacopan (see CS figure 4, p.36).

The co-primary endpoints were haematological responses defined using two different cut-points for haemoglobin level: an increase of ≥2 g/dL from baseline or maintenance of ≥12 g/dL in the absence of RBC transfusions at the end of 24-week treatment period.

Points for critique

Like APPOINT-PNH, APPLY-PNH was an open-label study, so subjective outcomes (fatigue and health-related quality of life) may have been influenced by knowledge of the intervention being received. However, all the remaining study endpoints (including the primary endpoints of increase from baseline haemoglobin levels in the absence of transfusions) used objective measures and are at low risk of bias.

3.2.2.2 Population

Patient baseline demographics were presented in Table 6 of the CS (p.39). Corrected baseline disease characteristics for APPLY-PNH were presented in the follow-up Addendum and are reproduced in Table 13 below for ease of reference.

Table 13 APPLY-PNH baseline disease characteristics

	Iptacopan 200 mg BD N=62	**C5 inhibitor N=35**	**Overall N=97**
Disease duration, years			
Mean (SD)	11.88 (9.813)	13.54 (10.947)	12.48 (10.211)
Median (min–max)	NR (0.7–40.2)	NR (1.5–42.0)	NR (0.7–42.0)
Length of time since diagnosis, n (%)			
<3 years	NR	NR	NR
≥3 years	NR	NR	NR
C5 inhibitor medication history – 6 months prior to randomisation -n (%)			
Eculizumab	40 (64.5)	23 (65.7)	63 (64.9)
Ravulizumab	22 (35.5)	12 (34.3)	34 (35.1)

	Iptacopan 200 mg BD N=62	C5 inhibitor N=35	Overall N=97
Duration of C5 inhibitor treatment (years)			
Mean (SD)	3.80 (3.567)	4.23 (3.868)	3.96 (3.665)
Median (min–max)	2.56 (0.5–16.6)	2.74 (0.4–16.3)	2.61 (0.4–16.6)
Eculizumab dose administered (mg)			
Median (min–max)	900.0 (900–1,200)	900.0 (900–1,500)	900.0 (900–1,500)
Ravulizumab dose administered (mg)			
Median (min–max)	3,300.0 (3,000–3,600)	3,300.0 (3,000–3,600)	3,300.0 (3,000–3,600)
Baseline Hb, n (%)			
Mean (SD)	8.927 (0.7038)	8.850 (0.8949)	8.899 (0.7745)
Baseline LDH level (U/L)			
Mean (SD)	269.1 (70.14)	272.7 (84.80)	270.4 (75.34)
≤1.5 x ULN, n (%)	58 (93.5)	32 (91.4)	90 (92.8)
>1.5 x ULN, n (%)	4 (6.5)	3 (8.6)	7 (7.2)
Transfusion in the last 12 months prior to screening, n (%)			
Yes	37 (59.7)	22 (62.9)	59 (60.8)
Transfusion in the last 6 months prior to randomisation, n (%)			
Yes	35 (56.5)	21 (60.0)	56 (57.7)
Number of transfusions in the last 6 months prior to study treatment			
<2	38 (61.3)	21 (60.0)	59 (60.8)
≥2	24 (38.7)	14 (40.0)	38 (39.2)
Number of transfusions in the last 6 months prior to study treatment among patients who had a transfusion			
N	35	21	56
Mean (SD)	3.1 (2.58)	4.0 (4.34)	3.4 (3.34)
Median (min–max)	2.0 (1–13)	2.0 (1–19)	2.0 (1–19)
Platelets (10^9/L)			
Mean (SD)	160.2 (63.83)	147.3 (77.01)	155.6 (68.77)
Absolute reticulocyte counts (109/L)			
Mean (SD)	193.22 (83.637)	190.59 (80.922)	192.27 (82.254)
Baseline FACIT-Fatigue total score			
Mean (SD)	34.7 (9.82)	30.8 (11.45)	33.4 (10.52)
Median (min–max)	34.8 (11–52)	31.5 (10–50)	33.0 (10–52)
Total PNH RBC clone size (%)†			
Mean (SD)	64.645 (27.4543)	57.391 (29.7258)	62.028 (28.3576)
History of MAVE			
Yes	12 (19.4)	10 (28.6)	22 (22.7)
History of aplastic anaemia			
Yes	9 (14.5)	5 (14.3)	14 (14.4)

Source: Novartis, Data on file, APPOINT-PNH CSR, Table 10.6, Table 14.1-3.2; Novartis, Data on file, APPLY-PNH Supplementary Report, Table 3-1, Table 3-2
All values have been updated to match those presented in the company's addendum.
†Total PNH clone size is calculated as sum of percentages of positive RBC of Type II and Type III.
Abbreviations: BD, twice daily; CSR, clinical study report; FACIT, Functional Assessment of Chronic Illness Therapy; Hb, haemoglobin; LDH, lactate dehydrogenase; NA, not applicable; NR, not reported; SD, standard deviation.

Points for critique

Baseline characteristics appeared to be similar between treatment arms and the EAG's clinical advisor considered the participant characteristics to be broadly reflective of those seen in NHS practice.

3.2.2.3 Effectiveness

Section B.2.6.2 of the CS summarises the clinical effectiveness results of APPLY-PNH.

Updated and corrected 24-week effectiveness data for APPLY-PNH were presented in the follow-up Addendum, and 48-week data were provided in response to the EAG's points for clarification (PfC A3). For ease of reference, these data are reproduced in tables 6-13 below.

24-week effectiveness data

During the randomised period, haematological response (defined as either an increase of ≥2 g/dL from baseline or maintenance of ≥12 g/dL in the absence of RBC transfusions) was significantly greater for iptacopan than C5 inhibitors (Table 14 and Table 15), and this result was robust to a series of sensitivity analyses (Table 16).

The secondary endpoints of transfusion avoidance, fatigue, and change from baseline in haemoglobin and absolute reticulocyte counts similarly favoured iptacopan over C5 inhibitors, though the ratio to baseline in LDH was similar between treatment arms (Table 17 to Table 20), suggesting similar control of IVH.

Fewer patients experienced clinical breakthrough haemolysis (BTH) in the iptacopan arm (n=2) than those in the C5 inhibitor arm (n=6).

A single major adverse vascular event (MAVE) was observed over the randomised period, occurring in the iptacopan arm.

The CS reported exploratory endpoints (section B.2.6.2.3 and Appendix N). This includes PNH-related signs and symptoms.

Table 14: APPLY-PNH: Summary of changes in primary and secondary endpoints (24-week analysis) due to APPLY-PNH data changes

Endpoint		Iptacopan (N=62)	C5 inhibitor (N=35)	Iptacopan vs C5 inhibitor treatment effect (95% CI) adjusted for covariates	Unadjusted two–sided p–value
Primary endpoints					
		Number of patients meeting criterion[#] Marginal proportion		**Difference between % responding[†]**	
≥2 g/dL increase in Hb from baseline‡ in the absence of RBC transfusions¶	Original values	51/60 82.3%	0/35 2.0%	80.3 (71.3, 87.6)	<0.0001
	Updated values	51/60 82.3%	0/35 2.0%	80.2 (71.2, 87.6)	<0.0001
Hb ≥12 g/dL‡ in the absence of RBC transfusions¶	Original values	42/60 68.8%	0/35 1.8%	67.0 (56.3, 76.9)	<0.0001
	Updated values	42/60 68.8%	0/35 1.8%	67.0 (56.4, 76.9)	<0.0001
Secondary endpoints					
Transfusion avoidance¶	Original values	60/62 96.4%	14/35 26.1%	70.3 (52.6, 84.9)	<0.0001
	Updated values	59/62 94.8%	14/35 25.9%	68.9 (51.4, 83.9)	<0.0001
		Mean	**Mean**	**Difference between means**	
Change from baseline in Hb (g/dL)‡	Original values	3.59	–0.04	3.63 (3.18, 4.08)	<0.0001
	Updated values	3.60	–0.06	3.66 (3.20, 4.12)	<0.0001
Change from baseline in FACIT–Fatigue scores‡	Original values	8.6	0.3	8.3 (5.3, 11.3)	<0.0001
	Updated values	No change			
Change from baseline in absolute reticulocyte counts (10^9/L)‡	Original values	–115.9	0.37	–116.3 (–132.2, –100.4)	<0.0001
	Updated values	–115.8	0.34	–116.2 (–132.0, –100.3)	<0.0001
		Geometric mean	**Geometric mean**	**Ratio of geometric means**	
Ratio to baseline in LDH (U/L)‡	Original values	0.96	0.98	0.99 (0.89, 1.10)	0.8345
	Updated values	0.96	0.98	0.99 (0.89, 1.10)	0.8361
		Number of patients with an event	**Number of patients with an event**	**Annualised rate ratio**	
Clinical BTH[§]	Original values	2	6	0.10 (0.02, 0.61)	0.0118

Endpoint		Iptacopan (N=62)	C5 inhibitor (N=35)	Iptacopan vs C5 inhibitor treatment effect (95% CI) adjusted for covariates	Unadjusted two–sided p–value
	Updated values	No change			
MAVEs§	Original values	1	0	Not estimable	0.3173
	Updated values	No change			

Source: Novartis, Data on file, APPLY-PNH Supplementary Report, Table 3-3, Table 3-4, Table 3-6, Table 3-8
All values have been updated to match those presented in the company's addendum
†Model-based estimate; ‡assessed between Day 126–168; ¶ between Day 14–168; § between Day 1–168; # among patients with evaluable/non-missing data.
Abbreviations: BTH, breakthrough haemolysis; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy – Fatigue; FAS, full analysis set; N, number of patients in the FAS; Hb, haemoglobin; LDH, lactate dehydrogenase; MAVE, major adverse vascular event; RBC, red blood cells

Primary endpoints: Haematological response

Table 15: APPLY-PNH: Responder analysis of Hb between Day 126 and Day 168 in the absence of RBC transfusions between Day 14 and Day 168 (FAS) [Update to company submission Table 13]

Responder criterion	n/M	Marginal proportion (95% CI)†	Diff. in marginal proportion (95% CI)†	Ratio of marginal proportion (95% CI)†	Unadjusted for multiplicity
					Two-sided p-value‡
Increase in Hb levels ≥2g/dL¶ from baseline without requiring RBC transfusions§					
Iptacopan 200 mg BD N=62	51/60	82.3 (73.4, 90.2)	80.2 (71.2, 87.6)	40.20 (20.73, 74.82)	<0.0001
C5 inhibitor N=35	0/35	2.0 (1.1, 4.0)	–	–	–
Hb levels ≥12 g/dL¶ without requiring RBC transfusions§					
Iptacopan 200 mg BD N=62	42/60	68.8 (58.4, 78.9)	67.0 (56.4, 76.9)	38.22 (16.87, 78.63)	<0.0001
C5 inhibitor N=35	0/35	1.8 (0.9, 4.0)	–	–	–

Source: Novartis, Data on file, APPLY-PNH Supplementary Report, Table 3-4
All values have been updated to match those presented in the company's addendum.
†Logistic regression model using Firth correction with common intercept and randomization strata, sex, indicator variable of age ≥45 years, indicator variable of baseline Hb ≥9 g/dL as factors. The 95% CI is computed using bootstrap. ‡Logistic regression model using Firth correction with randomisation strata, sex, indicator variable of age ≥45 years, indicator variable of baseline Hb ≥9 g/dL as factors. ¶Between Day 126 and 168 (≥ 3 out of 4 scheduled measurements); §Between Day 14 and Day 168. Requiring RBC transfusions refers to any patient receiving transfusions or meeting protocol defined criteria for transfusion.
Abbreviations: BD, twice daily; CI, confidence interval; FAS, full analysis set; Hb, haemoglobin; M, evaluable patients; n, the number of patients who responded based on non-missing data; RBC, red blood cell.

Table 16: APPLY-PNH: Summary of primary and sensitivity analyses for the primary endpoints – analysis of Hb between Day 126 and Day 168 in the absence of RBC transfusions between Day 14 and Day 168 (FAS) [Update to company submission Table 14]

Analysis description	Iptacopan 200 mg BD vs C5 inhibitor Difference between % achieving endpoint (95% CI)	Unadjusted two-sided p-value
Increase in Hb levels ≥2g/dL† from baseline without requiring RBC transfusions‡		
Primary analysis	80.2 (71.2, 87.6)	<0.0001
Tipping point analysis • Imputed Hb values were lowered by a value delta (2 g/dL in the iptacopan group)¶	76.8 (66.9, 85.4)	NR
Analysis including local lab data • If central lab data missing, local laboratory data was included	80.3 (71.2, 87.6)	<0.0001
Cochran-Mantel-Haenszel • Hypothesis testing using a CMH test	NA	<0.0001
Post-hoc sensitivity analysis • With MI Hb between >7 and ≤9 g/dL were considered by default as not having signs and/or symptoms and therefore not meeting the criteria for transfusion	80.3 (71.3, 87.6)	<0.0001
Post-hoc sensitivity analysis • Determining transfusion avoidance without imputation	80.3 (71.3, 87.6)	<0.0001
Hb levels ≥12 g/dL† without requiring RBC transfusions‡		
Primary analysis	67.0 (56.4, 76.9)	<0.0001
Tipping point analysis • Imputed Hb values were lowered by a value delta (2 g/dL in the iptacopan group)¶	64.1 (52.9, 74.0)	NR
Analysis including local labs • If central lab data missing, local laboratory data was included	67.0 (56.4, 76.8)	<0.0001
Cochran-Mantel-Haenszel • Hypothesis testing using a CMH test	NA	<0.0001
Post-hoc sensitivity analysis • With MI Hb between >7 and ≤9 g/dL were considered by default as not having signs and/or symptoms and therefore not meeting the criteria for transfusion	67.0 (56.4, 76.9)	<0.0001
Post-hoc sensitivity analysis • Determining transfusion avoidance without imputation	67.0 (56.4, 76.9)	<0.0001

Source: Novartis, Data on file, APPLY-PNH Supplementary Report, Table 3-5
All values have been updated to match those presented in the company's addendum
†Between Day 126 and 168 (≥3 out of 4 scheduled measurements); ‡Between Day 14 and Day 168. Requiring RBC transfusion refers to any patient receiving transfusions or meeting protocol defined criteria for transfusion; ¶Missing Hb values in each treatment group were imputed as for the primary analysis but an adjustment for the iptacopan group was applied to the imputed values. Missing haemoglobin values were imputed and missing values in the iptacopan arm were decreased by a value delta. Delta ranged from 0 g/dL (primary analysis) to 2 g/dL (considered clinically meaningful change).
Abbreviations: CI, confidence interval; CMH, Cochran Mantel Haenszel; CSR, clinical study report; Hb, haemoglobin; FAS, full analysis set; MI, multiple imputation; NA, not applicable; NR, not reported; RBC, red blood cell.

Secondary endpoints

Table 17: APPLY-PNH: Transfusion avoidance between Day 14 and Day 168 (FAS) [Update to company submission Table 15]

	Iptacopan 200 mg BD N=62	C5 inhibitor N=35
n/M	59/62	14/35
Marginal proportion (95% CI)†	94.8 (88.1, 100.0)	25.9 (11.6, 42.4)
Difference in marginal proportion (95% CI)†	68.9 (51.4, 83.9)	–
Ratio of marginal proportion (95% CI)†	3.70 (2.23, 8.17)	–
Unadjusted for multiplicity OR (95% CI)‡	108.41 (17.25, 681.24)	–
Unadjusted for multiplicity p-value‡	<0.0001	–

Source: Novartis, Data on file, APPLY-PNH Supplementary Report, Table 3-6
All values have been updated to match those presented in the company's addendum
†Logistic regression model with common intercept and randomisation strata, sex, indicator variable of age ≥45 years, indicator variable of baseline Hb ≥9 g/dL as factors. The 95% CI is computed using bootstrap. ‡Conditional logistic regression model with randomisation strata, sex, indicator variable of age ≥45 years, indicator variable of baseline Hb ≥9 g/dL as factors.
Abbreviations: BD, twice daily; CI, confidence interval; CSR, clinical study report; FAS, full analysis set; Hb, haemoglobin; M, The number of patients in the treatment group with response variable defined based on non-missing data (evaluable patients); n, the number of patients who did not receive transfusions nor meet protocol defined criteria between Day 14 and Day 168; OR, odds ratio.

Table 18: APPLY-PNH: Change from baseline in Hb levels (g/dL) (assessed between Day 126 and Day 168) (FAS) [Update for company submission, Section B.2.6.2.2.2 text on p. 60]

	Iptacopan 200 mg BD N=62	C5 inhibitor N=35
n	62	29
Adjusted mean (95% CI)	3.60 (3.33, 3.88)	–0.06 (–0.45, 0.34)
Adjusted mean difference (95% CI)	3.66 (3.20, 4.12)	–
Unadjusted for multiplicity p-value‡	p<0.0001	–

Source: Novartis, Data on file, APPLY-PNH Supplementary Report, Table 3-8
All values have been updated to match those presented in the company's addendum..
Change from baseline is analysed using a MMRM which includes randomisation strata, age indicator variable of age ≥45 years, sex, treatment, visit, baseline Hb, timepoint as fixed effects, treatment*timepoint and timepoint*baseline Hb as interaction terms. The correlations between visits within patients were modelled using an unstructured covariance matrix.
Abbreviations: BD, twice daily; CI, confidence interval; FAS, full analysis set; Hb, haemoglobin; MMRM, mixed model of repeated measures; n, number of patients with values non-missing/ not imputed as per the intercurrent event handling strategy.

Table 19: APPLY-PNH: Change from baseline in absolute reticulocyte counts (10^9/L) (assessed between Day 126 and Day 168) (FAS) [Update for company submission, Section B.2.6.2.2.4 text on p. 61]

	Iptacopan 200 mg BD N=62	C5 inhibitor N=35
n	62	35
Adjusted mean (95% CI)	–115.81 (–126.40, –105.23)	0.34 (–13.04, 13.72)
Adjusted mean difference (95% CI)	–116.15 (–132.04, –100.26)	–
Unadjusted for multiplicity p-value‡	p<0.0001	–

Source: Novartis, Data on file, APPLY-PNH Supplementary Report, Table 3-11
All values have been updated to match those presented in the company's addendum
Change from baseline is analysed using a MMRM which includes randomisation strata, age indicator variable of age ≥45 years, sex, treatment, visit, baseline reticulocyte counts, timepoint as fixed effects, treatment*timepoint and timepoint*baseline reticulocyte counts as interaction terms. The correlations between visits within patients were modelled using an unstructured covariance matrix.
Abbreviations: BD, twice daily; CI, confidence interval; FAS, full analysis set; MMRM, mixed model of repeated measures.

Table 20: APPLY-PNH: Log-transformed LDH (U/L) ratio to baseline (assessed between Day 126 and Day 168)† (FAS) [Update to company submission Table 17]

	Iptacopan 200 mg BD N=62	C5 inhibitor N=35
n	62	35
Geometric adjusted mean (95%CI)	0.96 (0.90, 1.03)	0.98 (0.89, 1.07)
Geometric mean ratio (95% CI)	0.99 (0.89, 1.10)	–
% Reduction (95% CI)	1.14 (–10.19, 11.31)	
Two-sided p-value	0.8361	

Source: Novartis, Data on file, APPLY-PNH Supplementary Report, Table 3-13
All values have been updated to match those presented in the company's addendum
†Log transformed ratio to baseline is analysed using a mixed model of repeated measures which was stratified by randomisation strata, and includes age indicator variable of age >=45 years, sex, treatment, visit, log-transformed baseline LDH level, timepoint as fixed effects, treatment*timepoint and timepoint*log- transformed baseline LDH level as interaction terms. The correlations between visits within patients were modelled using an unstructured covariance matrix. The log transformation used refers to the natural log (base of e). Results are back-transformed and expressed as geometric means.
Abbreviations: BD, twice daily; CI, confidence interval; CSR, clinical study report; FAS, full analysis set; LDH, lactate dehydrogenase.

48-week effectiveness data

In response to the EAG's request for clarification, the company provided 48-week efficacy data for APPLY-PNH, which is reproduced in Table 21 below.

These data suggest that haematological response among patients randomised to the iptacopan arm was maintained during the 24-week extension period, and substantially increased among patients who switched from C5 inhibitors. A similar pattern of findings was observed for change from baseline in haemoglobin, fatigue scores and absolute reticulocyte counts.

After 48 weeks, 86.4% of patients initially randomised to the iptacopan arm had a ≥2 g/dL increase from baseline in Hb; the percentage of patients with Hb ≥12 g/dL was 67.8%. Among the patients who switched from C5 inhibitor to iptacopan at 24-weeks, the proportion of patients achieving these haematological response endpoints were 72.4% and 58.6%, respectively. As noted by the company, haematological response endpoints in the 48-week analysis included all Hb values irrespective of RBC transfusions, whereas the primary analysis at 24 weeks required the absence of transfusions as an integral part of the endpoints. However, the large majority of patients did not require transfusions after 14 days of iptacopan treatment, with the proportion of transfusion-avoidant patients in the iptacopan arm 91.9% (Day 14 to Day 336) and in the C5 inhibitor-to-iptacopan arm 94.1% (Day 14 to Day 168 of iptacopan treatment).

Figure 2 to Figure 5 illustrate the changes in continuous endpoints across to the randomised and extension periods of APPLY-PNH. These suggest that the majority of improvements in haemoglobin, fatigue scores and absolute reticulocyte counts were achieved four weeks from starting or switching to iptacopan.

Based on the data reported in Table 14 and Table 21, there were relatively few BTH events during the extension period, though there appeared to be numerically more events among patients remaining on iptacopan (n=4) than among patients switching from C5 inhibitors (n=1). There appeared to a single MAVE event in each arm during the extension period.

Table 21: APPLY-PNH: Summary of efficacy results at the 48-week analysis

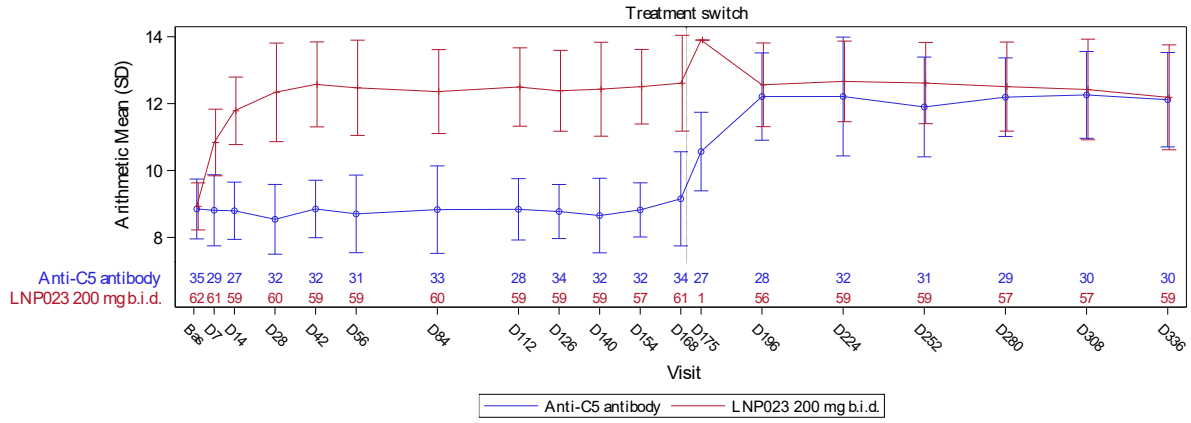
Endpoint	Arm#	Time	Summary measure	
		Iptacopan exposure	Patients achieving the haematological response endpoint (n/M (%))	
≥2 g/dL increase from baseline in Hb, irrespective of transfusions	Iptacopan	48 weeks	51/62 (86.4)	
	C5 inhibitor to iptacopan	24 weeks[III]	21/34 (72.4)	
Hb ≥12 g/dL, irrespective of transfusions	Iptacopan	48 weeks	40/62 (67.8)	
	C5 inhibitor to iptacopan	24 weeks[III]	17/34 (58.6)	
		Iptacopan exposure	Adj mean CFB (95% CI) at Day 336	Adj mean difference in CFB (95% CI): Day 336 vs Day 168
Change from baseline* in Hb level (g/dL)†	Iptacopan	48 weeks	+3.35 (3.04, 3.67)	−0.41 (−0.80, −0.01)
	C5 inhibitor to iptacopan	24 weeks[III]	+3.36 (2.94, 3.79)	+3.02 (2.49, 3.56)
Change from baseline‡ in FACIT-Fatigue score	Iptacopan	48 weeks	+9.80 (8.04, 11.56)	+0.73 (−1.14, 2.60)
	C5 inhibitor to iptacopan	24 weeks[III]	+10.96 (8.58, 13.34)	+10.79 (8.12, 13.47)
Change from baseline§ in absolute reticulocyte counts (109/L)	Iptacopan	48 weeks	−106.26 (−117.57, −94.96)	+9.92 (−4.40, 24.25)
	C5 inhibitor to iptacopan	24 weeks[III]	−107.95 (−123.18, −92.73)	−102.29 (−121.57, −83.02)
		Iptacopan exposure	Geometric adj mean ratio to baseline (95% CI) at Week 48	Geometric adj mean ratio (95% CI): Day 336 vs Day 168
Ratio to baseline‖ in log-transformed LDH (U/L)	Iptacopan	48 weeks	1.11 (1.02, 1.22)	1.12 (1.00, 1.25)
	C5 inhibitor to iptacopan	24 weeks[III]	0.99 (0.88, 1.11)	0.99 (0.85, 1.15)
		Time period	Patients not requiring an RBC transfusion since 2 weeks after initiation of iptacopan monotherapy (n [%])	
Transfusion avoidance¶	Iptacopan	Day 14 to Day 336	57 (91.9)	
	C5 inhibitor to iptacopan	Day 182 to Day 336 (iptacopan)	32 (94.1)**	
		Time period	n/N	Overall adj annualised rate of events since initiation of iptacopan monotherapy, including both treatment arms (95% CI)
Clinical BTH††	Iptacopan	Baseline to Day 336	6/62	0.11 (0.05, 0.23)
	C5 inhibitor to iptacopan	Day 169 to Day 336 (iptacopan)	1/34	
MAVEs	Iptacopan	Baseline to Day 336	2/62	0.04 (0.01, 0.13)
	C5 inhibitor to iptacopan	Day 169 to Day 336 (iptacopan)	1/34	

Source: Novartis data on file, 48-week APPLY-PNH CSR (2023)

[#] Iptacopan N=62; C5 inhibitor to iptacopan N=35; *Mean (SD) baseline Hb levels were 8.93 (0.70) and 8.85 (0.89) g/dL in the iptacopan and C5 inhibitor-to-iptacopan arms, respectively; [†]Analysis includes all central lab Hb data, including post-transfusion data; [‡]Mean (SD) baseline FACIT-F scores were 34.7 (9.8) and 30.8 (11.5) in the iptacopan and C5 inhibitor-to-iptacopan arms, respectively; [§]Mean (SD)

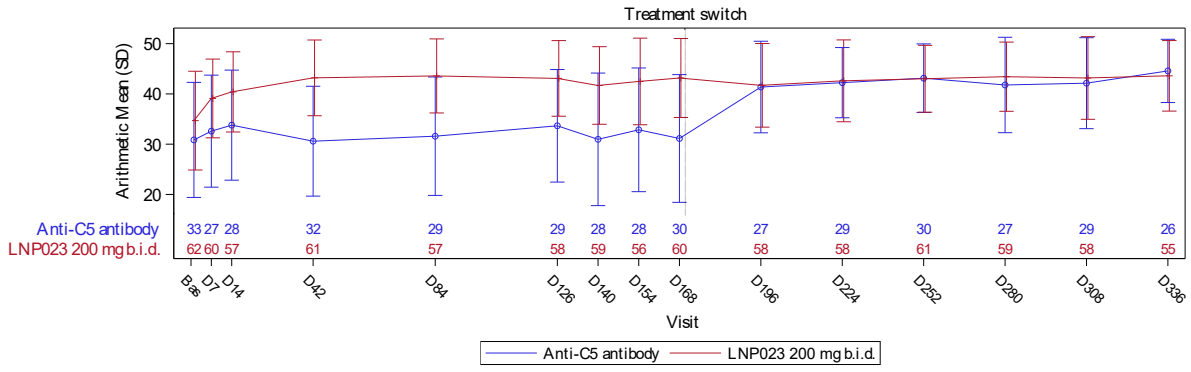
baseline absolute reticulocyte counts were 193.2 (83.6) and 190.6 (80.9) × 10^9/L in the iptacopan and C5 inhibitor-to-iptacopan arms, respectively; [‡]Mean (SD) baseline LDH levels were 269.1 (70.1) and 272.7 (84.8) U/L in the iptacopan and C5 inhibitor-to-iptacopan arms, respectively; [¶]Defined as neither receiving nor meeting the criteria to receive a packed RBC transfusion; **34 of 35 patients in the C5 inhibitor-to-iptacopan arm received iptacopan in the treatment extension period; [††]Events that met the protocol-specified criteria for clinical BTH; [‖]Received iptacopan from Day 169 to Day 336 (treatment extension period).
Abbreviations: Adj, adjusted; BTH, breakthrough haemolysis; CFB, change from baseline; CI, confidence interval; Hb, haemoglobin; LDH, lactate dehydrogenase; M, number of patients with evaluable/non-missing data; MAVE, major adverse vascular event; n, number of patients with event; N, number of patients treated with iptacopan; RBC, red blood cells; SD, standard deviation.

Figure 2: APPLY-PNH: Arithmetic mean (SD) of Hb (g/dL) by visit up to Day 336 (FAS)



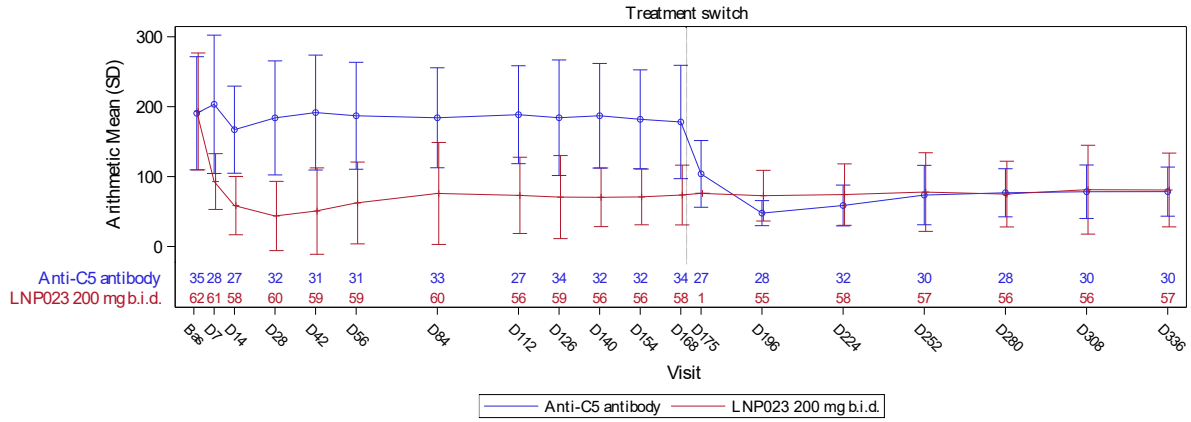
Source: Novartis data on file, 48-week APPLY-PNH CSR (2023)
At each visit-window, only patients with a value at both baseline and that visit-window are included.
Abbreviations: Bas = baseline; FAS, full analysis set; Hb, haemoglobin; SD, standard deviation.

Figure 3: APPLY-PNH: Arithmetic mean (SD) of FACIT-Fatigue scores by visit up to Day 336 (FAS)



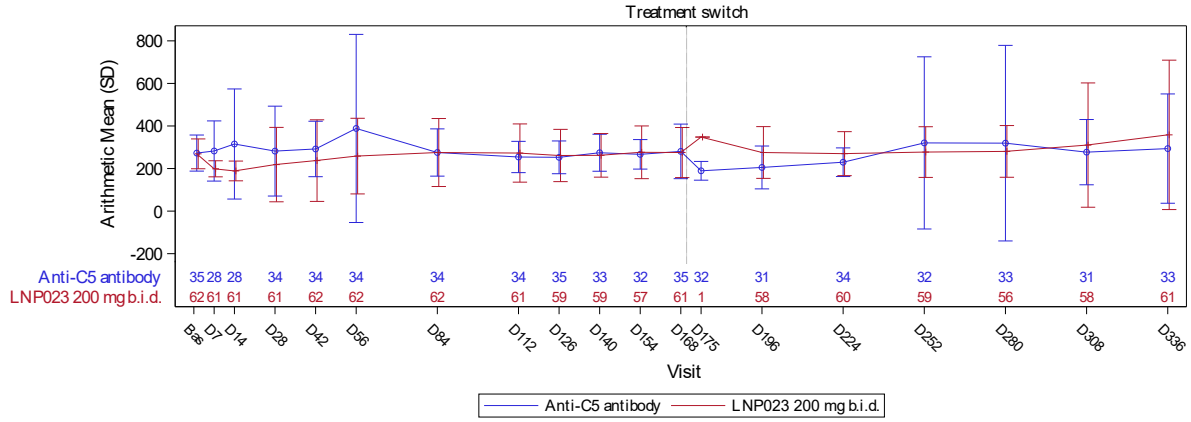
Source: Novartis data on file, 48-week APPLY-PNH CSR (2023)
At each visit-window, only patients with a value at both baseline and that visit-window are included.
Abbreviations: Bas = baseline; FAS, full analysis set; SD, standard deviation.

Figure 4: APPLY-PNH: Arithmetic mean (SD) of absolute reticulocyte counts (10^9/L) by visit up to Day 336 (FAS)



Source: Novartis data on file, 48-week APPLY-PNH CSR (2023)
At each visit-window, only patients with a value at both baseline and that visit-window are included.
Abbreviations: Bas = baseline; FAS, full analysis set; SD, standard deviation.

Figure 5: APPLY-PNH: Arithmetic mean (SD) of LDH (U/L) by visit up to Day 336 (FAS)



Source: Novartis data on file, 48-week APPLY-PNH CSR (2023)

At each visit-window, only patients with a value at both baseline and that visit-window are included.

Abbreviations: Bas = baseline; FAS, full analysis set; LDH, lactate dehydrogenase; SD, standard deviation.

Points for critique

Study duration and sample size

As noted in section 3.2.1.3 there is little long-term evidence available for proximal inhibitors, including the longer-term risks of BTH and thrombosis. APPLY-PNH only provides evidence of the comparative effects of iptacopan relative to C5 inhibitors for 24-weeks, with a further 24 weeks of non-comparative evidence. Consequently, the efficacy of iptacopan beyond a year is currently unknown.

The sample size of APPLY-PNH was restricted by the ultra-rare nature of PNH. While the study was powered to detect a difference on its primary haematological response outcomes, it was not powered to detect rare but clinically significant events.

Discontinuation, treatment compliance and missed doses

Very few patients discontinued treatment during the randomised or extension periods (see Table 22). With the exception of one patient from the C5 inhibitor arm who did not enter the treatment extension period, the only iptacopan treatment discontinuations were due to pregnancy.

Table 22 Discontinuations reported in the APPLY-PNH clinical study report[6]

	Randomised treatment period (24 weeks)		**Extension treatment period (24 weeks)**
Number of patients at start of treatment period	Iptacopan (n=62)	Anti-C5 antibody (n=35)	Iptacopan (n=95)*
Discontinuations	1/62 (1.6%) Pregnancy	0	1/95 (1.0%) Pregnancy

* One patient from the C5 inhibitor arm did not enter the treatment extension period due to the investigator's decision (patient's clinical condition)

The draft SmPC for iptacopan recommends 200 mg iptacopan taken orally twice daily (i.e. 400mg total daily dose) and discourages discontinuation. The CS did not present any information on treatment compliance or missed doses. However, the EAG have extracted this information from the APPLY-PNH clinical study report in Table 23 below. The company also provided compliance data in response to points for clarification (PfC B13).

These data suggest that around [redacted] of patients missed at least one daily dose of oral iptacopan. The proportion missing at least one full day of iptacopan treatment increased from [redacted] during the randomised period to [redacted] at the analysis cut-off date. No doses of C5 inhibitors were missed. No AEs or evidence of haemolysis was reported among patients who missed treatment doses.

Table 23 Treatment compliance and missed doses reported in APPLY-PNH clinical study report[4]

	Core treatment period (24 weeks)		**Analysis at data cut-off 26th Sept 2022***
	Iptacopan (n=62)	**C5 inhibitor (n=35)**	**Iptacopan (n=95)**
Completed treatment period, n/N (%)	[redacted]	[redacted]	[redacted]
Treatment ongoing, n/N (%)	[redacted]	[redacted]	[redacted]
Mean (SD) relative dose intensity, %	[redacted]	[redacted]	[redacted]
Dose interruptions At least one full day with no dose, n/N (%)	[redacted]	[redacted]	[redacted]
Missing doses	[redacted]	[redacted]	[redacted]

At least one missing capsule of iptacopan 200mg/day), n/N(%) Mean (SD) cumulative duration of missed dose, days	[redacted]	[redacted]	[redacted]

*Full 48-week follow-up data unavailable to EAG

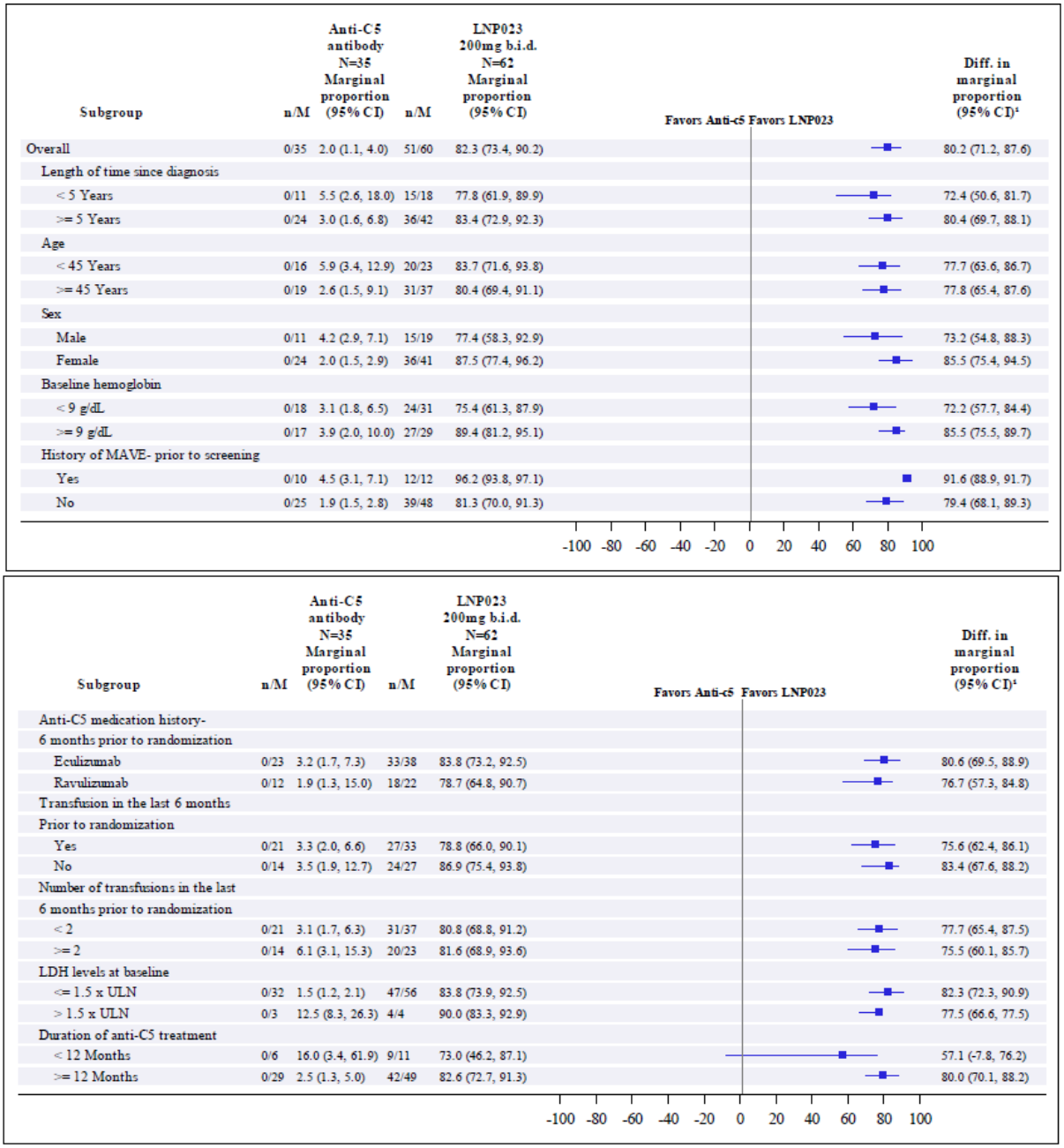
3.2.2.4 Subgroup data

24-week APPLY-PNH subgroup data for the haematological response co-primary outcomes were presented in section B.2.7 of the CS. Updated and corrected plots were presented in the follow-up addendum, and reproduced in Figure 6 and Figure 7 below for ease of reference.

Subgroup analyses for secondary outcomes were presented in supplementary files in response to the EAG's points for clarification.

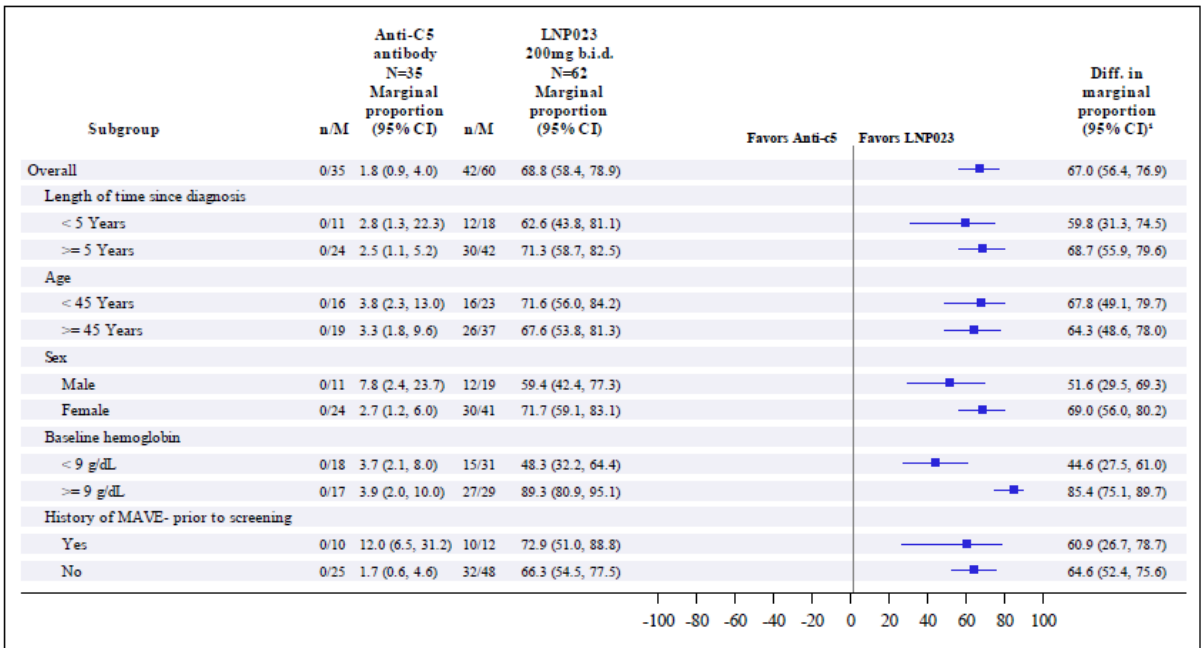
For both the primary and secondary effects of iptacopan versus C5 inhibitors were broadly consistent across all specified subgroups.

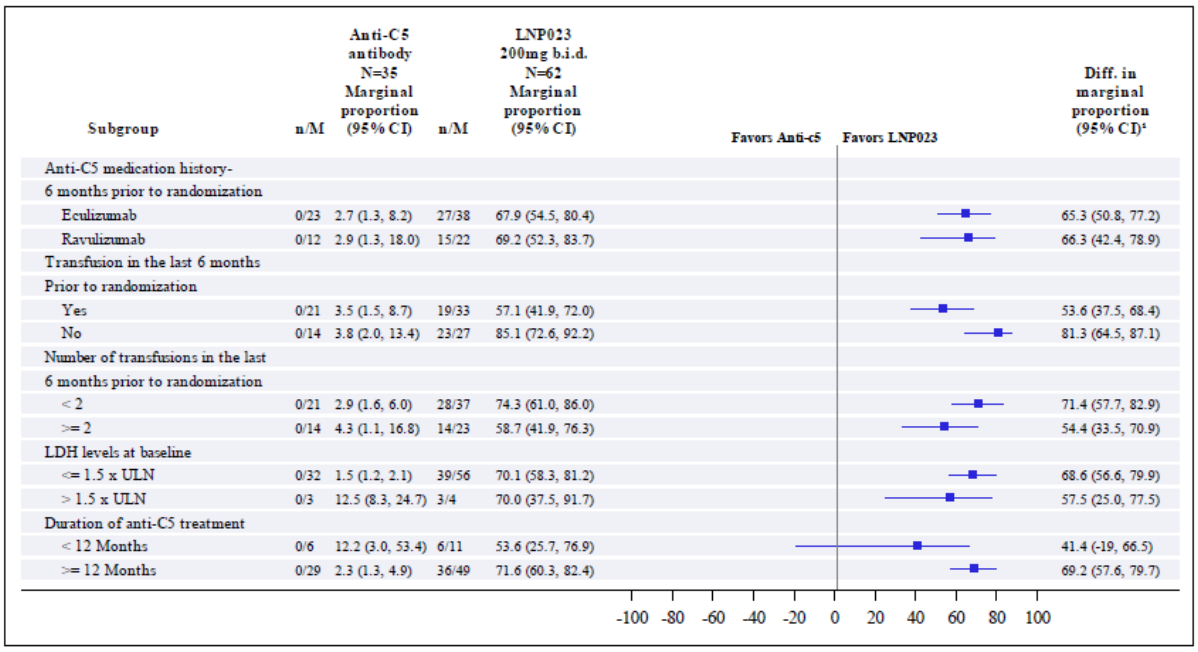
Figure 6: Forest plot of subgroup analysis of response based on increase in Hb (≥2 g/dL) between Day 126 and Day 168 in the absence of requirement of pRBC transfusions between Day 14 and Day 168 (FAS) [Updated]



Source: Novartis, Data on file, APPLY-PNH Supplementary Report, Figure 3-1
Abbreviations: b.i.d, twice daily; CFB, change from baseline; CI, confidence interval; FAS, full analysis set; Hb, haemoglobin; LDH, lactate dehydrogenase; LNP023, iptacopan; MAVE, major adverse vascular event; pRBC, packed red blood cell; ULN, upper limit of normal.

Figure 7: Forest plot of subgroup analysis of response based on Hb absolute level ≥12 g/dL between Day 126 and Day 168 in the absence of requirement of RBC between Day 14 and Day 168 (FAS) [Updated]





Source: Novartis, Data on file, APPLY-PNH Supplementary Report, Figure 3-2

Abbreviations: b.i.d, twice daily; CI, confidence interval; FAS, full analysis set; Hb, haemoglobin; LDH, lactate dehydrogenase; LNP023, iptacopan; MAVE, major adverse vascular event; RBC, red blood cell; ULN, upper limit of normal.

Points for critique

Type of C5 inhibitor as comparator

While ravulizumab is the preferred C5 inhibitor for most patients in practice, only 35% of patients in APPLY-PNH received ravulizumab, compared with 65% of patients receiving eculizumab. However, the subgroup data suggest that outcomes at 24 weeks were broadly similar for the two C5 inhibitors.

Of note, the subgroup figures show that 37/97 (38.1%) of patients in APPLY-PNH received two or more transfusions in the 6 months prior to randomisation. In practice, patients on C5 inhibitors who still require transfusion would typically be offered a switch to a proximal inhibitor (currently pegcetacoplan). Similarly 7.2% of patients in APPLY-PNH (7/97) had LDH levels more than 1.5 times the upper limit of normal (ULN), suggesting that these patients are not responding optimally to C5 inhibitor treatment. Registry data suggest that LDH > 1.5 x ULN is a risk for thrombosis and mortality. However, the risk of thrombosis in patients with an LDH level consistently >1.5 x ULN while on C5 inhibition is currently uncertain.

3.2.3 Adverse events

Sections B.2.10 (p.80) of the CS reported safety data from APPOINT-PNH and APPLY-PNH. Final 48-week data were presented in response to the EAG's PfC A3. For ease of reference, an overview of AEs from all reported analyses for both studies has been combined in Table 24 below.

In general, iptacopan appeared to be well-tolerated with no discontinuations due to AEs, either among complement inhibitor-naïve patients in APPOINT-PNH, or among complement inhibitor-experienced patients in APPLY-PNH.

Section B.2.10 of the CS further described serious adverse events, deaths and adverse events of special interest (AESI) for the 24-week and interim analyses of APPOINT-PNH and APPLY-PNH. Table 25 below provides an overview of all AESI data reported in the CS (the 48-week update provided to the EAG included no additional data on AESIs).

The largest risk differences in AESIs in the randomized comparison of APPLY-PNH related to BTH, which was less common with iptacopan (2/62, 3.2%) than C5 inhibitors (6/35, 17.1%), and 'decreased platelets', which was more common with iptacopan (6/62, 6.5%) than C5 inhibitors (0 events). One decreased platelets event was considered serious and was suspected to be related to iptacopan.

Points for critique

As an ultra-rare condition, sample sizes of PNH studies are inevitably restricted. While the available safety evidence from APPOINT-PNH and APPLY-PNH suggest iptacopan is well tolerated, these studies are insufficiently large to reliably detect rare or infrequent adverse events. In addition, the

currently available evidence on iptacopan is limited to 48-weeks, so there is no evidence on the longer-term safety of iptacopan.

Table 24 APPOINT-PNH and APPLY-PNH: Overview of AEs until the data cut-off dates (2nd Nov 2022 / 26th Sep 2022) and 48-week follow-up (SAS)

	APPOINT-PNH (complement inhibitor-naïve)			APPLY-PNH (complement inhibitor-experienced with residual anaemia)				
	Iptacopan 200 mg BD, N=40 n (%)			Randomised treatment period		Combined iptacopan safety analysis (randomised + extension treatment period until cut-off date)** N=95 n (%)	Final 48-week data	
	Core treatment period (24 weeks)	Overall (core + extension treatment period until cut-off date)*	Final 48-week data	Iptacopan 200 mg BD N=62 n (%)	C5 inhibitor N=35 n (%)		Iptacopan 200 mg BD N=62 n (%)	Combined iptacopan safety analysis N=96 n (%)
AEs	37 (92.5)	37 (92.5)	37 (92.5)	51 (82.3)	28 (80.0)	75 (78.9)	58 (93.5)	85 (88.5)
Suspected to be treatment related	14 (35.0)	16 (40.0)	17 (42.5)	16 (25.8)	3 (8.6)	21 (22.1)	17 (27.4)	21 (21.9)
Severe AEs	1 (2.5)	3 (7.5)	4 (10.0)	3 (4.8)	3 (8.6)	8 (8.4)	6 (9.7)	9 (9.4)
Suspected to be treatment related	0	1 (2.5)	1 (2.5)	0	0	1 (1.1)	0	1 (1.0)
SAEs	4 (10.0)	6 (15.0)	8 (20.0)	6 (9.7)	5 (14.3)	12 (12.6)	9 (14.5)	13 (13.5)
Suspected to be treatment related	0	1 (2.5)	2 (5.0)	1 (1.6)	0	2 (2.1)	0	1 (1.0)
Fatal SAEs	0	0	0	0	0	0	0	0
AEs leading to treatment discontinuation	0	0	0	0	0	0	0	0
AEs leading to interruption	0	0	0	0	0	0	1 (1.6)	1 (1.0)
AEs requiring additional therapy	24 (60.0)	30 (75.0)	33 (82.5)	40 (64.5)	18 (51.4)	62 (65.3)	53 (85.5)	73 (76.0)

Source: Novartis, Data on file, APPOINT-PNH CSR, Table 12.1. Novartis, Data on file, APPLY-PNH CSR, Table 12.1 and Table 12.12 Company response to points for clarification A3
A patient with multiple occurrences of an AE under one treatment is counted only once.
*Median Treatment duration 317.5 days (range 170 – 339)
**Median treatment duration 245 days (range 28 – 344)
Abbreviations: AE, adverse event; BD, twice daily; CSR, clinical study report; SAE, serious adverse event; SAS, safety analysis set

Table 25 APPOINT-PNH and APPLY-PNH: Overview of adverse events of special interest (AESIs) until the data cut-off dates (2nd Nov 2022 / 26th Sep 2022) (SAS)

	APPOINT-PNH (complement inhibitor-naïve)		APPLY-PNH (complement inhibitor-experienced with residual anaemia)			
	Iptacopan 200 mg BD, N=40 n (%)		Randomised treatment period			Combined iptacopan safety analysis (randomised + extension treatment period until cut-off date)** N=95 n (%)
	Core treatment period (24 weeks)	Overall (core + extension treatment period until cut-off date)*	Iptacopan 200 mg BD N=62 n (%)	C5 inhibitor N=35 n (%)	Risk difference (95% CI)	
Severe or serious infections	**2 (5.0)**	**4 (10.0)**	**2 (3.2)**	**3 (8.6)**	**–5.35 (–15.61, 4.92)**	**5 (5.3)**
COVID-19 infections	1 (2.5)	2 (5.0)	1 (1.6)	2 (5.7)	–4.10 (–12.41, 4.20)	1 (1.1)
Cellulitis						1 (1.1)
Pneumonia bacterial	1 (2.5)	1 (2.5)				
Pneumonia	0	1 (2.5)				
Pyelonephritis			1 (1.6)	0	1.61 (–1.52, 4.75)	1 (1.1)
Septic Shock						1 (1.1)
Systemic infection						1 (1.1)
Urinary tract infection			1 (1.6)	0	1.61 (–1.52, 4.75)	1 (1.1)
Arthritis bacterial			0	1 (2.9)	–2.86 (–8.38, 2.66)	
Intervertebral discitis			0	1 (2.9)	–2.86 (–8.38, 2.66)	
Sepsis			0	1 (2.9)	–2.86 (–8.38, 2.66)	
Infections capsular bacteria	**1 (2.5)**	**2 (5.0)**	**1 (1.6)**	**0**	**1.61 (–1.52, 4.75)**	**1 (1.1)**
Bronchitis haemophilus			1 (1.6)	0	1.61 (–1.52, 4.75)	1 (1.1)
Pneumonia bacterial	1 (2.5)	1 (2.5)				
Staphylococcal skin infection	0	1 (2.5)				
PNH haemolysis and thrombosis	**1 (2.5)**	**2 (5.0)**	**10 (16.1)**	**10 (28.6)**	**–12.44 (–29.99, 5.10)**	**12 (12.6)**
Blood LDH increased			4 (6.5)	3 (8.6)	–2.12 (–13.23, 8.99)	5 (5.3)
BTH	0	1 (2.5)	2 (3.2)	6 (17.1)	–13.92 (–27.15, –0.68)	5 (5.3)
Blood creatinine increased	1 (2.5)	1 (2.5)	1 (1.6)	0	1.61 (–1.52, 4.75)	1 (1.1)
Extravascular haemolysis						1 (1.1)
Haemoglobin decreased						1 (1.1)
Haemoglobinuria			1 (1.6)	0	1.61 (–1.52, 4.75)	1 (1.1)
Hemiparesis			1 (1.6)	0	1.61 (–1.52, 4.75)	1 (1.1)
Ocular icterus			1 (1.6)	0	1.61 (–1.52, 4.75)	1 (1.1)
Transient ischaemic attack			1 (1.6)	0	1.61 (–1.52, 4.75)	1 (1.1)

	APPOINT-PNH (complement inhibitor-naïve)		APPLY-PNH (complement inhibitor-experienced with residual anaemia)			
	Iptacopan 200 mg BD, N=40 n (%)		Randomised treatment period			Combined iptacopan safety analysis (randomised + extension treatment period until cut-off date)** N=95 n (%)
	Core treatment period (24 weeks)	Overall (core + extension treatment period until cut-off date)*	Iptacopan 200 mg BD N=62 n (%)	C5 inhibitor N=35 n (%)	Risk difference (95% CI)	
Extravascular haemolysis			0	2 (5.7)	–5.71 (–13.40, 1.98)	
Jaundice			0	1 (2.9)	–2.86 (–8.38, 2.66)	
Testicular effects	**1 (2.5)**	**1 (2.5)**	**1 (1.6)**	**0**	**1.61 (–1.52, 4.75)**	**1 (1.1)**
Blood follicle stimulating hormone increased	1 (2.5)	1 (2.5)				
Dihydrotestosterone decreased	1 (2.5)	1 (2.5)	1 (1.6)	0	1.61 (–1.52, 4.75)	1 (1.1)
Thyroid changes	**1 (2.5)**	**1 (2.5)**	**1 (1.6)**	**0**	**1.61 (–1.52, 4.75)**	**1 (1.1)**
Reverse tri-iodothyronine increased	1 (2.5)	1 (2.5)				
Hypothyroidism			1 (1.6)	0	1.61 (–1.52, 4.75)	1 (1.1)
Decreased platelets	**9 (9.5)**		**4 (6.5)**	**0**	**6.45 (0.34, 12.57)**	**9 (9.5)**
Thrombocytopenia			3 (4.8)	0	4.84 (–0.50, 10.18)	5 (5.3)
Platelet count decreased			1 (1.6)	0	1.61 (–1.52, 4.75)	4 (4.2)

Source: Novartis, Data on file, APPOINT-PNH CSR, APPLY-PNH CSR, Company response to points for clarification A3
*Median Treatment duration 317.5 days (range 170 – 339)
**Median treatment duration 245 days (range 28 – 344)
Abbreviations: AE, adverse event; BD, twice daily; CSR, clinical study report; SAE, serious adverse event; SAS, safety analysis set

3.2.4 Summary of critique of clinical effectiveness and safety evidence for iptacopan

The evidence for iptacopan is based on two small, open-label studies (APPOINT-PNH and APPLY-PNH) that were powered to detect a difference on the objective primary outcome(s) of haematological response. Secondary and exploratory outcomes such as fatigue and health-related quality of life were more likely to have been at risk of bias and/or subject to chance.

Though APPOINT-PNH recruited a majority of patients from East Asia, the disease characteristics of the study populations are broadly representative of UK practice population.

APPOINT-PNH showed a large statistically significant change from baseline for iptacopan in reducing blood transfusions and increasing haemoglobin levels in complement-inhibitor naïve PNH patients. This appeared to be associated with some improvement in fatigue scores. However, there

was no direct comparative evidence in the complement inhibitor naïve group, as APPOINT was single arm study (see section 3.4 for discussion of indirect treatment comparison).

The APPLY-PNH study showed significant greater effects of iptacopan over continued C5-inhibitor treatment for haemoglobin, blood transfusions, and fatigue among complement-inhibitor experienced PNH patients with residual anaemia. Iptacopan and continued C5-inhibitor treatment appeared to have a similar effect on LDH ratios, suggesting similar control of IVH. The randomised phase of APPLY-PNH was only 24 weeks, so there is currently no longer-term evidence on the relative effects of iptacopan and C5 inhibitors.

There is no direct evidence comparing iptacopan against the only currently licenced proximal inhibitor (pegcetacoplan). See section 3.4 for discussion of indirect treatment comparisons.

The available safety data suggest that iptacopan is generally well tolerated, with no clear excess risks of adverse effects relative to C5 inhibitors. However, no data are available beyond 48 weeks of treatment, and the relatively small available studies were not designed to detect rare events. The possibility of more BTH over longer term follow-up is plausible, particularly given the unknown risk of medication non-adherence outside of a trial setting. This risk may be mitigated by the close supervision provided under the national PNH service arrangements, but there is a lack of real-world evidence on compliance with twice-daily oral iptacopan and its effects over the medium-to-long term. Similarly, while the observed incidence of MAVEs among iptacopan-treated patients was low, the APPOINT-PNH and APPLY-PNH do not add to the limited available evidence on the longer-term effects of proximal complement inhibitors in preventing thrombosis.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

3.3.1 Comparator interventions considered

The CS presented indirect comparisons of iptacopan with:

- C5 inhibitors (eculizumab or ravulizumab)
- Pegcetacoplan (for the complement inhibitor-experienced population with residual anaemia only)

Due to limitation of the available evidence, the company used a variety of methods to obtain estimates of the effect of iptacopan compared to C5 inhibitors and pegcetacoplan. A discussion of these methods is provided in section 3.4.

3.3.2 Trials in the indirect treatment comparisons

Details of all eligible trials were presented in Appendix D of the CS. The company appear to have selected the most suitable available study for each comparator.

Table 26 presents summary of the studies considered for the ITC analyses. Further discussion of the suitability of these studies is provided in section 3.4.

Table 26 Summary of trials considered for the ITC analyses

Comparator	Trial	Sample size	Trial design	Notes
Complement inhibitor-naive population: comparator studies considered for the unanchored ITC versus APPOINT-PNH				
Eculizumab	Study 301	125	Phase III RCT	Selected over TRIUMPH for main comparison on the basis of similarity to APPOINT-PNH population, better reflection of complement inhibitor-naïve patients seen in UK clinical practice, comparator (ravulizumab), and sample size (CS, p.67)
	TRIUMPH	43	Phase III placebo-controlled RCT	Excluded from main comparison, but ITC using TRIUMPH presented in appendix D. Placebo arm not used in the ITC.
Ravulizumab	Study 301	121	Phase III RCT	
C5 inhibitors	APPEX	85	Real world cohort	APPEX was classed as a study of 'C5 inhibitors' in the CS, though 84/85 patients received eculizumab, and just 1 received ravulizumab
Complement inhibitor-experienced population: comparator studies considered for the anchored and unanchored ITC versus APPLY-PNH				
Pegcetacoplan	PEGASUS	41	Phase III RCT	No other trials evaluating licenced treatments for complement-experienced patients with residual anaemia were identified.
Eculizumab	PEGASUS	39	Phase III RCT	

The quality of the included trials was assessed (see section 3.1). We note the generally small sample sizes, particularly for pegcetacoplan. While none of the identified RCTs were blinded, haemoglobin response and transfusion endpoints are objectively measured and at low risk of bias. FACIT-Fatigue scores may potentially be at higher risk of bias.

While the method of allocation concealment for Study 301 was not explicitly stated, it seems likely that allocation was concealed as part of its clearly described stratified randomisation procedure.

Missing outcomes data and more infrequent assessments in clinical practice when compared to a clinical trial were recognised as potential sources of bias in APPEX.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

The CS documents (original Doc B, revised Doc B, and the addendum) report indirect treatment comparisons of iptacopan in the complement inhibitor-naïve and complement inhibitor-experienced populations. For the complement naïve population, iptacopan has only been evaluated in a single-arm trial (APPOINT-PNH) and so has not been directly compared with any other eligible treatment.

While iptacopan was compared with C5 inhibitors (eculizumab and ravulizumab) in the complement inhibitor-experienced population (APPLY-PNH), it has not been directly compared to pegcetacoplan. Therefore, indirect treatment comparison approaches were used to compare iptacopan with other treatments in the complement inhibitor-naïve and -experienced populations.

Study 301 (RCT) and APPEX (real-world evidence) were used to carry out an unanchored matching-adjusted indirect comparison (MAIC) and augmented inverse probability weighting (AIPW) comparisons, respectively, in the complement inhibitor-naive population, and PEGASUS (clinical trial) was used to carry out both anchored and unanchored MAICs in the complement inhibitor-experienced population ITC.

Section B.2.9 of the CS included a summary of the process used to select studies for the ITCs, the baseline characteristics of patients in all studies included in the ITC analyses, the methods used in the ITC analysis, the results, the uncertainties, and the implications. A fuller explanation is provided in the Appendix D and the addendum.

It is important to note that, according to the CS, the estimates from the clinical effectiveness section (B.2.9) were not used in the economic model because "the definition of model health states required the consideration of Hb and transfusion outcomes in combination" (page 95 of CS).

3.4.1. Indirect treatment comparisons in the complement inhibitor-naïve group

Iptacopan has been evaluated among complement-inhibitor naïve patients in a single-arm trial (APPOINT-PNH). Assessment timepoints for APPOINT-PNH were 24 weeks and 48 weeks (see section 3.2 of this report). However, at the time of the original company submission, only 24-week data were available for inclusion in the ITC; the ITC was not updated in the revised Document B or in the addendum submitted by the company.

3.4.1.1 APPOINT-PNH vs Study 301

Study selection and methods

As described in section B.2.9.1.2 of the CS, the company undertook a systematic review to identify studies eligible for the complement-inhibitor naïve ITC. Of the identified studies, STUDY 301[3] and TRIUMPH[2] were considered most suitable for an ITC including 24-week timepoint data from APPOINT-PNH. The company preferred STUDY 301 over TRIUMPH; both trials included eculizumab as comparators, but STUDY 301 also included ravulizumab which is commonly used in current UK clinical practice. STUDY 301 also included more participants than TRIUMPH. An analysis including TRIUMPH is presented in Appendix D of the CS.

Unanchored MAIC analyses were used to estimate the relative clinical effectiveness of iptacopan versus eculizumab and ravulizumab. APPOINT-PNH endpoint data were adjusted to align with Study 301 trial definitions where possible. The entropy balancing technique was used to reweight individual participant data (IPD) from APPOINT-PNH to adjust for differences with STUDY 301, as set out in the relevant NICE DSU Technical Support Document 18.[7] The prognostic factors adjusted for were age, sex, percentage transfusion free in prior 12 months, baseline LDH, history of MAVE. However, differences in baseline Hb could not be adjusted for, as the analysis did not converge. While APPOINT-PNH recruited patients with Hb < 10 g/dL Study 301 did not specify a level of Hb (to define anaemia) as an eligibility criterion, and so included patients with Hb ≥ 10 g/dL.

Table 20 of the CS compared the baseline characteristics of the patients in APPOINT-PNH and Study 301, before and after weighting. For ease of reference, this is reproduced below as Table 27.

Table 27: Comparison of baseline characteristics between Study 301 and APPOINT-PNH, before and after weighting [sourced from Document B, Table 20]

Baseline Characteristics	Study 301	APPOINT-PNH Unweighted		APPOINT-PNH Weighted†	
	N = 246	N=40	SMDs	ESS=31	SMDs
Age, years: mean (SD)	45.5 (15.7)	42.1 (15.8)	0.216	45.5 (15.7)	0.000
LDH, U/L: mean (SD)	1,606.4 (752.7)	1,698.8 (683.3)	0.129	1,606.4 (684.7)	0.000
Transfusion free, 12 months prior: n (%)	44 (17.9%)	13 (32.5%)	0.342	17.8%	0.000
History of MAVE, n (%)	42 (17.1%)	5 (12.5%)	0.129	17.1%	0.001
Sex, male: n (%)	134 (54.5%)	23 (57.5%)	0.061	54.5%	0.001
Weight, kg: mean (SD)	68.7 (15.2)	70.1 (12.7)	0.100	68.6 (12.3)	0.005
Height, cm: mean (SD)	166.2 (9.8)	168.2 (9.1)	0.208	167.1 (9.0)	0.100

Race, white: n (%)	94 (38.2%)	12 (30%)	0.174	28.4%	0.210
Hb, g/dL: mean (SD)	9.5 (1.6)	8.15 (1.09)	0.983	7.9 (1.2)	1.127
Baseline FACIT-Fatigue score: mean (SD)	NR	32.8 (10.2)	NA	32.3 (10.0)	NA
Reticulocyte count: mean (SD), per mm^3	NR	154,325 (63,666)	NA	143,231 (609,11)	NA

Green = SMD ≤ 0.1 (small difference); Yellow = 0.1 > SMD ≤ 0.2 (moderate difference); Red = SMD > 0.2 (substantial difference). These conservative thresholds were informed by Austin 2009 and 2011 [8, 9].†Reweights APPOINT-PNH data to balance with Study 301 on age (means and SD), proportion of males, LDH level at baseline (mean and SD), transfusion free 12 months prior, and history of MAVE; Abbreviations: ESS, effective sample size; FACIT, Functional Assessment of Chronic Illness Therapy; Hb, haemoglobin; LDH, lactate dehydrogenase; MAVE, major adverse vascular event; NA, not applicable; NR, not reported; SD, standard deviation; SMD, standardised mean difference.

The outcomes evaluated were change from baseline (CFB) of LDH, CFB in FACIT-fatigue score, and transfusion avoidance. The CFB of LDH and FACIT were reported as mean difference. Transfusion avoidance was reported using odd ratio (OR). Haematological response and CFB in Hb endpoints were not reported for Study 301, so could not be included in the indirect comparison. Confidence intervals were calculated using bootstrapping.

Results

The results of the ITC were reported in Table 21 (CS Doc B). For ease of reference, this is replicated in Table 28 below. This shows that estimates obtained using Study 301 favoured iptacopan as having a better clinical treatment effect for all outcomes analysed (i.e., transfusion avoidance, % CFB in LDH, and CFB in FACIT-Fatigue score) compared to both eculizumab and ravulizumab. However, the effects were not statistically significant except for % CFB in LDH.

The estimates obtained from the ITCs were uncertain in that the 95% confidence interval of all the estimates were wide. Sensitivity analyses reported in the CS Appendix D (D.5.3.3.1).

Table 28: Overview of results for iptacopan vs ravulizumab or eculizumab in the complement inhibitor-naïve population: ITC using APPOINT-PNH vs Study 301 [sourced from Document B, Table 21]

	Transfusion avoidance	**% CFB in LDH**	**CFB in FACIT-Fatigue score**
Iptacopan (ESS=31†)	78.6%	% CFB = –85.08 (95% CI –87.84, –82.32)	CFB =10.85 (95% CI 7.23, 14.47)
Ravulizumab (N=125)	73.5%	% CFB = –76.84 (95% CI –79.96, –73.73)	CFB = 7.07 (95% CI 5.55, 8.60)
Eculizumab (N =121)	66.1%	% CFB = –76.02 (95% CI –79.20, –72.83)	CFB = 6.40 (95% CI 4.85, 7.96)
Iptacopan (ESS=31†) vs ravulizumab (N=125)	OR = 1.32 (95% CI 0.47, 3.73) p=0.6011	**MD = –8.24 (95% CI –13.28, –3.20) p=0.0013**	MD = 3.78 (95% CI –1.38, 8.94), p=0.1514
Iptacopan (ESS=31†) vs	OR = 1.88 (95% CI 0.67, 5.28) p=0.2281	**MD = –9.06 (95% CI –14.14, –3.98) p=0.0005**	MD = 4.45 (95% CI –0.72, 9.62), p=0.0918

	Transfusion avoidance	% CFB in LDH	CFB in FACIT-Fatigue score
eculizumab (N =121)			

OR >1 implies higher odds of remaining transfusion-free for iptacopan vs ravulizumab or eculizumab; MD >0 implies higher LDH for iptacopan vs ravulizumab or eculizumab; MD >0 implies higher FACIT Fatigue score for iptacopan vs ravulizumab or eculizumab; **Bold** values indicate statistical significance and corresponds to a two-tailed p-value <0.05.† APPOINT-PNH results using Study 301 endpoint definitions and population adjusted to balance with Study 301 on age (means and SD), proportion of males, transfusion free 12 months prior, baseline LDH (mean and SD), and history of MAVE.
Abbreviations: CFB, change from baseline; CI, confidence interval; ESS, effective sample size; FACIT, Functional Assessment of Chronic Illness Therapy; ITC, indirect treatment comparison; LDH, lactate dehydrogenase; MAVE, major adverse vascular event; MD, mean difference (in CFB); OR, odds ratio; SD, standard deviation.

Points for critique

The EAG agrees that STUDY 301 is the best available study to use in the ITC given the larger sample size compared to TRIUMPH and the inclusion of ravulizumab, which is widely used in UK clinical practice. APPOINT-PNH is a 24-week study with a further 24-week extension period (48-weeks in total). While the company provided the 48-week data in response to the EAG's points for clarification (see section 3.3), only the 24-week data were used in the ITCs.

The company assumed that there is reasonable overlap in the eligibility criteria between APPOINT-PNH and Study 301, which is required when using MAIC, so that participant characteristics in APPOINT-PNH can be re-weighted to match Study 301. However, with the non-adjustment for baseline Hb (which is used to define anaemia) in Study 301 due to convergence issues encountered in the company's analysis, the substantial differences in baseline Hb could have biased the assumption of sufficient "population overlap" for MAIC. As baseline Hb was lower in APPOINT-PNH compared to Study 301, this bias would be against iptacopan. The fact that this key characteristic could not be adjusted for, in addition to the comparison being unanchored, means that the findings of this indirect comparison are highly uncertain.

No data are available on the relative effect of iptacopan versus eculizumab or ravulizumab on the APPOINT-PNH primary outcome of Hb response.

3.4.1.2 APPOINT-PNH vs APPEX

The CS also presented a complement-inhibitor naïve population ITC analysis using a real-world cohort data (APPEX). While the APPEX study was classified as evidence on C5 inhibitors, almost all patients received eculizumab (only one of the 85 included patients received ravulizumab).

An unanchored population-adjusted comparison using a doubly robust augmented inverse probability weighting (AIPW) was used to estimate the relative effects of iptacopan (using the APPOINT-PNH study) versus C5 inhibitors (using the APPEX cohort data). The propensity score model was used to

weight IPD from APPEX and APPOINT-PNH taking into consideration the factors of age, sex, baseline Hb, baseline reticulocyte count, transfusion needs, ongoing aplastic anaemia/ bone marrow disease, and history of MAVE. The company validated these prognostic factors with UK clinicians and they were also considered appropriate by the EAG's clinical advisor.

Tables comparing the baseline characteristics of the patients in APPOINT-PNH alongside patients in APPEX were reported in the CS Doc B (table 22), before and after weighting. For ease of reference, this is reproduced below as Table 29.

Table 29: Comparison of baseline characteristics between APPEX and APPOINT-PNH, before and after weighting [sourced from Document B, Table 22]

Characteristic Categories/statistics	Before weighting			After weighting	
	APPOINT-PNH trial cohort (N=40)	APPEX real-world cohort (N=85)	SMD	APPEX real-world cohort (N=41)	SMD
Age, years: mean (SD)	42.1 (15.85)	47.8 (19.07)	−0.362	42.5 (17.47)	−0.023
Sex, male: n (%)	23 (57.5)	34 (40.0)	0.354	22 (53.8)	0.074
Baseline Hb, g/dL: mean (SD)	8.2 (1.09)	8.4 (1.27)	−0.200	8.1 (1.49)	0.035
Number of transfusions in the 24 weeks prior to index date: mean (SD)	2.2 (2.25)	1.9 (2.93)	0.114	2.5 (3.65)	–0.148
Number of units of RBC transfused in the 24 weeks prior to index date: mean (SD)	3.98 (4.08)	3.24 (4.04)	0.181	4.01 (4.66)	–0.009
Transfusions in the 24 weeks prior to index date, yes: n (%)	28 (70.0)	49 (57.6)	0.270	25 (61.1)	0.195
Number of transfusions in the 24 weeks prior to index date among patients who had a transfusion: mean (SD)	3.1 (2.09)	3.3 (3.21)	–0.103	4.1 (3.93)	–0.476
Number of transfusions in the 24 weeks prior to index date among patients who had a transfusion: n (%)					
<2	7 (25.0)	16 (32.7)	–0.177	7 (26.1)	–0.025
≥2	21 (75.0)	33 (67.3)	0.177	18 (73.9)	0.025
Number of units of RBC transfused in the 24 weeks prior to index date among patients who had a transfusion: mean (SD)	5.7 (3.74)	5.6 (3.86)	0.018	6.6 (4.33)	–0.239
Absolute reticulocyte counts, $\times 10^9$/litre: mean (SD)	154.3 (63.67)	149.3 (83.73)	0.079	155.3 (91.28)	–0.015
History of MAVE, yes: n (%)	5 (12.5)	15 (17.6)	–0.156	5 (12.9)	0.013
Ongoing aplastic anaemia, yes: n (%)	16 (40.0)	18 (21.2)	0.384	15 (36.7)	0.068

Abbreviations: Hb, haemoglobin; MAVE, major adverse vascular event; RBC, red blood cells; SD, standard deviation; SMD, standardised mean difference, defined as the difference in mean or **proportion** estimates between the APPOINT-PNH trial and APPEX real-world cohorts (trial - real-world) divided by the SD in the trial cohort.

The outcomes evaluated were CFB in reticulocyte count, increase in Hb from baseline in the absence of red blood cell (RBC) transfusions, percentage CFB LDH, and transfusion avoidance. The increase in Hb from baseline in the absence of RBC transfusion and transfusion avoidance were reported as percentage difference in proportions, CFB in reticulocyte count was reported as difference in CFB and

percentage CFB in LDH was reported as ratio of percentage levels to baseline. All estimates were reported alongside their 95% confidence interval, which were calculated using bootstrapping.

Results

The results of the AIPW ITC were reported in Table 23 of the CS. For ease of reference, they are replicated in Table 30 below which shows iptacopan is favoured as having a better clinical treatment effect on the increase in Hb from baseline in the absence of RBC transfusion, transfusion avoidance, %CFB in LDH and CFB in reticulocyte count, compared to a C5 inhibitor.

The estimates obtained from the AIPW ITCs were uncertain in that the 95% confidence intervals of the estimates were wide. Sensitivity analyses are reported in the CS Appendix D (D.5.3.3.1).

Table 30: Overview of results for iptacopan vs C5 inhibitors in the complement inhibitor-naïve population: ITC using APPOINT-PNH vs APPEX [sourced from Document B, Table 23]

Endpoint	Estimate	Iptacopan vs C5 inhibitors, average treatment effect (95% CI)§
≥2 g/dL increase in Hb from baseline† in the absence of RBC transfusions‡	Difference in proportions (%)	68.4 (41.0, 95.8)
Hb levels ≥12 g/dL† in the absence of RBC transfusions‡	Difference in proportions (%)	53.5 (31.6, 75.5)
Transfusion avoidance‡	Difference in proportions (%)	38.9 (15.1, 62.6)
% CFB in LDH (U/L)‡	Ratio of % levels to baseline	0.52 (0.40, 0.67)
CFB in reticulocyte count (x10⁹/L)¶	Difference in CFB	–75.8 (–107.2, –44.4)

*Of 85 patients in APPEX, 84 received eculizumab, 1 patient received ravulizumab
†Endpoint for C5 inhibitors included measurements between Day 100 and Day 200 (mean of all available measurements); ‡Endpoint for C5 inhibitors included measurements between Day 15 and Day 200; ¶Endpoint for C5 inhibitors included measurements between Day 1 and Day 200.
§Estimates of differences between treatments derived as average treatment effect in the treated using debiased 4-fold cross-fitting of orthogonalised scores from efficient influence function; confidence bounds comparisons including multiple imputations in APPOINT-PNH are combined using Rubin's combination rules.
Abbreviations: CFB, change from baseline; CI, confidence interval; Hb, haemoglobin; ITC, indirect treatment comparison; LDH, lactate dehydrogenase; RBC, red blood cell.

Points for critique

The EAG agrees that using data from the APPEX real world evidence (RWE) study helps to understand the safety and effectiveness of treatment within clinical practice settings. However, unlike RCT or clinical trials, RWE lack elements to control for potential selection bias and confounding, which can lead to over- or under-estimated treatment effects. The company also raised concerns around outcome measurement variability between the sources included in this comparison, noting "differences between the irregular measurements practiced in real-world clinical practice, which may in some case be driven by clinical events as opposed to regularly scheduled measurements in clinical trial" (B.2.9.2.4 p74).

The EAG agrees with the choice of method the company employed to analyse the data which is in line with NICE TSD 17.[10]

As stated in the CS (p.71), the APPEX study was designed to contextualise findings of APPOINT-PNH in a target trial framework, so the primary and secondary endpoints as well as patient eligibility criteria were fully aligned between the two studies. In addition, as the company had the relevant IPD, they could adjust the APPEX data to APPOINT-PNH, which is preferable to adjusting APPOINT-PNH to aggregate comparator study data using MAIC (as was done for the comparison with Study 301). However, this remains an unanchored comparison where it is assumed that all prognostic and effect modifying covariates are known and adjusted for, which is hard to support in practice.

The APPEX data used in the analysis was derived from a larger cohort of patients from two participating trial centres, with all French patients and a random selection of UK patients included. The company responded to an EAG point for clarification (PfC A5), explaining the rationale for this approach (i.e. to obtain a similar number of patients from the two participating centres). Attempts appear to have been made to minimise selection bias, and the EAG's clinical advisor considered the cohort used for the analysis to reflect that seen in UK clinical practice.

As noted previously, only one patient (of 85) from the APPEX study received ravulizumab. Thus, the analyses essentially compare iptacopan with eculizumab and not C5 inhibitors as a class.

The EAG requested for the dataset and R-code used in the ITC to rerun the analysis. The company provided their R-code (PfC A8) but the APPOINT-PNH and APPEX datasets could not be shared due to participant confidentiality. Consequently, the analysis could not be rerun to ascertain if estimates are as reported in the CS. However, the code appeared to be correct, and the required software packages and procedures for adjusted indirect comparisons appear to have been correctly implemented.

3.4.2 Indirect treatment comparisons in the complement inhibitor-experienced population with residual anaemia

Study selection and methods

Iptacopan was directly compared to C5 inhibitor treatments among complement-inhibitor experienced patients with residual anaemia in a two-arm RCT (APPLY-PNH). Assessment timepoints for APPLY-PNH were 24 weeks and 48 weeks (see section 3.2 of this report). However, at the time of the company submission, only 24-week data were available for inclusion in the ITC.

No 48-week data were used for ITC in the complement inhibitor-experienced group, however a revised CS document B and addendum included revised 24-week clinical trial data for APPLY-PNH.

For ease of reference, the results of the updated analyses from the addendum have been reproduced in this EAG report.

Of the studies identified in the systematic review, PEGASUS was considered the most appropriate to use in an ITC with APPLY-PNH. PEGASUS evaluated the treatment effectiveness of pegcetacoplan and eculizumab. It is a two-arm trial with three periods: a 4-week run-in period where all patients received both eculizumab and pegcetacoplan, then a 16-week period where patients were randomised to receive either pegcetacoplan or eculizumab (day 1 to day 112), followed by a 32-week open label period where patients received pegcetacoplan (those who had been randomised to eculizumab continued to receive it for the first 4-weeks of this period). For the ITC, the company used the timeframe of 20-weeks, including the run-in and randomised periods (day -28 to day 112).

The company used a matched indirect adjusted comparison (MAIC) to compare iptacopan to pegcetacoplan. The entropy balancing technique was used to reweight the IPD from APPLY-PNH to adjust for differences with PEGASUS. The prognostic factors adjusted for were age, sex, percentage transfusion free in prior 12 months, baseline LDH, baseline Hb, and screening reticulocytes. The company validated these factors with UK clinicians. A table comparing the baseline characteristics of the patients in the company's trial APPLY-PNH alongside patients in the PEGAGUS trial was reported in the original CS (Table 25, p78), before and after weighting. The updated version of this table reported in the company addendum, including revised data for APPLY-PNH, is reported below as Table 31.

Table 31: Comparison of baseline characteristic between iptacopan (APPLY-PNH) and pegcetacoplan (PEGASUS): ITT population (N= 62), and analysis set (N = 54) before and after weighting [sourced from Addendum, Table 9]

Characteristics	Pegcetacoplan (PEGASUS)	Iptacopan (APPLY-PNH)					
		ITT		ITC analysis dataset† Unweighted		ITC analysis dataset† Weighted‡	
	N=41	N=62	SMDs	N=54	SMDs	ESS=15	SMDs
Hb, g/dL: mean (SD)¶	8.7 (1.1)	8.9 (0.7)	0.186	8.8 (0.7)	0.146	8.7 (1.1)	0.000
LDH (U/L): mean (SD)	257.5 (97.6)	269.1 (70.1)	0.137	263.5 (71.5)	0.070	257.5 (73.5)	0.000
Age, years: mean (SD)	50.2 (16.3)	51.7 (16.9)	0.091	51.7 (16.6)	0.092	50.2 (16.5)	0.001
Screening reticulocytes (10^9/L): mean (SD)	217.5 (75.0)	204.0 (84.1)	0.169	210.7 (84.1)	0.086	217.6 (76.3)	0.002
Sex female: n (%)	27 (65.9)	43 (69.4)	0.075	37 (68.5)	0.057	66%	0.003
Transfusion free, 12 months prior: n (%)	10 (24.4)	25 (40.3)	0.346	22 (40.7)	0.354	24%	0.008
Duration of C5 inhibitor, years: mean (SD)	5.5 (3.9)	3.8 (3.6)	0.454	3.9 (3.7)	0.430	5.4 (4.0)	0.018
Screening platelet count (10^9/L): mean (SD)	166.6 (98.3)	160.9 (55.9)	0.071	167.4 (55.1)	0.010	152.2 (66.2)	0.172
FACIT-F score: mean (SD)	32.2 (11.4)	34.7 (9.8)	0.234	35.1 (10.1)	0.274	35.1 (10.8)	0.257
Time since diagnosis, years: mean (SD)	8.7 (7.4)	11.9 (9.8)	0.362	11.9 (9.6)	0.372	10.9 (6.9)	0.309
BMI (kg/m^2): mean (SD)	26.7 (4.3)	24.9 (5.0)	0.385	24.5 (4.3)	0.523	25.2 (4.4)	0.344
History of aplastic anaemia: n (%)	11 (26.8)	9 (14.5)	0.308	8 (14.8)	0.299	12.5%	0.368
Race, white: n (%)	24 (58.5)	48 (77.4)	0.413	42 (77.8)	0.422	34.8 (84.5)	0.602
≥4 transfusions of pRBCs, 12 months prior: n (%)	21 (51.2)	16 (25.8)	0.541	15 (27.8)	0.494	20.2%	0.684
History of MAVE: n (%)	NR	12 (19.4)	NA	11 (20.4)	NA	14.6%	NA

Updated values to original company evidence submission underlined and in red font.
Green = SMD ≤0.1 (small difference); Yellow = 0.1 > SMD ≤ 0.2 (moderate difference); Red = SMD > 0.2 (substantial difference). These conservative thresholds were informed by Austin 2009 and 2011 (104, 105).
†8 patients removed from the APPLY-PNH iptacopan dataset, who were not eligible for PEGASUS based on criteria for reticulocyte count, platelet count and BMI; ‡Reweights APPLY-PNH data to balance with PEGASUS on baseline Hb per PEGASUS definition, sex, proportion transfusion-free within 12 months prior to baseline, reticulocyte count at screening, baseline LDH, and age; ¶Baseline Hb was calculated as per PEGASUS definition, as an average of values recorded prior to run-in dosing including local and central laboratory values.
Abbreviations: BMI, body mass index; ESS, effective sample size; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; ITT, intent-to-treat; LDH, lactate dehydrogenase; MAVE, major adverse vascular event; NA, not applicable; NR, not reported; pRBC packed red blood cell; SD, standard deviation; SMD, standardised mean difference.

Both unanchored and anchored MAIC analyses were used to estimate the clinical effectiveness of iptacopan compared to pegcetacoplan. An anchored ITC technique was also used but not clearly explained in the CS. It was described in response to an EAG point for clarification (PfC A8) as: "Anchored ITCs for iptacopan vs pegcetacoplan were computed as the difference between (a) the reweighted outcome for iptacopan minus the reweighted outcome for the C5 inhibitor control arm of APPLY-PNH and (b) the published estimate of the outcome for pegcetacoplan minus that of the C5 inhibitor control arm of PEGASUS. Consequently, the anchored ITC analysis performed may be viewed

as…a weighted form of contrast-based evidence synthesis methods described in the NICE TSD2, which differs from a Bucher ITC which does not incorporate reweighting".

The outcomes measured in the ITCs were CFB in Hb excluding post-transfusion data, CFB in Hb including post-transfusion data and transfusion avoidance. CFB in Hb data were reported using mean difference (with 95% confidence intervals). Transfusion avoidance was reported using odds ratio (OR) (with 95% confidence interval).

Results

The results of the revised ITCs were reported in Table 10 of the Addendum, reproduced in Table 32 below. The results favoured iptacopan over eculizumab on transfusion avoidance, CFB in Hb including and excluding post-transfusion data.

Table 32: Overview of results for iptacopan vs pegcetacoplan in the complement inhibitor-experienced population with residual anaemia: ITC using APPLY-PNH vs PEGASUS [sourced from Addendum, Table 10]

	CFB in Hb, excluding post-transfusion data (95% CI)	CFB in Hb, including post-transfusion data (95% CI)	Transfusion avoidance
Iptacopan (ESS=15†)	3.38 (2.99, 3.77)	3.42 (3.02, 3.82)	98.7%
Pegcetacoplan (N=41)	2.37 (1.66, 3.08)	2.66 (2.17, 3.15)	85.4%
Eculizumab/ ravulizumab APPLY-PNH (ESS=7†)	[redacted]	[redacted]	[redacted]
Eculizumab PEGASUS (N=39)	*–1.47 (–2.78, –0.16)*	*–0.03 (–0.54, 0.48)*	*15.4%*
Unanchored MAIC results			
Iptacopan vs pegcetacoplan	**MD 1.01 (95% CI 0.21, 1.82) p=0.014**	**MD 0.76 (95% CI 0.13, 1.39) p=0.018**	**OR 12.71 (95% CI 1.87, 86.22) p=0.009**
Anchored results			
Iptacopan vs pegcetacoplan	MD [redacted] (95% CI [redacted]) p=0.873	MD [redacted] (95% CI [redacted]) p=0.141	OR [redacted] (95% CI [redacted]) p=0.392

Updated values to original company evidence submission underlined and in red font.
MD >0 implies higher value for iptacopan vs pegcetacoplan; OR >1 implies higher odds for iptacopan vs pegcetacoplan; **Bold** values indicate statistical significance and corresponds to a two-tailed p-value <0.05.
†APPLY-PNH results using PEGASUS endpoint definitions and population adjusted, reweighted to balance with PEGASUS on baseline Hb (mean and SD), proportion of females, proportion transfusion-free within 12 months prior, screening reticulocyte (mean and SD), baseline LDH (mean and SD), and age (mean and SD).
Abbreviations: CFB, change from baseline; CI, confidence interval; ESS, effective sample size; Hb, haemoglobin; ITC, indirect treatment comparison; LDH, lactate dehydrogenase; MD, mean difference (in CFB); OR, odds ratio

Points for critique

While PEGASUS appears to be the closest and only eligible trial available for the ITC of iptacopan in the complement inhibitor-experienced population, there are important methodological inconsistencies between PEGASUS and APPLY-PNH. While APPLY-PNH was a 24-week parallel RCT comparing iptacopan versus C5 inhibitors (eculizumab or ravulizumab), PEGASUS was a 20-week controlled trial incorporating a 4-week run-in period, during which all patients were administered pegcetacoplan + eculizumab (combined therapy), before being randomised to either pegcetacoplan or eculizumab monotherapy without any wash-out period. Hence, the treatment effectiveness estimated in PEGASUS seems compromised, as the combined treatment effect (pegcetacoplan + eculizumab) from this run-in period was not accounted or differentiated from the treatment effect when administered as a monotherapy (pegcetacoplan or eculizumab). This difference in the C5 comparator arms undermines the validity of the anchored comparison including PEGASUS and APPLY-PNH.

The method used by the company in the unanchored MAIC followed the recommended method in NICE TSD 18. While the company explained their anchored ITC approach in the response to point of clarification (PfC A8), there was no justification why their approach was preferred over the standard Bucher method, which is discussed in TSD 18 as an appropriate method to use for anchored comparisons when effect modifiers are assumed to be well-balanced across studies. Even when there is a suspicion that effect modifiers may not be balanced across studies, a standard Bucher indirect comparison[11, 12] can serve as a reference point for comparison to the adjusted analyses. The EAG performed an anchored ITC using the Bucher method to estimate the indirect effect of iptacopan versus pegcetacoplan for the transfusion avoidance endpoint. The estimated odd ratio is 1.43 (95% CI 0.20, 10.40), compared with the company's anchored MAIC estimate of [redacted] (95% CI [redacted]). While the point estimates differ and the Bucher analysis has narrower confidence intervals, neither analysis indicates a statistically significant difference between iptacopan and pegcetacoplan.

The estimates obtained using the anchored and unanchored comparisons were notably different. The anchored comparison showed no statistically significant differences between iptacopan and pegcetacoplan, though estimates were uncertain. In contrast, the estimates obtained in the unanchored MAIC favoured iptacopan over pegcetacoplan, though again with some degree of uncertainty. Furthermore, the ESS after reweighting was very small compared to the unweighted sample size (see Table 31). TSD 18 advises that where both an anchored and unanchored indirect comparison is possible, the anchored comparison should be preferred. The company provided justification in section B.2.9.3.2.3 of the CS why this might not apply here, therefore the EAG prefers to base conclusions on results of the anchored comparison.

The ITC analyses reported in the CS addendum included revised 24-week clinical trial data for APPLY-PNH. The revised clinical data caused a substantial difference in the estimated odds ratio for the transfusion avoidance endpoint compared to the original analysis, due to an additional patient in the APPLY-PNH dataset receiving a transfusion despite minimal changes in the baseline characteristics. For example, the original anchored comparison OR estimate was [redacted] and the revised is [redacted]. The EAG sent a PfC (PfC follow-up Q4) regarding this difference. The company responded that the number of patients with transfusion events increased from one to two; this decreased the proportion of transfusion–avoidant patients in the iptacopan arm in the APPLY-PNH trial (PfC follow-up response Q4), leading to the decrease in the odd ratio of iptacopan compared to pegcetacoplan. This illustrates how sensitive the transfusion avoidance ITC is to very small changes in the number of transfusion events and how uncertain the transfusion avoidance results are.

Given the above inconsistencies and uncertainties, the EAG suggests interpreting these clinical effectiveness results with caution.

3.5 Conclusions of the clinical effectiveness section

The CS reflects the decision problem defined in the final scope and presents evidence on the effects of iptacopan in two PNH populations: (1) complement inhibitor-naïve patients who have haemolysis with clinical symptoms and (2) complement inhibitor-experienced patients with residual anaemia. It is likely to have included the currently available relevant evidence.

3.5.1 Complement inhibitor-naïve patients who have haemolysis with clinical symptoms

A small single-armed study (APPOINT-PNH) provided direct evidence on the treatment effects of iptacopan in the complement inhibitor-naïve population. This showed a large statistically significant change from baseline to 24 weeks for iptacopan in reducing blood transfusions and increasing haemoglobin levels in complement-inhibitor naïve PNH patients. This appeared to be associated with some improvement in fatigue scores.

In the absence of direct evidence, two unanchored ITCs were conducted to estimate the treatment effects of iptacopan relative to C5 complement inhibitors.

One unanchored MAIC using study 301 (an RCT that compared ravulizumab with eculizumab), showed a significantly greater reduction in LDH from baseline for iptacopan than ravulizumab or eculizumab, but no significant difference in transfusion avoidance or change from baseline FACIT-Fatigue score. Relative effect on haemoglobin levels could not be estimated. The results of this ITC are uncertain due to the inability to adjust for baseline differences between 301 and APPOINT-PNH.

A second ITC used a propensity score model to match to data from a real-world dataset (APPEX) to APPOINT-PNH. This showed significantly greater improvements in haemoglobin response, transfusion avoidance, change from baseline LDH, and reticulocyte count for iptacopan than eculizumab. However, this unanchored comparison was also subject to uncertainty, and could not estimate the treatment effect of iptacopan relative to ravulizumab (the preferred C5 inhibitor for most patients in current NHS practice).

While iptacopan appears to be efficacious among complement inhibitor-naïve PNH patients, its longer-term effectiveness and effects relative to eculizumab and ravulizumab in this population are not well-established.

3.5.2 Complement inhibitor-experienced patients with residual anaemia

A single RCT (APPLY-PNH) showed significantly greater treatment effects for iptacopan over continued C5 inhibitor treatment for haemoglobin response and blood transfusion measures, while iptacopan and continued C5 inhibitor treatment appeared to have a similar effect on LDH ratios. The randomised phase of APPLY-PNH was only 24 weeks, so there is currently no longer-term evidence on the relative effects of iptacopan and C5 inhibitors.

Anchored and unanchored MAICs were conducted to estimate the treatment effects of iptacopan relative to the only currently licenced proximal inhibitor (pegcetacoplan). Both employed the PEGASUS RCT, which compared pegcetacoplan versus eculizumab. The two ITCs were inconsistent in their estimates of relative treatment effect on haemoglobin and transfusion avoidance outcomes, however results from the anchored comparison are considered more reliable by the EAG. These results were also highly uncertain due to a very small effective sample size for the iptacopan group, and discrepancies in C5 inhibitor comparator arms due to PEGASUS incorporating a pegcetacoplan-plus-eculizumab run-in period. Consequently, the relative treatment effects of iptacopan versus pegcetacoplan among complement inhibitor-experienced patients with residual anaemia are not well-established.

3.5.3 Adverse events

The available safety data suggest that iptacopan is generally well tolerated, with no clear excess risks of adverse effects relative to C5 inhibitors. However, no data are available beyond 48 weeks of treatment, and the relatively small available studies were not designed to detect rare events. The risks of BTH and MAVE associated with longer-term iptacopan treatment have yet to be established.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

The company's systematic literature review did not identify any economic evaluations of iptacopan for the treatment of adults with PNH, while several cost-effectiveness studies were identified for pegcetacoplan, ravulizumab and eculizumab for the treatment of PNH. Table 37 of the CS provides a summary of the included cost-effectiveness studies relevant to the decision problem, while Appendix G of the CS provides a detailed description of the searches and results of the review. The company summarised the two previous cost-effectiveness models used in NICE Technology Appraisals to evaluate PNH treatments (Tables 37 and 38 of the CS): TA698, ravulizumab for treating paroxysmal nocturnal haemoglobinuria in adults; and TA778, pegcetacoplan for treating paroxysmal nocturnal haemoglobinuria in adults who have anaemia after at least 3 months of treatment with a C5 inhibitor.

Points for critique

The literature searching for the company's review of cost-effectiveness evidence appears to have been conducted to a high standard and is well reported – See Appendix 1 for details. The EAG considers that all relevant publications are likely to have been identified. Table 37 of the CS provides a sufficiently detailed summary of the model structures, patient populations and cost-effectiveness results included in previous studies of treatments for PNH in adults, while Table 38 provides a comparison of the key features of the company's economic analysis with the previous NICE appraisals (TA698 and TA778). Of note, the company also summarises Hakimi et al., (2022), [13] which is a cost-effectiveness study of pegcetacoplan compared with ravulizumab for the treatment of PNH in a UK setting, funded by Apellis Pharmaceuticals, Inc and Swedish Orphan Biovitrum AB (pegcetacoplan), which includes much of the redacted economic information contained in TA778.

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

The company submitted a *de-novo* model to compare the cost-effectiveness of iptacopan with relevant comparator complement inhibitors in two separate populations: (i) iptacopan with C5 inhibitors of ravulizumab and eculizumab in adult patients with PNH who are naïve to treatment with complement inhibitors and have haemolysis with clinical symptom(s); and (ii) iptacopan with pegcetacoplan and C5 inhibitors (ravulizumab and eculizumab) in a complement inhibitor-experienced PNH adult population with residual anaemia.

A semi-Markov cohort model is used to estimate long-term health outcomes and costs based on patients transitioning between three PNH health states representing anaemia and transfusion requirements over a lifetime horizon, while all patients are at a risk of all-cause mortality, which is assumed not to be affected by treatment. When patients discontinue treatment with one complement

inhibitor, a switch to another complement inhibitor is modelled, with a maximum of one subsequent line of therapy included (i.e., patients continue on the subsequent line of treatment over their remaining lifetime).

Iptacopan is modelled to affect quality-adjusted life years (QALYs) by increasing the proportion of patients who are not receiving transfusions and do not have anaemia, which is associated with improved health-related quality of life, compared to the comparator complement inhibitors, and, to a lesser extent, reducing the proportion of patients requiring transfusions, which is associated with lower health-related quality of life. Treatment-specific health state utility values are also included in the company's base case analysis, with iptacopan modelled to have better health-related quality of life compared to treatment with C5 inhibitors.

The largest component of cost associated with treatment for PNH relates to drug acquisition costs, with a much smaller relative proportion associated with health state resource use (including blood transfusions), adverse event costs (including breakthrough haemolysis events) and drug administration costs.

The company's *de-novo* model relies heavily on the approach used in NICE technology appraisal TA778 for pegcetacoplan, with the same model structure, cycle length and modelled health states used in the company's base case analysis, and similarities in the approach used to estimate treatment effectiveness, in terms of treatment-specific transition probabilities between health states, while the population (aligned with the anticipated license for iptacopan) and the source of data used to inform treatment effectiveness, treatment discontinuations, utility values and costs is based on evidence from the relevant treatment-specific clinical trials and clinician input (see Table 38 of CS for comparison of key features of the company's analysis with previous NICE appraisals, including TA698 and TA778).

The EAG considers that the company's model base case differs from the previous NICE appraisals in the following key elements:

- The model structure based on three health states for transfusion status and anaemia differs from TA698 (although the same as TA778), where eight health states related to breakthrough haemolysis (BTH) events were modelled and one related to spontaneous remission (scenario only).
- One subsequent line of therapy is included in the company's model, with the same three health states based on transfusion and anaemia status, whereby after discontinuing their initial complement inhibitor treatment patients transition to another complement inhibitor and continue that therapy for the remainder of the time horizon. A subsequent line of treatment was not considered in either of TA698 or TA778.

- Treatment-specific discontinuation rates are included in the company's model, which differ from the previous appraisals and may not reflect clinical practice.
- Health-related quality of life utility values are based on EQ-5D data collected in the iptacopan clinical trials, while EORTC-QLQ-C30 data collected in the pegcetacoplan and ravulizumab trials was mapped to EQ-5D to derive utility estimates for TA778 and TA698, respectively.
- Treatment-specific utility values by health state are used in the company's model, whereas treatment-independent health state utility values were accepted by the appraisal committee in TA778 and TA698.

The appropriateness and implications of these differences between previous NICE appraisals and the CS for the treatment of adults with PNH are discussed in the relevant sections below.

4.2.1 NICE reference case checklist

The model submitted by the company is assessed in relation to the NICE reference case in Table 33.

Table 33 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The CS is appropriate.
Perspective on costs	NHS and PSS	The CS is appropriate.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The CS is appropriate.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The CS is appropriate. The time horizon is lifetime (up to age 100 years).
Synthesis of evidence on health effects	Based on systematic review	The CS is appropriate. The systematic review identified two clinical trials for iptacopan in the relevant patient populations: APPOINT-PNH for complement inhibitor-naïve and APPLY-PNH for complement inhibitor-experienced with residual anaemia.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life (HRQoL) in adults.	The CS is appropriate. HRQoL was measured with EQ-5D-5L and valued using the UK tariff. The EQ-5D-5L was converted to EQ-5D-3L using an appropriate algorithm by Hernández Alava et al (2020). [14]
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	The CS is appropriate.

Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The CS is appropriate.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	The CS is appropriate.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	The CS is appropriate.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	The CS is appropriate.
CS: company submission; PSS: personal social services; QALYs: quality-adjusted life years; HRQoL, health-related quality of life; EQ-5D: standardised instrument for use as a measure of health outcome.		

4.2.2 Model structure

4.2.2.1 Summary of company submission

The model is a cohort semi-Markov model, whereby patients' transition between three mutually exclusive health states over time and at risk of all-cause mortality (see Figure 8):

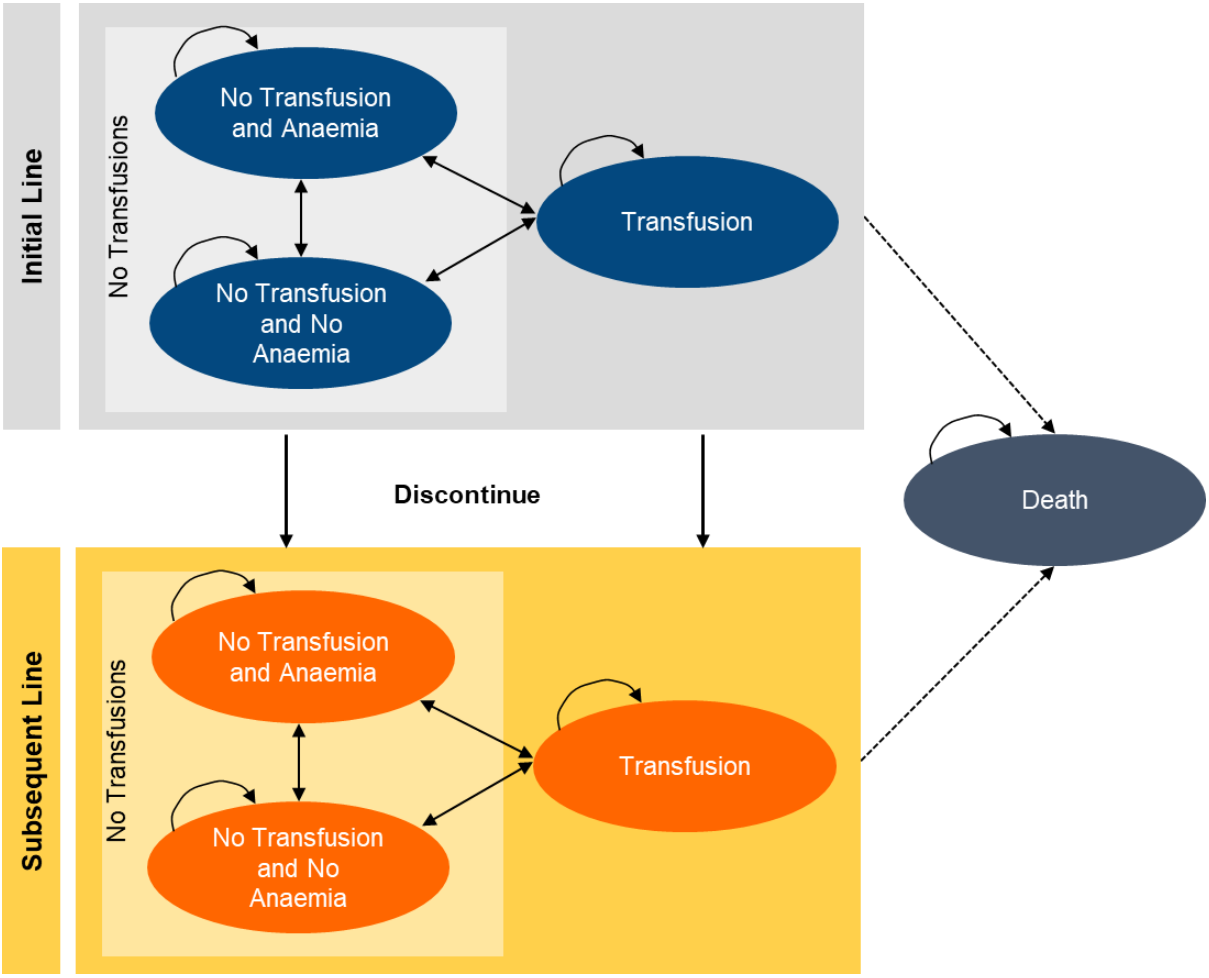
- No Transfusion and Anaemia (patients who are not receiving transfusions and have anaemia);
- No Transfusion and No Anaemia (patients who are not receiving transfusions and do not have anaemia);
- Transfusion (patients who receive transfusions); and
- Death (due to any cause).

The starting distribution of patients across health states is based on the patient characteristics at baseline in the APPOINT-PNH and APPLY-PNH trials in the respective populations. During each model cycle of length 4 weeks (with half-cycle correction implemented), patients either remain in their current health state or move to another health state based on treatment-specific transition probabilities (see Section 4.2.6). A subsequent line of therapy is modelled based on the same health states as the initial line of therapy, whereby patients may transition to another complement inhibitor treatment after discontinuing their initial complement inhibitor and remain on the subsequent therapy for the remainder of the time horizon. Different treatment discontinuation approaches are included in the model for the different therapies (see Section 4.2.6).

The health states are defined based on transfusion status and anaemia, where anaemia is represented by Hb level. The company's base case analysis uses Hb level above and below a threshold level of 10.5 g/dL (i.e., no anaemia is defined as Hb ≥ 10.5 g/dL and anaemia defined as Hb < 10.5 g/dL), in order to be in line with that used in TA778, which was consistent with the inclusion criteria of Hb <

10.5 g/dL used in the PEGASUS trial for pegcetacoplan. The APPOINT-PNH and APPLY-PNH trials for iptacopan used inclusion criteria of Hb < 10.0 g/dL, which is considered in a scenario analysis but not used in the base case analysis because the only transition probabilities published for the comparator pegcetacoplan were based on the threshold of Hb < 10.5 g/dL.

Figure 8: Cost-effectiveness model structure (reproduced from CS Figure 12, page 105)



Points for critique

The model structure is consistent with that used in TA778 (pegcetacoplan), which was considered by the Appraisal Committee to be suitable for decision making. During TA778 the committee noted that the company's model structure was different to the model presented in TA698 (ravulizumab), which had eight health states related to BTH events (with distinction between BTH events related to suboptimal C5 inhibition and those related to complement-amplifying condition, CAC BTH) and one related to spontaneous remission (scenario only), in addition to the death state. The committee accepted that the ravulizumab model was not appropriate for capturing the benefits associated with pegcetacoplan such as preventing extravascular breakthrough haemolysis, which results in a drop in haemoglobin level and blood transfusions, both of which were captured in the pegcetacoplan model. Spontaneous remission was not modelled as it is not expected to vary by treatment. The EAG

considers that the same reasoning holds for iptacopan; BTH due to suboptimal C5 inhibition is only an issue for eculizumab where BTH is managed by adjusting the dosage or frequency of maintenance doses of eculizumab to achieve and maintain efficacy of treatment, while CAC BTH events are not expected to vary by treatment. The company's model structure for iptacopan considers BTH as a separate discrete event with associated costs and disutility because BTH events were rare in the iptacopan clinical trials, although this may be due to short trial follow-up. Therefore, overall, the EAG considers the model structure in TA778 (pegcetacoplan) to be more appropriate for evaluating the cost-effectiveness of iptacopan than the model structure in TA698 (ravulizumab). However, unlike TA778, the company's model also considers a subsequent line of treatment after discontinuation from the initial treatment. The EAG considers this to be appropriate in light of the fact that additional treatment options are now available. The appropriateness of the treatment discontinuation assumptions and approaches used for the different therapies are discussed in Section 4.2.6.

The anaemia health states (with and without anaemia) are defined in terms of the Hb threshold level of 10.5 g/dL, in line with TA778, rather than 10.0 g/dL as used in the APPOINT-PNH and APPLY-PNH trials. This was to allow the company to incorporate the published transition probabilities for pegcetacoplan in the model. The EAG's clinical advisor considered this small 0.5 g/dL difference to have limited clinical importance. The company presents cost-effectiveness results of a scenario analysis using transition probabilities based on a threshold of Hb < 10.0 g/dL for iptacopan and C5 inhibitors. The company submission also includes health-related quality of life utility values for the threshold of 10.0 g/dL. The EAG considers it appropriate to incorporate the utility values for the threshold of 10.0 g/dL with the transition probabilities based on this threshold in the scenario analysis (see Section 6.1) in order to ensure that the health states are aligned with the quality of life outcomes; however, the EAG agrees with the company that the same definition of anaemia should be used across all treatment options in the base case analysis and, therefore, the threshold level of 10.5 g/dL seems appropriate for the base case results.

4.2.3 Population

4.2.3.1 Summary of company submission

Two subpopulations of adult patients with PNH are considered in the model, in line with the anticipated license wording and evidence available from the APPOINT-PNH and APPLY-PNH trials:

1. Adult patients with PNH who are naïve to treatment with complement inhibitors and have haemolysis with clinical symptom(s) (i.e., complement inhibitor-naïve); and
2. Adult patients with PNH who have been treated with a complement inhibitor and have anaemia (i.e., complement inhibitor-experienced with residual anaemia).

The cost-effectiveness of iptacopan with the relevant comparator complement inhibitors is presented separately for the two subpopulations.

The patient characteristics at baseline and initial distribution of patients across health states are based on the APPOINT-PNH and APPLY-PNH trials in the complement inhibitor-naïve and complement inhibitor-experienced with residual anaemia populations, respectively (see Tables 40 and 41, page 112 of CS and baseline distribution for the complement inhibitor-experienced population updated in Table 11 of addendum to B.3 of CS).

Points for critique

As discussed in Section 2.3, the EAG has expressed some concerns about how well the patient populations of the APPOINT-PNH and APPLY-PNH trials align with the PNH population seen in UK clinical practice (e.g., the APPOINT-PNH trial mostly enrolled East Asian patients and had a low proportion of participants with a history of thrombosis compared to what might be expected to be seen in UK patients); however, the EAG is satisfied that iptacopan is expected to work in a similar way in a UK population and the trial results are generalisable to UK clinical practice.

For the complement inhibitor-naïve population, the APPEX study provides data on 85 patients treated with C5 inhibitors (84 with eculizumab and 1 with ravulizumab) of which 45% (38 patients) were from the UK National PNH service registry at St. James's University Hospital, Leeds. The EAG considers that the baseline characteristics of participants in the APPEX study is likely to be more representative of complement inhibitor-naïve patients in NHS practice over participants in the APPOINT-PNH trial; however, to inform the effectiveness of C5 inhibitors in the model for the complement inhibitor-naïve population, the company have reweighted the APPEX data to match the APPOINT-PNH population (See Table 22 of CS, page 73 for a comparison of APPEX patient characteristics before and after reweighting to balance baseline characteristics with the APPOINT-PNH population), which makes the populations more comparable (with an effective sample size of 41 in the APPEX real-world cohort following reweighting and a sample of 40 in APPOINT-PNH cohort). The EAG considers the weighted adjustment approach used by the company to be appropriate since there is not expected to be a mortality effect associated with the treatments. A similar approach was also used to balance participant baseline characteristics in the APPLY-PNH and PEGASUS trials to adjust for differences between trial populations for the complement inhibitor-experienced cohort.

4.2.4 Intervention and comparators

4.2.4.1 Summary of company's submission

The intervention is iptacopan with a dose of 200 mg taken twice daily (BD) in oral capsule. The comparators are eculizumab, ravulizumab and pegcetacoplan; although pegcetacoplan is only included as an option for patients with residual anaemia after ≥3 months of treatment with a C5 inhibitor, as per its license and TA778. Therefore, pegcetacoplan is only considered as a comparator in the complement inhibitor-experienced population, but may be included as a subsequent line of therapy in the complement inhibitor-naïve population in patients who remain anaemic after ≥3 months of treatment with a C5 inhibitor. The dosing regimens for the comparator drugs are largely in line with their respective SmPC (see Table 39, page 110 of CS). For eculizumab, based on clinical practice, some patients were assumed to receive higher than label maintenance doses (see Table 51, page 128 of CS). A similar approach was taken in the pegcetacoplan submission.

The model allows a maximum of one line of subsequent treatment after the initial therapy in both subpopulations. The sequence of treatments in the complement inhibitor-naïve and -experienced populations is shown in Table 34, alongside the timepoint at which patients are permitted to switch treatment in the model.

Table 34 Treatment sequences for each subpopulation included in the model

Initial treatment	Discontinuation approach	Timepoint for treatment switch	Subsequent treatment
Complement inhibitor-naïve population			
Iptacopan	Continuous discontinuation	per model cycle	Ravulizumab
Eculizumab	One-time discontinuation	24 weeks	Pegcetacoplan
Ravulizumab	One-time discontinuation	24 weeks	Pegcetacoplan
Complement inhibitor-experienced population			
Iptacopan	Continuous discontinuation	per model cycle	Ravulizumab
Eculizumab	No discontinuation	-	-
Ravulizumab	No discontinuation	-	-
Pegcetacoplan	Continuous discontinuation	per model cycle	Ravulizumab

Points for critique

The comparators included in the CS are modelled in line with their licensed dose. However, by allowing only a maximum of one line of subsequent treatment after initial therapy, the choice of modelled treatment sequences does not reflect the full range of sequence possibilities in the treatment pathway. For example, in the population that is complement inhibitor-naïve, it may be expected that the treatment sequence starting with iptacopan would include ravulizumab then pegcetacoplan given that, in this same population, the comparator sequence starting with C5 inhibitors includes pegcetacoplan. The previous NICE appraisals, TA778 and TA698, only considered a single treatment option, where patients did not discontinue from their initial treatment in the model (except that in TA778, a small proportion of patients at week 16 were modelled to discontinue pegcetacoplan after a

'settle in period' when clinicians could identify a select number of patients for whom pegcetacoplan is unsuitable). The EAG notes that the final NICE scope did not specifically define a comparison of treatment sequences for the cost-effectiveness analysis; therefore, it is unclear whether the modelling of treatment sequences is appropriate for the decision problem. Modelling a subsequent line of treatment in the complement inhibitor-naïve population creates a question about whether or not the patients in the subsequent line of treatment in the naïve population, after discontinuing from their initial therapy, should be considered complement inhibitor-experienced patients, with residual anaemia. The EAG believes that the answer to this question depends on the reasons for discontinuation from initial therapy in the naïve population. Importantly, the EAG notes that, in the complement inhibitor-naïve population, the company have used the transition probabilities from the complement inhibitor-experienced population with residual anaemia for pegcetacoplan to model the transitions between the three mutually exclusive health states over time when pegcetacoplan is used as a subsequent line of therapy, while the transition probabilities from the complement inhibitor-naïve population is used for second-line ravulizumab in the naïve population. This creates an inconsistency in approach for second-line pegcetacoplan and ravulizumab in the complement inhibitor-naïve population, and makes it less clear whether it is appropriate to model a subsequent line of therapy in the naïve population if these patients are now classified as complement inhibitor-experienced with residual anaemia, after discontinuation from their initial therapy.

For the complement inhibitor-naïve population, the EAG considers it more appropriate to model the sequence: iptacopan to ravulizumab vs. ravulizumab (no discontinuation) [or eculizumab, with no discontinuation, as both ravulizumab and eculizumab are assumed to have equal clinical effectiveness], and using the transition probabilities from the naïve population for C5 inhibitors at first and second-line, in order to avoid the inconsistency in approach used by the company. In addition, this modelled sequence is in line with the approach used in the complement inhibitor-experienced population, where a subsequent line of treatment is not considered for C5 inhibitors.

The EAG's clinical advisor indicated that eculizumab is increasingly used infrequently in UK clinical practice, with ravulizumab considered the first line of therapy when complement inhibitor therapy is initiated. However, the choice of eculizumab or ravulizumab for treatment initiation largely depends on the individual patient and circumstances, e.g., eculizumab is mainly used in patients with acute renal failure and pregnancy, while ravulizumab is used, in general, for a presentation of thrombosis. Pegcetacoplan is only licensed for use in the complement inhibitor-experienced population after ≥3 months on a C5 inhibitor. The EAG's clinical advisor indicated that in clinical practice pegcetacoplan is typically given about 6 months after a C5 inhibitor (rather than 3 months) for patients who remain anaemic, while C5 inhibitors are used in acutely thrombotic patients, where they are known to be effective (longer history of use compared to pegcetacoplan). Therefore, the EAG considers the

modelled sequence of treatments in the complement inhibitor-experienced population with residual anaemia to be appropriate, but the modelled one-time discontinuation at 24 weeks for C5 inhibitors (modelled to affect 30% of patients in the 'Transfusion' and 'No Transfusion and Anaemia' health states) in the complement inhibitor-naïve population to pegcetacoplan is likely to mask the cost-effectiveness of iptacopan relative to C5 inhibitors in the naïve population because this subset of patients would be considered complement inhibitor-experienced with residual anaemia, while pegcetacoplan is not a relevant comparator in the naïve population given its licence and NICE recommendation as per TA778.

> ***item 1. The modelled treatment sequence in the complement inhibitor-naïve population with pegcetacoplan as a subsequent line of treatment after one-time discontinuation from C5 inhibitors at 24 weeks for 30% of patients who still have anaemia or receive transfusions is likely to mask the cost-effectiveness of iptacopan relative to C5 inhibitors in the naïve population. Furthermore, the company have used an inconsistent approach to modelling the transition probabilities for the subsequent line of therapy in the iptacopan sequence vs. the C5 inhibitors sequence in the complement inhibitor-naïve population.***

4.2.5 Perspective, time horizon and discounting

4.2.5.1 Summary of company's submission

The analysis is conducted from the perspective of the NHS and Personal Social Services (PSS) in England and Wales over a lifetime time horizon up to age 100 years, which leads to a modelled time horizon of 58 years in the complement inhibitor-naïve population and 49 years in the complement inhibitor-experienced population (due to the starting age of 42.1 and 51 years in the respective populations based on the APPOINT-PNH and APPLY-PNH trials). A 3.5% annual discount rate is used for both costs and health effects.

Points for critique

The CS adheres to the NICE health technology evaluations manual [15] and the EAG considers the approach used by the company to be appropriate.

4.2.6 Treatment effectiveness and extrapolation

4.2.6.1 Summary of company's submission

The effectiveness of the treatments used in the model are based on treatment-specific transition probabilities that describe the probability of moving between the three mutually exclusive health states over time, where every four weeks patients either remain in their current health state or move to another health state. The model assumes that the treatment effect is maintained throughout the duration of therapy for each treatment, and lifelong treatment is considered. An annual probability of

discontinuation is included for iptacopan and pegcetacoplan, while a one-time discontinuation at 24 weeks is considered for C5 inhibitors in the complement inhibitor-naïve population for 30% of patients in the 'Transfusion' and 'No Transfusion and Anaemia' health states.

The transition probabilities were derived from IPD from APPOINT-PNH for iptacopan in the complement inhibitor-naïve population (single arm trial) and APPLY-PNH for iptacopan and C5 inhibitors in the complement inhibitor-experienced population with residual anaemia. For C5 inhibitors in the naïve population, the transition probabilities were derived from IPD from the APPEX study, using the same methods as applied to the APPOINT-PNH data. As the company did not have access to IPD for pegcetacoplan, and in the absence of head-to-head data comparing iptacopan and pegcetacoplan, transition probabilities for pegcetacoplan were based on the PEGASUS trial as reported in Hakimi et al (2022) [13]. Eculizumab and ravulizumab are assumed to have equivalent efficacy in the model. Pooled eculizumab and ravulizumab data from APPLY-PNH and APPEX was used to obtain a single set of transition probabilities for C5 inhibitors for the complement inhibitor-experienced and -naïve populations, respectively.

Treatment effectiveness for iptacopan in the CS is based on data up to Day 168 from the iptacopan trials, which marks the end of the 24-week randomised treatment period of APPLY-PNH and 24-week core treatment period of APPOINT-PNH – this is labelled the 24-week data analysis. The CS was followed with an addendum in December 2023, which provides supplementary analyses based on the full 48-week trial duration of APPLY-PNH and APPOINT-PNH, where a 24-week treatment extension was included after the core treatment period – this is labelled the 48-week data analysis. The 48-week data analysis is based on trial data up to Day 336 (end of study) for iptacopan and is used to inform the transition probabilities, annual discontinuation rate and BTH event rates. The extension treatment period of the iptacopan trials did not provide additional data for C5 inhibitors because after the core 24-week treatment period participants randomised to C5 inhibitors switched to iptacopan. The available data up to week 24 from APPLY-PNH was used for C5 inhibitors in the 48-week data analysis, while the same transition probabilities for C5 inhibitors and pegcetacoplan from APPEX and PEGASUS, respectively were used in the 24-week and 48-week data analysis. The assessment window for Hb assessments and transfusion occurrence in the APPEX study was up to Day 200, which is slightly longer than 24 weeks, while PEGASUS trial data from the randomised controlled period from weeks 4-16 was used to inform the transition probabilities for pegcetacoplan.

At EAG points for clarification, the company provided an addendum to the CS to account for data changes and errors discovered after the original submission to NICE. These data corrections included changes to the transition probabilities estimated from APPLY-PNH, in addition to updates to the utility values estimated from iptacopan trial data and baseline distribution of patients across health states. An error was also discovered in how transition probabilities for C5 inhibitors in the

complement inhibitor-naïve population had been estimated from APPEX data. The model inputs were updated accordingly and a revised economic model submitted alongside the response to EAG points for clarification. The transition probabilities and other model inputs reported in the subsequent sections are based on the company's updated analysis and data corrections.

Points for critique

The EAG's primary concern in relation to the treatment effectiveness used in the economic model is that there is no direct link between the statistical analysis of iptacopan trial endpoints reported in Section B.2.4 of the CS and the transition probabilities between health states used in the model, which makes a comparison and validation of the transition probabilities informing the cost-effectiveness of iptacopan challenging as it is not clear if the model findings are in line with the primary and secondary outcomes of the trials. In response to EAG points for clarification the company agreed that a direct comparison of modelled transfusion outcomes with transfusion outcomes from the iptacopan trials is challenging because the trials focus on the proportion of patients that are transfusion-avoidant or transfusion-dependent over the trial duration, without consideration of whether transfusion-dependent patients receive transfusions once or at multiple timepoints during the trial. In contrast, the model considers that multiple transfusions are possible because it incorporates data on patients receiving transfusions in 4-week time periods. The company also agreed that a comparison for haemoglobin endpoints and modelled anaemia status was challenging because the trials reported change from baseline in Hb level and endpoints assessing the proportion of patients with an increase from baseline in Hb of ≥2 g/dL, or proportion of patients with Hb ≥12 g/dL without requiring a transfusion, while the model defined health states based on a haemoglobin threshold of Hb <10.5 g/dL for defining anaemia. Therefore, the company argues that a direct comparison of trial endpoints and model results is not feasible.

The company justifies the exclusion of the trial endpoints in the economic model because it would have precluded a comparison of iptacopan with pegcetacoplan. The CS uses the same health states as used in TA778 for the pegcetacoplan model in order to allow a comparison of the cost-effectiveness of iptacopan with pegcetacoplan, on the basis of published transition probabilities for pegcetacoplan that considers a threshold of Hb <10.5 g/dL when defining anaemia. The EAG acknowledges the reasons for the approach taken by the company but considers there to be uncertainty in the treatment effectiveness evidence informing the model without a comparison of modelled inputs and results with trial endpoints.

> ***item 2. There is uncertainty in the treatment effectiveness evidence informing the model because a comparison of iptacopan trial endpoints with modelled inputs and results is not feasible.***

A further key concern relates to the lack of randomisation and indirect comparison of iptacopan with C5 inhibitors in the complement inhibitor-naïve population, and iptacopan with pegcetacoplan in the complement inhibitor-experienced population with residual anaemia. The single arm design of the APPOINT-PNH trial has precluded a randomised comparison in the naïve population. An unanchored ITC of APPOINT-PNH and Study 301 is described in Section B.2.9.1.3.3. of CS, but since Study 301 did not report Hb endpoints, no ITC could be conducted on Hb outcomes. Therefore, the APPEX study, with observational study design, was the only source used to evaluate haematological response after initiation of C5 inhibitor treatment in previously complement inhibitor-naïve adult patients with PNH and anaemia. Similarly, in the complement inhibitor-experienced population with residual anaemia there is no head-to-head comparison of iptacopan with pegcetacoplan. At EAG points for clarification, the EAG requested an indirect treatment comparison of the transition probabilities for iptacopan with pegcetacoplan from APPLY-PNH and PEGASUS trial populations, using C5 inhibitors as the common comparator. The company attempted this for individual transitions but since the transition probabilities for the three health states are dependent on each other, this produced nonsensical results. The company indicated that it was not feasible within the time available to consider other methods for the ITC such as constructing pseudo-IPD data from the published PEGASUS transition probabilities. Further, the company argues that the validity of any transition probabilities for iptacopan with pegcetacoplan from APPLY-PNH and PEGASUS derived from an anchored ITC using the C5 inhibitors arms as the common comparator would be severely limited due to large differences observed in outcomes of the C5 inhibitor arms across the two trials, which the company believes is a consequence of the 4-week run-in period in the PEGASUS trial where all patients received combination therapy of eculizumab and pegcetacoplan before entering the randomised period with monotherapy at week 4. These differences in transition probabilities for the C5 inhibitor arms between trials are discussed below in Section 4.2.6.3. Importantly, the EAG considers that the company's concerns about differences between APPLY-PNH and PEGASUS, and the validity of any comparison of iptacopan with pegcetacoplan, still holds true even if an ITC of the transition probabilities is not undertaken because the transition probabilities for pegcetacoplan and iptacopan used in the model are independently derived from the PEGASUS and APPLY-PNH trials, respectively.

> ***item 3. The transition probabilities used in the model are based on a lack of randomisation in the complement inhibitor-naïve population, and a lack of direct (head-to-head) or indirect comparison of iptacopan and pegcetacoplan in the complement inhibitor-experienced population with residual anaemia.***

A further concern relates to the assessment time period (or data cut) from the iptacopan trials that is used to inform the cost-effectiveness of iptacopan and the comparator complement inhibitors. The 48-

week time period provides additional data for iptacopan, which is used to update the transition probabilities, annual discontinuation rate and BTH event rates in the model for iptacopan only, while the 24-week data from APPLY-PNH is used for C5 inhibitors in the 48-week data analysis and the same transition probabilities for C5 inhibitors and pegcetacoplan are used in the 24-week and 48-week data analysis. In the 48-week data analysis, the 24-week data for utility values from the APPOINT-PNH and APPLY-PNH trials is used for iptacopan and the comparators, which creates inconsistencies in the data cut used to inform the different parameters in the model. While the EAG considers the use of longer follow-up data to be best practice, in general, the EAG is concerned that the 48-week data analysis is not making a fair comparison of iptacopan and the comparator complement inhibitors because of the variation in length of assessment time period used for the comparators and inconsistencies in data cut used across modelled parameters. Therefore, the EAG considers that all cost-effectiveness results should be reported separately using the 24-week and 48-week data, in order to understand the implications of the variation in assessment time period used for iptacopan and the comparator complement inhibitors.

> ***item 4. There is variation in the assessment time period used for iptacopan and the comparator complement inhibitors, and across modelled parameters, in the 48-week data analysis.***

For the assumption of equivalent efficacy for eculizumab and ravulizumab, the EAG notes that this is in line with the approach adopted in TA778 for pegcetacoplan, where the committee concluded that the company's assumption of equal efficacy and safety profile between ravulizumab and eculizumab in the PEGASUS trial population was reasonable based on the non-inferiority of the two treatments demonstrated in Study 302 and the fact that ravulizumab is a re-engineered form of eculizumab with both technologies biologically very similar with over 99% homology. The EAG's clinical advisor considered that the efficacy of both treatments is likely to be equal in any population and therefore also holds for the iptacopan trial populations. Therefore, the EAG is satisfied with the company's assumption of equivalent efficacy for eculizumab and ravulizumab and with the data for the separate treatments being combined to provide transition probabilities for C5 inhibitors. Further, the company conducted a scenario analysis using separate sets of transition probabilities for eculizumab and ravulizumab, which was shown to have limited impact on the cost-effectiveness results and confirmed by the EAG.

Without access to the IPD, the EAG is unable to validate the data corrections and errors provided as an addendum to the CS. The EAG did follow-up with the company on a few concerns about the changes to the data, to which the company responded in the document named 'Follow-up questions on addendum to company evidence submission'. The EAG cannot validate the data but notes that due to a programming error in the estimation of the original transition probabilities from the APPEX study

the proportion of patients in the transfusion health state for C5 inhibitors is substantially higher than in the initial analysis for the complement inhibitor-naïve population.

4.2.6.2 Methods used to derive transition probabilities

The methods used to derive the transition probabilities were based on those used in TA778 (pegcetacoplan) and described in Hakimi et al (2022). [13] Patients were classified by the model health states according to their Hb level and transfusion dependency during the study visits collected over 4-week intervals of the APPLY-PNH and APPOINT-PNH trials, up to the end of the randomised controlled period at Day 168 for the 24-week analysis and up to the end of the trial extension period for the 48-week analysis. The transfusion health state was defined as receipt of packed RBC transfusions within 4 weeks prior to a study visit. A multinomial logistic regression model was fitted using current health state as the dependent variable, with independent covariates of lagged health state (prior 4 weeks health state), treatment (iptacopan or C5 inhibitors for APPLY-PNH), time from first treatment dose to study visit (in weeks), and interaction terms for time x treatment and time x lagged health state. The fitted model was used to estimate the probability of being in each health state conditional on study visit, lagged health state and treatment arm. The predicted probabilities were then averaged over study visits by lagged health state and treatment arm to derive transition probabilities for the model. Since APPOINT-PNH was a single arm trial with iptacopan as the only treatment option, the multinomial model was specified without the treatment terms. Similarly, the APPEX data was specified without the treatment terms as it was only used to inform the transition probabilities for C5 inhibitors in the complement inhibitor-naïve population. Missing information for Hb levels in the APPEX data was imputed using last observation carried forward (LOCF) prior to fitting the multinomial logistic regression model.

To adjust the health state transition probabilities from APPEX to the APPOINT-PNH population, the model was fit using estimation weights based on a propensity score model, where baseline patient characteristics and propensity scores were balanced between the two population cohorts (see Table 22 of CS for comparison of baseline characteristics between APPEX and APPOINT-PNH before and after weighting). The analyses derived the potential outcomes had the APPOINT-PNH cohort received treatment with C5 inhibitors, by weighting the observed outcomes from patients in APPEX to obtain treatment weights (see company response to question B5 of EAG points for clarification for further details). The treatment weights were then used as estimation weights when fitting the multinomial regression model for health states and the corresponding weighted transition probabilities used in the company's base case analysis. The company conducted a scenario analysis exploring unweighted transition probabilities.

The company also adjusted the health state transition probabilities from APPLY-PNH to the PEGASUS trial population by using weights derived from the ITC described in Section B.2.9.3.2 of

CS. In brief, patients who would not have been eligible for inclusion in PEGASUS were removed from the APPLY-PNH dataset and then the remaining patients from APPLY-PNH were weighted within treatment arm using entropy balancing to adjust for differences between the two populations (see Table 9 of addendum to CS for comparison of baseline characteristics between APPLY-PNH and PEGASUS before and after weighting). The weights obtained from this approach were used as estimation weights when fitting the multinomial regression model for health states and the corresponding weighted transition probabilities used in the company's base case analysis. Weights were applied to both the iptacopan and C5 inhibitor arms. The company also conducted a scenario analysis exploring unweighted transition probabilities.

Uncertainty in the transition probabilities from the multinomial logistic regression model was captured using a Dirichlet distribution, where transition probabilities from each health state were varied simultaneously.

Points for critique

The main drawback of the company's approach to the derivation of transition probabilities for the model was the desire to closely follow the approach used in TA778 in order to compare iptacopan and pegcetacoplan in the complement inhibitor-experienced population using the published transition probabilities for pegcetacoplan reported in Hakimi et al (2022). [13] The company decided a priori to use the same methods and set of model covariates as was applied in the analysis of PEGASUS. As a result, a single model specification was applied across all analyses and model fit was not considered (see company response to question B2 of EAG points for clarification). The EAG acknowledges the need to include the published transition probabilities for pegcetacoplan in the absence of IPD from PEGASUS but believes it is an oversight not to consider other potential alternative model specifications (i.e., inclusion and exclusion of potentially relevant covariates and interaction terms) that may produce a better fit to the iptacopan trial data, which could be considered for the comparison of iptacopan with C5 inhibitors, particularly since pegcetacoplan is a relevant comparator only in the complement inhibitor-experienced population.

At EAG points for clarification, the EAG requested details on the number of participants in the trials with data available at each study visit used to generate transition probabilities in order to assess the level of uncertainty in the transition probabilities. Tables 14 and 15 of the company's response to EAG clarification question B3 provides an overview of the level of missing data in APPOINT-PNH, APPLY-PNH and the APPEX study. Missing observations in APPOINT-PNH ranged between 7.5% and 22.5% of the sample size (N=40) over the 4-week intervals up to the end of the core treatment period of 24 weeks, while missing observations in APPLY-PNH ranged between 3.2% and 6.4% in the iptacopan arm (N=62) and between 5.7% and 20% in the C5 inhibitors arm (N=35) over the 4-week intervals up to the end of the randomised period at 24 weeks. The corresponding level of

missing information was not provided for the treatment extension period up to 48 weeks. The company did not impute any missing data from the iptacopan trials for the estimation of transition probabilities. In contrast, multiple imputation using LOCF was used to impute missing information on Hb across consecutive 4-week periods in the APPEX data because it was subject to very high levels of missing information (ranging from 56-92%), reflecting less frequent Hb measurements in routine clinical practice. As a result, the dataset from the APPEX study contained no missing data prior to fitting the multinomial logistic regression model for the derivation of transition probabilities. The EAG notes that the company conducted a scenario analysis using transition probabilities generated without data imputation (complete case analysis), which was shown to have limited impact on the cost-effectiveness results and confirmed by the EAG. Therefore, the EAG has no major concerns regarding the handling of missing data.

In order to reflect uncertainty in the transition probabilities, the company used a Dirichlet distribution to vary the transition probabilities for each health state simultaneously. Although this method is appropriate, the EAG notes that uncertainty would be more adequately captured by varying the parameters directly in the multinomial logistic regression model and using the corresponding variance-covariance matrix to reflect the correlation between parameters for the derivation of transition probabilities.

Without access to the IPD, the EAG is unable to validate the methods used to adjust the health state transition probabilities for differences between populations. However, in general the EAG considers the methods used to be appropriate and that the weighted transition probabilities, as used in the company's base case analysis, is more appropriate than the use of unweighted transition probabilities.

4.2.6.3 Transition probabilities used in the model

Table 35 presents the health state transition probabilities used in the company's base case 24-week and 48-week analysis for the complement inhibitor-naïve population, derived from APPOINT-PNH for iptacopan and APPEX for C5 inhibitors.

Table 35 Health state transition probabilities for the complement inhibitor-naïve population (reproduced from Table 1 of company's supplementary analyses based on 48-week data)

From	To		
	No Transfusion and No Anaemia	No Transfusion and Anaemia	Transfusion
Based on 24-week data			
Iptacopan			
No Transfusion and No Anaemia	99.1%	0.9%	0.0%
No Transfusion and Anaemia	49.4%	48.2%	2.4%
Transfusion	18.0%	80.1%	1.9%
C5 inhibitors (eculizumab/ravulizumab)			
No Transfusion and No Anaemia	94.1%	4.5%	1.4%
No Transfusion and Anaemia	9.6%	76.1%	14.3%
Transfusion	2.5%	43.3%	54.2%
Based on 48-week data†			
Iptacopan			
No Transfusion and No Anaemia	98.0%	1.8%	0.2%
No Transfusion and Anaemia	37.6%	62.3%	0.1%
Transfusion	5.8%	36.5%	57.7%
C5 inhibitors (eculizumab/ravulizumab)			
No Transfusion and No Anaemia	94.1%	4.5%	1.4%
No Transfusion and Anaemia	9.6%	76.1%	14.3%
Transfusion	2.5%	43.3%	54.2%

†Iptacopan transition probabilities estimated from APPOINT-PNH 48-week data. C5 inhibitor transition probabilities estimated from APPEX data.
Anaemia defined as haemoglobin <10.5 g/dL.

Table 36 presents the health state transition probabilities used in the company's base case 24-week and 48-week analysis for the complement inhibitor-experienced population, derived from APPLY-PNH for iptacopan and C5 inhibitors, and from PEGASUS for pegcetacoplan as reported in Hakimi et al (2022). [13] Note that due to joint estimation of iptacopan and C5 inhibitor transition probabilities in one regression model, small changes in the C5 inhibitor transition probabilities are observed between the 48-week and 24-week analysis, although the 24-week data is used for C5 inhibitors in the 48-week analysis.

Table 36 Health state transition probabilities for the complement inhibitor-experienced population (reproduced from Table 2 of company's supplementary analyses based on 48-week data)

From	To		
	No Transfusion and No Anaemia	No Transfusion and Anaemia	Transfusion
Based on 24-week data			
Iptacopan			
No Transfusion and No Anaemia	97.9%	2.0%	0.0%
No Transfusion and Anaemia	51.0%	44.3%	4.7%
Transfusion	50.7%	32.4%	17.0%
C5 inhibitors (eculizumab/ravulizumab)			
No Transfusion and No Anaemia	45.5%	47.9%	6.6%
No Transfusion and Anaemia	7.7%	65.7%	26.6%
Transfusion	6.2%	33.6%	60.2%
Pegcetacoplan			
No Transfusion and No Anaemia	96.6%	3.1%	0.3%
No Transfusion and Anaemia	49.1%	43.7%	7.2%
Transfusion	61.2%	26.6%	12.2%
Based on 48-week data†			
Iptacopan			
No Transfusion and No Anaemia	93.5%	6.5%	0.0%
No Transfusion and Anaemia	41.1%	56.5%	2.4%
Transfusion	54.6%	39.0%	6.4%
C5 inhibitors (eculizumab/ravulizumab)			
No Transfusion and No Anaemia	43.1%	56.9%	0.0%
No Transfusion and Anaemia	3.9%	69.1%	27.0%
Transfusion	3.2%	30.3%	66.5%
Pegcetacoplan			
No Transfusion and No Anaemia	96.6%	3.1%	0.3%
No Transfusion and Anaemia	49.1%	43.7%	7.2%
Transfusion	61.2%	26.6%	12.2%

†Iptacopan and C5 inhibitor transition probabilities estimated in a joint multinomial logistic regression model utilising APPLY-PNH 48-week data for iptacopan and 24-week data for C5 inhibitors. Pegcetacoplan transition probabilities based on PEGASUS as published in Hakimi et al 2022. [13]
Anaemia defined as haemoglobin <10.5 g/dL.

Points for critique

The EAG noted that the transition probabilities reported in the CS were not validated with clinical experts, and no description of what the transition probabilities imply was presented in the CS. The EAG considered it very difficult to interpret the transition probabilities as presented in Table 35 and Table 36 above. To overcome this issue the EAG considers the Markov trace output from the model, which shows the expected proportion of patients in each health state over the modelled lifetime horizon for each treatment and for each population, to provide a clearer picture to understand the implications of the transition probabilities on the relative proportion of patients in each health state

over time and the corresponding implications on the cost-effectiveness of iptacopan vs. comparators. These are shown under the relevant population subheading below.

The EAG also requested validation of the transition probabilities derived from the trials with expert clinical opinion at EAG points for clarification. The company consulted one UK clinical expert in November 2023 (see company response to clarification question B8), where the distribution of patients across health states at baseline, transition probability matrices for each treatment (based on corrected 24-week data), and model outputs showing the distribution of patients across health states up to 5 years for each treatment was shown to the clinician, and separately for both populations. Treatment discontinuation was set to zero for all treatments in order to exclude the impact of treatment switches. The company states that the clinician confirmed overall good face validity of the model predictions in terms of patient distribution across health states for all treatments in both populations. Comments from the clinician specific to each population, as stated in the company's response to clarification question B8, are presented below under the relevant population subheading.

Complement inhibitor-naïve population

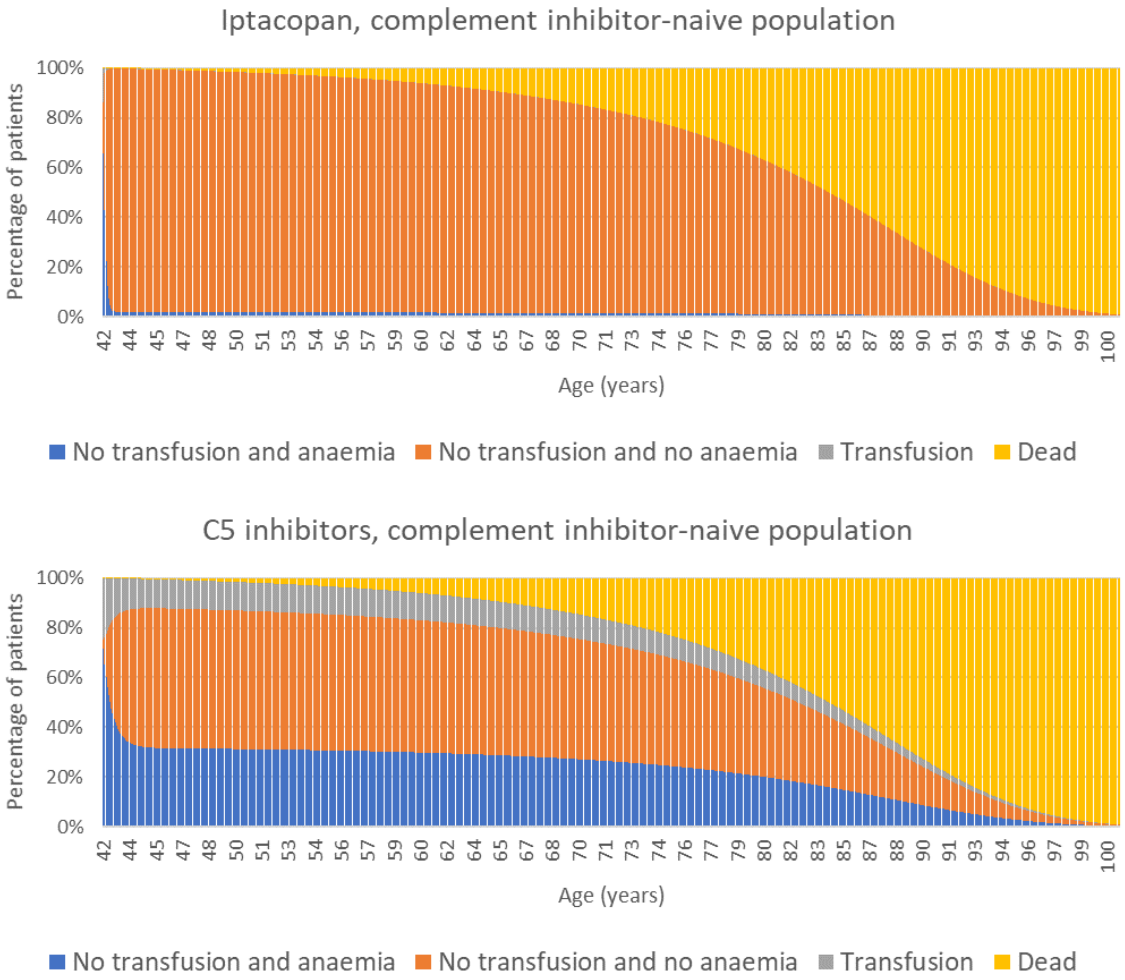
In the complement inhibitor-naïve population, the EAG considers that Table 35 shows:

- A much higher percentage of patients will require transfusions and remain transfusion dependent on C5 inhibitors than on iptacopan.
- Based on 48-week data for iptacopan, a very high percentage of patients remain transfusion dependent compared to the 24-week data, but due to a small percentage of patients requiring transfusions on iptacopan, the total proportion requiring transfusions for iptacopan is very small.
- Of those with uncontrolled anaemia in the 'No transfusion and anaemia' health state, a much higher percentage of patients will remain with uncontrolled anaemia on C5 inhibitors compared with iptacopan.
- For patients who achieve controlled anaemia in the 'No transfusion and no anaemia' health state they are very likely to remain controlled on either C5 inhibitors or iptacopan, with a slightly higher percentage remaining controlled for iptacopan.

Figure 9 shows the corresponding Markov trace for iptacopan and C5 inhibitors for the 24-week data, with treatment discontinuation set to zero for both treatments (i.e., no treatment switches). The company states that the model predicts that approximately 12% of patients treated with C5 inhibitors require transfusions long-term in this population, which was considered relatively low compared to the UK clinician experience of approximately 20%. Therefore, the company states that the model can be considered conservative for C5 inhibitors in this population (see response to clarification question B8). The company did not comment on the percentage of patients with uncontrolled anaemia in the 'No transfusion and anaemia' health state for C5 inhibitors compared to iptacopan, but the EAG notes

that the long-term projections are in line with the much higher percentage of patients expected to remain with uncontrolled anaemia on C5 inhibitors from the APPEX data. The corresponding Markov trace for iptacopan and C5 inhibitors for the 48-week data is very similar to Figure 9 (figure not shown) because the only substantial difference between the 48-week and 24-week data is the higher percentage of patients that remain transfusion dependent for iptacopan in the 48-week data, but given that there are few patients requiring transfusions on iptacopan, this has very minor implications on the percentage of patients in the transfusion health state over time. Overall, the EAG considers the projections shown in Figure 9 to be reasonable for the complement inhibitor-naïve population without treatment discontinuation, on the basis of the transition probabilities in Table 35 but acknowledging the concerns about the lack of comparison with trial endpoints and the lack of randomised comparison of iptacopan with C5 inhibitors in this population.

Figure 9 Model projections of the percentage of patients in each health state over time from the starting age used in the model for iptacopan and C5 inhibitors in the complement inhibitor-naïve population for the 24-week analysis, with treatment discontinuation set to zero for both treatments.



As discussed in Section 4.2.4.1, the company have modelled more than one line of treatment such that after discontinuation from iptacopan (with an annual discontinuation rate of 3.43% in the 24-week data and 2.72% in the 48-week data) patients move to ravulizumab, while 30% of patients who still have anaemia or receive transfusions initially treated with C5 inhibitors discontinue treatment at 24 weeks and receive pegcetacoplan and remain on these subsequent therapies over their remaining lifetime. Therefore, the resulting modelled proportion of patients in each health state informing the company's base case analysis for the 24-week data is presented in Figure 10. As discussed previously, the EAG has a concern that the company have been inconsistent in their approach to modelling second-line therapies in the complement inhibitor-naïve population, where the transition probabilities for pegcetacoplan from the experienced population (Table 36) are used in the model, while the transition probabilities for ravulizumab from the naïve population (Table 35) are used as second-line therapy following discontinuation from iptacopan. Furthermore, discontinuation from the subsequent

line therapies is not considered for the naïve population, while an annual discontinuation rate for pegcetacoplan in the experienced population is considered. Therefore, for the complement inhibitor-naïve population, the EAG considers it more appropriate to model the sequence: iptacopan to C5 inhibitors vs. C5 inhibitors (no discontinuation), with the transition probabilities for the naïve population used for C5 inhibitors at first and second-line (Table 35), because this avoids the inconsistency in approach used by the company and is in line with the approach used in the complement inhibitor-experienced population, where a subsequent line of treatment is not considered for C5 inhibitors. Furthermore, once patients move to subsequent lines of treatment in the naïve population they are effectively considered complement inhibitor-experienced patients. The company's modelled one-time discontinuation at 24 weeks for C5 inhibitors to pegcetacoplan in the naïve population is likely to mask the cost-effectiveness of iptacopan relative to C5 inhibitors in this population because these patients would be considered complement inhibitor-experienced with residual anaemia and pegcetacoplan is not a relevant comparator in the naïve population. For completeness, Figure 11 shows the EAG's preferred base case model projections of the percentage of patients in each health state over time for the complement inhibitor-naïve population based on the 24-week data (note that this corresponds to a comparison of iptacopan from the company's base case in Figure 10 and C5 inhibitors with no treatment discontinuation in Figure 9).

Figure 10 Company's 24-week base case model projections of the percentage of patients in each health state over time from the starting age used in the model for iptacopan and C5 inhibitors for the complement inhibitor-naïve population, with treatment switches permitted.

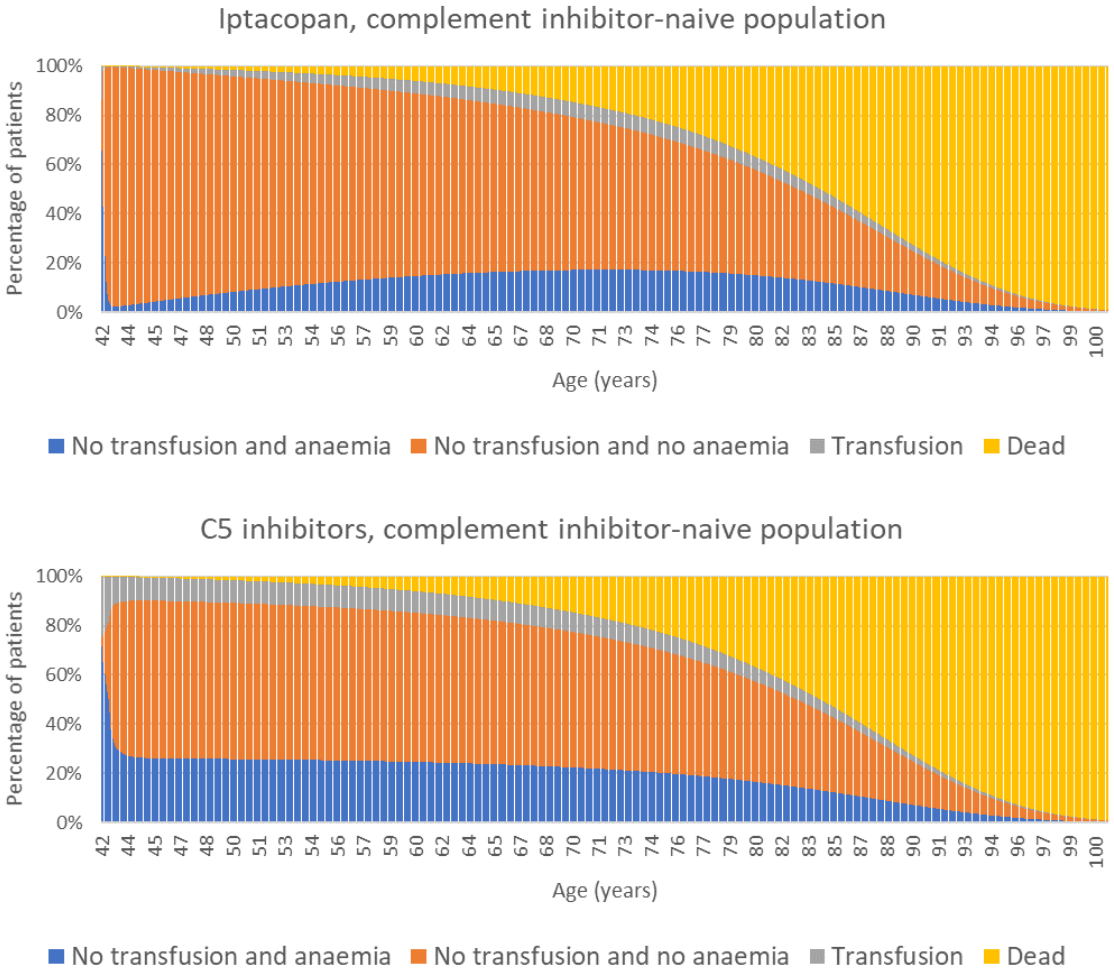
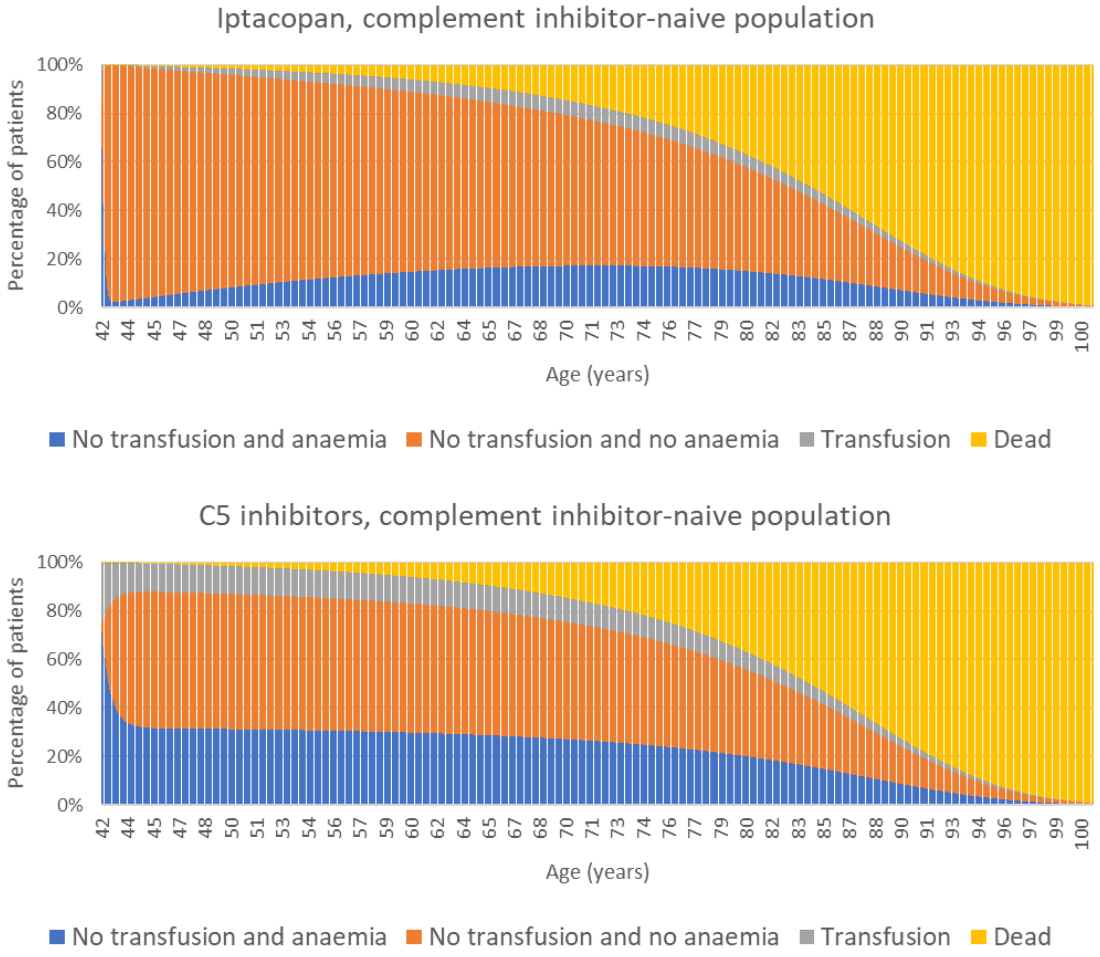


Figure 11 EAG's preferred 24-week model projections of the percentage of patients in each health state over time from the starting age used in the model for iptacopan and C5 inhibitors for the complement inhibitor-naïve population.



Complement inhibitor-experienced population with residual anaemia

In the complement inhibitor-experienced population with residual anaemia, the EAG considers that Table 36 shows:

- A much higher percentage of patients will require transfusions and remain transfusion dependent on C5 inhibitors than on iptacopan or pegcetacoplan; for the comparison of iptacopan with pegcetacoplan, a slightly higher percentage of patients will require transfusions on pegcetacoplan, while those remaining transfusion-dependent is higher with iptacopan based on the 24-week data but lower based on the 48-week data.
- Of those with uncontrolled anaemia in the 'No transfusion and anaemia' health state, a much higher percentage of patients will remain with uncontrolled anaemia on C5 inhibitors compared with iptacopan or pegcetacoplan; for the comparison of iptacopan with pegcetacoplan, a similar percentage of patients will remain with uncontrolled anaemia based on the 24-week data, while a higher percentage will remain uncontrolled for iptacopan compared to pegcetacoplan based on the 48-week data.
- For patients who achieve controlled anaemia in the 'No transfusion and no anaemia' health state they are very likely to remain controlled on either iptacopan or pegcetacoplan; in contrast, the percentage of patients who remain controlled on C5 inhibitors is reduced by approximately 50% (unlike the complement inhibitor-naïve population where patients on C5 inhibitors were shown to largely remain controlled).

Figure 12 shows the corresponding Markov trace for iptacopan, C5 inhibitors and pegcetacoplan for the 24-week data, with treatment discontinuation set to zero for all treatments (i.e., no treatment switches). The percentage of patients across the health states over time is similar for iptacopan and pegcetacoplan, with a slightly lower percentage of transfusions for iptacopan. The difference for C5 inhibitors is stark with a much larger proportion of patients with uncontrolled anaemia and requiring transfusions compared to either iptacopan or pegcetacoplan. The EAG's clinical advisor did not consider the percentages for C5 inhibitors to be reasonable and would expect to see a much higher percentage of patients with 'No transfusion and no anaemia' and a lower proportion requiring transfusions on C5 inhibitors. Based on the study by Kelly et al (2023)[16] of treatment outcomes of complement C5 inhibition in 509 UK patients with PNH, about 20% of patients achieve a normal Hb on C5 inhibitors (i.e., >13.5 g/dL in men and >11.5 g/dL in women) at 24 months after treatment initiation (complement inhibitor-naïve population), while the threshold for 'No transfusion and no anaemia' as used in the model is lower at 10.5 g/dL. In the most recent 12 months on C5 inhibitors, 123 out of 446 (27.6%) patients needed transfusions with 94 of the 123 (76.4%) requiring 3 or more transfusions. Kelly et al (2023)[16] also notes that one in four patients on C5 inhibitors have ongoing transfusion requirements.[16] Therefore, the model predictions of around 35% of patients require

transfusions with continued C5 inhibitor treatment may be too high. The company also states that their clinician advised that the proportion requiring transfusions would be considered too high for the overall population, but that it is a realistic estimate for a population with partial response to a C5 inhibitor (see response to clarification question B8). The company states that the model predictions of around 10% of patients reaching the non-anaemic state with continued C5 inhibitor treatment was considered too optimistic by their clinician, which is in contrast to the experience of the EAG's clinical advisor, who suggested a higher value of around 20%. The corresponding Markov trace for iptacopan, C5 inhibitors and pegcetacoplan for the 48-week data is similar to Figure 12 based on the 24-week data (figure not shown).

As discussed in Section 4.2.4.1, the company have modelled more than one line of treatment such that after discontinuation from either iptacopan or pegcetacoplan patients switch to ravulizumab, while no discontinuation is modelled for C5 inhibitors in this population. The EAG notes that although the subsequent line of treatment for iptacopan and pegcetacoplan is the same, the annual discontinuation rate is different for iptacopan and pegcetacoplan (see Section 4.2.6.4) of 3.43% for iptacopan in the 24-week data (2.72% in the 48-week data) and 16.13% for pegcetacoplan. Therefore, the resulting modelled proportion of patients in each health state informing the company's base case analysis for the 24-week data is presented in Figure 13. In contrast to Figure 12, Figure 13 shows a stark difference between iptacopan and pegcetacoplan in terms of the proportion of patients distributed across health states, with a substantially higher percentage of patients with uncontrolled anaemia for pegcetacoplan compared to iptacopan, and a substantially higher percentage of patients' transfusion dependent on pegcetacoplan. This difference between iptacopan and pegcetacoplan is solely driven by the differential discontinuation rates between the two treatments, which is discussed further in Section 4.2.6.4.

Figure 12 Model projections of the percentage of patients in each health state over time from the starting age used in the model for iptacopan, C5 inhibitors and pegcetacoplan in the complement inhibitor-experienced population for the 24-week analysis, with treatment discontinuation set to zero for all treatments.

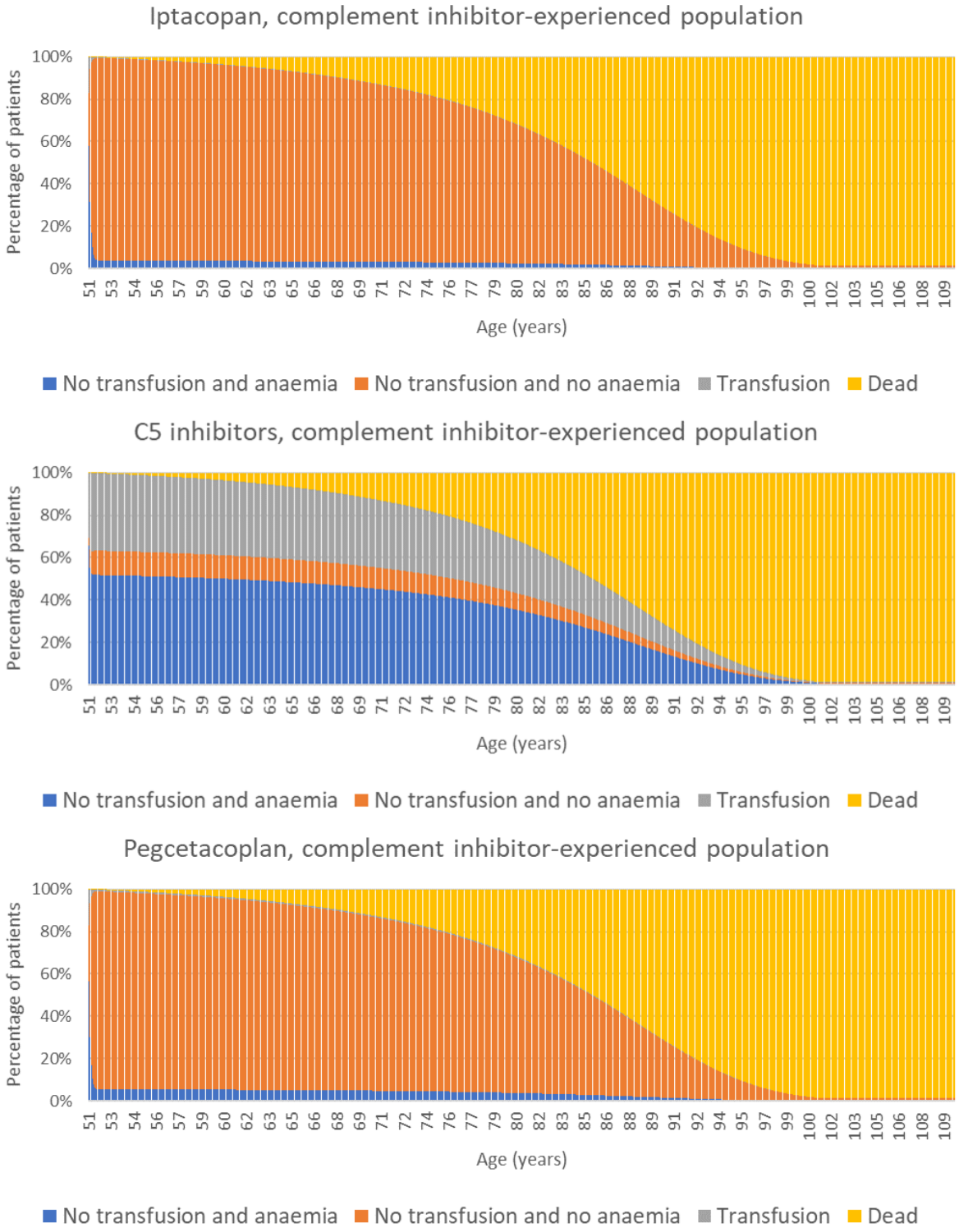
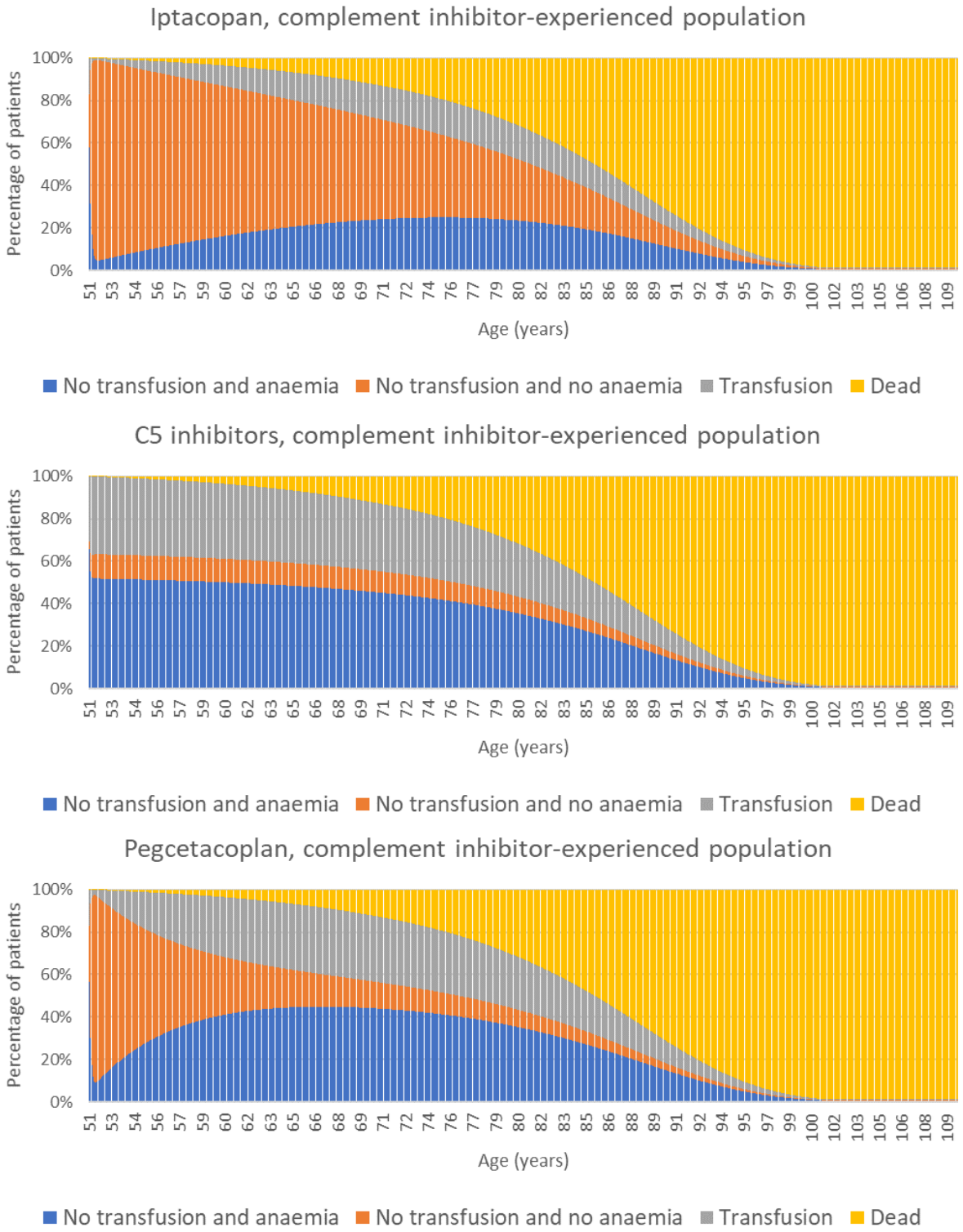


Figure 13 Company's 24-week base case model projections of the percentage of patients in each health state over time from the starting age used in the model for iptacopan, C5 inhibitors and pegcetacoplan for the complement inhibitor-experienced population, with treatment switch to ravulizumab following discontinuation from iptacopan (3.43% per annum) or pegcetacoplan (16.13% per annum).



A further key concern, as noted previously, relates to the lack of direct or indirect comparison of iptacopan with pegcetacoplan. A comparison of transition probabilities for C5 inhibitors in APPLY-PNH (iptacopan) and PEGASUS (pegcetacoplan) are shown in Table 37, where the values derived from APPLY-PNH are used in the model. Large differences are observed in outcomes of the C5 inhibitor arms across the two trials:

- A much higher percentage of patients require transfusions in PEGASUS compared to APPLY-PNH, while the percentage of patients who remain transfusion dependent is similar across the two trials.
- A much higher percentage of patients in the controlled anaemia health state become uncontrolled (i.e., movement from the 'No transfusion and no anaemia' health state to 'No transfusion and anaemia' health state) per 4-week cycle in PEGASUS compared to APPLY-PNH, while the percentage of patients with uncontrolled anaemia who remain with uncontrolled anaemia on C5 inhibitors is similar across the two trials.

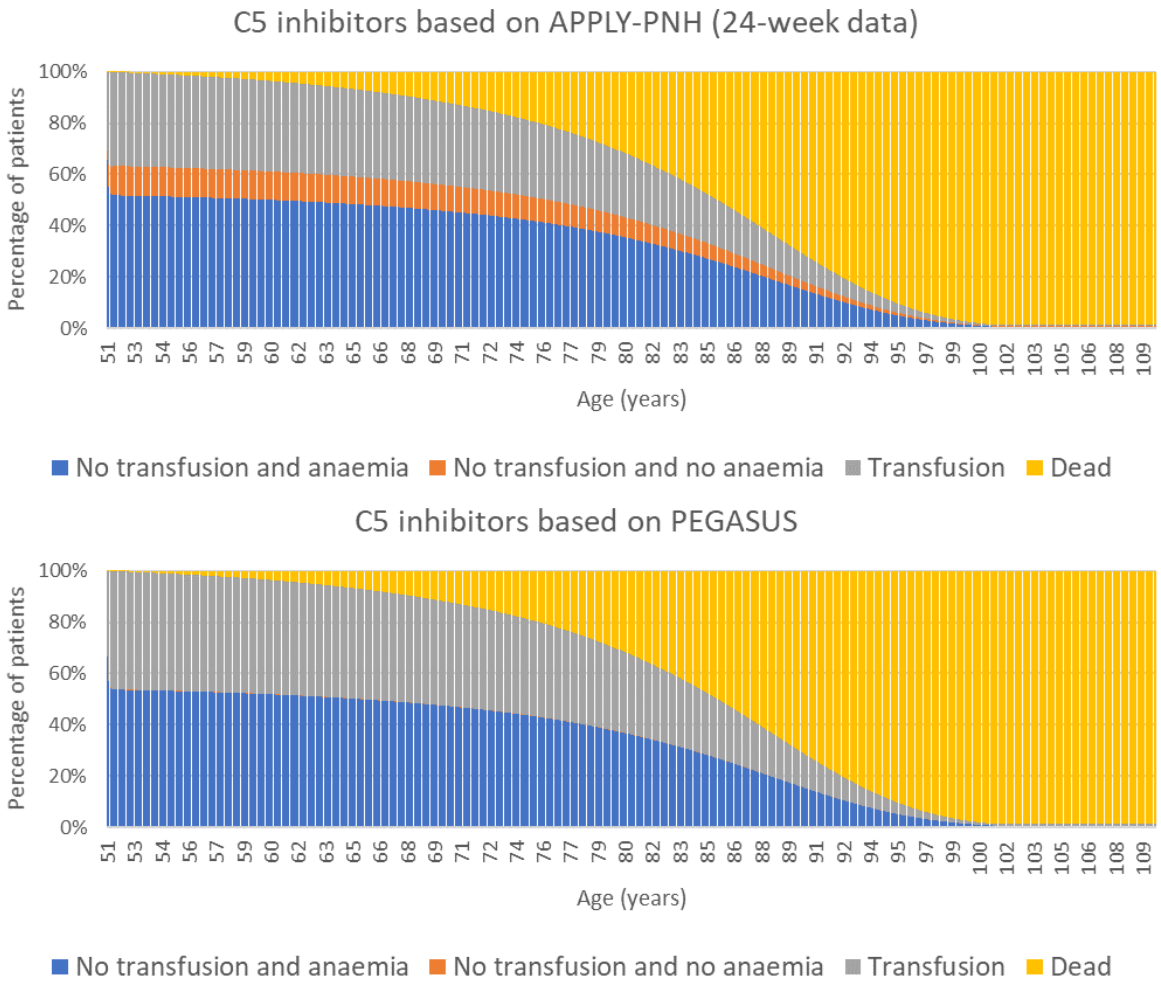
These differences in C5 inhibitors between APPLY-PNH and PEGASUS translate to the Markov trace shown in Figure 14, where there are very few patients (<0.1%) in the 'No transfusion and no anaemia' health state for C5 inhibitors in PEGASUS and a substantially higher percentage of patients' transfusion dependent in PEGASUS compared to APPLY-PNH. The company indicates that the lack of similarity between the C5 inhibitor comparator arms of APPLY-PNH and PEGASUS is a consequence of the 4-week run-in period in the PEGASUS trial where all patients received combination therapy of eculizumab and pegcetacoplan before entering the randomised period with monotherapy, whereas in the APPLY-PNH trial patients randomised to the C5 inhibitor arm continued the same C5 inhibitor treatment as prior to the trial (monotherapy without addition of iptacopan at any time). However, the EAG notes that the transition probabilities from the PEGASUS trial reported in Hakimi et al (2022) [13] are based on the randomised controlled period from weeks 4-16, in which patients had either pegcetacoplan or eculizumab, and not the 4-week run-in period in which both treatments were given, or the first 4 weeks of the randomised controlled period where a 'hangover' effect of the run-in period is observed (only the prior 4-weeks' health state is included as a covariate in the model). In TA778, the transition probabilities used data from the PEGASUS trial from week 4 to week 16 in order to mitigate any 'hangover' effect of the run-in period (i.e., a 4-week washout period was included to mitigate the effects of the run-in period) because the efficacy data from the PEGASUS trial shows that after week 4 of the randomised controlled period, haemoglobin stabilises for both pegcetacoplan and eculizumab (see Figure 9 of the company's response to EAG points for clarification). Therefore, the EAG considers it unlikely that the 4-week run-in period in the PEGASUS trial is the primary reason for the differences observed in C5 inhibitors between APPLY-

PNH and PEGASUS. The EAG is concerned that the comparison of iptacopan and pegcetacoplan from two distinctively different trial populations may not be appropriate, with transition probabilities for pegcetacoplan and iptacopan independently derived from PEGASUS and APPLY-PNH, respectively.

Table 37 Comparison of transition probabilities for C5 inhibitors in APPLY-PNH and PEGASUS

From	To		
	No Transfusion and No Anaemia	No Transfusion and Anaemia	Transfusion
APPLY-PNH (based on corrected 24-week data)			
No Transfusion and No Anaemia	45.5%	47.9%	6.6%
No Transfusion and Anaemia	7.7%	65.7%	26.6%
Transfusion	6.2%	33.6%	60.2%
PEGASUS (as reported in Hakimi et al., 2022 [13])			
No Transfusion and No Anaemia	3.0%	74.2%	22.8%
No Transfusion and Anaemia	0.1%	65.2%	34.7%
Transfusion	0.1%	40.4%	59.5%

Figure 14 Model projections of the percentage of patients in each health state over time for C5 inhibitors in APPLY-PNH (based on 24-week data) and PEGASUS.



4.2.6.4 Discontinuation rates

An annual probability of discontinuation for iptacopan and pegcetacoplan was informed by treatment-specific all-cause discontinuation rates from APPLY-PNH and PEGASUS, respectively, with data adjusted to reflect 52-week discontinuation. The model assumes that discontinuation occurs at an equal rate from all health states, i.e., the discontinuation rate is independent of the health state that patients are in. A summary of the treatment discontinuation rates and subsequent therapy used in the company's base case analysis is provided in Table 44, p119 of CS.

In the iptacopan arm of APPLY-PNH, during the 24-week randomised treatment period, there was one discontinuation due to pregnancy in 28.66 patient-years of follow-up, giving a discontinuation probability of 3.43% per year. Based on the 48-week data of all patients treated with iptacopan in APPLY-PNH, there was one discontinuation due to pregnancy in the extension treatment period, giving a total of two discontinuations in 72.47 patient-years of follow-up and a corresponding annual probability of discontinuation of 2.72%. In APPOINT-PNH, there were no discontinuations over the

full 48-week study duration. Therefore, the company applied the annual probability of discontinuation from the iptacopan arm of APPLY-PNH for both the complement inhibitor-naïve and -experienced populations.

In PEGASUS, a total of 13 patients discontinued pegcetacoplan over the 48-week study duration (Table 38). Four discontinuations in PEGASUS due to BTH, and one discontinuation due to fatal COVID-19 infection, were excluded from the calculation of pegcetacoplan discontinuation rate because UK clinicians advised the company that BTH is not a reason for discontinuation of pegcetacoplan in clinical practice. The resulting annual probability of discontinuation with pegcetacoplan based on the remaining eight discontinuations in 45.48 patient-years of follow-up is 16.13%.

There were no discontinuations from the C5 inhibitor treatment arm of APPLY-PNH or PEGASUS. In the complement inhibitor-experienced population, patients on C5 inhibitors are assumed not to discontinue and remain on the same treatment throughout the modelled time horizon. In the complement inhibitor-naïve population, it is assumed that a proportion of patients (30% who still have anaemia and require transfusions) will discontinue treatment at 24 weeks (i.e., a one-time discontinuation rather than annual probability of discontinuation) and switch to pegcetacoplan due to insufficient response to a C5 inhibitor, which is applied only to patients in the 'Transfusion' and 'No Transfusion and Anaemia' health states.

Table 38 Reasons for discontinuation of iptacopan and pegcetacoplan in trials (reproduced from Table 17 of the company's response to EAG points for clarification)

Treatment (Study)	Study period	Reason for discontinuation
Iptacopan (APPOINT-PNH)	Core and extension treatment period	NA (no discontinuations)
Iptacopan (APPLY-PNH)	Randomised treatment period	Pregnancy
	Extension treatment period	Pregnancy
Pegcetacoplan (PEGASUS)	Randomised controlled period	Breakthrough haemolysis
	Randomised controlled period	Breakthrough haemolysis
	Randomised controlled period	Breakthrough haemolysis
	Open-label period	Haemolysis
	Open-label period	Haemolytic anaemia
	Open-label period	Hypersensitivity pneumonitis
	Open-label period	Breakthrough haemolysis
	Open-label period	Acute myeloid leukaemia
	Open-label period	Diffuse large B cell lymphoma
	Open-label period	Fatal COVID-19 infection
	Open-label period	Pancytopenia[a]
	Open-label period	Bone marrow failure
	Follow-up period	Mesenteric ischaemia

Points for critique

The EAG is concerned that the use of treatment-specific annual discontinuation rates for iptacopan and pegcetacoplan informed by their respective clinical trials may not reflect how patients are

managed in the NHS. The company's base case uses a substantially higher discontinuation rate of 16.13% per annum for pegcetacoplan compared to the rate of 3.43% per annum for iptacopan from the 24-week data, or 2.72% per annum from the 48-week data. This differential discontinuation rate results in a stark difference between iptacopan and pegcetacoplan in terms of the proportion of patients distributed across health states over time because once patients discontinue either iptacopan or pegcetacoplan in the complement inhibitor-experienced population they are modelled to receive ravulizumab treatment, which is associated with a higher percentage of patients with uncontrolled anaemia and a higher percentage of patients transfusion-dependent.

Although the trial-specific discontinuation rates are likely to reflect the development of haemolysis, the greater number of discontinuations in PEGASUS compared to APPOINT-PNH and APPLY-PNH is likely to be partly explained by events that are not necessarily treatment-specific, e.g., reasons for discontinuation of pegcetacoplan in PEGASUS include diffuse large B cell lymphoma or acute myeloid leukaemia; if these events had occurred in the iptacopan trials, it is likely that patients would also have discontinued treatment with iptacopan.

The EAG's clinical advisor indicated that there is no known reason to expect a substantial difference in the long-term discontinuation rates between pegcetacoplan and iptacopan, beyond what has been observed for BTH. He suggested a slightly higher discontinuation rate for pegcetacoplan but not a substantial difference of 16.13% vs. 3.43% (or 2.72%). The treatment-specific discontinuation rates used in the company's model is an important driver of cost-effectiveness (see Section 6.3) and therefore the evidence supporting the difference between treatments needs to be carefully considered. Importantly, clinical trial data on treatment persistence does not usually generalise directly to clinical practice. Therefore, the EAG considers the treatment-specific discontinuation rates used in the model as an important source of uncertainty for the cost-effectiveness of iptacopan in the complement inhibitor-experienced population with residual anaemia.

> ***item 5: The use of treatment-specific discontinuation rates for iptacopan and pegcetacoplan from the clinical trials is a key driver of cost-effectiveness but is informed by limited data that may not reflect how patients are managed in the NHS.***

4.2.6.5 Mortality

All-cause mortality is estimated based on National Life Tables for the UK [17]. The model assumes patients do not have an increased risk of mortality due to PNH, which the EAG considers to be appropriate.

4.2.7 BTH and adverse events

4.2.7.1 Summary of adverse events

BTH was incorporated into the model as a discrete event associated with a one-off cost and disutility. For iptacopan, the rate of BTH events was based on APPOINT-PNH in the complement inhibitor-naïve population and APPLY-PNH in the complement inhibitor-experienced population with residual anaemia. For eculizumab and ravulizumab, the rate of BTH events was based on Study 301 for the naïve population and APPLY-PNH for the experienced population. For pegcetacoplan, the rate of BTH events was based on PEGASUS (48-week data). Table 39 summarises the BTH event rates included in the model. With the exception of BTH events, no other adverse events were modelled.

Table 39 Summary of BTH events rates

Treatment	Complement inhibitor-naïve population			Complement inhibitor-experienced population		
	Annual Rate	Proportion Treated	Source	Annual Rate	Proportion Treated	Source
Iptacopan	24-week data: 0.00 48-week data: 0.05	10%	APPOINT-PNH	24-week data: 0.07 48-week data: 0.11	10%	APPLY-PNH
Eculizumab	0.21	10%	Study 301	0.67	10%	APPLY-PNH
Ravulizumab	0.08	10%	Study 301	0.67	10%	APPLY-PNH
Pegcetacoplan	NA	NA	NA	0.13	10%	PEGASUS (48-week data)

Abbreviations: BTH, breakthrough haemolysis. NA, not applicable (pegcetacoplan is not licensed or used in complement inhibitor-naïve patients).

Points for critique

The EAG considers the approach used by the company for modelling BTH and adverse events to be reasonable. However, the EAG notes that there is variability in the rates reported across studies and the EAG is not entirely clear why the BTH events rates would be expected to differ between the complement inhibitor-naïve and -experienced populations.

Some BTH events may require blood transfusions and the costs of these are assumed to be captured within the costs of the transfusion health state in the model, which the EAG considers to be reasonable. For severe BTH events, an additional one-off dose of eculizumab (900mg) is included for 10% of BTH events, but the EAG notes that the definition of severe BTH is not clear.

The EAG conducted some exploratory scenarios on the BTH events rates to assess the impact on the cost-effectiveness of iptacopan relative to the comparator complement inhibitors; the EAG is satisfied that the BTH events rates have no material impact on cost-effectiveness.

4.2.8 Health-related quality of life

4.2.8.1 Summary of company's submission

Health state utility values are applied to time spent in health states in the model, in order to calculate quality-adjusted life years (QALYs) that reflect the improvement in health-related quality of life (HRQoL) associated with treatment. The company undertook a literature review to identify studies assessing the HRQoL of adults with PNH (see Appendix H of the CS for full details about the systematic literature review, including methodology, study selection process, inclusion and exclusion criteria and results). The company identified 10 studies that generated EQ-5D utility values in patients with PNH. Further, the company provides an analysis of EQ-5D data from the APPOINT-PNH and APPLY-PNH trials. Some information on the performed analyses is presented in the CS and in response to EAG points for clarification.

The CS summarises the data collected in the APPOINT-PNH and APPLY-PNH trials using the EORTC-QLQ-C30 and EQ-5D-5L instruments. The company considered the data obtained through the EQ-5D-5L instrument to represent the most suitable HRQoL and utility data for use in the model. Therefore, the trial-based utility values were used to inform the company's base-case analysis. Importantly, all utility values are based on 24-week trial results, even in the 48-week analysis.

The CS describes three elements relating to the quantification of HRQoL: (i) mapping the EQ-5D-5L responses to EQ-5D-3L utility values for the UK; (ii) derivation of health state utility values for use in the model; and (iii) adjustment for general population utility values.

4.2.8.2 Mapping the EQ-5D-5L responses to EQ-5D-3L utilities for the UK

The company used EQ-5D-3L utilities for the UK to inform the model used in the submission. These utility values were obtained using EQ-5D-5L responses from APPOINT-PNH and APPLY-PNH and the mapping function from Hernandez et al (2020). [14] These mapped values were summarized descriptively by treatment arm for patients with complete EQ-5D-5L responses at baseline, and used in the base-case analysis. The CS includes a scenario analysis that used EQ-5D-3L utility values obtained by applying the EORTC-QLQ-C30 data and mapping function by Longworth et al (2014). [18]

Points for critique

The EAG considers the approach used by the company to be appropriate and in line with the 2022 NICE evaluation methods manual. The EAG agrees that the data from EQ-5D-5L instrument and mapping algorithm from Hernandez et al (2020) [14] represent the appropriate approach to estimate the utility values to inform the model. The EAG performed a scenario analysis applying the EORTC-QLQ-C30 data and found it did not impact the final results.

The company have not indicated whether EQ-5D-5L response data were collected in the treatment extension period of the APPLY-PNH and APPOINT-PNH trials, but since the utility values from the 24-week core treatment period is used in the 48-week analysis, the EAG can only assume that utility values from the trials were not available in the trial extension period.

4.2.8.3 Derivation of health state utility values for use in the model

The utility values used in the model based on response to treatment were derived from a mixed (repeated measures) linear regression model which was fit to all utility values obtained at Day 1 (baseline) and all other visits where patients completed the EQ-5D questionnaire (i.e., Day 14, 42, 84, 126, 140, 154 and 168). The company provided the number of participants who reported EQ-5D data in APPOINT-PNH and APPLY-PNH trials, which are presented in Table 40 Data from APPLY-PNH and APPOINT-PNH were pooled for model fitting to enhance sample size and precision of model coefficients, which resulted in a total of 960 observations. Further, in the company's response to EAG points for clarification, the company explained that the missing EQ-5D values were not imputed because linear mixed models are based on the missing at random assumption.

Table 40 Number of participants providing EQ-5D data in APPOINT-PNH and APPLY-PNH

Visit	APPOINT-PNH iptacopan (N=40)	APPLY-PNH iptacopan (N=62)	APPLY-PNH C5 inhibitor (N=35)
Day 1	40	60	32
Day 14	35	56	30
Day 42	39	61	33
Day 84	38	57	29
Day 126	35	58	30
Day 140	37	59	29
Day 154	36	56	29
Day 168	37	60	31

All models were fit using random individual-level intercepts to account for correlation in utility values within patients across visits. The models were fit using the lme4 package in R. Model selection was performed among all models using information criteria such as the Akaike information criterion (AIC) and Bayesian information criterion (BIC). Covariates included in the final model, selected for best fit, were health state, treatment (iptacopan vs C5 inhibitors), baseline utility value, follow-up visit, and study (APPLY-PNH vs APPOINT-PNH). In the company's response to EAG points for clarification, coefficient estimates for the final model and the results for the model fit were provided Table 41). No results for the other models that were considered were provided.

Table 41 Multivariable regression results for selected utility model

Covariate	Coefficient (SE)	95% CI
Intercept	0.790 (0.028)	0.735, 0.845
Health state (reference: Transfusion)		
No transfusion and Anaemia	0.007 (0.014)	-0.021, 0.035
No transfusion and No Anaemia	0.029 (0.016)	-0.003, 0.061
Treatment (iptacopan vs C5 inhibitor)	0.071 (0.022)	0.027, 0.114
Baseline utility	0.487 (0.038)	0.412, 0.562
Study (APPLY-PNH vs APPOINT-PNH)	-0.019 (0.018)	-0.055, 0.017
Study visit (reference: Day 168)		
Baseline (Day 1)	-0.076 (0.016)	-0.107, -0.045
Day 14	-0.026 (0.014)	-0.054, 0.002
Day 42	-0.013 (0.013)	-0.039, 0.013
Day 84	-0.003 (0.013)	-0.029, 0.023
Day 126	-0.013 (0.013)	-0.039, 0.014
Day 140	-0.019 (0.013)	-0.045, 0.007
Day 154	-0.010 (0.013)	-0.036, 0.016
Model fit		
AIC	-1318.8	
BIC	-1245.8	
Marginal R^2	0.461	
Conditional R^2	0.667	

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CI, confidence interval; SE, standard error.

After fitting the model to the pooled data, predicted utilities were computed for all patients in APPLY-PNH and APPOINT-PNH, conditional on study enrolment, study visit, health state at study visit, baseline utility, and treatment. The company indicated in their response to EAG points for clarification that the data from APPOINT-PNH and APPLY-PNH were pooled to increase statistical power because there were few observations available in some of the health states. The company further stated that the differences in utility between the naïve and experienced populations were expected to be driven by the proportion of patients that required transfusion or continued to experience anaemia. For patients receiving the same treatment, with comparable baseline characteristics and in the same health state, the company did not expect that there would be a difference in utility values.

Treatment-specific means and SDs of the predicted utilities were then pooled by treatment arm across studies, study visit, and observed baseline utilities. The models predicted patients treated with iptacopan to experience better health-related quality of life (HRQoL) compared with those treated with C5 inhibitors. The company states that this could be due to the oral mode of administration of iptacopan and patients treated with iptacopan having higher mean Hb levels and experiencing less fatigue. This was investigated by assessing mean Hb values of patients receiving iptacopan vs patients

receiving a C5 inhibitor in APPLY-PNH for each health state. The values were provided in the response to EAG points for clarification and are shown in Table 42. The company stated that because of the higher Hb levels, patients treated with iptacopan were expected to feel less fatigued and provided the mean FACIT-Fatigue score in each health state in APPLY-PNH for iptacopan and C5 inhibitors to support that statement. The FACIT-Fatigue scores are provided in Table 43.

Table 42 Difference in mean Hb between iptacopan and C5 inhibitors in APPLY-PNH for each health state

Health state	Treatment	Observations	Mean Hb (g/dL)	SD	Difference iptacopan vs C5 inhibitor within health state (g/dL)
No transfusion and no anaemia	Iptacopan	568	12.58	1.03	1.49 (p=0.011)
	C5 inhibitor	8	11.09	1.23	
No transfusion and anaemia	Iptacopan	50	9.58	0.80	0.74 (p<0.001)
	C5 inhibitor	226	8.85	0.83	
Transfusion	Iptacopan	35	10.72	1.29	2.19 (p<0.001)
	C5 inhibitor	110	8.53	1.23	

Abbreviations: Hb, haemoglobin; SD, standard deviation.

Table 43 Difference in mean FACIT-Fatigue score between iptacopan and C5 inhibitors in APPLY-PNH for each health state

Health state	Treatment	Observations	Mean score	SD	Difference iptacopan vs C5 inhibitor within health state
No transfusion and no anaemia	Iptacopan	396	42.61	7.84	7.94 (p=0.166)
	C5 inhibitor	6	34.67	11.96	
No transfusion and anaemia	Iptacopan	34	38.76	8.99	6.02 (p=0.002)
	C5 inhibitor	147	32.74	13.07	
Transfusion	Iptacopan	26	39.35	5.96	7.81 (p<0.001)
	C5 inhibitor	76	31.54	8.44	

Abbreviations: Hb, haemoglobin; SD, standard deviation.

The company used these treatment-specific utility values in their base-case analysis (Table 44). The utility values used in the base-case analysis for pegcetacoplan were assumed equal to iptacopan, which the company considered a conservative assumption.

Table 44 Health state utility values applied in the submitted model

Health State	Iptacopan*		C5 inhibitors	
	Mean	SE	Mean	SE
No Transfusion and No Anaemia	0.879	0.004	0.775	0.056
No Transfusion and Anaemia	0.822	0.008	0.743	0.015
Transfusion	0.791	0.015	0.695	0.021

*Iptacopan health state utility values were also applied to pegcetacoplan.
Anaemia defined as Hb <10.5 g/dL.
Abbreviations: Hb, haemoglobin; SE, standard error.

The company also estimated treatment-independent means and SDs of utilities (Table 45), which were derived by pooling across studies, study visits, baseline utilities, and treatment arms. No further details on the model specifications to estimate the treatment-independent utility values were provided. These values were used in a scenario analysis.

Table 45 Treatment-independent utility values used in a scenario analysis

Health State	Pooled utility values	
	Mean	SE
No Transfusion and No Anaemia	0.878	0.004
No Transfusion and Anaemia	0.785	0.009
Transfusion	0.733	0.015

Anaemia defined as Hb <10.5 g/dL.
Abbreviations: Hb, haemoglobin; SE, standard error.

Points for critique

The EAG considers the general regression-based approach used by the company to be appropriate, in light of the correlation between clinical measures of disease burden and HRQoL outcomes in PNH. Although the EAG has no major concerns with the methods used, it notes that limited details are presented on the selection process of the regression-based models and the assessment of the goodness-of-fit. Consequently, the EAG could not thoroughly assess the methods used to obtain the utility values. Furthermore, the company provided scarce information on the estimation of the pooled treatment-independent utility values. It is unclear how the values were pooled across the treatment arms.

The EAG wishes to highlight a number of key points in relation to the utility values applied in the model:

- The utility values for iptacopan are substantially higher than for C5 inhibitors for each health state. That is, 0.10 higher for the health state No transfusion and no anaemia, 0.08 higher for No transfusion and anaemia and 0.11 for Transfusion. These differences are considered substantial, for example, the difference between health state No Transfusion and no anaemia and health state Transfusion is 0.08 in both populations treated with iptacopan and C5 inhibitors.

- The baseline mapped EQ-5D-3L utilities collected at Day 1 differ substantially between iptacopan (0.79 [SD, 0.17] in APPLY-PNH and 0.77 [SD, 0.17] in APPOINT-PNH) and C5 inhibitor (0.69 [SD, 0.28]).

- The utility values are based on the 24-week data for both the complement-inhibitor naïve and experienced populations for the 48-week analysis.

The EAG has a concern about the use of treatment-dependent utility values. The difference in HRQoL between iptacopan and C5 inhibitors is substantial and the underlying evidence for this difference is weak. The company states that the difference in the utility values might be due to higher Hb levels and present the evidence to support this statement. However, the provided evidence is assessed as weak given the substantial differences in the datasets between treatments. For example, the mean Hb for the health state 'No transfusion no anaemia' was based on 568 observations for iptacopan and only 8 observations for C5 inhibitors. The number of observations used to estimate the mean Hb for other health states and the mean FACIT-Fatigue score for all health states differ substantially. These substantial differences in the number of observations and the small number of observations used to estimate some of the mean values results in weak evidence for comparative purposes. Further, if there are significant differences in Hb levels between the treatments, it should be reflected in the structure of the model by creating additional health states with different Hb levels. In the company's model, patients treated with iptacopan have higher utility values than C5 inhibitors due to both the treatment effect associated with movement to better health states (e.g., higher transition probability of moving to the 'No transfusion and no anaemia' health state) and a higher utility value associated with treatment itself, despite being in the same health state (e.g., the 'No transfusion and no anaemia' health state has a utility value of 0.879 for iptacopan, while for C5 inhibitors, the utility value for this same health state is 0.775). The EAG considers that the only plausible explanation for a difference in health state utility by treatment is due to the disutility associated with mode of treatment administration, where administration by IV infusion may be associated with a disutility compared with oral therapy; however, the EAG does not consider the magnitude of the difference in treatment-dependent utility values between iptacopan and C5 inhibitors to be realistic. Furthermore, the EAG's clinical advisor indicated that some patients who receive C5 inhibitors administrated by IV infusion every 8th week do not need to think about their disease for 2 months, which may be more convenient for those patients than taking tablets twice a day. Thus, the increased quality of life associated with taking an oral therapy twice a day every day is unclear. Consequently, the EAG considers that the application of treatment-specific utility values may lead to double-counting of the treatment effect. Furthermore, the baseline utility value (utility value at Day 1) differed substantially between populations treated with iptacopan and C5 inhibitors indicating that the difference in the utility values could be due to small sample sizes and differences in the characteristics of patients treated with iptacopan and C5 inhibitors.

The EAG considers that the company's model differs from the previous NICE appraisals in the following key elements:

- The company used treatment-specific utility values while treatment-independent values were used in TA778 and TA698.

- Utility values for each health state used in TA778 were lower than the treatment-specific values for iptacopan and also lower than the pooled treatment-independent values in CS. The values used in TA778 are presented in Table 46. Model used in TA698 submission had different health states making it difficult to directly compare the applied utility values.

Table 46 Utility values used in TA778 submission for pegcetacoplan, eculizumab and ravulizumab

Health State	TA778 Mean
No Transfusion and No Anaemia	0.809
No Transfusion and Anaemia	0.738
Transfusion	0.695

Based on PEGASUS trial EORTC QLQ-C30 mapped to EQ-5D-3L values

item 6. The EAG considers it more appropriate to use treatment-independent health state utility values rather than treatment-specific utility values because the benefits of treatment are already captured in the transitions between health states.

4.2.8.4 Adjustment for general population utility values

The company adjusted the utility values for age, in line with the NICE manual. It was done by using general population utility values for the UK derived from the HSE 2014 dataset reported by Hernandez-Alava et al, 2022. [19] Furthermore, the company used a multiplicative method to adjust utility values in each cycle.

Points for critique

The EAG assessed the application of the adjustment in the submitted model and does not have any concerns.

4.2.9 Resource use and costs

4.2.9.1 Summary of company's submission

The company conducted a systematic literature review to identify relevant cost and healthcare resource use data in adult patients with PNH (see Appendix I of CS for details). Of the studies identified, the resource use and cost data included in the model follows a similar approach to that used in TA778 (pegcetacoplan) and TA698 (ravulizumab).

The CS includes costs related to (i) drug acquisition and administration; (ii) treatment-related resource use; (iii) health state related resource use; and (iv) BTH events. Unit costs were informed by national published sources, such as the National schedule of NHS costs, BNF, PSSRU costs and eMIT, inflated to 2021/22 prices where appropriate and discounted at an annual rate of 3.5%. The dosing

regimen for each drug was based on the respective SmPC. Table 47 summarises the costs included in the company's base case analysis.

Table 47 Costs used in the company's base case analysis

Item	Model input	Source
Drug acquisition costs per year		
Iptacopan (cPAS)	Complement inhibitor-naïve: first year: [redacted] subsequent years: [redacted] Complement inhibitor-experienced: first year: [redacted] subsequent years: [redacted]	Calculated based on the dosing of iptacopan in PNH: 200 mg taken orally twice daily. The annual cost for iptacopan considering list price is [redacted] per patient per year. Includes confidential PAS discount ([redacted] discount off the list price) for iptacopan (confidential price is [redacted] per pack of 56*200mg capsules).
Eculizumab (List price)	Complement inhibitor-naïve: first year: £ 261,941.91 subsequent years: £ 263,390.91 Complement inhibitor-experienced: first year: £ 263,390.91 subsequent years: £ 263,390.91	Calculated based on the weighted average drug cost for all patients as per different up-dosing regimen in maintenance period.
Ravulizumab (List price)	Complement inhibitor-naïve: first year: £ 360,904.71 subsequent years: £ 320,787.66 Complement inhibitor-experienced: first year: £ 319,427.64 subsequent years: £ 319,427.64	Calculated as weight-based average cost by weight categories reported in APPOINT-PNH and APPLY_PNH. Patients' weights distribution is reported in the CS, Table 51, p129. Loading dose and maintenance doses aligned with the SmPC.
Pegcetacoplan (List price)	Complement inhibitor-experienced: first year: £ 324,822.98 subsequent years: £ 323,507.14	Calculated based on the maintenance dose of 1,080mg Q2W and proportion of patients receiving concomitant eculizumab for first four weeks.
Administration costs (one-off cost)		
One-time administration costs	Complement inhibitor-naïve: Iptacopan: £0.00 Eculizumab: £99.92 Ravulizumab: £99.92 Complement inhibitor-experienced: Iptacopan: £0.00 Eculizumab: £0.00 Ravulizumab: £0.00 Pegcetacoplan: £74.67	Calculated as one-off costs in the first model cycle for each drug informed by the respective SmPC. The administration costs for IV infusion are assumed to be in hospital setting in first cycle and homecare thereafter which is covered by manufacturer.
Treatment related resource use associated with vaccinations, antibiotics, and iron overload treatment		
Neisseria (N.) meningitidis vaccine Streptococcus (S.) pneumoniae vaccine Haemophilus (H.) influenzae type B vaccine Antibiotics Chelation therapy	iptacopan & pegcetacoplan: first cycle cost: £ 104.17subsequent cycle cost: £ 6.56 eculizumab & ravulizumab: first cycle cost: £ 53.64 subsequent cycle cost: £ 53.64	The cost of treatment-related resource use is estimated according to the frequency of treatment needed and the proportion of patients in need of taking the specific treatment. The proportion of patients required to take vaccinations is based on the SmPC of each drug, while the proportion of patients on iron chelation therapy or venesection is informed by TA778 and the company's UK clinical advisory board respectively. All patients need to take antibiotics penicillin (500mg BD) as per National PNH service. The treatment-related resource use and unit costs are presented in CS Table 56 and 57, p134.

Venesection		
Health state related resource use		
Health-state related resource use	Health state costs per cycle: No transfusion and No Anaemia: £ 30.57 No transfusion and Anaemia: £ 30.57 Transfusion: £ 798.32	Based on inputs from the UK medical advisory board, health-state related resource use, including - blood transfusion, - haematologists visit and - blood test, was applied in different frequency per model cycle as per health states, which is summarised in CS Table 60, p136.
Breakthrough haemolysis costs per model cycle		
Severe BTH events	Complement inhibitor-naïve: Iptacopan: £3.62 Eculizumab: £15.50 Ravulizumab: £5.80 Complement inhibitor-experienced: Iptacopan: £7.97 Eculizumab: £48.54 Ravulizumab: £48.54 Pegcetacoplan: £9.56	Calculated based on the occurrence rate of BTH events per model cycle multiplied by unit cost per event. Model assumes that 10% of BTH events would be treated with a one-off dose of eculizumab (900 mg). Transfusion was not considered for BTH event since already captured in health state resource use.

Abbreviations: PNH: Paroxysmal nocturnal haemoglobinuria; BD: twice daily; CS: Company submission; IV: Intravenous; SC: Subcutaneous; SmPC: Summary of product characteristics; C5: Complement component 5; CS: Company submission; QW: once weekly; BTH: Breakthrough haemolysis.

4.2.9.2 Drug acquisition and administration costs

The drug acquisition costs for iptacopan were sourced from APPOINT-PNH and APPLY-PNH and the expected licensed dosing regimen (200 mg BD). There is no difference in dosage between the complement inhibitor-naïve and -experienced populations.

For eculizumab, up-dosing higher than the label maintenance dose was assumed. The treatment regimen is 600 mg QW loading dose for the first 4 weeks in the complement inhibitor-naïve population and maintenance dose of 900 mg Q2W starting at week 5 to month 6, with the percentage of patients receiving up-dosing applied according to the treatment schedule of patients in APPLY-PNH, while in the complement inhibitor-experienced population with residual anaemia, it was assumed that at the start of the model, patients who required higher maintenance doses were already on such a dose. Table 48 presents the percentage of patients on each dose as used in the model.

Ravulizumab's dosing is weight-based, based on the proportion of patients in each weight category from APPOINT-PNH and APPLY-PNH for the complement inhibitor-naïve and -experienced populations, respectively. Up-dosing was not considered for ravulizumab. For the complement inhibitor-naïve population, patients started on a loading dose then received a maintenance dose according to the label, while complement inhibitor-experienced patients were assumed to start on the maintenance dose (Table 48).

Pegcetacoplan had a 4-week overlap transition period for patients switching from C5 inhibitors, specifically 12% from eculizumab and 88% from ravulizumab, which was claimed based on clinical expert response in the UK medical advisory board. But since patients switching from ravulizumab Q8W had covered the first initial loading period (i.e., 4 weeks) for pegcetacoplan, they were not assumed to have additional ravulizumab at that duration, thus only concomitant acquisition costs of eculizumab were included for pegcetacoplan.

Table 48 Drug acquisition costs (reproduced from CS, Table 51, p128)

Drug	Unit costs, £	Formulation size	Proportion of patients
Iptacopan (Oral)	[redacted] (list price) [redacted] (PAS price)	200mg*56	200mg BD: 100%
Eculizumab (IV infusion)	£3,150	300mg*1	Complement inhibitor-naïve population - Loading dose (week 1-4) 600mg QW: 100% - Maintenance dose (week 5 up to month 6) 900mg Q2W: 100% - Maintenance dose (month 6 and afterwards) 900mg Q2W: 81.0% 1,200mg Q2W: 17.5% 1,500mg Q2W: 1.5% Complement inhibitor-experienced population - Maintenance dose (week 1 and afterwards) 900mg Q2W: 81.0% 1,200mg Q2W: 17.5% 1,500mg Q2W: 1.5%
Ravulizumab (IV infusion)	£4,533	300mg*1	Complement inhibitor-naïve population - Loading dose (week 1) [40,60) kg/2,400 mg: 17.5% [60,100) kg/2,700 mg: 80.0% [100,3000) kg/3,000 mg: 2.5% - Maintenance dose (week 3 and afterwards) [40,60) kg/3,000 mg/ Q8W: 17.5% [60,100) kg/3,300 mg/ Q8W: 80.0% [100,3000) kg/3,600 mg/ Q8W: 2.5% Complement inhibitor-experienced population - Maintenance dose (week 1 and afterwards) [40,60) kg/3,000 mg/ Q8W: 26.8% [60,100) kg/3,300 mg/ Q8W: 66.0% [100,3000) kg/3,600 mg/ Q8W: 7.2%
Pegcetacoplan (SC infusion)	£3,100	1080mg*1	Switching from C5 inhibitors (week 1-4) - 1080mg twice weekly with eculizumab: 12% - 1080mg twice weekly with ravulizumab: 88% Maintenance (week 5 and afterwards) - 1,080mg twice weekly: 100%

Abbreviations: PAS: Patient access scheme; IV: Intravenous; SC: Subcutaneous; QW: Once weekly; Q2W: Once every two weeks; Q8W: once every eight weeks.

Drug administration costs were determined according to the route of administration and the site of care. Given that iptacopan is administrated orally, no administration costs were assumed.

For eculizumab and ravulizumab, which are administrated through an IV infusion, the administration costs were estimated based on the assumptions used in TA698. More specifically, the cost of administrating the drug through an IV infusion consisted of the first administration at the hospital and

subsequent doses provided through a home care service. The cost of the first administration consisted of: i) 35 min administration time of band 6 nurse time; ii) 60 min observation time of band 6 nurse specialist (hospital based) time; and iii)15 min Band 7 pharmacist specialist time. Subsequent doses would be delivered through home care service covered by the manufacturer.

Pegcetacoplan is administered through SC infusion. The administration costs at the first cycle (reference source: TA778) were associated with self-administration training consisting of: i) 20 min Band 6 hospital nurse time; and ii) two home self-administration trainings, each 30min by Band 6 nurse.

Points for critique

The EAG notes that in TA698 the costs associated with exceeding the dose of 1200 mg for eculizumab were not taken into account because they would be covered by Alexion. Consequently, only 900 mg and 1200 mg doses were taken into account. Furthermore, in TA778 (9th March 22), eculizumab's dosing escalation was 900 mg every 11 days, 1200 mg Q2W, 1500mg Q2W. In the CS for iptacopan, the dosing escalation is 1200 mg or 1500 mg every 14 days..

In general, the dosing regimens used for drug acquisition costs in the CS are in accordance with the SmPC for each drug. The proportion of patients involved in up-dosing schedule for eculizumab is sourced from APPLY-PNH, which seems reasonable, and the weight-based dosing for ravulizumab is based on the average weight of patients in APPOINT-PNH and APPLY-PNH.

The EAG considers that concomitant eculizumab acquisition costs for patients initiating pegcetacoplan should be excluded from the model. The transition probabilities used in the model for pegcetacoplan are based on data from the randomised controlled period of the PEGASUS trial from weeks 4-16, in which patients had either pegcetacoplan or eculizumab, and not the 4-week run-in period in which both treatments were given, or the first 4 weeks of the randomised controlled period (only the prior 4-weeks' health state is included as a covariate in the model) where a 'hangover' effect of the run-in period was observed, i.e., the transition probabilities are estimated based on weeks 4-16 after the 4-week washout period in order to mitigate any 'hangover' effect of the run-in period in PEGASUS. Therefore, the EAG considers it inappropriate to include concomitant eculizumab acquisition costs for patients initiating pegcetacoplan.

> ***item 7: The EAG considers that concomitant eculizumab acquisition costs for patients initiating pegcetacoplan should be excluded from the model.***

4.2.9.3 Confidential pricing arrangements for drug acquisition costs

The EAG notes that there are confidential commercial arrangements in place for the comparators of ravulizumab and pegcetacoplan. The drug acquisition costs used in the company submission and EAR (Section 5 & Section 6) include only the confidential pricing agreement for iptacopan.

Table 49 presents details of the comparators with confidential prices which differ from the publicly available list prices used to generate the results in this report. These prices were made available to the EAG and were used to replicate all analyses presented in the EAR for consideration by the Appraisal Committee. Details of all confidential pricing arrangements and all results inclusive of these arrangements are provided in the confidential appendix to this report. These prices are correct as of 08th November 2023.

Table 49 Source of the confidential prices used in the confidential appendix

Treatment	Form	Dose per unit	Pack size	Source of price used in model/type of confidential arrangement sent by NICE
Ravulizumab	IV infusion	300 mg	1 vial	cPAS
Pegcetacoplan	SC infusion	1080 mg	1 vial	cPAS
Phenoxymethylpenicillin	Tablets	250 mg	28	CMU

Abbreviations: cPAS, confidential patient access scheme.

4.2.9.4 Treatment-related and health state related resource use

Except for the drug acquisition costs and administration costs considered in the CS, i) treatment-related resource use, including vaccinations, antibiotics and iron overload treatments, and ii) health state related resource use, consisting of blood transfusions, haematologist visits and blood tests were also included in the model. The resource use counted into each cycle of the model was assumed not to differ between the complement inhibitor-naïve and -experienced populations for each treatment which is shown on Table 50.

Table 50 Treatment related resource use

Treatment	One-off cost in the first cycle (proportion of patients)	Per cycle costs (proportion of patients)
Iptacopan	- H. influenzae type B (100%); - venesection (17.5%)	- N. meningitidis types A, C, W, Y, and B vaccinations (100%); - S. pneumoniae (100%); - antibiotics penicillin (100%)
eculizumab	N/A	- N. meningitidis types A, C, W, Y, and B vaccinations (100%); - antibiotics penicillin (100%); - chelation therapy (17.5%)
ravulizumab	N/A	- N. meningitidis types A, C, W, Y, and B vaccinations (100%); - antibiotics penicillin (100%); - chelation therapy (17.5%)

pegcetacoplan	H. influenzae type B (100%); venesection (17.5%)	- N. meningitidis types A, C, W, Y, and B vaccinations (100%); - S. pneumoniae (100%); - antibiotics penicillin (100%)

Neisseria (N.) meningitidis types A, C, W, Y, and B vaccinations every 5 years are required for all the interventions and Streptococcus (S.) pneumoniae at every 5 years frequency and one-off Haemophilus (H.) influenzae type B are required for proximal inhibitors iptacopan and pegcetacoplan were assumed in the model. Prophylactic antibiotics penicillin (500mg BD) was included as repeated 365 days every year.

Based on APPLY-PNH, 17.5% patients treated with C5 inhibitors would require chelation therapy which required average dose deferasirox 21mg/kg once daily, consistent with TA778, according to the average patient weight from APPOIN-PNH and APPLY-PNH, to control iron overload.

According to APPLY-PNH and information provided through the company's UK advisory board, venesection was assumed been taken monthly lasting for 12 months for 17.5 % patients receiving proximal inhibitors (iptacopan and pegcetacoplan), as a one-off cost in the first cycle. The frequency and unit costs of these items were summarised in Section B.3.5.2.1, CS, Table 56 and Table 57.

Health-related resource use encompasses of blood transfusions, haematologist, and blood tests. Patients in transfusion periods would receive transfusion and blood tests every cycle and haematologist visit every two months, while patients in the other two health states ('No transfusion and no anaemia' and 'No transfusion and anaemia') would only incur haematologist visit and blood tests every 6 months. See Section B.3.5.2.2, CS, Table 59 and Table 61 for the unit costs and costs incurred per cycle.

Points for critique

The EAG considers the health care resource use to be appropriately sourced, well informed and implemented correctly in the model. The EAG also notes that the health care resource use costs have no material impact on the cost-effectiveness of iptacopan relative to the comparator complement inhibitors.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

5.1.1 Summary of company's submission

All analyses presented in the CS used the confidential PAS price for iptacopan and list price for comparators. A summary of the inputs and variables used in the company's base case analysis is presented in Table 19, p21 of the CS addendum and assumptions used in the model are summarised in Table 65, p140 of the CS.

Table 51 shows the company's base case deterministic cost-effectiveness results in the complement inhibitor-naïve population using 24-week and 48-week data. In the complement inhibitor-naïve population, iptacopan is cost-effective vs eculizumab and ravulizumab, [redacted]. Iptacopan total costs [redacted] and total QALYs slightly increase based on the 48-week data vs 24-week data.

Table 52 presents the net health benefit (NHB) for the complement inhibitor-naïve population (24-week and 48-week data). Iptacopan has a positive net health benefit in all comparisons.

Table 51: Base-case results, complement inhibitor-naïve population (reproduced from Table 5, p11, Supplementary analyses)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
Based on 24-week data								
Iptacopan (PAS price)	[redacted]	21.05	16.59	–	–	–	–	–
Eculizumab	[redacted]	21.05	15.52	[redacted]	0.00	–1.07	[redacted]	[redacted]
Ravulizumab	[redacted]	21.05	15.53	[redacted]	0.00	–1.06	[redacted]	[redacted]
Based on 48-week data								
Iptacopan (PAS price)	[redacted]	21.05	16.68	–	–	–	–	–
Eculizumab	[redacted]	21.05	15.52	[redacted]	0.00	–1.17	[redacted]	[redacted]
Ravulizumab	[redacted]	21.05	15.53	[redacted]	0.00	–1.16	[redacted]	[redacted]

Analysis uses PAS price for iptacopan and list price for comparators.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 52: Net health benefit, complement inhibitor-naïve population (reproduced from Table 6, p11, Supplementary analyses)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Based on 24-week data						
Iptacopan (PAS price)	[redacted]	16.59	–	–	–	–
Eculizumab	[redacted]	15.52	[redacted]	–1.07	[redacted]	[redacted]
Ravulizumab	[redacted]	15.53	[redacted]	–1.06	[redacted]	[redacted]
Based on 48-week data						
Iptacopan (PAS price)	[redacted]	16.68	–	–	–	–
Eculizumab	[redacted]	15.52	[redacted]	–1.17	[redacted]	[redacted]
Ravulizumab	[redacted]	15.53	[redacted]	–1.16	[redacted]	[redacted]

Analysis uses PAS price for iptacopan and list price for comparators.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 53 shows the company's base case deterministic cost-effectiveness results in the complement inhibitor-experienced population with residual anaemia using 24-week and 48-week data. In the complement inhibitor-experienced population, based on 24-week data, iptacopan is cost-effective vs ravulizumab and pegcetacoplan, [redacted]. Compared with eculizumab, iptacopan is more costly and more effective, with an ICER above the threshold range ([redacted]). However, iptacopan total costs [redacted] and total QALYs slightly increase based on 48-week data vs 24-week data. Based on 48-week data, iptacopan is cost-effective vs all comparators ([redacted]).

Table 54 presents the net health benefit (NHB) for the complement inhibitor-experienced population (24-week and 48-week data). Iptacopan has a positive net health benefit in all comparisons.

Table 53: Base-case results, complement inhibitor-experienced population (reproduced from Table 7, p12, Supplementary analyses)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
Based on 24-week data								
Eculizumab	[redacted]	18.89	12.68	–	–	–	–	–
Iptacopan (PAS price)	[redacted]	18.89	14.42	[redacted]	0.00	1.74	[redacted]	[redacted]
Ravulizumab	[redacted]	18.89	12.68	[redacted]	0.00	0.00	[redacted]	[redacted]
Pegcetacoplan	[redacted]	18.89	13.35	[redacted]	0.00	0.67	[redacted]	[redacted]
Based on 48-week data								
Iptacopan (PAS price)	[redacted]	18.89	14.47	–	–	–	–	–
Eculizumab	[redacted]	18.89	12.60	[redacted]	0.00	–1.86	[redacted]	[redacted]
Ravulizumab	[redacted]	18.89	12.60	[redacted]	0.00	–1.86	[redacted]	[redacted]
Pegcetacoplan	[redacted]	18.89	13.29	[redacted]	0.00	–1.18	[redacted]	[redacted]

Analysis uses PAS price for iptacopan and list price for comparators.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 54: Net health benefit, complement inhibitor-experienced population (reproduced from Table 8, p13, Supplementary analyses)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Based on 24-week data						
Eculizumab	[redacted]	12.68	–	–	–	–
Iptacopan (PAS price)	[redacted]	14.42	[redacted]	1.74	[redacted]	[redacted]
Ravulizumab	[redacted]	12.68	[redacted]	0.00	[redacted]	[redacted]
Pegcetacoplan	[redacted]	13.35	[redacted]	0.67	[redacted]	[redacted]
Based on 48-week data						
Iptacopan (PAS price)	[redacted]	14.47	–	–	–	–
Eculizumab	[redacted]	12.60	[redacted]	–1.86	[redacted]	[redacted]
Ravulizumab	[redacted]	12.60	[redacted]	–1.86	[redacted]	[redacted]
Pegcetacoplan	[redacted]	13.29	[redacted]	–1.18	[redacted]	[redacted]

Analysis uses PAS price for iptacopan and list price for comparators.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; PAS, patient access scheme; QALY, quality-adjusted life year.

Points for critique

To aid understanding of the key drivers of the cost-effectiveness results, Table 55 and Table 56 provide a summary of the disaggregated costs and QALYs, respectively. The total costs are driven by drug acquisition costs for iptacopan and comparators in the complement inhibitor-naïve and -experienced populations. In the complement inhibitor-naïve population, the QALYs gained is driven by the gains in HRQoL associated with the health state of 'No transfusion and no anaemia'. In the complement inhibitor-experienced population with residual anaemia, the QALYs gained for iptacopan are driven by the gains in HRQoL associated with the health state of 'No transfusion and no anaemia',

but the QALYs gained for C5 inhibitors and pegcetacoplan are driven by the gains in HRQoL associated with the health state of 'No transfusion and anaemia'.

Table 55 Summary of the disaggregated costs in the company's deterministic base case results

Item	Cost of Iptacopan (£)	Cost of Eculizumab (£)	Cost of Ravulizumab (£)	Cost of Pegcetacoplan (£)
Complement inhibitor-naïve population (based on 24-week data)				
Drug acquisition cost	[redacted]	[redacted]	[redacted]	-
Drug administration cost	£ 46	£ 115	£ 115	-
Healthcare Resource Use Costs	£ 24,350	£ 40,916	£ 40,543	-
Adverse Events Costs	£ 601	£ 3,373	£ 1,261	-
Total	[redacted]	[redacted]	[redacted]	-
Complement inhibitor-naïve population (based on 48-week data)				
Drug acquisition cost	[redacted]	[redacted]	[redacted]	-
Drug administration cost	£ 39	£ 115	£ 115	-
Healthcare Resource Use Costs	£ 23,087	£ 40,916	£ 40,543	-
Adverse Events Costs	£ 1,186	£ 3,373	£ 1,261	-
Total	[redacted]	[redacted]	[redacted]	-
Complement inhibitor-experienced population (based on 24-week data)				
Drug acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration cost	£ 43	£ 0	£ 0	£ 156
Healthcare Resource Use Costs	£ 37,282	£ 89,935	£ 89,935	£ 70,085
Adverse Events Costs	£ 4,939	£ 11,959	£ 11,959	£ 9,587
Total	[redacted]	[redacted]	[redacted]	[redacted]
Complement inhibitor-experienced population (based on 48-week data)				
Drug acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration cost	£ 37	£ 0	£ 0	£ 156
Healthcare Resource Use Costs	£ 35,905	£ 100,050	£ 100,050	£ 77,516
Adverse Events Costs	£ 4,866	£ 11,959	£ 11,959	£ 9,587
Total	[redacted]	[redacted]	[redacted]	[redacted]

Table 56 Summary of the disaggregated QALYs in the company's deterministic base case results

Item	QALYs of Iptacopan	QALYs of Eculizumab	QALYs of Ravulizumab	QALYs of Pegcetacoplan
Complement inhibitor-naïve population (based on 24-week data)				
No Transfusion and Anaemia	1.95	4.05	4.05	-
No Transfusion and No Anaemia	14.05	10.13	10.13	-
Transfusion	0.59	1.35	1.35	-
Disutility associated with BTH	0.00	-0.02	-0.01	-
Total	16.59	15.52	15.53	-
Complement inhibitor-naïve population (based on 48-week data)				

Item	QALYs of Iptacopan	QALYs of Eculizumab	QALYs of Ravulizumab	QALYs of Pegcetacoplan
No Transfusion and Anaemia	2.10	4.05	4.05	-
No Transfusion and No Anaemia	14.03	10.13	10.13	-
Transfusion	0.56	1.35	1.35	-
Disutility associated with BTH	-0.01	-0.02	-0.01	-
Total	16.68	15.52	15.53	-
Complement inhibitor-experienced population (based on 24-week data)				
No Transfusion and Anaemia	2.65	6.75	6.75	5.24
No Transfusion and No Anaemia	10.29	1.55	1.55	4.85
Transfusion	1.50	4.44	4.44	3.30
Disutility associated with BTH	-0.02	-0.05	-0.05	-0.04
Total	14.42	12.68	12.68	13.35
Complement inhibitor-experienced population (based on 48-week data)				
No Transfusion and Anaemia	3.33	6.77	6.77	5.27
No Transfusion and No Anaemia	9.71	0.80	0.80	4.30
Transfusion	1.45	5.09	5.09	3.77
Disutility associated with BTH	-0.02	-0.05	-0.05	-0.04
Total	14.47	12.60	12.60	13.29

5.2 Company's sensitivity analyses

5.2.1 Summary of company's submission

5.2.1.1 Probabilistic sensitivity analysis

Joint parameter uncertainty was explored through probabilistic sensitivity analysis (PSA), in which all parameters were assigned distributions and varied jointly. 10,000 Monte Carlo simulations were recorded.

Table 57 and Table 58 show the company's PSA results in the complement inhibitor-naïve and -experienced populations, respectively. In the complement inhibitor-naïve population, PSA results are congruent with the deterministic results, and iptacopan remains cost-effective ([redacted]) at the iptacopan PAS price and comparator list prices. Based on 24-week data, Figure 1 of CS Addendum, p30, presents the cost-effectiveness plane. The CEAC (Figure 2 of CS Addendum, p30) shows that iptacopan [redacted] and cost-effective in [redacted]% of simulations at a willingness-to-pay (WTP) threshold of £20,000 per QALY, and [redacted]% of simulations at a WTP threshold of £30,000 per QALY. Based on 48-week data, Figure 1 of Supplementary Analyses, p16 presents the cost-effectiveness plane. The CEAC (Figure 2 of Supplementary Analyses, p16) shows that iptacopan [redacted] was cost-effective in [redacted]% of simulations at a willingness-to-pay (WTP) threshold of £20,000 per QALY, and [redacted]% of simulations at a WTP threshold of £30,000 per QALY.

In the complement inhibitor-experienced population, PSA results are congruent with the deterministic results. Changes in the results of the PSA using the 48-week data vs 24-week data are aligned with the changes in the deterministic analysis. Based on 24-week data, Figure 3 of CS Addendum, p31 presents the cost-effectiveness plane. The CEAC (Figure 3 of CS Addendum, p31) shows that iptacopan [redacted] and was cost-effective in [redacted]% of simulations at a willingness-to-pay (WTP) threshold of £20,000 per QALY, and [redacted]% of simulations at a WTP threshold of £30,000 per QALY. Based on 48-week data, Figure 3 of Supplementary Analyses, p17 presents the cost-effectiveness plane. The CEAC (Figure 4 of Supplementary Analyses, p17) shows that iptacopan [redacted] was cost-effective in [redacted]% of simulations at a willingness-to-pay (WTP) threshold of £20,000 per QALY, and [redacted]% of simulations at a WTP threshold of £30,000 per QALY.

Table 57: PSA results, complement inhibitor-naïve population (reproduced from Table 9, p14, Supplementary analyses)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
Based on 24-week data						
Iptacopan (PAS price)	[redacted]	16.56	–	–	–	–
Eculizumab	[redacted]	15.51	[redacted]	–1.05	[redacted]	[redacted]
Ravulizumab	[redacted]	15.51	[redacted]	–1.05	[redacted]	[redacted]
Based on 48-week data						
Iptacopan (PAS price)	[redacted]	16.65	–	–	–	–
Eculizumab	[redacted]	15.49	[redacted]	–1.15	[redacted]	[redacted]
Ravulizumab	[redacted]	15.50	[redacted]	–1.15	[redacted]	[redacted]

Analysis uses PAS price for iptacopan and list price for comparators.
Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year

Table 58: PSA results, complement inhibitor-experienced population (reproduced from Table 10, p15, Supplementary analyses)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
Based on 24-week data						
Eculizumab	[redacted]	12.68	–	–	–	–
Iptacopan (PAS price)	[redacted]	14.40	[redacted]	1.72	[redacted]	[redacted]
Ravulizumab	[redacted]	12.68	[redacted]	0.00	[redacted]	[redacted]
Pegcetacoplan	[redacted]	13.35	[redacted]	0.67	[redacted]	[redacted]
Based on 48-week data						
Iptacopan (PAS price)	[redacted]	14.44	–	–	–	–
Eculizumab	[redacted]	12.61	[redacted]	–1.84	[redacted]	[redacted]
Ravulizumab	[redacted]	12.61	[redacted]	–1.84	[redacted]	[redacted]
Pegcetacoplan	[redacted]	13.30	[redacted]	–1.15	[redacted]	[redacted]

Analysis uses PAS price for iptacopan and list price for comparators.
Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

5.2.1.2 Scenario analysis

The company conducted twelve scenario analyses related to patient characteristics, transition probabilities, treatment discontinuation, utility values, resource use and cost, and reports the corresponding results in the complement inhibitor-naïve and -experienced populations in Table 59 and Table 60, respectively. Sensitivity analyses are mostly well aligned with the deterministic base-case results.

Scenario analyses for the complement inhibitor-naïve based on 24-week data shows that iptacopan remains cost-effective vs ravulizumab in all scenario analyses, and vs eculizumab in all but one scenario over the threshold of £30,000 per QALY. The scenario is the scenario without discounting applied. Scenario based on 48-week data in the complement inhibitor-naïve population shows that iptacopan remains cost-effective vs ravulizumab and eculizumab in all scenario analyses.

Scenario analyses for the complement inhibitor-experienced based on 24-week data shows that iptacopan remains cost-effective vs ravulizumab and pegcetacoplan in all scenario analyses. The ICER vs eculizumab mostly well aligned with the deterministic base-case results, except two scenarios [redacted]. The first of these is also the scenario without discontinuation applied. The second is the comparator dosing based on UK clinical input. Iptacopan is cost-effective vs all comparators in all scenarios based on the 48-week data, except for the scenario with no discounting vs eculizumab (ICER [redacted]). In the scenario without discontinuations, iptacopan now generates slightly lower QALYs than pegcetacoplan, but remains cost-effective at the iptacopan PAS price and comparator list prices ([redacted]).

No subgroup analyses were conducted by the company.

Table 59: Scenario analyses for iptacopan in the complement inhibitor-naïve population (reproduced from Table 11, p18 of the supplementary analyses)

Scenario	Iptacopan vs eculizumab			Iptacopan vs ravulizumab		
	Inc. costs	Inc. QALYs	ICER	Inc. costs	Inc. QALYs	ICER
Based on 24-week data						
Base case	[redacted]	**1.07**	[redacted]	[redacted]	**1.06**	[redacted]
Definition of anaemia	[redacted]	1.11	[redacted]	[redacted]	1.10	[redacted]
No imputation for APPEX data	[redacted]	1.23	[redacted]	[redacted]	1.22	[redacted]
Unweighted transition probabilities	[redacted]	1.08	[redacted]	[redacted]	1.07	[redacted]
Comparator dosing	[redacted]	1.07	[redacted]	[redacted]	1.06	[redacted]
No discontinuation for any treatment	[redacted]	2.46	[redacted]	[redacted]	2.44	[redacted]
No discontinuation for iptacopan	[redacted]	1.96	[redacted]	[redacted]	1.95	[redacted]
Treatment independent utilities	[redacted]	0.44	[redacted]	[redacted]	0.43	[redacted]
EORTC QLQ-C30 utilities	[redacted]	1.08	[redacted]	[redacted]	1.07	[redacted]
No BTH cost	[redacted]	1.07	[redacted]	[redacted]	1.06	[redacted]
No chelation therapy or venesection	[redacted]	1.07	[redacted]	[redacted]	1.06	[redacted]
TA778 resource use	[redacted]	1.07	[redacted]	[redacted]	1.06	[redacted]
No discounting	[redacted]	1.52	[redacted]	[redacted]	1.51	[redacted]
Based on 48-week data						
Base case	[redacted]	**1.17**	[redacted]	[redacted]	**1.16**	[redacted]
Definition of anaemia	[redacted]	1.22	[redacted]	[redacted]	1.21	[redacted]
No imputation for APPEX data	[redacted]	1.35	[redacted]	[redacted]	1.34	[redacted]
Unweighted transition probabilities	[redacted]	1.18	[redacted]	[redacted]	1.17	[redacted]
Comparator dosing	[redacted]	1.17	[redacted]	[redacted]	1.16	[redacted]
No discontinuation for any treatment	[redacted]	2.40	[redacted]	[redacted]	2.39	[redacted]
No discontinuation for iptacopan	[redacted]	1.91	[redacted]	[redacted]	1.90	[redacted]
Treatment independent utilities	[redacted]	0.43	[redacted]	[redacted]	0.42	[redacted]

Scenario	Iptacopan vs eculizumab			Iptacopan vs ravulizumab		
	Inc. costs	Inc. QALYs	ICER	Inc. costs	Inc. QALYs	ICER
EORTC QLQ-C30 utilities	[redacted]	1.18	[redacted]	[redacted]	1.17	[redacted]
No BTH cost	[redacted]	1.17	[redacted]	[redacted]	1.16	[redacted]
No chelation therapy or venesection	[redacted]	1.17	[redacted]	[redacted]	1.16	[redacted]
TA778 resource use	[redacted]	1.17	[redacted]	[redacted]	1.16	[redacted]
No discounting	[redacted]	1.76	[redacted]	[redacted]	1.74	[redacted]
New scenario: Pooled discontinuation rate for iptacopan	[redacted]	1.37	[redacted]	[redacted]	1.36	[redacted]
New scenario: Pooled BTH event rate for iptacopan	[redacted]	1.16	[redacted]	[redacted]	1.15	[redacted]

Analysis uses PAS price for iptacopan and list price for comparators.
Abbreviations: BTH, breakthrough haemolysis; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TA, technology appraisal

Table 60: Scenario analyses for iptacopan in the complement inhibitor-experienced population (reproduced from Table 12, p20 of the supplementary analyses)

Scenario	Iptacopan vs eculizumab			Iptacopan vs ravulizumab			Iptacopan vs pegcetacoplan		
	Inc. costs	Inc. QALYs	ICER	Inc. costs	Inc. QALYs	ICER	Inc. costs	Inc. QALYs	ICER
Based on 24-week data									
Base case	[redacted]	**1.74**	[redacted]	[redacted]	**1.74**	[redacted]	[redacted]	**1.07**	[redacted]
Definition of anaemia	[redacted]	1.58	[redacted]	[redacted]	1.58	[redacted]	[redacted]	0.98	[redacted]
Unweighted transition probabilities	[redacted]	1.78	[redacted]	[redacted]	1.78	[redacted]	[redacted]	1.10	[redacted]
C5 inhibitor efficacy by treatment	[redacted]	1.50	[redacted]	[redacted]	2.12	[redacted]	[redacted]	1.30	[redacted]
C5 inhibitor efficacy from PEGASUS	[redacted]	1.84	[redacted]	[redacted]	1.84	[redacted]	[redacted]	1.13	[redacted]
Comparator dosing	[redacted]	1.74	[redacted]	[redacted]	1.74	[redacted]	[redacted]	1.07	[redacted]
No discontinuation	[redacted]	2.61	[redacted]	[redacted]	2.61	[redacted]	[redacted]	0.03	[redacted]
Treatment independent utilities	[redacted]	1.17	[redacted]	[redacted]	1.17	[redacted]	[redacted]	0.72	[redacted]
EORTC QLQ-C30 utilities	[redacted]	1.63	[redacted]	[redacted]	1.63	[redacted]	[redacted]	1.01	[redacted]
No BTH cost	[redacted]	1.74	[redacted]	[redacted]	1.74	[redacted]	[redacted]	1.07	[redacted]
No chelation therapy or venesection	[redacted]	1.74	[redacted]	[redacted]	1.74	[redacted]	[redacted]	1.07	[redacted]
TA778 resource utilisation	[redacted]	1.74	[redacted]	[redacted]	1.74	[redacted]	[redacted]	1.07	[redacted]
No discounting	[redacted]	2.60	[redacted]	[redacted]	2.60	[redacted]	[redacted]	1.81	[redacted]
Based on 48-week data									
Base case	[redacted]	**1.86**	[redacted]	[redacted]	**1.86**	[redacted]	[redacted]	**1.18**	[redacted]
Definition of anaemia	[redacted]	1.82	[redacted]	[redacted]	1.82	[redacted]	[redacted]	1.17	[redacted]
Unweighted transition probabilities	[redacted]	1.89	[redacted]	[redacted]	1.89	[redacted]	[redacted]	1.21	[redacted]
C5 inhibitor efficacy by treatment[§]	[redacted]	1.60	[redacted]	[redacted]	2.22	[redacted]	[redacted]	1.40	[redacted]
C5 inhibitor efficacy from PEGASUS	[redacted]	1.91	[redacted]	[redacted]	1.91	[redacted]	[redacted]	1.21	[redacted]

Scenario	Iptacopan vs eculizumab			Iptacopan vs ravulizumab			Iptacopan vs pegcetacoplan		
	Inc. costs	Inc. QALYs	ICER	Inc. costs	Inc. QALYs	ICER	Inc. costs	Inc. QALYs	ICER
Comparator dosing	[redacted]	1.86	[redacted]	[redacted]	1.86	[redacted]	[redacted]	1.18	[redacted]
No discontinuation	[redacted]	2.59	[redacted]	[redacted]	2.59	[redacted]	[redacted]	–0.07	[redacted]
Treatment independent utilities	[redacted]	1.24	[redacted]	[redacted]	1.24	[redacted]	[redacted]	0.76	[redacted]
EORTC QLQ-C30 utilities	[redacted]	1.74	[redacted]	[redacted]	1.74	[redacted]	[redacted]	1.10	[redacted]
No BTH cost	[redacted]	1.86	[redacted]	[redacted]	1.86	[redacted]	[redacted]	1.18	[redacted]
No chelation therapy or venesection	[redacted]	1.86	[redacted]	[redacted]	1.86	[redacted]	[redacted]	1.18	[redacted]
TA778 resource utilisation	[redacted]	1.86	[redacted]	[redacted]	1.86	[redacted]	[redacted]	1.18	[redacted]
No discounting	[redacted]	2.84	[redacted]	[redacted]	2.84	[redacted]	[redacted]	2.03	[redacted]
New scenario: With C5 inhibitor transition probabilities - 24 weeks†	[redacted]	1.81	[redacted]	[redacted]	1.81	[redacted]	[redacted]	1.14	[redacted]
New scenario: Pooled discontinuation rate for iptacopan	[redacted]	2.07	[redacted]	[redacted]	2.07	[redacted]	[redacted]	1.38	[redacted]
New scenario: Pooled BTH event rate for iptacopan	[redacted]	1.86	[redacted]	[redacted]	1.86	[redacted]	[redacted]	1.18	[redacted]

§Scenario analysis using iptacopan transition probabilities estimated in the multinomial logistic regression model based on APPLY-PNH 48-week data and eculizumab and ravulizumab transition probabilities estimated in the model based on APPLY-PNH 24-week data. Due to insufficient time, no joint regression model could be run. However, given the direction of changes with the 48-week transition probabilities, it is expected that the results presented here are conservative.
†Scenario analysis using C5 inhibitor transition probabilities estimated in the multinomial logistic regression model based on APPLY-PNH 24-week data.
Analysis uses PAS price for iptacopan and list price for comparators.
Abbreviations: BTH, breakthrough haemolysis; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TA, technology appraisal.

5.3 Model validation and face validity check

5.3.1 Summary of company submission

The company undertook both internal and external validation of the model. Internal validation included cell-by-cell checks and logical checks by the model developers and by health economists not involved in the development of the model. Expert clinical input was sought to validate sources of clinical evidence and approaches to analyse, key prognostic factors and treatment effect modifiers for population adjustments, the model structure, treatment discontinuations, utility values and key model assumptions.

For the external model validation, the company compared the model outcomes (based on 24-week data) with published cost-effectiveness analyses. The cost-effectiveness analysis published by Hakimi et al [13] compares pegcetacoplan to ravulizumab in complement inhibitor-experienced patients with residual anaemia, using an analysis that is closely aligned with the pegcetacoplan NICE appraisal TA778. The model structure used in this submission is also closely aligned with the TA778 model and so outcomes of these analyses should be comparable. Modelled outcomes for ravulizumab and pegcetacoplan are comparable to those from Hakimi et al. [13] Both costs and QALYs in this analysis are smaller, however this may be explained by the population characteristics, which patients in the Hakimi et al [13] analysis being younger and having a higher mean weight. The detailed comparison is provided in the Table 28, Table 29, p36, the CS addendum and the Section B.3.13.1.2 of the CS.

Points for critique

The EAG considers that the company's validation procedure was appropriate. The EAG reviewed the company model in detail. The EAG considered the model to be well coded and presented in a clear and transparent manner that did not hinder model validation. The EAG did not identify any errors affecting the cost-effectiveness results.

6 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

A summary of the key issues identified and critiqued in Section 4, along with the scenario where the EAG addresses each issue in its additional analyses, is shown in Table 61. The EAG identified a number of limitations and areas of uncertainty in the company's cost-effectiveness analysis. Where possible, the EAG explored alternative assumptions to the company's base-case analysis, focusing on those issues that are expected to have the most impact (EAG Scenarios 1-7). A description of the EAG scenario analyses are presented in Section 6.1.1, while the impact on the cost-effectiveness results is presented in Section 6.2.

The EAG's base case consists of the set of assumptions and model inputs that the EAG considers to be most appropriate for assessing the cost-effectiveness of iptacopan compared with C5 inhibitors in the complement inhibitor-naïve population, and iptacopan compared with C5 inhibitors or pegcetacoplan in the complement inhibitor-experienced population with residual anaemia. The effect of making changes simultaneously on elements that are considered to form part of the EAG's preferred base case assumptions are presented in Section 6.3.

All additional analyses conducted by the EAG are presented separately using the 24-week and 48-week data from the iptacopan trials.

Table 61 Summary of the key issues identified by the EAG in Section 4 and EAG scenarios

Critique item and description The EAG considers that:		Dealt with in the		Area of remaining uncertainty	Significant impact on ICER
		EAG Scenarios	EAG Base-case		
1	***The modelled treatment sequence in the complement inhibitor-naïve population with pegcetacoplan as a subsequent line of treatment after one-time discontinuation from C5 inhibitors at 24 weeks for 30% of patients who still have anaemia or receive transfusions is likely to mask the cost-effectiveness of iptacopan relative to C5 inhibitors in the naïve population.***	Scenarios 3, 4	Yes	No	Yes
2	***There is uncertainty in the treatment effectiveness evidence informing the model because a comparison of iptacopan trial endpoints with modelled inputs and results is not feasible.***	No	No	Yes	Unclear
3	***The transition probabilities used in the model are based on a lack of randomisation in the complement inhibitor-naïve population, and a lack of direct (head-to-head) or indirect comparison of iptacopan and pegcetacoplan in the complement inhibitor-experienced population with residual anaemia.***	No (partially considered in Scenario 2)	No	Yes	Unclear
4	***There is variation in the assessment time period used for iptacopan and the comparator complement inhibitors, and across modelled parameters, in the 48-week data analysis.***	All scenarios reported separately for 24-week and 48-week data	Yes	No	Only in complement inhibitor-experienced population
5	***The use of treatment-specific discontinuation rates for iptacopan and pegcetacoplan from the clinical trials is a key driver of cost-effectiveness but is informed by limited data that may not reflect how patients are managed in the NHS.***	Scenarios 5a, 5b, 5c	Yes	Yes	Yes
6	***It is more appropriate to use treatment-independent health state utility values rather than treatment-specific utility values because the benefits of treatment are already captured in the transitions between health states.***	Scenario 6	Yes	No	Yes
7	***Concomitant eculizumab acquisition costs for patients initiating pegcetacoplan should be excluded from the model.***	Scenario 7	Yes	No	No

6.1.1 Issues explored by the EAG in additional analyses

6.1.1.1 Scenario 1: Hb threshold level of 10.0 g/dL

As discussed in Section 4.2.2.1, the health states used in the company's model are defined based on transfusion status and anaemia, where anaemia is represented by Hb level above and below a threshold level of 10.5 g/dL. The threshold of 10.5 g/dL was used in the model in order to incorporate the published transition probabilities for pegcetacoplan based on the inclusion criteria of Hb < 10.5 g/dL in the PEGASUS trial, whereas the APPOINT-PNH and APPLY-PNH trials for iptacopan used inclusion criteria of Hb < 10.0 g/dL.

Scenario 1 considers the cost-effectiveness of iptacopan relative to the comparator complement inhibitors when the transition probabilities and utility values informing the model are based on a threshold of Hb < 10.0 g/dL for iptacopan and C5 inhibitors from the trials (Hb < 10.5 g/dL for pegcetacoplan). The results of Scenario 1 are presented separately for each population.

6.1.1.2 Scenario 2: Transition probabilities from PEGASUS for C5 inhibitors

As discussed in Section 4.2.6.1, the transition probabilities used in the model are based on a lack of direct (head-to-head) or indirect comparison of iptacopan and pegcetacoplan in the complement inhibitor-experienced population with residual anaemia, while in Section 4.2.6.3 it was noted that large differences were observed in outcomes of the C5 inhibitor arms of APPLY-PNH (iptacopan) and PEGASUS (pegcetacoplan). The EAG is concerned that the comparison of iptacopan and pegcetacoplan from two distinctively different trial populations may not be appropriate, with transition probabilities for pegcetacoplan and iptacopan independently derived from PEGASUS and APPLY-PNH, respectively.

Scenario 2 assesses the implications for the cost-effectiveness of iptacopan relative to the comparator complement inhibitors when the transition probabilities for C5 inhibitors are based on PEGASUS rather than APPLY-PNH, as used in the company's base case for the complement inhibitor-experienced population with residual anaemia. The EAG notes that this scenario does not address the EAG's primary concern for the comparison of iptacopan and pegcetacoplan, but it provides an indication of how sensitive the company's cost-effectiveness results are to the differences observed in C5 inhibitors between APPLY-PNH and PEGASUS.

6.1.1.3 Scenario 3: One treatment line (no discontinuation)

As discussed in Section 4.2.4.1 the final NICE scope did not specifically define a comparison of treatment sequences for the cost-effectiveness of iptacopan. In TA778 (pegcetacoplan) and TA698 (ravulizumab) only one treatment line was considered, where patients did not discontinue from their initial treatment in the model (except in TA778, a small proportion of patients were permitted to

discontinue pegcetacoplan after a 'settle in period' when it became known that pegcetacoplan was unsuitable). When alternative treatment options are available, the EAG considers modelling subsequent lines of treatment to be more appropriate than a single treatment line; however, the EAG notes a number of inconsistencies in the approach used by the company to model subsequent treatments that are likely to mask the cost-effectiveness of iptacopan relative to C5 inhibitors in the complement inhibitor-naïve population.

Scenario 3 considers the cost-effectiveness of iptacopan relative to the comparator complement inhibitors when treatment discontinuation is set to zero for all treatments in order to exclude the impact of treatment switches, i.e., one treatment line is modelled in Scenario 3.

6.1.1.4 Scenario 4: Modelled treatment sequence in the complement inhibitor-naïve population

As discussed in Section 4.2.4.1, in the complement inhibitor-naïve population the company modelled the treatment sequence:

Iptacopan to ravulizumab vs. C5 inhibitors (ravulizumab/ eculizumab) to pegcetacoplan

and used the transition probabilities from the complement inhibitor-experienced population with residual anaemia for pegcetacoplan when used as the second line therapy after C5 inhibitors, while the transition probabilities from the complement inhibitor-naïve population was used for second-line ravulizumab after iptacopan. The EAG notes the inconsistency in approach for second-line pegcetacoplan and ravulizumab in the complement inhibitor-naïve population. The EAG also considers it not entirely clear whether pegcetacoplan should be included as a subsequent line of treatment in the naïve population when it is only considered as a relevant comparator for the complement inhibitor-experienced population for patients with residual anaemia after ≥3 months of treatment with a C5 inhibitor. Importantly, the modelled one-time discontinuation at 24 weeks for C5 inhibitors to pegcetacoplan (modelled to affect 30% of patients remaining in the 'Transfusion' and 'No Transfusion and Anaemia' health states) is likely to mask the cost-effectiveness of iptacopan relative to C5 inhibitors in the complement inhibitor-naïve population because this subset of patients become complement inhibitor-experienced with residual anaemia.

In the complement inhibitor-naïve population, the EAG considers it more appropriate to model the treatment sequence:

Iptacopan to ravulizumab vs. C5 inhibitors (ravulizumab/ eculizumab),

where C5 inhibitors is considered the current standard of care in the NHS in the treatment naïve population.

Scenario 4 considers the cost-effectiveness of iptacopan using the EAG's preferred modelled treatment sequence in the complement inhibitor-naïve population, and using the transition probabilities from the naïve population for C5 inhibitors at first and second-line. The modelled sequence in Scenario 4 is also in line with the approach used by the company in the complement inhibitor-experienced population with residual anaemia, where a subsequent line of treatment is not considered for C5 inhibitors, and ravulizumab is considered the subsequent treatment after iptacopan or pegcetacoplan.

6.1.1.5 Scenario 5: Annual discontinuation rates for iptacopan and pegcetacoplan

As discussed in Section 4.2.6.4, the EAG is concerned that the use of treatment-specific annual discontinuation rates for iptacopan and pegcetacoplan informed by their respective clinical trials may not reflect how patients are managed in the NHS. The company's base case uses a substantially higher discontinuation rate of 16.13% per annum for pegcetacoplan compared to the rate of 3.43% per annum for iptacopan from the 24-week data, or 2.72% per annum from the 48-week data. This differential discontinuation rate results in a stark difference between iptacopan and pegcetacoplan in terms of the proportion of patients distributed across health states over time, with a substantially higher percentage of patients with uncontrolled anaemia for pegcetacoplan compared to iptacopan, and a substantially higher percentage of patients' transfusion dependent on pegcetacoplan, because once patients discontinue either iptacopan and pegcetacoplan they are modelled to receive ravulizumab treatment.

The EAG's clinical advisor indicated that there is no known reason to expect a substantial difference in the long-term discontinuation rates between pegcetacoplan and iptacopan, except for differences observed for BTH. He suggested a slightly higher discontinuation rate for pegcetacoplan but not a substantial difference of 16.13% vs. 3.43% (or 2.72%).

Scenario 5 is split into three scenarios 5a, 5b, and 5c, where alternative assumptions for the annual discontinuation rate of pegcetacoplan compared to iptacopan in NHS clinical practice are considered, in the complement inhibitor-experienced population with residual anaemia:

- Scenario 5a uses the same annual discontinuation rate for pegcetacoplan and iptacopan of 3.43% per year (24-week data analysis, or 2.72% per year in the 48-week data analysis);
- Scenario 5b uses a slightly higher discontinuation rate for pegcetacoplan of 5% per year compared to iptacopan of 3.43% per year (24-week data analysis, or 2.72% in the 48-week data analysis);
- Scenario 5c uses a higher discontinuation rate for pegcetacoplan of 10% per year compared to iptacopan of 3.43% per year (24-week data analysis, or 2.72% in the 48-week data analysis).

6.1.1.6 Scenario 6: Treatment-independent health state utility values

As discussed in Section 4.2.8.1, the company used treatment-specific health state utility values in the model. The EAG notes that the difference in utility values between iptacopan and C5 inhibitors are substantial despite being in the same health state; for example, the 'No transfusion and no anaemia' health state has a utility value of 0.879 for iptacopan and 0.775 for C5 inhibitors. The EAG considers that the only plausible explanation for a difference in health state utility by treatment is due to the disutility associated with mode of treatment administration; however, the EAG does not consider the magnitude of the difference in treatment-dependent utility values between iptacopan and C5 inhibitors to be realistic. The underlying evidence for this difference is weak and the baseline utility value (utility value at Day 1) differed substantially between patients treated with iptacopan and C5 inhibitors in APPLY-PNH indicating that the difference in the utility values could be due to small sample sizes and differences in the characteristics of patients treated with iptacopan and C5 inhibitors. The EAG considers it more appropriate to use treatment-independent health state utility values because the benefits of treatment are already captured in the transitions between health states. Furthermore, treatment-independent health state utility values were used in TA778 (pegcetacoplan) and TA698 (ravulizumab).

Scenario 6 considers the cost-effectiveness of iptacopan relative to the comparator complement inhibitors when treatment-independent health state utility values are used in the model. The results of Scenario 6 are presented separately for each population.

6.1.1.7 Scenario 7: Exclusion of concomitant eculizumab acquisition costs for patients initiating pegcetacoplan

As discussed in Section 4.2.9, the EAG considers that concomitant eculizumab acquisition costs for patients initiating pegcetacoplan should be excluded from the model because the transition probabilities used in the model for pegcetacoplan are based on the randomised controlled period of the PEGASUS trial from weeks 4-16, in which patients had either pegcetacoplan or eculizumab, and not the 4-week run-in period in which both treatments were given, or the first 4 weeks of the randomised controlled period where a 'hangover' effect of the run-in period was observed, i.e., the transition probabilities are based on week 4-16 after the 4-week washout period in order to mitigate any 'hangover' effect of the run-in period in PEGASUS. Therefore, the EAG considers it inappropriate to include concomitant eculizumab acquisition costs for patients initiating pegcetacoplan.

Scenario 7 considers the cost-effectiveness of iptacopan relative to the comparator complement inhibitors when concomitant eculizumab acquisition costs for patients initiating pegcetacoplan are excluded in the complement inhibitor-experienced population with residual anaemia.

6.2 *Impact on the ICER of additional clinical and economic analyses undertaken by the EAG*

Table 62 and Table 63 show the results of the EAG scenarios (Scenarios 1, 3, 4 and 6) for the complement inhibitor-naïve population using 24-week data and 48-week data, respectively. Table 64 and Table 65 show the results of the EAG scenarios (Scenarios 1, 2, 3, 5a, 5b, 5c, 6 and 7) for the complement inhibitor-experienced population with residual anaemia using 24-week data and 48-week data, respectively.

In the complement inhibitor-naïve population, the only scenario that changes the company's base case ICER of [redacted] is Scenario 4, where the modelled treatment sequence is iptacopan to ravulizumab vs. C5 inhibitors (no discontinuation) compared to the company's base case modelled treatment sequence that includes discontinuation from C5 inhibitors to pegcetacoplan at 24 weeks for 30% of patients who still have anaemia and require transfusions. In Scenario 4, [redacted] This is driven by lower QALYs associated with eculizumab treatment (a greater proportion in the anaemia and transfusion health states compared to iptacopan) [redacted]

The other EAG scenarios that have a large impact on the company's base case results in the complement inhibitor-naïve population are Scenario 3, one treatment line modelled with no discontinuations, and Scenario 6, treatment-independent health state utility values. Scenario 3 improves the cost-effectiveness of iptacopan compared to the company's base case because the benefits of iptacopan from APPOINT-PNH are extrapolated over a lifetime horizon with no discontinuation and because C5 inhibitors generate lower QALYs since anaemic/ transfusion-dependent patients are not switching to pegcetacoplan (that is more effective for patients with residual anaemia). Scenario 6 does not change the company's base case conclusion that [redacted] but the QALY gain from iptacopan compared to C5 inhibitors is substantially reduced (over 50% reduction) relative to the company's base case. This is because the treatment-specific utility value for the same health state in the company's base case is significantly higher for iptacopan compared to C5 inhibitors, which the EAG considers to be double counting the effects of iptacopan.

In the complement inhibitor-naïve population, Scenario 1 using a lower threshold level of 10.0 g/dL for defining anaemia had the least impact on the company's base case results. Furthermore, the use of

48-week data compared to 24-week data for specific model parameters for iptacopan did not affect the conclusions in the naïve population, except for the changes to the ICER noted above for Scenario 4.

In the complement inhibitor-experienced population with residual anaemia, the EAG scenarios with the largest impact on the company's base case ICER are: (i) Scenario 6 with treatment-independent health state utility values, where the QALY gains for iptacopan vs. the comparator complement inhibitors are reduced by 30% [redacted]); (ii) Scenarios 5a, 5b and 5c, using alternative annual discontinuation rates for pegcetacoplan of 3.43% (24-week data, or 2.72% with 48-week data), 5% and 10%, respectively, where the QALY gains for iptacopan compared to pegcetacoplan in the company's base case are substantially reduced to near zero, using the same discontinuation rates for iptacopan and pegcetacoplan (because the company assumes the same treatment-specific health state utility values for pegcetacoplan and iptacopan), reduced by 75% using a discontinuation rate of 5% for pegcetacoplan compared to 16.13% in the company's base case (and 24-week data for iptacopan), and reduced by 29% with a discontinuation rate of 10% for pegcetacoplan.

Scenario 3, with only one treatment line modelled and no discontinuations, has a large impact on both costs and QALYs in the complement inhibitor-experienced population, but the EAG considers this scenario less relevant for the complement inhibitor-experienced population because of the availability of alternative treatment options. Scenario 2, which uses the transition probabilities from PEGASUS for C5 inhibitors rather than those from APPLY-PNH used in the company's base case analysis demonstrates that the cost-effectiveness of iptacopan is sensitive to the differences observed between the APPLY-PNH and PEGASUS trial populations. Therefore, the EAG is concerned that the comparison of iptacopan and pegcetacoplan, with transition probabilities derived from two distinctively different trial populations, may not be appropriate.

In the complement inhibitor-experienced population with residual anaemia, Scenario 1 using a lower threshold level of 10.0 g/dL for defining anaemia and Scenario 7, excluding concomitant eculizumab acquisition costs for patients initiating pegcetacoplan, had the least impact on the company's base case results. The use of 48-week data vs. 24-week data is more favourable for the cost-effectiveness of iptacopan relative to the comparator complement inhibitors in the experienced population, [redacted]

Table 62 Cost-effectiveness results of the EAG scenario analyses for the complement inhibitor-naïve population using 24-week data

	Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER	NHB at 20,000	NHB at 30,000
Scenario #	company base-case	Iptacopan	[redacted]	16.59	-	-	-	-	-
		Eculizumab	[redacted]	15.52	[redacted]	-1.07	[redacted]	[redacted]	[redacted]
		Ravulizumab	[redacted]	15.53	[redacted]	-1.06	[redacted]	[redacted]	[redacted]
		Pairwise comparison							
		Iptacopan vs. Eculizumab			[redacted]	1.07	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Ravulizumab			[redacted]	1.06	[redacted]	[redacted]	[redacted]
1	Hb threshold level of 10.0 g/dL	Iptacopan	[redacted]	16.52					
		Eculizumab	[redacted]	15.41	[redacted]	-1.11	[redacted]	[redacted]	[redacted]
		Ravulizumab	[redacted]	15.42	[redacted]	-1.10	[redacted]	[redacted]	[redacted]
		Pairwise comparison							
		Iptacopan vs. Eculizumab			[redacted]	1.11	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Ravulizumab			[redacted]	1.10	[redacted]	[redacted]	[redacted]
3	One treatment line (no discontinuation)	Iptacopan	[redacted]	17.48					
		Eculizumab	[redacted]	15.02	[redacted]	-2.46	[redacted]	[redacted]	[redacted]
		Ravulizumab	[redacted]	15.03	[redacted]	-2.44	[redacted]	[redacted]	[redacted]
		Pairwise comparison							
		Iptacopan vs. Eculizumab			[redacted]	2.46	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Ravulizumab			[redacted]	2.44	[redacted]	[redacted]	[redacted]
4	Modelled treatment sequence	Eculizumab	[redacted]	15.02					
		Iptacopan	[redacted]	16.59	[redacted]	1.57	[redacted]	[redacted]	[redacted]
		Ravulizumab	[redacted]	15.03	[redacted]	-1.55	[redacted]	[redacted]	[redacted]
		Pairwise comparison							

		Iptacopan vs. Eculizumab			[redacted]	1.57	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Ravulizumab			[redacted]	1.55	[redacted]	[redacted]	[redacted]
6	**Treatment-independent health state utility values**	Iptacopan	[redacted]	17.12					
		Eculizumab	[redacted]	16.68	[redacted]	-0.44	[redacted]	[redacted]	[redacted]
		Ravulizumab	[redacted]	16.69	[redacted]	-0.43	[redacted]	[redacted]	[redacted]
		Pairwise comparison							
		Iptacopan vs. Eculizumab			[redacted]	0.44	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Ravulizumab			[redacted]	0.43	[redacted]	[redacted]	[redacted]

Table 63 Cost-effectiveness results of the EAG scenario analyses for the complement inhibitor-naïve population using 48-week data

	Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER	NHB at 20,000	NHB at 30,000
Scenario #	company base-case	Iptacopan	[redacted]	16.68	-	-	-	-	-
		Eculizumab	[redacted]	15.52	[redacted]	-1.17	[redacted]	[redacted]	[redacted]
		Ravulizumab	[redacted]	15.53	[redacted]	-1.16	[redacted]	[redacted]	[redacted]
		Pairwise comparison							
		Iptacopan vs. Eculizumab			[redacted]	1.17	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Ravulizumab			[redacted]	1.16	[redacted]	[redacted]	[redacted]
1	Hb threshold level of 10.0 g/dL	Iptacopan	[redacted]	16.63					
		Eculizumab	[redacted]	15.41	[redacted]	-1.22	[redacted]	[redacted]	[redacted]
		Ravulizumab	[redacted]	15.42	[redacted]	-1.21	[redacted]	[redacted]	[redacted]
		Pairwise comparison							
		Iptacopan vs. Eculizumab			[redacted]	1.22	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Ravulizumab			[redacted]	1.21	[redacted]	[redacted]	[redacted]
3	One treatment line (no discontinuation)	Iptacopan	[redacted]	17.42					
		Eculizumab	[redacted]	15.02	[redacted]	-2.40	[redacted]	[redacted]	[redacted]
		Ravulizumab	[redacted]	15.03	[redacted]	-2.39	[redacted]	[redacted]	[redacted]
		Pairwise comparison							
		Iptacopan vs. Eculizumab			[redacted]	2.40	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Ravulizumab			[redacted]	2.39	[redacted]	[redacted]	[redacted]
4	Modelled treatment sequence	Eculizumab	[redacted]	15.02					
		Iptacopan	[redacted]	16.68	[redacted]	1.66	[redacted]	[redacted]	[redacted]
		Ravulizumab	[redacted]	15.03	[redacted]	-1.65	[redacted]	[redacted]	[redacted]
		Pairwise comparison							

		Iptacopan vs. Eculizumab			[redacted]	1.66	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Ravulizumab			[redacted]	1.65	[redacted]	[redacted]	[redacted]
6	**Treatment-independent health state utility values**	Iptacopan	[redacted]	17.11					
		Eculizumab	[redacted]	16.68	[redacted]	-0.43	[redacted]	[redacted]	[redacted]
		Ravulizumab	[redacted]	16.69	[redacted]	-0.42	[redacted]	[redacted]	[redacted]
		Pairwise comparison							
		Iptacopan vs. Eculizumab			[redacted]	0.43	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Ravulizumab			[redacted]	0.42	[redacted]	[redacted]	[redacted]

Table 64 Cost-effectiveness results of the EAG scenario analyses for the complement inhibitor-experienced population using 24-week data

	Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER	NHB at 20,000	NHB at 30,000
Scenario #	company base-case	Eculizumab	[redacted]	12.68	-	-	-	-	-
		Iptacopan	[redacted]	14.42	[redacted]	1.74	[redacted]	[redacted]	[redacted]
		Ravulizumab	[redacted]	12.68	[redacted]	-1.74	[redacted]	[redacted]	[redacted]
		Pegcetacoplan	[redacted]	13.35	[redacted]	-1.07	[redacted]	[redacted]	[redacted]
		Pairwise comparison							
		Iptacopan vs. Eculizumab			[redacted]	1.74	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Ravulizumab			[redacted]	1.74	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Pegcetacoplan			[redacted]	1.07	[redacted]	[redacted]	[redacted]
1	Hb threshold level of 10.0 g/dL	Eculizumab	[redacted]	12.86	-	-	-	-	-
		Iptacopan	[redacted]	14.44	[redacted]	1.58	[redacted]	[redacted]	[redacted]
		Ravulizumab	[redacted]	12.86	[redacted]	-1.58	[redacted]	[redacted]	[redacted]
		Pegcetacoplan	[redacted]	13.47	[redacted]	-0.98	[redacted]	[redacted]	[redacted]
		Pairwise comparison							
		Iptacopan vs. Eculizumab			[redacted]	1.58	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Ravulizumab			[redacted]	1.58	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Pegcetacoplan			[redacted]	0.98	[redacted]	[redacted]	[redacted]
2	Transition probabilities from PEGASUS for C5 inhibitors	Eculizumab	[redacted]	12.54	-	-	-	-	-
		Iptacopan	[redacted]	14.37	[redacted]	1.84	[redacted]	[redacted]	[redacted]
		Ravulizumab	[redacted]	12.54	[redacted]	-1.84	[redacted]	[redacted]	[redacted]
		Pegcetacoplan	[redacted]	13.24	[redacted]	-1.13	[redacted]	[redacted]	[redacted]
		Pairwise comparison							
		Iptacopan vs. Eculizumab			[redacted]	1.84	[redacted]	[redacted]	[redacted]

		Iptacopan vs. Ravulizumab			[redacted]	1.84	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Pegcetacoplan			[redacted]	1.13	[redacted]	[redacted]	[redacted]
3	**One treatment line (no discontinuation)**	Iptacopan	[redacted]	15.29	-	-	-	-	-
		Eculizumab	[redacted]	12.68	[redacted]	-2.61	[redacted]	[redacted]	[redacted]
		Pegcetacoplan	[redacted]	15.26	[redacted]	-0.03	[redacted]	[redacted]	[redacted]
		Ravulizumab	[redacted]	12.68	[redacted]	-2.61	[redacted]	[redacted]	[redacted]
		Pairwise comparison							
		Iptacopan vs. Eculizumab			[redacted]	2.61	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Ravulizumab			[redacted]	2.61	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Pegcetacoplan			[redacted]	0.03	[redacted]	[redacted]	[redacted]
5a	**Same discontinuation rates for iptacopan and pegcetacoplan (3.43% per year)**	Eculizumab	[redacted]	12.68	-	-	-	-	-
		Iptacopan	[redacted]	14.42	[redacted]	1.74	[redacted]	[redacted]	[redacted]
		Ravulizumab	[redacted]	12.68	[redacted]	-1.74	[redacted]	[redacted]	[redacted]
		Pegcetacoplan	[redacted]	14.40	[redacted]	-0.02	[redacted]	[redacted]	[redacted]
		Pairwise comparison							
		Iptacopan vs. Eculizumab			[redacted]	1.74	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Ravulizumab			[redacted]	1.74	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Pegcetacoplan			[redacted]	0.02	[redacted]	[redacted]	[redacted]
5b	**Higher discontinuation rate for pegcetacoplan of 5% per year compared to iptacopan**	Eculizumab	[redacted]	12.68	-	-	-	-	-
		Iptacopan	[redacted]	14.42	[redacted]	1.74	[redacted]	[redacted]	[redacted]
		Ravulizumab	[redacted]	12.68	[redacted]	-1.74	[redacted]	[redacted]	[redacted]
		Pegcetacoplan	[redacted]	14.15	[redacted]	-0.27	[redacted]	[redacted]	[redacted]
		Pairwise comparison							
		Iptacopan vs. Eculizumab			[redacted]	1.74	[redacted]	[redacted]	[redacted]

		Iptacopan vs. Ravulizumab			[redacted]	1.74	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Pegcetacoplan			[redacted]	0.27	[redacted]	[redacted]	[redacted]
5c	**Higher discontinuation rate for pegcetacoplan of 10% per year compared to iptacopan**	Eculizumab	[redacted]	12.68	-	-	-	-	-
		Iptacopan	[redacted]	14.42	[redacted]	1.74	[redacted]	[redacted]	[redacted]
		Ravulizumab	[redacted]	12.68	[redacted]	-1.74	[redacted]	[redacted]	[redacted]
		Pegcetacoplan	[redacted]	13.65	[redacted]	-0.77	[redacted]	[redacted]	[redacted]
		Pairwise comparison							
		Iptacopan vs. Eculizumab			[redacted]	1.74	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Ravulizumab			[redacted]	1.74	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Pegcetacoplan			[redacted]	0.77	[redacted]	[redacted]	[redacted]
6	**Treatment-independent health state utility values**	Eculizumab	[redacted]	13.51	-	-	-	-	-
		Iptacopan	[redacted]	14.68	[redacted]	1.17	[redacted]	[redacted]	[redacted]
		Ravulizumab	[redacted]	13.51	[redacted]	-1.17	[redacted]	[redacted]	[redacted]
		Pegcetacoplan	[redacted]	13.95	[redacted]	-0.72	[redacted]	[redacted]	[redacted]
		Pairwise comparison							
		Iptacopan vs. Eculizumab			[redacted]	1.17	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Ravulizumab			[redacted]	1.17	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Pegcetacoplan			[redacted]	0.72	[redacted]	[redacted]	[redacted]
7	**Exclusion of concomitant eculizumab acquisition costs for patients initiating pegcetacoplan**	Eculizumab	[redacted]	12.68	-	-	-	-	-
		Iptacopan	[redacted]	14.42	[redacted]	1.74	[redacted]	[redacted]	[redacted]
		Ravulizumab	[redacted]	12.68	[redacted]	-1.74	[redacted]	[redacted]	[redacted]
		Pegcetacoplan	[redacted]	13.35	[redacted]	-1.07	[redacted]	[redacted]	[redacted]
		Pairwise comparison							
		Iptacopan vs. Eculizumab			[redacted]	1.74	[redacted]	[redacted]	[redacted]

		Iptacopan vs. Ravulizumab	[redacted]	1.74	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Pegcetacoplan	[redacted]	1.07	[redacted]	[redacted]	[redacted]

Table 65 Cost-effectiveness results of the EAG scenario analyses for the complement inhibitor-experienced population using 48-week data

	Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER	NHB at 20,000	NHB at 30,000
Scenario #	company base-case	Iptacopan	[redacted]	14.47	-	-	-	-	-
		Eculizumab	[redacted]	12.60	[redacted]	-1.86	[redacted]	[redacted]	[redacted]
		Ravulizumab	[redacted]	12.60	[redacted]	-1.86	[redacted]	[redacted]	[redacted]
		Pegcetacoplan	[redacted]	13.29	[redacted]	-1.18	[redacted]	[redacted]	[redacted]
		Pairwise comparison							
		Iptacopan vs. Eculizumab			[redacted]	1.86	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Ravulizumab			[redacted]	1.86	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Pegcetacoplan			[redacted]	1.18	[redacted]	[redacted]	[redacted]
1	Hb threshold level of 10.0 g/dL	Iptacopan	[redacted]	14.50	-	-	-	-	-
		Eculizumab	[redacted]	12.68	[redacted]	-1.82	[redacted]	[redacted]	[redacted]
		Ravulizumab	[redacted]	12.68	[redacted]	-1.82	[redacted]	[redacted]	[redacted]
		Pegcetacoplan	[redacted]	13.33	[redacted]	-1.17	[redacted]	[redacted]	[redacted]
		Pairwise comparison							
		Iptacopan vs. Eculizumab			[redacted]	1.82	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Ravulizumab			[redacted]	1.82	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Pegcetacoplan			[redacted]	1.17	[redacted]	[redacted]	[redacted]
2	Transition probabilities from PEGASUS for C5 inhibitors	Iptacopan	[redacted]	14.45	-	-	-	-	-
		Eculizumab	[redacted]	12.54	[redacted]	-1.91	[redacted]	[redacted]	[redacted]
		Ravulizumab	[redacted]	12.54	[redacted]	-1.91	[redacted]	[redacted]	[redacted]
		Pegcetacoplan	[redacted]	13.24	[redacted]	-1.21	[redacted]	[redacted]	[redacted]
		Pairwise comparison							
		Iptacopan vs. Eculizumab			[redacted]	1.91	[redacted]	[redacted]	[redacted]

		Iptacopan vs. Ravulizumab			[redacted]	1.91	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Pegcetacoplan			[redacted]	1.21	[redacted]	[redacted]	[redacted]
3	**One treatment line (no discontinuation)**	Iptacopan	[redacted]	15.19	-	-	-	-	-
		Eculizumab	[redacted]	12.60	[redacted]	-2.59	[redacted]	[redacted]	[redacted]
		Pegcetacoplan	[redacted]	15.26	[redacted]	0.07	[redacted]	[redacted]	[redacted]
		Ravulizumab	[redacted]	12.60	[redacted]	-2.66	[redacted]	[redacted]	[redacted]
		Pairwise comparison							
		Iptacopan vs. Eculizumab			[redacted]	2.59	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Ravulizumab			[redacted]	2.59	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Pegcetacoplan			[redacted]	-0.07	[redacted]	[redacted]	[redacted]
5a	**Same discontinuation rates for iptacopan and pegcetacoplan (2.72% per year)**	Iptacopan	[redacted]	14.47	-	-	-	-	-
		Eculizumab	[redacted]	12.60	[redacted]	-1.86	[redacted]	[redacted]	[redacted]
		Ravulizumab	[redacted]	12.60	[redacted]	-1.86	[redacted]	[redacted]	[redacted]
		Pegcetacoplan	[redacted]	14.51	[redacted]	0.05	[redacted]	[redacted]	[redacted]
		Pairwise comparison							
		Iptacopan vs. Eculizumab			[redacted]	1.86	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Ravulizumab			[redacted]	1.86	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Pegcetacoplan			[redacted]	-0.05	[redacted]	[redacted]	[redacted]
5b	**Higher discontinuation rate for pegcetacoplan of 5% per year compared to iptacopan**	Iptacopan	[redacted]	14.47	-	-	-	-	-
		Eculizumab	[redacted]	12.60	[redacted]	-1.86	[redacted]	[redacted]	[redacted]
		Ravulizumab	[redacted]	12.60	[redacted]	-1.86	[redacted]	[redacted]	[redacted]
		Pegcetacoplan	[redacted]	14.12	[redacted]	-0.35	[redacted]	[redacted]	[redacted]

		Pairwise comparison							
		Iptacopan vs. Eculizumab			[redacted]	1.86	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Ravulizumab			[redacted]	1.86	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Pegcetacoplan			[redacted]	0.35	[redacted]	[redacted]	[redacted]
5c	**Higher discontinuation rate for pegcetacoplan of 10% per year compared to iptacopan**	Iptacopan	[redacted]	14.47	-	-	-	-	-
		Eculizumab	[redacted]	12.60	[redacted]	-1.86	[redacted]	[redacted]	[redacted]
		Ravulizumab	[redacted]	12.60	[redacted]	-1.86	[redacted]	[redacted]	[redacted]
		Pegcetacoplan	[redacted]	13.61	[redacted]	-0.86	[redacted]	[redacted]	[redacted]
		Pairwise comparison							
		Iptacopan vs. Eculizumab			[redacted]	1.86	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Ravulizumab			[redacted]	1.86	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Pegcetacoplan			[redacted]	0.86	[redacted]	[redacted]	[redacted]
6	**Treatment-independent health state utility values**	Iptacopan	[redacted]	14.62	-	-	-	-	-
		Eculizumab	[redacted]	13.37	[redacted]	-1.24	[redacted]	[redacted]	[redacted]
		Ravulizumab	[redacted]	13.37	[redacted]	-1.24	[redacted]	[redacted]	[redacted]
		Pegcetacoplan	[redacted]	13.85	[redacted]	-0.76	[redacted]	[redacted]	[redacted]
		Pairwise comparison							
		Iptacopan vs. Eculizumab			[redacted]	1.24	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Ravulizumab			[redacted]	1.24	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Pegcetacoplan			[redacted]	0.76	[redacted]	[redacted]	[redacted]
7	**Exclusion of concomitant eculizumab acquisition costs for patients initiating pegcetacoplan**	Iptacopan	[redacted]	14.47	-	-	-	-	-
		Eculizumab	[redacted]	12.60	[redacted]	-1.86	[redacted]	[redacted]	[redacted]
		Ravulizumab	[redacted]	12.60	[redacted]	-1.86	[redacted]	[redacted]	[redacted]
		Pegcetacoplan	[redacted]	13.29	[redacted]	-1.18	[redacted]	[redacted]	[redacted]

		Pairwise comparison					
		Iptacopan vs. Eculizumab	[redacted]	1.86	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Ravulizumab	[redacted]	1.86	[redacted]	[redacted]	[redacted]
		Iptacopan vs. Pegcetacoplan	[redacted]	1.18	[redacted]	[redacted]	[redacted]

6.3 EAG's preferred assumptions

In the complement inhibitor-naïve population, the EAG's preferred assumptions include the following changes from the company's base case:

- The modelled treatment sequence: iptacopan to ravulizumab vs. C5 inhibitors, where C5 inhibitors are considered the current standard of care in the NHS in the treatment naïve population, rather than the company's modelled sequence of iptacopan to ravulizumab vs. C5 inhibitors to pegcetacoplan – Scenario 4;
- The use of treatment-independent health state utility values rather than treatment-specific utility values – Scenario 6.

In the complement inhibitor-experienced population with residual anaemia, the EAG's preferred assumptions include the following changes from the company's base case:

- A higher discontinuation rate for pegcetacoplan of 10% per annum compared to iptacopan of 3.43% per annum (24-week data, or 2.72% per annum in 48-week data), but lower than the company's base case discontinuation rate of 16.13% per annum for pegcetacoplan – Scenario 5c;
- The use of treatment-independent health state utility values rather than treatment-specific utility values – Scenario 6;
- Exclusion of concomitant eculizumab acquisition costs for patients initiating pegcetacoplan – Scenario 7

Table 66 and Table 67 show the cumulative impact of the EAG's preferred assumptions on the ICER in the complement inhibitor-naïve population using 24-week data and 48-week data, respectively, while Table 68 and Table 69 show the cumulative impact of the EAG's preferred assumptions on the ICER in the complement inhibitor-experienced population with residual anaemia using 24-week data and 48-week data, respectively.

In the complement inhibitor-naïve population [redacted]

In the complement inhibitor-experienced population with residual anaemia, [redacted] The change in the ICER for iptacopan compared to eculizumab using the EAG's preferred assumptions is due to the lower incremental QALY gains for iptacopan associated with using treatment-independent health state utility values. [redacted] because there is a higher relative proportion of patients requiring transfusions on eculizumab compared to iptacopan in the 48-week data vs. 24-week data. The lower discontinuation rate for pegcetacoplan of 10% per annum compared to the company's base case discontinuation rate of 16.13% per annum increases the total QALYs for pegcetacoplan, [redacted] The exclusion of concomitant eculizumab acquisition costs for patients initiating pegcetacoplan has minimal effect on the cost-effectiveness results, but the EAG considers it appropriate to exclude these costs because the transition probabilities for pegcetacoplan have excluded the effects of the 4-week concomitant treatment period in the PEGASUS trial.

Table 66 Cumulative cost-effectiveness results for the EAG's preferred assumptions in the complement inhibitor-naïve population using 24-week data

Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER	NHB at 20,000	NHB at 30,000
company base-case	Iptacopan	[redacted]	16.59	-	-	-	-	-
	Eculizumab	[redacted]	15.52	[redacted]	-1.07	[redacted]	[redacted]	[redacted]
	Ravulizumab	[redacted]	15.53	[redacted]	-1.06	[redacted]	[redacted]	[redacted]
	Pairwise comparison							
	Iptacopan vs. Eculizumab			[redacted]	1.07	[redacted]	[redacted]	[redacted]
	Iptacopan vs. Ravulizumab			[redacted]	1.06	[redacted]	[redacted]	[redacted]
4	Eculizumab	[redacted]	15.02					
	Iptacopan	[redacted]	16.59	[redacted]	1.57	[redacted]	[redacted]	[redacted]
	Ravulizumab	[redacted]	15.03	[redacted]	-1.55	[redacted]	[redacted]	[redacted]
	Pairwise comparison							
	Iptacopan vs. Eculizumab			[redacted]	1.57	[redacted]	[redacted]	[redacted]
	Iptacopan vs. Ravulizumab			[redacted]	1.55	[redacted]	[redacted]	[redacted]
4+6 (EAG base case)	Eculizumab	[redacted]	16.51					
	Iptacopan	[redacted]	17.12	[redacted]	0.61	[redacted]	[redacted]	[redacted]
	Ravulizumab	[redacted]	16.52	[redacted]	-0.60	[redacted]	[redacted]	[redacted]
	Pairwise comparison							
	Iptacopan vs. Eculizumab			[redacted]	0.61	[redacted]	[redacted]	[redacted]
	Iptacopan vs. Ravulizumab			[redacted]	0.60	[redacted]	[redacted]	[redacted]

Table 67 Cumulative cost-effectiveness results for the EAG's preferred assumptions in the complement inhibitor-naïve population using 48-week data

Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER	NHB at 20,000	NHB at 30,000
company base-case	Iptacopan	[redacted]	16.68	-	-	-	-	-
	Eculizumab	[redacted]	15.52	[redacted]	-1.17	[redacted]	[redacted]	[redacted]
	Ravulizumab	[redacted]	15.53	[redacted]	-1.16	[redacted]	[redacted]	[redacted]
	Pairwise comparison							
	Iptacopan vs. Eculizumab			[redacted]	1.17	[redacted]	[redacted]	[redacted]
	Iptacopan vs. Ravulizumab			[redacted]	1.16	[redacted]	[redacted]	[redacted]
4	Eculizumab	[redacted]	15.02					
	Iptacopan	[redacted]	16.68	[redacted]	1.66	[redacted]	[redacted]	[redacted]
	Ravulizumab	[redacted]	15.03	[redacted]	-1.65	[redacted]	[redacted]	[redacted]
	Pairwise comparison							
	Iptacopan vs. Eculizumab			[redacted]	1.66	[redacted]	[redacted]	[redacted]
	Iptacopan vs. Ravulizumab			[redacted]	1.65	[redacted]	[redacted]	[redacted]
4+6 (EAG base case)	Eculizumab	[redacted]	16.51					
	Iptacopan	[redacted]	17.11	[redacted]	0.60	[redacted]	[redacted]	[redacted]
	Ravulizumab	[redacted]	16.52	[redacted]	-0.59	[redacted]	[redacted]	[redacted]
	Pairwise comparison							
	Iptacopan vs. Eculizumab			[redacted]	0.60	[redacted]	[redacted]	[redacted]
	Iptacopan vs. Ravulizumab			[redacted]	0.59	[redacted]	[redacted]	[redacted]

Table 68 Cumulative cost-effectiveness results for the EAG's preferred assumptions in the complement inhibitor-experienced population using 24-week data

Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER	NHB at 20,000	NHB at 30,000
company base-case	Eculizumab	[redacted]	12.68	-	-	-	-	-
	Iptacopan	[redacted]	14.42	[redacted]	1.74	[redacted]	[redacted]	[redacted]
	Ravulizumab	[redacted]	12.68	[redacted]	-1.74	[redacted]	[redacted]	[redacted]
	Pegcetacoplan	[redacted]	13.35	[redacted]	-1.07	[redacted]	[redacted]	[redacted]
	Pairwise comparison							
	Iptacopan vs. Eculizumab			[redacted]	1.74	[redacted]	[redacted]	[redacted]
	Iptacopan vs. Ravulizumab			[redacted]	1.74	[redacted]	[redacted]	[redacted]
	Iptacopan vs. Pegcetacoplan			[redacted]	1.07	[redacted]	[redacted]	[redacted]
5c	Eculizumab	[redacted]	12.68	-	-	-	-	-
	Iptacopan	[redacted]	14.42	[redacted]	1.74	[redacted]	[redacted]	[redacted]
	Ravulizumab	[redacted]	12.68	[redacted]	-1.74	[redacted]	[redacted]	[redacted]
	Pegcetacoplan	[redacted]	13.65	[redacted]	-0.77	[redacted]	[redacted]	[redacted]
	Pairwise comparison							
	Iptacopan vs. Eculizumab			[redacted]	1.74	[redacted]	[redacted]	[redacted]
	Iptacopan vs. Ravulizumab			[redacted]	1.74	[redacted]	[redacted]	[redacted]
	Iptacopan vs. Pegcetacoplan			[redacted]	0.77	[redacted]	[redacted]	[redacted]
5c+6	Eculizumab	[redacted]	13.51	-	-	-	-	-
	Iptacopan	[redacted]	14.68	[redacted]	1.17	[redacted]	[redacted]	[redacted]
	Ravulizumab	[redacted]	13.51	[redacted]	-1.17	[redacted]	[redacted]	[redacted]
	Pegcetacoplan	[redacted]	14.16	[redacted]	-0.52	[redacted]	[redacted]	[redacted]
	Pairwise comparison							
	Iptacopan vs. Eculizumab			[redacted]	1.17	[redacted]	[redacted]	[redacted]
	Iptacopan vs. Ravulizumab			[redacted]	1.17	[redacted]	[redacted]	[redacted]
	Iptacopan vs. Pegcetacoplan			[redacted]	0.52	[redacted]	[redacted]	[redacted]
5c+6+7 (EAG base case)	Eculizumab	[redacted]	13.51	-	-	-	-	-
	Iptacopan	[redacted]	14.68	[redacted]	1.17	[redacted]	[redacted]	[redacted]
	Ravulizumab	[redacted]	13.51	[redacted]	-1.17	[redacted]	[redacted]	[redacted]
	Pegcetacoplan	[redacted]	14.16	[redacted]	-0.52	[redacted]	[redacted]	[redacted]
	Pairwise comparison							
	Iptacopan vs. Eculizumab			[redacted]	1.17	[redacted]	[redacted]	[redacted]
	Iptacopan vs. Ravulizumab			[redacted]	1.17	[redacted]	[redacted]	[redacted]
	Iptacopan vs. Pegcetacoplan			[redacted]	0.52	[redacted]	[redacted]	[redacted]

Table 69 Cumulative cost-effectiveness results for the EAG's preferred assumptions in the complement inhibitor-experienced population using 48-week data

Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER	NHB at 20,000	NHB at 30,000
company base-case	Iptacopan	[redacted]	14.47	-	-	-	-	-
	Eculizumab	[redacted]	12.60	[redacted]	-1.86	[redacted]	[redacted]	[redacted]
	Ravulizumab	[redacted]	12.60	[redacted]	-1.86	[redacted]	[redacted]	[redacted]
	Pegcetacoplan	[redacted]	13.29	[redacted]	-1.18	[redacted]	[redacted]	[redacted]
	Pairwise comparison							
	Iptacopan vs. Eculizumab			[redacted]	1.86	[redacted]	[redacted]	[redacted]
	Iptacopan vs. Ravulizumab			[redacted]	1.86	[redacted]	[redacted]	[redacted]
	Iptacopan vs. Pegcetacoplan			[redacted]	1.18	[redacted]	[redacted]	[redacted]
5c	Iptacopan	[redacted]	14.47	-	-	-	-	-
	Eculizumab	[redacted]	12.60	[redacted]	-1.86	[redacted]	[redacted]	[redacted]
	Ravulizumab	[redacted]	12.60	[redacted]	-1.86	[redacted]	[redacted]	[redacted]
	Pegcetacoplan	[redacted]	13.61	[redacted]	-0.86	[redacted]	[redacted]	[redacted]
	Pairwise comparison							
	Iptacopan vs. Eculizumab			[redacted]	1.86	[redacted]	[redacted]	[redacted]
	Iptacopan vs. Ravulizumab			[redacted]	1.86	[redacted]	[redacted]	[redacted]
	Iptacopan vs. Pegcetacoplan			[redacted]	0.86	[redacted]	[redacted]	[redacted]
5c+6	Iptacopan	[redacted]	14.62	-	-	-	-	-
	Eculizumab	[redacted]	13.37	[redacted]	-1.24	[redacted]	[redacted]	[redacted]
	Ravulizumab	[redacted]	13.37	[redacted]	-1.24	[redacted]	[redacted]	[redacted]
	Pegcetacoplan	[redacted]	14.07	[redacted]	-0.55	[redacted]	[redacted]	[redacted]
	Pairwise comparison							
	Iptacopan vs. Eculizumab			[redacted]	1.24	[redacted]	[redacted]	[redacted]
	Iptacopan vs. Ravulizumab			[redacted]	1.24	[redacted]	[redacted]	[redacted]
	Iptacopan vs. Pegcetacoplan			[redacted]	0.55	[redacted]	[redacted]	[redacted]
5c+6+7 (EAG base case)	Iptacopan	[redacted]	14.62	-	-	-	-	-
	Eculizumab	[redacted]	13.37	[redacted]	-1.24	[redacted]	[redacted]	[redacted]
	Ravulizumab	[redacted]	13.37	[redacted]	-1.24	[redacted]	[redacted]	[redacted]
	Pegcetacoplan	[redacted]	14.07	[redacted]	-0.55	[redacted]	[redacted]	[redacted]
	Pairwise comparison							
	Iptacopan vs. Eculizumab			[redacted]	1.24	[redacted]	[redacted]	[redacted]
	Iptacopan vs. Ravulizumab			[redacted]	1.24	[redacted]	[redacted]	[redacted]
	Iptacopan vs. Pegcetacoplan			[redacted]	0.55	[redacted]	[redacted]	[redacted]

6.4 Conclusions of the cost effectiveness section

The company submitted a decision model to compare the cost-effectiveness of iptacopan with C5 inhibitors in adult patients with PNH who are naïve to treatment with complement inhibitors, and to compare the cost-effectiveness of iptacopan with pegcetacoplan and C5 inhibitors in a complement inhibitor-experienced PNH adult population with residual anaemia. The company's approach relies heavily on the approach used in NICE technology appraisal TA778 for pegcetacoplan, with the same model structure, cycle length and modelled health states and similarities in the approach used to estimate treatment effectiveness, in terms of treatment-specific transition probabilities between health states, while the populations are aligned with the anticipated license for iptacopan and the source of data used to inform treatment effectiveness, discontinuations, utility values and costs for iptacopan is based on evidence from APPOINT-PNH (single arm trial) in the naïve population and APPLY-PNH in the experienced population. Data from the APPEX study and PEGASUS trial are used to support the effectiveness of C5 inhibitors in the naïve population and pegcetacoplan in the experienced population, respectively.

The EAG's primary concern in relation to the data used in the cost-effectiveness model is that there is no direct link between the iptacopan trial endpoints and the transition probabilities used in the model, which makes a comparison and validation of the transition probabilities informing the cost-effectiveness of iptacopan challenging as it is not clear if the model findings are in line with the primary and secondary outcomes of the trials. A further key concern relates to the lack of randomisation and indirect comparison of iptacopan with C5 inhibitors in the complement inhibitor-naïve population, and iptacopan with pegcetacoplan in the complement inhibitor-experienced population with residual anaemia. Importantly, the EAG is concerned about the validity of any comparison of iptacopan with pegcetacoplan because of the differences observed in outcomes for C5 inhibitors between the APPLY-PNH and PEGASUS trials. The EAG believes that these differences are not a result of the 4-week run-in period of the PEGASUS trial when concomitant eculizumab and pegcetacoplan was given because the transition probabilities from the PEGASUS trial are based on week 4 to week 16 of the randomised controlled period of the trial in order to mitigate any 'hangover' effect of the run-in period because the efficacy data from the PEGASUS trial shows that after week 4 of the randomised controlled period, haemoglobin stabilises for both pegcetacoplan and eculizumab. Therefore, the EAG is concerned about the validity of the comparison of iptacopan and pegcetacoplan from two distinctively different trial populations.

A further concern relates to the assessment time period (or data cut) from the iptacopan trials that is used to inform the cost-effectiveness of iptacopan and the comparator complement inhibitors. The 48-week data provides a longer period of follow-up to inform the transition probabilities, discontinuation

and BTH events rates for iptacopan, but the 24-week data from APPLY-PNH is used for C5 inhibitors in the 48-week data analysis and the same transition probabilities for C5 inhibitors and pegcetacoplan are used in the 24-week and 48-week data analysis. In addition, the 24-week data for utility values from the APPOINT-PNH and APPLY-PNH trials is used for iptacopan in the 48-week data analysis. While the EAG considers the use of longer follow-up data to be best practice, in general, the EAG is concerned that the 48-week data analysis is not making a fair comparison of iptacopan and the comparator complement inhibitors because of the variation in length of assessment time period used for the comparators and inconsistencies in data cut used across modelled parameters.

An annual probability of discontinuation for iptacopan (3.43% using 24-week data, or 2.72% using 48-week data) and pegcetacoplan (16.13%) was informed by treatment-specific all-cause discontinuation rates from APPLY-PNH and PEGASUS, respectively. The EAG notes that the cost-effectiveness of iptacopan and pegcetacoplan is largely determined by the differential discontinuation rates between the two treatments because after discontinuation from either iptacopan or pegcetacoplan the model assumes that patients switch to ravulizumab, which is associated with a higher percentage of patients with uncontrolled anaemia and a higher percentage of patients' transfusion dependent. The EAG is concerned that the use of treatment-specific annual discontinuation rates from the short-term clinical trials may not reflect long-term treatment persistence, or how patients are managed in the NHS.

The model uses treatment-specific health state utility values and the difference in utility between iptacopan and C5 inhibitors is substantial despite being in the same health state. The EAG considers that the only plausible explanation for a difference in health state utility by treatment is due to the disutility associated with mode of treatment administration; however, the EAG does not consider the magnitude of the difference in treatment-dependent utility values between iptacopan and C5 inhibitors to be realistic. The underlying evidence for this difference is weak and the baseline utility value (utility value at Day 1) differed substantially between patients treated with iptacopan and C5 inhibitors in APPLY-PNH indicating that the difference in the utility values could be due to small sample sizes and differences in the characteristics of patients treated with iptacopan and C5 inhibitors. The EAG considers it more appropriate to use treatment-independent health state utility values because the benefits of treatment are already captured in the transition probabilities between health states.

The modelled assumptions with the largest impact on the cost-effectiveness results in the complement inhibitor-naïve population are those relating to: (i) subsequent line of treatment after complement inhibitor initiation, and (ii) treatment-independent health state utility values, while in the complement inhibitor-experienced population with residual anaemia it is those relating to: (i) rates of treatment

discontinuation; (ii) treatment-independent health state utility values; and (iii) transition probabilities for C5 inhibitors.

In the complement inhibitor-naïve population, the EAG's preferred assumptions include the following changes from the company's base case: (i) modelled treatment sequence (iptacopan to ravulizumab vs. C5 inhibitors) and (ii) use of treatment-independent health state utility values rather than treatment-specific utility values. The resulting ICER for the comparison of iptacopan and ravulizumab is unchanged from the company's base case, [redacted] The resulting ICER for the comparison of iptacopan and eculizumab is [redacted] using 24-week data and [redacted] using 48-week data, which differs from the company's base case [redacted]

In the complement inhibitor-experienced population with residual anaemia, the EAG's preferred assumptions include: (i) a higher discontinuation rate for pegcetacoplan of 10% per annum compared to iptacopan of 3.43% per annum (24-week data, or 2.72% per annum in 48-week data), but lower than the company's base case discontinuation rate of 16.13% per annum; (ii) use of treatment-independent health state utility values rather than treatment-specific utility values; and (iii) exclusion of concomitant eculizumab acquisition costs for patients initiating pegcetacoplan. The resulting ICER for the comparison of iptacopan and ravulizumab or pegcetacoplan is unchanged from the company's base case, [redacted]. The resulting ICER for iptacopan compared to eculizumab is [redacted] using 24-week data [redacted] using 48-week data.

7 SEVERITY MODIFIER

The CS demonstrates that severity weights are not applicable for the two populations of adult patients with PNH. The EAG considers this to be appropriate based on the QALY shortfall calculations, which support a QALY severity weight of 1.0.

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APPENDICES

Appendix 1 Appraisal of evidence searches

Clinical Evidence Searches – Appendix D

Search strategy:

The original company submission included searches to identify clinical evidence for adult patients with paroxysmal nocturnal haemoglobinuria (PNH). A description of the searches and some of the search strategies were included in Appendix D, pp. 1-16.

In response to the EAG's PfCs (points for clarification), the company provided additional search strategies and corrections to errors identified by the EAG.

Strategies for the indirect treatment comparison (ITC) report were not included in the document, which was raised as a PfC. In their response, the company clarified that no separate searches were conducted for the ITC and that relevant trials were taken from the results of the clinical evidence searches included in Appendix D, pp. 1-16. Appropriate search terms for comparators were included in these clinical evidence searches. More thorough documentation for the ITC would have been helpful in appraising the methodology.

Table 70 EAG appraisal of evidence identification

TOPIC	EAG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	YES	In the original company submission, the search strategies for conference proceedings; clinical trial registries; health technology agencies (HTA); and health authority websites were not provided. This was raised as a PfC. In their response, the company provided further details of these sources, the date of the searches, and the terms used. However, these searches were not formally documented with the number of hits per source. In the original company submission, the PRISMA did not include the number of records obtained from: the searches of conference proceedings; clinical trial registries; health technology agencies (HTA); and health authority websites. This was raised as a PfC. In their response, the company provided a detailed PRISMA.

Were appropriate sources searched?	YES	A limited selection of relevant databases and conference proceedings were searched. No dedicated HTA databases were searched (though HTA sources were searched).
Was the timespan of the searches appropriate?	YES	The searches were not limited by date in the strategy and undertaken recently on 20th April 2023.
Were appropriate parts of the PICOS included in the search strategies?	PARTLY	The searches combined the population with the comparators and the study types. As PNH is a rare disorder it would have been more sensitive to combine the population with fewer or no additional PICO elements. For example, it would have been better to use the following PICO structures: • Population AND Study Types • Population AND (Comparators OR Study Types)
Were appropriate search terms used?	PARTLY	Search terms for the condition were relatively comprehensive, although the population term: marchiafava micheli syndrome was missed in all strategies. In addition, line 2 of the Embase strategy contains the search term: 'paroxysmal nocturnal h? emoglobinuria' with a space after the optional wildcard symbol (?). This error was raised as a PfC. In their response, the company clarified that no relevant papers were missed as a result. Numerous search terms were missed for the intervention and no specific biosimilars were searched for eculizumab. As an example, the following are some missed terms for eculizumab: abp959, bcd148, bow080, elizaria, isu305, monoclonal antibody 5G1.1. However, there are missed drug names for many of the interventions. This was raised as a PfC. In their response, the company clarified that no relevant papers were missed as a result. It is more sensitive if intervention search terms with numbers are searched for with a space, without a space, and with a hyphen, in order to pick up variations of the drug name. It would have been more sensitive to truncate drug names to pick up names with symbols such as (R) on the end. It would also have been more sensitive to search drug names with additional field codes for drugs on Embase. In the Embase strategy all the intervention Emtree headings are exploded but there are no narrower terms, so this is misleading. In the Embase strategy the Emtree term randomized controlled trial/ is not used.
Were any search restrictions applied appropriate?	PARTLY	It would have been more sensitive to remove non-English language papers during screening rather than in the search strategy.
Were any search filters used validated and referenced?	PARTLY	Search filters were used but not fully referenced, as there is no description of which specific filter was used. The filter was not validated as it was modified.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

Cost and Healthcare Resource Identification, Measurement, and Valuation Searches – Appendix I

Search strategy:

The original company submission included searches to identify cost and healthcare resource identification, measurement, and valuation studies for adult patients with paroxysmal nocturnal haemoglobinuria (PNH). A description of the searches and some of the search strategies were included in Appendix I, pp. 1-10.

In response to the EAG's PfCs (points for clarification), the company provided additional search strategies and further information.

Table 71 EAG appraisal of evidence identification

TOPIC	EAG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	YES	In the original company submission, the search strategies for conference proceedings; health technology agencies (HTA); and grey literature databases were not provided. This was raised as a PfC. In their response, the company provided further details of these sources, the date of the searches, and the terms used. However, these searches were not formally documented with the number of hits per source. In the original company submission, the PRISMA did not include the number of records obtained from grey literature databases. This was raised as a PfC. In their response, the company provided a detailed PRISMA.
Were appropriate sources searched?	YES	A good selection of relevant databases and sources were searched.
Was the timespan of the searches appropriate?	YES	The searches were limited from 2014 – Current.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the population with the study type.
Were appropriate search terms used?	YES	Search terms for the condition were relatively comprehensive, although the population term: marchiafava micheli syndrome was missed in all strategies.
Were any search restrictions applied appropriate?	PARTLY	It would have been more sensitive to remove non-English language papers during screening rather than in the search strategy.
Were any search filters used validated and referenced?	PARTLY	Search filters were used but not fully referenced, as there is no description of which specific filter was used. The filter is not validated as it has been modified.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

Cost-Effectiveness Searches – Appendix G

Search strategy:

The original company submission included searches to identify cost-effectiveness studies for adult patients with paroxysmal nocturnal haemoglobinuria (PNH). A description of the searches and some of the search strategies were included in Appendix G, pp. 1-11.

In response to the EAG's PfCs (points for clarification), the company provided additional search strategies and corrections to errors identified by the EAG.

Table 72 EAG appraisal of evidence identification

TOPIC	EAG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	YES	In the original company submission, the search strategies for conference proceedings; health technology agencies (HTA); and grey literature databases were not provided. This was raised as a PfC. In their response, the company provided further details of these sources, the date of the searches, and the terms used. However, these searches were not formally documented with the number of hits per source. In the original company submission, the PRISMA did not include the number of records obtained from grey literature databases. This was raised as a PfC. In their response, the company provided a detailed PRISMA.
Were appropriate sources searched?	YES	A limited selection of relevant databases and conference proceedings were searched.
Was the timespan of the searches appropriate?	YES	The searches were not limited by date in the strategy and were quite recent.
Were appropriate parts of the PICOS included in the search strategies?	PARTLY	The searches combined the population with the comparators and the study type. As paroxysmal nocturnal haemoglobinuria is a rare disorder it would have been more sensitive to combine the population with fewer or no additional PICO elements.
Were appropriate search terms used?	PARTLY	Search terms for the condition were relatively comprehensive, although the population term: marchiafava micheli syndrome was missed in all strategies. In addition, line 2 of the Embase strategy contains the search term: 'paroxysmal nocturnal h? emoglobinuria' with a space after the optional wildcard symbol (?). This error was raised as a PfC. In their response, the company clarified that no relevant papers were missed as a result. Numerous search terms were missed for the intervention and no specific biosimilars were searched for eculizumab. As an example, the following are some missed terms for eculizumab: abp959, bcd148, bow080, elizaria, isu305, monoclonal antibody 5G1.1. However, there are missed drug names for many

		of the interventions. This was raised as a PfC. In their response, the company clarified that no relevant papers were missed as a result. It is more sensitive if intervention search terms with numbers are searched for with a space, without a space, and with a hyphen, in order to pick up variations of the drug name. It would have been more sensitive to truncate drug names to pick up names with symbols such as (R) on the end. It would also have been more sensitive to search drug names with additional field codes for drugs on Embase. In the Embase strategy all of the intervention Emtree headings are exploded but there are no narrower terms, so this is misleading.
Were any search restrictions applied appropriate?	PARTLY	It would have been more sensitive to remove non-English language papers during screening rather than in the search strategy.
Were any search filters used validated and referenced?	PARTLY	Search filters were used but not fully referenced, as there is no description of which specific filter was used. The filter was not validated as it was modified.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

Health-Related Quality of Life Searches – Appendix H

Search strategy:

The original company submission included searches to identify health-related quality of life studies evidence for adult patients with paroxysmal nocturnal haemoglobinuria (PNH). A description of the searches and some of the search strategies were included in Appendix H, pp. 1-11.

In response to the EAG's PfCs (points for clarification), the company provided additional search strategies and further information.

Table 73 EAG appraisal of evidence identification

TOPIC	EAG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	YES	In the original company submission, the search strategies for conference proceedings; health technology agencies (HTA); and grey literature databases were not provided. This was raised as a PfC. In their response, the company provided further details of these sources, the date of the searches, and the terms used. However, these searches were not formally documented with the number of hits per source. In the original company submission, the PRISMA did not include the number of records obtained from grey literature databases. This was raised as a PfC. In their response, the company provided a detailed PRISMA.
Were appropriate sources searched?	YES	A good selection of relevant databases and sources were searched.
Was the timespan of the searches appropriate?	YES	The searches were not limited by date in the strategy and were quite recent.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the population with the study type.
Were appropriate search terms used?	YES	Search terms for the condition were relatively comprehensive, although the population term: marchiafava micheli syndrome was missed in all strategies.
Were any search restrictions applied appropriate?	PARTLY	It would have been more sensitive to remove non-English language papers during screening rather than in the search strategy.
Were any search filters used validated and referenced?	PARTLY	Search filters were used but not fully referenced, as there is no description of which specific filter was used. It is not specified if the filter is validated.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

Single Technology Appraisal

Iptacopan for treating paroxysmal nocturnal haemoglobinuria [ID6176]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Wednesday 7 February 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Modelling of treatment discontinuation and switch in naïve population

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 97, paragraph one, sentence one: "[…], but the modelled one-time discontinuation at 24 weeks for C5 inhibitors (modelled to affect 30% of patients) in the complement inhibitor-naïve population to pegcetacoplan is likely to mask the cost-effectiveness of iptacopan in the naïve population because this subset of patients would be considered complement inhibitor-experienced with residual anaemia and pegcetacoplan is not a relevant comparator for the naïve population given its licence and NICE recommendation as per TA778." Page 97, last sentence, and page 98, first sentence: "[…] while a one-time discontinuation at 24 weeks is considered for C5 inhibitors in the complement inhibitor-naïve population for 30% of patients." Page 109, paragraph one, sentence one: "[…] while 30% of patients initially treated with C5 inhibitors discontinue treatment at 24 weeks and receive pegcetacoplan and remain	The EAG report states that in the company's model for the complement inhibitor-naïve population, 30% of patients discontinue C5 inhibitor treatment at 24 weeks and switch to pegcetacoplan. This is incorrect, since discontinuation and switch to pegcetacoplan is modelled only for 30% of patients who still have anaemia or receive transfusions after 24 weeks of C5 inhibitor treatment (one-time discontinuation applied exclusively to patients in 'Transfusion' or 'No Transfusion and Anaemia' health states after 24 weeks in the model). Details are provided in the company submission, section B.3.3.3 Discontinuation and subsequent therapy, page 118, paragraph 2, and Table 44, page 119. Please amend text accordingly in the EAG report, on page numbers as listed in column one of this table,	The EAG's description of the company's approach to modelling C5 inhibitor discontinuation and treatment switch in the complement inhibitor-naïve population is factually inaccurate.	The EAG have amended the text throughout the report to make it clear that the one-time discontinuation of C5 inhibitors at 24 weeks is for 30% of patients who still have anaemia or receive transfusions.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
on these subsequent therapies over their remaining lifetime." Page 150, paragraph three, sentence four: "Importantly, the modelled one-time discontinuation at 24 weeks for C5 inhibitors to pegcetacoplan (modelled to affect 30% of patients) is likely to mask the cost-effectiveness of iptacopan in the complement inhibitor-naïve population because this subset of patients become complement inhibitor-experienced with residual anaemia." Page 153 (labelled as page 166 in the document), paragraph two, sentence one: "[…] compared to the company's base case modelled treatment sequence that includes discontinuation from C5 inhibitors to pegcetacoplan at 24 weeks for 30% of patients"	for an accurate representation of the company's model.		
Page 97, paragraph one, sentence one: "[…], but the modelled one-time discontinuation at 24 weeks for C5 inhibitors (modelled to affect 30% of patients) in the complement inhibitor-naïve population to pegcetacoplan is likely to mask the cost-	Please remove all text stating that the company's modelling approach for C5 inhibitor discontinuation and treatment switch in the naïve population "is likely to mask the cost-effectiveness of iptacopan",	The statements underlying the EAG's conclusion are factually inaccurate, which also makes the	The EAG have amended the text throughout to say "is likely to mask the cost-effectiveness of

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
effectiveness of iptacopan in the naïve population because this subset of patients would be considered complement inhibitor-experienced with residual anaemia and pegcetacoplan is not a relevant comparator for the naïve population given its licence and NICE recommendation as per TA778. item 1. The modelled treatment sequence in the complement inhibitor-naïve population with pegcetacoplan as a subsequent line of treatment after one-time discontinuation from C5 inhibitors at 24 weeks is likely to mask the cost-effectiveness of iptacopan in the naïve population." Page 110, paragraph one, sentence four: "The company's modelled one-time discontinuation at 24 weeks for C5 inhibitors to pegcetacoplan in the naïve population is likely to mask the cost-effectiveness of iptacopan in this population because these patients would be considered complement inhibitor-experienced with residual anaemia and pegcetacoplan is not a relevant comparator for the naïve population." Page 148, Table 61, item 1:	and justifications "because this subset of patients would be considered complement inhibitor-experienced with residual anaemia and pegcetacoplan is not a relevant comparator for the naïve population given its licence and NICE recommendation as per TA778" (and similar wording). As highlighted in the previous row, discontinuation of C5 inhibitor treatment in the naïve population and subsequent switch to pegcetacoplan was only modelled for patients who still have anaemia or receive transfusions after C5 inhibitor treatment. Upon discontinuation, these patients represent a C5 inhibitor-experienced population with residual anaemia who are eligible to switch to pegcetacoplan. The company's modelling approach thus correctly reflects the	conclusion factually inaccurate.	iptacopan **relative to C5 inhibitors** in the complement inhibitor-naïve population". The EAG considers this to be factually accurate because the outcomes of the comparator arm C5 inhibitors is affected by subsequent line pegcetacoplan, which is only included as a comparator in the complement-inhibitor experienced population. The subset of patients who discontinue to

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"The modelled treatment sequence in the complement inhibitor-naïve population with pegcetacoplan as a subsequent line of treatment after one-time discontinuation from C5 inhibitors at 24 weeks is likely to mask the cost-effectiveness of iptacopan in the naïve population." Page 150, paragraph one, sentence two: "[…] however, the EAG notes a number of inconsistencies in the approach used by the company to model subsequent treatments that are likely to mask the cost-effectiveness of iptacopan in the complement inhibitor-naïve population." Page 150, paragraph three, sentence four: "Importantly, the modelled one-time discontinuation at 24 weeks for C5 inhibitors to pegcetacoplan (modelled to affect 30% of patients) is likely to mask the cost-effectiveness of iptacopan in the complement inhibitor-naïve population because this subset of patients become complement inhibitor-experienced with residual anaemia."	pegcetacoplan licence and NICE recommendation as per TA778, as well as UK clinical practice as confirmed by several UK clinicians (see company submission page 118, but also EAG report pages 28-29, 67, and 96). As the company's modelling approach reflects UK clinical practice, it does not mask cost-effectiveness, but rather is an element of it.		pegcetacoplan are now part of the complement-inhibitor experienced population, where the cost-effectiveness of iptacopan is assessed separately in the complement-inhibitor experienced population.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 96, paragraph two: "For the complement inhibitor-naïve population, the EAG considers it more appropriate to model the sequence: iptacopan to ravulizumab vs. ravulizumab (no discontinuation) [or eculizumab, with no discontinuation, as both ravulizumab and eculizumab are assumed to have equal clinical effectiveness], and using the transition probabilities from the naïve population for C5 inhibitors at first and second-line, in order to avoid the inconsistency in approach used by the company and because the reasons for discontinuation have not been explicitly modelled."	We ask the EAG to revise this statement, taking into account how discontinuation of C5 inhibitors in the complement inhibitor-naïve population has been implemented in the company's model, with 30% of patients in the 'Transfusion' or 'No Transfusion and Anaemia' health states after 24 weeks switching to pegcetacoplan (see above). Pegcetacoplan is only indicated and recommended by NICE (TA778) for patients who are anaemic after treatment with a C5 inhibitor, i.e. for treatment switches due to inadequate efficacy of C5 inhibitors. For iptacopan, all discontinuations in the Phase 3 trials were unrelated to treatment efficacy (two discontinuations due to pregnancy) and it was assumed that patients would discontinue equally from all health states (see response to clarification question B10).	The EAG's statement is inaccurate, since reasons for discontinuation were considered in modelling discontinuation and treatment switches differently between iptacopan and C5 inhibitors in the complement inhibitor-naïve population.	The EAG have deleted the part of the sentence "and because the reasons for discontinuation have not been explicitly modelled." The key point that the EAG is making in this statement is that the company have been inconsistent in their approach to modelling subsequent therapies. In the iptacopan arm, after treatment discontinuation, the company have used the transition probabilities from

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			the naïve population for ravulizumab, whereas in the C5 inhibitors arm, after treatment discontinuation, the company have used the transition probabilities from the complement-inhibitor experienced population for pegcetacoplan. The EAG's modelled treatment sequence avoids this inconsistency and also resolves the issue above, where the cost-effectiveness of iptacopan relative to C5 inhibitors in

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			the complement inhibitor-naïve population is affected by outcomes in the complement inhibitor-experienced population, even though the cost-effectiveness of the treatments are assessed separately in the complement inhibitor-experienced population.

Issue 2 Utilities

Description of problem	Description of proposed amendment	Justification for amendment	EAGresponse
Page 22, Issue 9 Table, row three:	Please add information about utility decrements associated with treatment	The current wording in the EAG report omits a key component of the utility modelling approach in	The EAG does not consider these statements to be factually inaccurate. The

Description of problem	Description of proposed amendment	Justification for amendment	EAGresponse
"The EAG considers it more appropriate to use treatment-independent health state utility values, which is in line with the approach used in TA778 and TA698." Page 90, bullet point three: "Treatment-specific utility values by health state are used in the company's model, whereas treatment-independent health state utility values were accepted by the appraisal committee in TA778 and TA698." Page 128, bullet point one: "The company used treatment-specific utility values while treatment-independent values were used in TA778 and TA698." Page 128, Table 46 Page 152, paragraph one, sentence six: "Furthermore, treatment-independent health state utility	administration being included and accepted in TA778 and TA698 in the EAG report.	previous PNH appraisals and is thus factually inaccurate. The EAG's summary of the utility modelling approach used in TA778 and TA698 omits that in these appraisals, utility decrements associated with treatment administration were included in the model and accepted by the NICE committees. This information is summarised in the company submission, section B.3.4.5.1 Disutility associated with mode of administration (page 124). This was considered accordingly in the company's scenario analysis using treatment-independent health state utility values, applying disutilities associated with treatment administration of eculizumab, in line with the approach taken in TA779 and TA698.	statements are referring to the health state utility values. Treatment-independent health state utility values were used in TA778 and TA698. Therefore, these statements are factually correct. In the previous appraisals of TA778 and TA698, a utility decrement associated with treatment administration was only included for eculizumab, not ravulizumab or pegcetacoplan. The EAG report clearly states "The EAG considers that the only plausible explanation for a difference in health state utility by treatment is due to the disutility associated with mode of treatment administration, where administration by IV infusion

Description of problem	Description of proposed amendment	Justification for amendment	EAGresponse
values were used in TA778 (pegcetacoplan) and TA698 (ravulizumab).”			may be associated with a disutility compared with oral therapy; however, the EAG does not consider the magnitude of the difference in treatment-dependent utility values between iptacopan and C5 inhibitors to be realistic.”
Page 138 and 139, Table 56, multiple rows: “Disutility associated with treatment administration”	Please amend to: “Disutility associated with **BTH**”	The current labelling is incorrect. Values reflected in Table 56 of the EAG report represent QALY losses from disutilities associated with breakthrough haemolysis (BTH). The company’s base case did not apply disutilities associated with treatment administration, given the use of treatment-specific health state utility values, to avoid double-counting. (Only the company’s scenario analysis using treatment-independent health state utility values applied disutilities associated with treatment administration, in line with the	Thank you for noting this. This was a typo, which was copied across multiple tables. The EAG have corrected the typo throughout.

Description of problem	Description of proposed amendment	Justification for amendment	EAGresponse
		approach taken in TA779 and TA698.)	
Page 15, bullet point three: "Treatment-specific health state utility values are included in the company's base case, with iptacopan modelled to have better health-related quality of life compared to treatment with C5 inhibitors due to its oral administration."	Please amend to: "Treatment-specific health state utility values are included in the company's base case, with iptacopan modelled to have better health-related quality of life compared to treatment with C5 inhibitors ~~due to its oral administration~~."	This statement does not correctly reflect the company's considerations in including treatment-specific utility values in the base case. While we acknowledge the EAG's view that the difference in health state utility values between iptacopan and C5 inhibitors is due to the disutility associated with mode of treatment administration, the company's view is that also higher mean Hb and higher mean FACIT-Fatigue values for iptacopan-treated patients compared to C5 inhibitor-treated patients within the same health state contribute to better quality of life (see response to clarification question B20).	The EAG have amended the statement by removing "due to its oral administration".
Page 127, paragraph four, sentence four: "However, the provided evidence is assessed as weak given the	Please revise this statement to reflect the number of observations in states other than 'No	The current statement selects only the health state with the starkest difference in the number of observations, and does not	This statement is not factually inaccurate. The EAG report provides the number of observations for

Description of problem	Description of proposed amendment	Justification for amendment	EAGresponse
substantial differences in the datasets between treatments. For example, the mean Hb for the health state 'No transfusion no anaemia' was based on 568 observations for iptacopan and only 8 observations for C5 inhibitors."	transfusion and no anaemia'.	provide a balanced description of the available evidence. The EAG concludes that this is weak evidence and uses this to justify the statement that "the only plausible explanation for a difference in health state utility by treatment is due to the disutility associated with mode of treatment administration". However, a reader given the full context may come to a different conclusion from the EAG.	the other health states (see Tables 42 and 43). The EAG also notes that there is a stark difference in the number of observations for iptacopan and C5 inhibitors across all the health states.
Page 128: "item 6. The EAG considers it more appropriate to use treatment-independent health state utility values rather than treatment-specific utility values because the benefits of treatment are already captured in the transitions between health states."	We ask the EAG to revise this statement. Treatment-independent health state utility values do not capture benefits associated with different modes of administration, which had been accepted by the NICE committees in the previous PNH appraisals TA778 and TA698, or the impact of higher mean Hb and	The EAG's statement is inconsistent with conclusions from previous appraisals of PNH treatments in not considering the impact of mode of administration on quality of life.	As above, the EAG does not consider this statement to be factually inaccurate. Treatment-independent health state utility values were used in the previous PNH appraisals. In the previous appraisals, a utility decrement associated with treatment administration was only included for eculizumab, not ravulizumab or

Description of problem	Description of proposed amendment	Justification for amendment	EAGresponse
Page 152, paragraph one, sentence five: "The EAG considers it more appropriate to use treatment-independent health state utility values because the benefits of treatment are already captured in the transitions between health states."	higher mean FACIT-Fatigue within health states.		pegcetacoplan.

Issue 3 Indirect treatment comparisons (ITCs)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 74, Table 26, eculizumab row, last column: "Selected over TRIUMPH for main comparison on the basis of sample size, comparator (ravulizumab), similarity to APPOINT-PNH population and better reflection of complement inhibitor-naïve patients seen in UK clinical practice (CS, p.67)"	Please rearrange the sequence of elements to: "Selected over TRIUMPH for main comparison on the basis of **similarity to APPOINT-PNH population, better reflection of complement inhibitor-naïve patients seen in UK clinical practice, comparator (ravulizumab), and sample size** (CS, p.67)"	The current wording does not accurately represent the company's decision-making process, as the decision to deprioritise TRIUMPH was mainly based on the study population, rather than sample size.	Not a factual error, but rephrased as proposed.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 78, paragraph two, sentence two: "However, with the non-adjustment for baseline Hb (which is used to define anaemia) in Study 301 due to convEAGence issues encountered in the company's analysis, the substantial differences in baseline Hb could have biased the assumption of sufficient "population overlap" for MAIC."	We ask for addition of the following text: "[…] **However, as baseline Hb was lower in APPOINT-PNH compared to Study 301, this bias would be against iptacopan.**"	The current wording does not recognise the direction of the bias, which may be misleading.	Not a factual error, but additional information added as proposed.
Page 81, paragraph three, sentence four: "However, the code appeared to be correct, and the required software packages and procedures for MAIC appear to have been correctly implemented."	Please amend to: "However, the code appeared to be correct, and the required software packages and procedures for **adjusted indirect comparisons** appear to have been correctly implemented."	The current wording is not accurate to describe the indirect comparison between APPOINT-PNH and APPEX.	Amendment accepted

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 82, paragraph one, sentence three: "The prognostic factors adjusted for were age, sex, percentage transfusion free in prior 12 months, baseline LDH, baseline Hb, and history of MAVE."	Please amend to: "The prognostic factors adjusted for were age, sex, percentage transfusion free in prior 12 months, baseline LDH, baseline Hb, and **screening reticulocytes**."	The current wording lists a wrong adjustment factor, and omits one correct adjustment factor	Amendment accepted
Page 85, paragraph two, sentence two: "While the company explained their anchored ITC approach in the response to point of clarification (PfC A8), there was no justification why their approach was preferred over the standard Bucher method, which is discussed in TSD 18 as an appropriate method to use for anchored comparisons when effect modifiers are assumed to be well-balanced across studies."	Please delete this statement: ~~"While the company explained their anchored ITC approach in the response to point of clarification (PfC A8), there was no justification why their approach was preferred over the standard Bucher method, which is discussed in TSD 18 as an appropriate method to use for anchored comparisons when effect modifiers are assumed to be well-balanced across studies."~~	The EAG's statement is not accurate. Table 25 in the company submission presents a comparison of patient characteristics in the two trials, providing evidence for substantial or moderate imbalances in key effect modifiers prior to population adjustments. The standard Bucher method is not justified on this basis.	Not a factual error. The following sentences describe the value of a Bucher analysis as a reference point for comparison.
Page 85, paragraph three, sentences five and six: "TSD 18 is clear that where both an anchored and unanchored	Please amend the texts to: Page 85: "TSD 18 ~~is clear~~ **advises** that where both an anchored and unanchored indirect comparison is	The current wording is not accurate. The company did provide a summary explanation in section	Not a factual error. These are statements of the EAG's opinion, based on the limitations

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
indirect comparison is possible, the anchored comparison should be preferred. The company has not provided sufficient explanation for why this might not apply here, therefore the EAG prefers to base conclusions on results of the anchored comparison." Page 87, paragraph four, sentence three: "The two ITCs were inconsistent in their estimates of relative treatment effect on haemoglobin and transfusion avoidance outcomes, however results from the anchored comparison are considered more reliable by the EAG."	possible, the anchored comparison should be preferred. The company ~~has not~~ provided ~~sufficient explanation for~~ **justification in section B.2.9.3.2.3 of the CS** why this might not apply here, ~~therefore~~ **and** the EAG ~~prefers to base conclusions on results of the anchored comparison~~ **also observed that differences in the C5 comparator arms undermine the validity of the anchored comparison**." Page 87: "The two ITCs were inconsistent in their estimates of relative treatment effect on haemoglobin and transfusion avoidance outcomes~~, however results from the anchored comparison are considered more reliable by the EAG~~."	B.2.9.3.2.3 of the company submission, with further details in D.4.5.4.2. Furthermore, the EAG report (page 86) also provides a critique of the anchored comparison and states "This difference in the C5 comparator arms undermines the validity of the anchored comparison including PEGASUS and APPLY-PNH." The conclusions that the EAG prefers the anchored comparison or considers its results more reliable contradict this statement.	of the evidence. All methods have limitations which are clearly outlined in the report. For clarity we have changed "is clear" to "advises" as suggested.
Page 86, paragraph one, sentence two: "The revised clinical data caused a substantial difference	Please add the following text to provide clarity: "The revised clinical data caused a substantial difference in the	The current wording is inaccurate as it implies that there was one additional patient in the dataset overall.	Amendment accepted

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
in the estimated odd ratio for the transfusion avoidance endpoint compared to the original analysis, due to an additional patient in the APPLY-PNH dataset despite minimal changes in the baseline characteristics."	estimated odd**s** ratio for the transfusion avoidance endpoint compared to the original analysis, due to an additional patient in the APPLY-PNH dataset **receiving a transfusion,** despite minimal changes in the baseline characteristics."		
Page 86, paragraph one, sentence five: "The company responded that the additional patient increased the number of patients with transfusion event from one to two"	Please amend the text to: "The company responded that ~~the additional patient increased~~ the number of patients with transfusion event **increased** from one to two."	The current wording is inaccurate as it implies that there was one additional patient in the dataset overall.	Amendment accepted
Page 86, paragraph one, sentence six: "This illustrates how sensitive the ITC is to very small changes in the number of transfusion events and how uncertain the results are."	Please amend the text to: "This illustrates how sensitive the **transfusion avoidance** ITC is to ~~very~~ small changes in the number of transfusion events and how uncertain the **transfusion avoidance** results are."	The current wording is inaccurate as the critique in this section relates to the transfusion avoidance outcome only. Changes in the Hb outcomes were minimal.	Not a factual error but proposed clarification added
Page 86, paragraph two, sentence one: "Given the above	Please amend the text to: "Given the above ~~inconsistencies and~~ uncertainties, the EAG	It is unclear what "the above inconsistencies" refers to, so we suggest that this	Not a factual error.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
inconsistencies and uncertainties, the EAG suggests interpreting these clinical effectiveness results with caution."	suggests interpreting these ~~clinical effectiveness~~ **transfusion avoidance** results with caution.	statement is removed. Furthermore, the section critiques the transfusion avoidance outcome only.	
Page 87, paragraph one, sentence one: "A second ITC used AIPW to match to data from a real-world dataset (APPEX)."	Please amend the text to: "A second ITC used ~~AIPW~~ **a propensity score model** to match ~~to~~ data from a real-world dataset (APPEX) **to APPOINT-PNH**."	The current text is inaccurate. As described in the company submission, section B.2.9.2.2, and noted on page 80 of the EAG report, the APPEX data were adjusted to match the APPOINT-PNH study population.	Amendment accepted
Page 94, paragraph four, sentence two: "[…] which makes the populations more comparable (with resulting loss of data from 44 APEX participants: N=41 in the APPEX real-world cohort and N=40 in APPOINT-PNH cohort following reweighting)."	Please amend the text to: "[…] which makes the populations more comparable (with ~~resulting loss of data from 44 APEX participants: N=~~ **an effective sample size of** 41 in the APPEX real-world cohort **following reweighting** and N=40 in APPOINT-PNH cohort ~~following reweighting~~)."	The current wording is misleading as it could be misunderstood as APPOINT-PNH being reweighted or that 44 patients were removed from the APPEX dataset.	The EAG have amended this statement as proposed.
Page 100, paragraph one,	Please amend the following text to	The reason why an ITC on Hb	The EAG have

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
sentence three: "An unanchored ITC of APPOINT-PNH and Study 301 is described in Section B.2.9.1.3.3. of CS, but due to differences in study inclusion criteria with regards to the presence of anaemia, where non-anaemic patients were eligible for inclusion in Study 301, no ITC could be conducted on Hb outcomes."	provide clarity: "An unanchored ITC of APPOINT-PNH and Study 301 is described in Section B.2.9.1.3.3. of CS, but ~~due to differences in study inclusion criteria with regards to the presence of anaemia, where non-anaemic patients were eligible for inclusion in Study 301~~ **since Study 301 did not report Hb endpoints**, no ITC could be conducted on Hb outcomes."	outcomes could not be conducted is currently stated incorrectly (please refer to the referenced section of the company submission, last sentence).	amended this statement as proposed.
Page 100, paragraph 1, sentence 11: "Importantly, the EAG considers that the company's concerns about differences between APPLY-PNH and PEGASUS, and the validity of any comparison of iptacopan with pegcetacoplan, still holds true even if an ITC of the transition probabilities is not undertaken because the transition probabilities for pegcetacoplan	Please delete this sentence: ~~"Importantly, the EAG considers that the company's concerns about differences between APPLY-PNH and PEGASUS, and the validity of any comparison of iptacopan with pegcetacoplan, still holds true even if an ITC of the transition probabilities is not undertaken because the transition probabilities for pegcetacoplan and iptacopan used in the model are independently derived from the~~	The company's concerns are only around anchored ITCs, as the unanchored comparisons do not rely on the C5 inhibitor control arms of the trials. Please refer to the company submission, section B.2.9.3.2.3, and the company response to clarification question B7.	The EAG does not consider this statement to be factually inaccurate. In this paragraph, the EAG is referring to the concerns that the company highlighted in response to clarification question B7. The text reflects the company's response to this clarification question.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
and iptacopan used in the model are independently derived from the PEGASUS and APPLY-PNH trials, respectively.”	~~PEGASUS and APPLY-PNH trials, respectively.”~~		

Issue 4 Link between trial results and model outputs

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 18, Issue 4 Table, row two: “There is no direct link between the iptacopan trial endpoints and the health state transition probabilities used in the model, which makes a comparison and validation of the transition probabilities informing the cost-effectiveness of iptacopan challenging as it is not clear if the model findings are in line with the primary and secondary outcomes of the trials.” Page 174, paragraph two, sentence one:	While the EAG reports agreement from the company that a direct comparison of clinical trial endpoints and model outputs is challenging, it does not mention or reflect data provided by the company in response to clarification questions in order to support comparison of observed trial data and model predictions. Please see response to clarification question B1 (pages 25-29), providing a comparison between observed and predicted	The current description does not provide a factually accurate and complete representation of what the company supplied in response to clarification questions.	The EAG does not consider these statements to be factually inaccurate. The EAG is making the point that there is no direct link between the iptacopan trial endpoints and the health state transition probabilities used in the model. The comparison of

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
“The EAG’s primary concern in relation to the data used in the cost-effectiveness model is that there is no direct link between the iptacopan trial endpoints and the transition probabilities used in the model, which makes a comparison and validation of the transition probabilities informing the cost-effectiveness of iptacopan challenging as it is not clear if the model findings are in line with the primary and secondary outcomes of the trials.”	health state membership over 24 weeks, which showed that the distribution of patients across health states in the trial and economic model is well aligned. This information should be added to the EAG report.		observed and predicted health state occupancy in response to clarification question B1 does not provide a comparison between the primary and secondary trial endpoints and the modelled transition probabilities. Instead, it provides a comparison between observed health state occupancy and predicted health state occupancy over 24 weeks, where the predicted health state occupancy is based on transition probabilities derived from observed health state occupancy. Therefore, one would expect these results

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			to agree. The EAG's primary concern is the lack of direct comparison of primary and secondary outcomes of the trial with the transition probabilities used in the model.
Page 113, paragraph 2 to page 114: sentence 2: "*Complement inhibitor-experienced population with residual anaemia* […] The difference for C5 inhibitors is stark with a much larger proportion of patients with uncontrolled anaemia and requiring transfusions compared to either iptacopan or pegcetacoplan. The EAG's clinical advisor did not consider the percentages for C5 inhibitors to be reasonable and would expect to see a much higher percentage of patients with 'No transfusion and no anaemia' and a lower proportion requiring transfusions on	We thank the EAG for providing details on the discussion with the clinical advisor and the referenced study. Based on this information, we believe that the context of the discussion may have been misunderstood. The values referenced from the study in the EAG report represent anaemia and blood transfusions in patients initiating C5 inhibitor treatment, i.e. (up to that point) a complement inhibitor-naïve population. However, the population of interest in this matter (EAG report	The information summarised in the EAG report is inaccurate in the context it is presented in (complement inhibitor-experienced patients with residual anaemia).	The EAG have amended the text in the report to reflect Kelly et al (2023). "In the most recent 12 months on C5 inhibitors, 123 out of 446 (27.6%) patients needed transfusions with 94 of the 123 (76.4%) requiring 3 or more transfusions." The EAG is not clear where the company have identified the

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
C5 inhibitors. Based on the study by Kelly et al (2023)[16] of treatment outcomes of complement C5 inhibition in 509 UK patients with PNH, about 20% of patients achieve a normal Hb on C5 inhibitors (i.e., >13.5 g/dL in men and >11.5 g/dL in women) at 24 months after treatment initiation, while the threshold for 'No transfusion and no anaemia' as used in the model is lower at 10.5 g/dL. He also noted that one in four patients on C5 inhibitors have ongoing transfusion requirements.[16] Therefore, the model predictions of around 35% of patients require transfusions with continued C5 inhibitor treatment is too high. The company also states that their clinician advised that the proportion requiring transfusions would be considered too high for the overall population, but that it is a realistic estimate for a population with partial response to a C5 inhibitor (see response to clarification question B8)."	page 113) are complement inhibitor-experienced patients with residual anaemia. In the study by Kelly et al (2023), after 12 months of treatment with a C5 inhibitor, 335/421 (79.6%) of patients had residual anaemia (a Hb value below the normal range). Among these patients with residual anaemia on C5 inhibitor treatment, 36.7% (123/335 patients) are reported to still require transfusions. This percentage (36.7%) is fully in line with the model prediction of around 35% of patients requiring transfusions with continued C5 inhibitor treatment, in a population who is complement inhibitor-experienced with residual anaemia.		figure of 36.7% (123/335 patients) are reported to still require transfusions.

Issue 5 Generalisability of trial data to UK practice

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 31, Table 6 Summary of decision problem, row: Population, column: EAG comment, sentence 2: "APPOINT-PNH population includes a substantially larger proportion of East Asian patients (67.5%) than would be seen in UK practice. However, the clinical differences between populations recruited in Asia and the UK are likely to be important for this evaluation (see	Please amend the text to: "APPOINT-PNH population includes a substantially larger proportion of East Asian patients (67.5%) than would be seen in UK practice. However, the clinical differences between populations recruited in Asia and the UK are **not** likely to be important for this evaluation (see section 3.2.1)."	We believe the word "not" may have been missed in error, given the EAG's conclusions elsewhere in the report that the trial population appears comparable with UK patients (including in section 3.2.1 which is cross-referenced in Table 6): "patients included in APPOINT-PNH were broadly similar to those treated in UK practice" (EAG report page 41) "The most notable difference between the study and NHS populations is the high proportion of East Asian patients (67%) in APPOINT-PNH. […] However, the study population appears comparable to NHS treatment population, in that all symptomatic patients with PNH have high LDH levels and anaemia." (EAG report page 42) This is reiterated in the economic section 4.2.3: "[…] the EAG has expressed some concerns about how well the patient	Amendment accepted

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
section 3.2.1)."		populations of the APPOINT-PNH and APPLY-PNH trials align with the PNH population seen in UK clinical practice (e.g., the APPOINT-PNH trial mostly enrolled East Asian patients and had a low proportion of participants with a history of thrombosis compared to what might be expected to be seen in UK patients); however, the EAG is satisfied that iptacopan is expected to work in a similar way in a UK population and the trial results are generalisable to UK clinical practice." (EAG report page 94)	

Issue 6 Concomitant eculizumab acquisition costs for patients initiating pegcetacoplan

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 15, paragraph one, sentence one: "[…] (iv) exclusion of concomitant eculizumab acquisition costs for patients initiating pegcetacoplan because overlap of treatments is unlikely to happen in NHS clinical practice."	The EAG report states that concomitant use of eculizumab in the first four weeks of pegcetacoplan initiation "is unlikely to happen in NHS clinical practice" but does not state a clear source for this. It should be clarified whether this statement is, for	The source of the EAG's assumption is currently unclear, and may be	The EAG have amended the text throughout to remove the reference to "overlap of

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 23, Issue 10 Table, row two, sentence two: "The EAG considers the inclusion of these costs to be inappropriate because overlap of treatments is unlikely to happen in NHS clinical practice." Page 132, paragraph six, sentence one, and page 133, paragraph one, sentence two: "The EAG considers that concomitant eculizumab acquisition costs for patients initiating pegcetacoplan should be excluded from the model because overlap of treatments is unlikely to happen in NHS clinical practice. […] Therefore, the EAG considers it inappropriate to include concomitant eculizumab acquisition costs for patients initiating pegcetacoplan." Page 133, paragraph two: "item 7: The EAG considers that concomitant eculizumab acquisition costs for patients initiating pegcetacoplan should be excluded from the model because overlap of treatments is unlikely to happen in NHS clinical practice."	example, based on input received from the EAG's clinical advisor, or an assumption by the EAG. In the company submission, the consideration of 4 weeks of concomitant eculizumab acquisition costs for patients switching from eculizumab to pegcetacoplan was based on the pegcetacoplan (Aspaveli) SmPC, which states in section 4.2 Posology and method of administration: "*Patients switching to ASPAVELI from a C5 inhibitor* For the first 4 weeks, pegcetacoplan is administered as twice weekly subcutaneous doses of 1 080 mg in addition to the patient's current dose of C5 inhibitor treatment to minimise the risk of haemolysis with abrupt treatment discontinuation. After 4 weeks, the patient should discontinue C5 inhibitor before continuing on monotherapy with ASPAVELI." One of the UK clinicians of the National	contradictory to clinical advice received by the company. In addition, information on the company's rationale for including concomitant cost should be reflected in the EAG's summary of the company's submission.	treatments is unlikely to happen in NHS clinical practice". The source of this statement was from the final recommendations for TA778, but the EAG considers it appropriate for the Appraisal Committee for iptacopan to come to their own conclusions. The EAG still considers it appropriate to exclude concomitant eculizumab acquisition costs for patients

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 148, Table 61, item 7: "Concomitant eculizumab acquisition costs for patients initiating pegcetacoplan should be excluded from the model because overlap of treatments is unlikely to happen in NHS clinical practice." Page 152, paragraph three: "[…] the EAG considers that concomitant eculizumab acquisition costs for patients initiating pegcetacoplan should be excluded from the model because overlap of treatments is unlikely to happen in NHS clinical practice. […] Therefore, the EAG considers it inappropriate to include concomitant eculizumab acquisition costs for patients initiating pegcetacoplan." Page 167, bullet point five: "• Exclusion of concomitant eculizumab acquisition costs for patients initiating pegcetacoplan because overlap of treatments is unlikely to happen in NHS clinical practice – Scenario 7" Page 168, last sentence:	PNH Service consulted by Novartis during preparation of the submission confirmed that patients already on C5 inhibitors when starting pegcetacoplan would have four weeks of concomitant therapy before discontinuing the C5 inhibitor (please see page 6 in the Iptacopan PNH Model & ITC External Validation Calls Report, 2023, provided in the reference pack to the company submission). In case the EAG's assumption that the overlap of treatments is unlikely to happen in NHS clinical practice was based on documents from the pegcetacoplan appraisal (TA778), we wish to highlight that the submission and committee meeting took place prior to the licence being granted, with the final SmPC wording likely not known, and that the company's and the ERG's clinical advisors had conflicting views on this matter (refer to TA778 committee papers,		initiating pegcetacoplan because the transition probabilities for pegcetacoplan have excluded the effects of the 4-week concomitant treatment period in the PEGASUS trial. The EAG also notes that the exclusion of concomitant eculizumab acquisition costs for patients initiating pegcetacoplan has minimal effect on the cost-

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"[…] but the EAG considers it appropriate to exclude these costs because overlap of treatments is unlikely to happen in NHS clinical practice […]"	ERG report pages 25-26).		effectiveness results.

Issue 7 Incorrect or mislabelled data

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 32, Table 6 Summary of decision problem, rows 'Economic analysis', 'Subgroups', 'Special considerations including issues related to equity or equality'	Please amend the labelling and content of rows six, seven, and eight (currently labelled economic analysis, subgroups, and special considerations, respectively). Row six (economic analysis) currently presents subgroups, row seven (subgroups) currently presents equality issues, and row eight (special considerations) presents a repeat of the population row.	Labelling and content of table rows are currently not aligned, and there appears to be no content covering economic analysis.	Amended
Page 43, Table 11, row '≥2 g/dL increase from baseline in Hb, irrespective of transfusions', 48 weeks column:	Please correct to: "38/39 patients **97.4%** ~~(95% CI: 92.5, 100.0)~~"	The stated percentage is incorrect (95% CI not reported)	Amended

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG response</th></tr>
<tr><td>“38/39 patients 97.5% (95% CI: 92.5, 100.0)”</td><td></td><td></td><td></td></tr>
<tr><td>Page 44, paragraph one, sentence two:
“[…] and this level of response was sustained at 48 weeks (97.5% (95% CI: 92.5, 100.0))”</td><td>Please correct to:
“[…] and this level of response was sustained at 48 weeks (97.4% <s>(95% CI: 92.5, 100.0)</s>)”</td><td>The stated percentage is incorrect (95% CI not reported)</td><td>Amended</td></tr>
<tr><td>Page 45, Table 12, rows “Completed treatment period” and “Treatment ongoing”, column “Extension treatment period”</td><td>Please correct values in this table from:
<table>
<tr><td></td><td>Core treatment period (24 weeks)</td><td>Extension treatment period (24-48 weeks)</td></tr>
<tr><td>Completed treatment period, n/N (%)</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Treatment ongoing, n/N (%)</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
to:
<table>
<tr><td></td><td>Core treatment period (24 weeks)</td><td>Extension treatment period (24-48 weeks)</td></tr>
</table></td><td>The stated figures are incorrect</td><td>Amended</td></tr>
</table>

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	Completed treatment period, n/N (%) [redacted] [redacted] Treatment ongoing, n/N (%) [redacted] [redacted]		
Page 63, Table 23 title: "Table 23 Treatment compliance and missed doses reported in APPOINT-PNH clinical study report[4]"	Please amend the title of Table 23 to: "Table 23 Treatment compliance and missed doses reported in **APPLY**-PNH clinical study report[4]"	The table title erroneously refers to APPOINT-PNH, while the presented data is from the APPLY-PNH study.	Amended
Page 81, paragraph two, sentence one: "As noted previously, only one patient (of 41) from the APPEX study received ravulizumab."	Please correct to: "As noted previously, only one patient (of **85**) from the APEX study received ravulizumab."	The stated figure is incorrect	Amended
Page 49, Table 3 Page 51 and 52, Table 14	The addendum to the company evidence submission documenting changes to APPLY-PNH trial data included red and underlined highlighting for all values that had changed. Tables transferred across from the company's addendum to the EAG report do not	The highlighting in tables in the EAG report does not accurately reflect	Red underlined highlighting has been

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 54, Table 15 Page 55, Table 16 Page 56, Table 17 Page 56, Table 18 Page 56, Table 19 Page 57, Table 20	consistently include the correct highlighting, while the table footnote "Updated values to original company evidence submission underlined and in red font" has been maintained. Please either a) remove all red and underlined highlighting from tables in the EAG report, including the table footnote describing the rationale for highlighting, or b) apply red and underlined highlighting consistently as reflected in the company's addendum (ID6176_Iptacopan_PNH_NICE_Addendum_4 Dec 2023_[CON]) Discrepancies can be found between underlining and red font colour on: EAG report page 49, Table 3 when compared with company's addendum, Table 1, pages 7-8 EAG report page 51 and 52, Table 14 when compared with company's addendum, Table 2, pages 9-10 EAG report page 54, Table 15 when compared with company's addendum, Table 3, page 11 EAG report page 55, Table 16 when compared with company's addendum, Table 4, page 12 EAG report page 56, Table 17 when compared with company's addendum, Table 5, Page 13 EAG report page 56, Table 18 when compared with company's addendum, Table 6, Page 13 EAG report page 56, Table 19 when compared with company's	where values have changed, as per the information provided within the company's addendum. One of the suggested two approaches for resolving this issue should be implemented, in order to avoid the EAG report giving an incorrect impression that the company had highlighted data changes in a selective manner.	removed from all EAR table cells, but links to the corresponding tables in the addendum have been retained in each table caption, and the footnotes updated to clarify that all values have been updated to match those presented in the company's addendum.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	addendum, Table 7, Page 14 EAG report page 57, Table 20 when compared with company's addendum, Table 8, Page 14		
Page 84, Table 32	Please add bold formatting to the row "Unanchored MAIC results", "Iptacopan vs pegcetacoplan", in order to indicate statistical significance as per the company submission and table footnote ("**Bold** values indicate statistical significance and corresponds to a two-tailed p-value <0.05."): **MD [redacted] (95% CI [redacted]) p=0.014** | **MD [redacted] (95% CI [redacted]) p=0.018** | **OR [redacted] (95% CI [redacted]) p=0.009**	Formatting update to indicate statistical significance in line with the table key	Amended

Issue 8 Other factual inaccuracies and text clarifications

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 30, last sentence: "While not reported in the CS, clinical study report data suggest high compliance with oral iptacopan in the short term, though longer-term data are not yet available (see section 0)."	Please amend the text to state that information on treatment compliance and missed doses was provided by the company in response to clarification question B13 (see page 47 of response document).	The current wording suggests that the company did not provide this information, while it was provided in the clarification question response document	Text amended in each case to show that the company also provided compliance data in response to point for clarification B13.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 45, paragraph four, sentence two: "The CS did not present any information on treatment compliance or missed doses. However, the EAG have extracted this information from the APPOINT-PNH clinical study report[4] in Table 12 below." Page 63, paragraph two, sentence two: "The CS did not present any information on treatment compliance or missed doses. However, the EAG have extracted this information from the APPLY-PNH clinical study report in Table 25 below."			
Page 43, Table 11, rows: "≥2 g/dL increase from baseline in Hb, irrespective of transfusions" and	Please amend the text for these two endpoints to: "≥2 g/dL increase from baseline in Hb~~, irrespective of transfusions~~" and	As reported on page 6 of the clarification questions response document, the definition of the haematological response endpoints differed between	Amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"Hb ≥12 g/dL, irrespective of transfusions"	"Hb ≥12 g/dL~~, irrespective of transfusions~~" In addition, we suggest adding a footnote to signify that haematological response endpoints in the 48-week analysis included all Hb values irrespective of red blood cell (RBC) transfusions, whereas the primary analysis at 24 weeks required the absence of transfusions as an integral part of the endpoints.	the week 24 and week 48 analyses.	
Page 62, paragraph one, sentence two: "APPLY-PNH only provides evidence of the comparative effects of iptacopan relative to C5 inhibitors for 24-weeks, with a further 24 weeks of observational evidence."	Please amend to: "APPLY-PNH only provides evidence of the comparative effects of iptacopan relative to C5 inhibitors for 24-weeks, with a further 24 weeks of ~~observational~~ **non-comparative** evidence"	The current wording has the potential to be misinterpreted – APPLY-PNH was not an observational study, and patients continued to be treated with iptacopan.	Amended
Page 63, Table 23, column three: "Interim analysis*"	Please amend the column title "Interim analysis*" to "**Analysis at data cut-off 26th Sept 2022***"	The suggested terminology is more accurate	Amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 76, paragraph one, sentence six: "While APPOINT-PNH that recruited patients with Hb ≤ 10 mg Study 301 did not specify a level of Hb (to define anaemia) as an eligibility criterion, and so included patients with Hb > 10mg."	Please amend to: "While APPOINT-PNH ~~that~~ recruited patients with Hb ~~≤ 10 mg~~ **<10 g/dL,** Study 301 did not specify a level of Hb (to define anaemia) as an eligibility criterion, and so included patients with Hb ~~>~~ ~~10mg~~ **≥10 g/dL**."	Incorrect unit for Hb and incorrect symbols	Amended
Page 88, paragraph four, sentence one: "A Markov cohort model is used to estimate long-term health outcomes and costs"	Please amend to: "A **semi-**Markov cohort model is used to estimate long-term health outcomes"	The current wording is not fully accurate	Amended
Page 89, paragraph five, sentence one: "The EAG considers that the company's model differs from the previous NICE appraisals in the following key elements"	Please amend to: "The EAG considers that the company's model **base case** differs from the previous NICE appraisals in the following key elements"	The current wording is not an accurate representation of the company submission as scenarios without discontinuation, with EORTC utilities, and treatment-independent utilities were provided	Amended
Page 94, paragraph four,	Please amend to:	The current wording is not	Amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
sentence one: "For the complement inhibitor-naïve population, the APPEX study provides data on UK patients, with 45% (38 patients from among the 85 patients included in the company's comparative analysis of participant characteristics in the APPOINT-PNH and APPEX studies) from the UK National PNH service registry at St. James's University Hospital, Leeds, who were treated with C5 inhibitors (84 with eculizumab and 1 with ravulizumab)."	"For the complement inhibitor-naïve population, the APPEX study provides data on ~~UK~~ **85 patients treated with C5 inhibitors (84 with eculizumab and 1 with ravulizumab) of which**~~, with~~ 45% (38 patients ~~from among the 85 patients included in the company's comparative analysis of participant characteristics in the APPOINT-PNH and APPEX studies)~~ **were** from the UK National PNH service registry at St. James's University Hospital, Leeds~~, who were treated with C5 inhibitors (84 with eculizumab and 1 with ravulizumab)~~."	accurate	
Page 95, paragraph one, sentence three: "Therefore, pegcetacoplan is only considered as a comparator in the complement inhibitor-experienced population, but may be included as a subsequent line of therapy in the complement	Please amend the text to: "Therefore, pegcetacoplan is only considered as a comparator in the complement inhibitor-experienced population, but may be included as a subsequent line of therapy in the complement inhibitor-naïve population **in patients who**	The current wording does not accurately represent the specific population (patients who remain anaemic), and the stated time frame might be misunderstood to refer to time since discontinuation	Amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
inhibitor-naïve population after discontinuation ≥3 months of a C5 inhibitor."	**remain anaemic** after ~~discontinuation~~ ≥3 months of **treatment with** a C5 inhibitor."	rather than treatment duration prior to discontinuation	
Page 95, paragraph one, sentence four: "The dosing regimens for the comparator drugs are in line with their respective SmPC (see Table 39, page 110 of CS)."	Please amend the text to: "The dosing regimens for the comparator drugs are **largely** in line with their respective SmPC (see Table 39, page 110 of CS). **For eculizumab, based on clinical practice, some patients were assumed to receive higher than label maintenance doses (see Table 51, page 128 of CS). A similar approach was taken in the pegcetacoplan submission."**	The current wording does not accurately represent the specific doses used in the model	Amended
Page 101, paragraph one, sentence two: "This means that in the 48-week data analysis a longer follow-up period is used to inform the transition probabilities, discontinuation and BTH events rates for iptacopan compared to	The EAG is correct that for transition probabilities, 48-week data was only available for iptacopan. However, discontinuation and BTH event rates for pegcetacoplan included in the model were also informed by 48-week trial data. This should	The current wording does not accurately represent the evidence included in the model	Amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
the comparator complement inhibitors."	be considered in the text.		
Page 113, bullet point one, sentence one: "[…] for the comparison of iptacopan with pegcetacoplan, a slightly higher percentage of patients will require transfusions on pegcetacoplan, while those remaining transfusion-dependent is lower for pegcetacoplan based on the 24-week data but higher based on the 48-week data"	Please amend the text to improve clarity: ""[…] for the comparison of iptacopan with pegcetacoplan, a slightly higher percentage of patients will require transfusions on pegcetacoplan, while those remaining transfusion-dependent is **higher with iptacopan** based on the 24-week data but **lower** based on the 48-week data"	The revised text improves clarity, since there is only one set of transition probabilities for pegcetacoplan, while it is the iptacopan transition probability matrix that changes between 24-week and 48-week data.	Amended
Page 23, Issue 10, row 2 column 2, sentence three: "In addition, the transition probabilities used in the model for pegcetacoplan are only based on the randomised controlled period of the PEGASUS trial from weeks 4-16, in which patients had either pegcetacoplan or eculizumab, and not the 4-week run-in period in which both treatments were	Please amend this sentence to acknowledge that data from the first 4 weeks of the randomised controlled period were used to define patients' prior health states for the multinomial regression model.	Transitions probabilities in Hakimi et al were based on observations from weeks 4-16, however include a covariate for the prior 4-weeks' health state, which includes data from the first 4 weeks of randomised controlled treatment.	The data for the transition probabilities are based on observations from week 4. The prior 4-weeks' health state is only included as a covariate in the model (starting baseline health state). Further details of the methods used are described in the company submission of TA778 where it states that "in

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
given, or the first 4 weeks of the randomised controlled period where a 'hangover' effect of the run-in period was observed, i.e., the transition probabilities are based only on week 4 to week 16 after the 4-week washout period in order to mitigate any 'hangover' effect of the run-in period in PEGASUS." Page 117, paragraph two, sentence three: "the EAG notes that the transition probabilities from the PEGASUS trial reported in Hakimi et al (2022) [13] are only based on the randomised controlled period from weeks 4-16, in which patients had either pegcetacoplan or eculizumab, and not the 4-week run-in period in which both treatments were given, or the first 4 weeks of the randomised controlled period where a 'hangover' effect of the			order to mitigate the impact of the run-in period, the base case analyses use transition probability calculated using data from week 4 to week 16…… Starting from week 4 also helps to start the analysis from a theoretically 'washed out' patient". For clarity, the report has been amended throughout to reflect the inclusion of the prior 4 week's health state as a covariate.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
run-in period is observed” Page 132, final paragraph, sentence two: “the transition probabilities used in the model for pegcetacoplan are only based on the randomised controlled period of the PEGASUS trial from weeks 4-16, in which patients had either pegcetacoplan or eculizumab, and not the 4-week run-in period in which both treatments were given, or the first 4 weeks of the randomised controlled period where a ‘hangover’ effect of the run-in period was observed, i.e., the transition probabilities are based only on week 4 to week 16 after the 4-week washout period in order to mitigate any ‘hangover’ effect of the run-in period in PEGASUS.” Page 153, Section 6.1.1.7,			

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
paragraph one, sentence two: “the transition probabilities used in the model for pegcetacoplan are only based on the randomised controlled period of the PEGASUS trial from weeks 4-16, in which patients had either pegcetacoplan or eculizumab, and not the 4-week run-in period in which both treatments were given, or the first 4 weeks of the randomised controlled period where a ‘hangover’ effect of the run-in period was observed, i.e., the transition probabilities are based only on week 4 to week 16 after the 4-week washout period in order to mitigate any ‘hangover’ effect of the run-in period in PEGASUS.”			
Page 130, Table 47, row ‘Treatment related resource use associated with vaccinations, antibiotics, and iron overload treatment’, column two:	Please change to: “iptacopan & pegcetacoplan:	The current wording is an inaccurate label of the cost. Additionally, two values were swapped.	Amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"iptacopan & pegcetacoplan: first cycle cost: £ 104.17 subsequent model cost: £ 53.64 eculizumab & ravulizumab: first cycle cost: £ 6.56 subsequent model cost: £ 53.64"	first cycle cost: £ 104.17 subsequent **cycle** cost: £ **6.56** eculizumab & ravulizumab: first cycle cost: £ **53.64** subsequent **cycle** cost: £ 53.64"		
Page 131, paragraph one, sentence one: "[…] while in the complement inhibitor-experienced population with residual anaemia, patients start on the maintenance dose of 900 mg Q2W."	Please amend to: "[…] while in the complement inhibitor-experienced population with residual anaemia, ~~patients start on the maintenance dose of 900 mg Q2W~~ **it was assumed that at the start of the model, patients who required higher maintenance doses were already on such a dose**."	The current wording is not an accurate representation of the doses used in the model.	Amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 131, Table 48, row 'Eculizumab (IV infusion)', column four: "Complement inhibitor-naïve population - Loading dose (week 1-4) 600mg QW: 100% - Maintenance dose (week 5 and afterwards) 900mg Q2W: 81.0% 1,200mg Q2W: 17.5% 1,500mg Q2W: 1.5%"	Please amend to: "Complement inhibitor-naïve population - Loading dose (week 1-4) 600mg QW: 100% - Maintenance dose (week 5 **up to month 6**) **900mg Q2W: 100%** - **Maintenance dose (Month 6 and afterwards)** 900mg Q2W: 81.0% 1,200mg Q2W: 17.5% 1,500mg Q2W: 1.5%"	The current wording is not an accurate representation of the doses used in the model. In the complement inhibitor-naïve population, updosing of eculizumab to a higher dose for a proportion of patients is assumed only from Month 6 onwards.	Amended
Page 132, paragraph four, sentence four: "However in the CS for iptacopan, the dosing escalation is 900 mg every 14 days The EAG does not consider this difference to be concerning because only 1.5% patients received 1,500 mg in APPLY-	Please amend to: "~~However~~ in the CS for iptacopan, the dosing escalation is ~~900~~ **1200 mg or 1500** mg every 14 days ~~The EAG does not consider this difference to be concerning because only 1.5% patients received 1,500 mg in APPLY-~~	The current wording is not an accurate representation of the doses used in the model. Since 1500 mg every 14 days was also an escalation dose used in TA778, the difference highlighted by the EAG in the next sentence is	Amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
PNH."	~~PNH.~~"	unclear.	
Page 134, Table 50, rows 'eculizumab' and 'ravulizumab': "- S. pneumoniae (100%)"	Please remove "~~S. pneumoniae (100%)~~"	Patients treated with C5 inhibitors do not receive this vaccine, and no cost for S. pneumoniae vaccination was considered for eculizumab- or ravulizumab-treated patients in the model.	Amended
Page 142, paragraph three, sentence three: "The first of these is also the scenario without discounting applied."	Please amend to: "The first of these is also the scenario without ~~discounting~~ **discontinuation** applied".	The current text incorrectly refers to the scenario without discounting, rather than the scenario without discontinuation (see Table 60 in EAG report).	Amended
Page 147, paragraph two, sentence one: "The EAG's base case consists of the set of assumptions and model inputs that the EAG considers to be most appropriate for assessing the cost-effectiveness of iptacopan with C5 inhibitors in the complement	Please amend the text to "The EAG's base case consists of the set of assumptions and model inputs that the EAG considers to be most appropriate for assessing the cost-effectiveness of iptacopan **compared** with C5 inhibitors in the complement inhibitor-naïve population, and	The current text is misleading, as it suggests iptacopan is used in combination with C5 inhibitors	Amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
inhibitor-naïve population, and iptacopan with C5 inhibitors or pegcetacoplan in the complement inhibitor-experienced population with residual anaemia."	iptacopan **compared** with C5 inhibitors or pegcetacoplan in the complement inhibitor-experienced population with residual anaemia		
Page 153 (labelled as page 166 in the document), paragraph 3, sentence 2: "Scenario 3 improves the cost-effectiveness of iptacopan compared to the company's base case because the benefits of iptacopan from APPOINT-PNH are extrapolated over a lifetime horizon with no discontinuation."	Please add an additional statement at the end of the following text to provide additional context: "Scenario 3 improves the cost-effectiveness of iptacopan compared to the company's base case because the benefits of iptacopan from APPOINT-PNH are extrapolated over a lifetime horizon with no discontinuation, **and because C5 inhibitors generate lower QALYs since anaemic/ transfusion-dependent patients are not switching to pegcetacoplan (the more effective treatment for patients with residual anaemia)**."	The current wording does not provide the full context for the differences in this scenario.	Amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 167, paragraph one, sentence one: "[…] and reduced by 29% with a higher discontinuation rate of 10% for pegcetacoplan."	Please amend the text to: "[…] and reduced by 29% with a ~~higher~~ discontinuation rate of 10% for pegcetacoplan."	The current wording suggests that this discontinuation rate is higher than in the company's base case, which is not accurate	Amended
Page 169, Table 66, row '4+6 (EAG base case)', 'Iptacopan vs. Ravulizumab', column: ICER: [redacted]	Please change to [redacted]	Current value is incorrect as iptacopan [redacted]	Amended
Page 170, Table 67, row '4+6 (EAG base case)', 'Iptacopan vs. Ravulizumab', column: ICER: [redacted]	Please change to [redacted]	Current value is incorrect as iptacopan [redacted]	Amended

Issue 9 Typographical and formatting errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 28, paragraph three, sentence two	Please amend "It's" to "Its"	Typographical error	Amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 30, paragraph four, sentence five	Please amend the cross reference from “section 0”, to the correct heading in the document	Incomplete cross reference	Amended
Page 32, Table 6, row: Subgroups, column five	Please amend the cross reference from “section 0”, to the correct heading in the document	Incomplete cross reference	Amended
Page 34, paragraph four, sentence one	Please amend the cross reference from “Appendix x”, to the correct appendix in the document	Incomplete cross reference	Amended
Page 35, paragraph two, sentence one	Please amend “assesments” to “assessments”	Typographical error	Amended
Page 45, paragraph two, sentence one	Please amend “ral” to “real”	Typographical error	Amended
Page 47, paragraph five, sentence two	Please amend: “However, the remaining all study endpoints” to “However, all the remaining study endpoints”	It would be useful to correct the word order to avoid confusion or misunderstanding	Amended
Page 57, paragraph four, sentence one	Please amend “Figure 2 Figure 5 illustrate” to “Figure 2 to Figure 5 illustrate”	It would be useful to add the missing word to avoid confusion or misunderstanding	Amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 64, paragraph one, sentence three	Please amend the cross reference from “Table 25 to “Table 23”	Incorrect cross reference	Amended
Page 67, paragraph two, sentence two	Please amend “pegcetocoplan” to “pegcetacoplan”	Typographical error	Amended
Page 68, sentence one	Please amend “iptacapan” to “iptacopan”	Typographical error	Amended
Page 72, paragraph four, sentence one	Please amend “iptacapan” to “iptacopan”	Typographical error	Amended
Page 73, paragraph one, sentence one	Please amend “thromobosis” to “thrombosis”	Typographical error	Amended
Page 73, paragraph three, sentence two	Please amend the cross reference from “section xx”, to the correct heading in the document.	Incomplete cross reference	Amended
Page 74, Table 26, row five, column five	Please amend “ravulzumab” to “ravulizumab”	Typographical error	Amended
Page 80, Table 30, footnote *	Please amend “paitents” to “patients”	Typographical error	Amended
Page 85, paragraph two, sentence four	Please amend “pegcetaplan” to “pegcetacoplan”	Typographical error	Amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 87, paragraph two, sentence one	Please amend “ravalizumab” to “ravulizumab”	Typographical error	Amended
Page 90, Table 33, row seven, column three	Please amend “HROoL” to “HRQoL”	Typographical error	Amended
Page 94, paragraph four, sentence two	Please amend “APEX” to “APPEX”	Typographical error	Amended
Page 139, Table 56, row eight and 14	Please amend “Tranfusion” to “Transfusion”	Typographical error	Amended
Page 153 to 156	Please fix the page numbering from page 152 to 157. Between these pages, the page numbers are all listed as page 166, rather than 153, 154, 155, and 156	Formatting error	Amended

Issue 10 Incorrect confidentiality markings

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Iptacopan EAG report, Table 21, pages 60 and 61	Table 21 results are marked CiC, however, this is not required	In Table 21: APPLY-PNH: Summary of efficacy results at the 48-week analysis, all confidentiality markings can be removed.	Amended

Page 63, paragraph three, sentence one and two	Please add CiC marking to the percentage values of patients missing iptacopan doses	“These data suggest that around [redacted] of patients missed at least one daily dose of oral iptacopan. The proportion missing at least one full day of iptacopan treatment increased from [redacted] during the randomised period to [redacted] at the analysis cut-off date.”	Amended
Page 86, paragraph one, sentence three	Please add CiC marking to the anchored comparison OR estimate	“For example, the original anchored comparison OR estimate was [redacted] and the revised is [redacted].”	Amended
Page 135, paragraph three, sentence three	Please amend the CiC marking for costs (needed) and QALYs (not needed)	“Iptacopan total costs [redacted] and total QALYs slightly increase based on the 48-week data vs 24-week data.”	Amended
Page 136, paragraph one, sentence four	Please amend the CiC marking for QALYs (not needed)	“However, iptacopan total costs [redacted] and total QALYs slightly increase based on 48-week data vs 24-week data.”	Amended
Page 141, paragraph three, sentence two	Please amend the CiC marking for results (needed)	“The ICER vs eculizumab mostly well aligned with the deterministic base-case results, except two scenarios [redacted].”	Amended
Page 141, paragraph three, last sentence	Please amend the CiC marking for results (needed, [redacted])	“In the scenario without discontinuations, iptacopan now generates slightly lower QALYs than pegcetacoplan, but remains cost-effective at the iptacopan PAS price and comparator list prices ([redacted]).”	Amended

Page 153 (labelled as page 166 in the document), paragraph three, sentences three and four	Please amend the CiC marking for QALYs (not needed)	“Scenario 6 does not change the company’s base case conclusion that [redacted], but the QALY gain from iptacopan compared to C5 inhibitors is substantially reduced (over 50% reduction) relative to the company’s base case. This is because the treatment-specific utility value for the same health state in the company’s base case is significantly higher for iptacopan compared to C5 inhibitors, which the EAG considers to be double counting the effects of iptacopan.”	Amended

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Iptacopan for treating paroxysmal nocturnal haemoglobinuria [ID6176]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **4 April 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating paroxysmal nocturnal haemoglobinuria and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Morag Griffin & Austin Kulasekararaj
2. Name of organisation	Leeds teaching hospitals & King's College Hospital (on behalf of the two NHSE commissioned services for PNH)
3. Job title or position	Consultant haematologist, PNH joint service lead & Consultant haematologist, PNH joint service lead
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with paroxysmal nocturnal haemoglobinuria? ☒ A specialist in the clinical evidence base for paroxysmal nocturnal haemoglobinuria or iptacopan? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

8. What is the main aim of treatment for paroxysmal nocturnal haemoglobinuria? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	PNH is a rare haemolytic and thrombotic condition. The main aim of treatment for PNH is of disease control, to reduce life threatening complications, improve patient quality of life, and normalise life expectancy. Treatment with eculizumab (approved in 2007) and latterly ravulizumab has enabled the service to treat patients, achieving the majority of the above aims, however patients develop extravascular haemolysis, which can affect quality of life and productivity. Both the above treatment are also intravenous.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	PNH disease control, with cessation of intravascular haemolysis and prevention of thrombosis. This is assessed clinically, and with an LDH and Hb response as well as patient symptoms. For proximal complement inhibition, clinically significant response including the above, also includes an improvement in Hb of >2g/dl, and a reduction in blood transfusion requirements.
10. In your view, is there an unmet need for patients and healthcare professionals in paroxysmal nocturnal haemoglobinuria?	Patients with PNH are currently reliant on intravenous treatment when diagnosed. This treatment is effective, lifesaving and stabilises patients, however patients are reliant on healthcare staff treating them at home. If patients develop extravascular haemolysis with a low Hb +/- a transfusion requirement, this significantly affects patient quality of life, and they have the option of pegcetacoplan, a subcutaneous twice a week infusion treatment. However some patient have needle aversion, or do not response to pegcetacoplan. It also makes travel more complicated due to transportation needles, infusion device and drug. Thus unmet needs are: 1. Fatigue – remains a significant issue for patients with PNH, leading to a reduction in work productivity and family life. 2. Burden of existing treatments (related to modality of administration ie either intravenous or subcutaneous, twice weekly)

11. How is paroxysmal nocturnal haemoglobinuria currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Clinical guidelines are nationally agreed treatment indications which are reflected also in centres worldwide https://pnhserviceuk.co.uk/healthcare-professionals/indications-for-treatment-with-eculizumab-ravulizumab-and-pegcetacoplan/ The pathway is well defined and does not vary from the 2 centres (Leeds and London). All patients with significant PNH are also discussed at a monthly joint MDT. Depending on approval indications, the PNH service would potentially use in both treatment naïve and complement inhibitor treated patients. It approved in the naive treatment setting, indications for treatment will be unchanged compared to patients starting on eculizumab or ravulizumab. If approved for patients already on a C5 inhibitor, reasons to change treatment will depend on approval process. Patient choice and anticipated response to treatment, as well as anticipated compliance to an oral treatment will be considered.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Iptacopan is the first oral treatment to be assessed for PNH. Healthcare resource: As the treatment is oral, homecare nursing would not be required, however delivery of treatment would need to be undertaken by a homecare service Clinical setting - Specialist clinics: PNH is an ultrarare condition, all patients should continue to be managed by the National PNH service, who have the expertise and experience in treating patients, advising about medication, and managing complications/infections if they arise.

	Investment: No investment should be required from the NHS, the PNH service is well established. Patients already attend clinic and treatment options are discussed regularly as part of a clinic consultation. Number of patients treated will not change, the type of treatment only would change.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Iptacopan would offer patients an oral treatment with the expectation of response similar to those of the clinical trial outcomes: Iptacopan would offer patients an oral treatment with the expectation of response similar to those of the clinical trial outcomes N Engl J Med. 2024 Mar 14;390(11):994-1008. doi: 10.1056/NEJMoa230869 Patients already on eculizumab or ravulizumab with extravascular haemolysis; anticipated response of 85% of patients achieving a haemoglobin increase at least 2 g/dl and 95% becoming transfusion free. If utilised in the naive treatment setting: 96% of patients anticipate an increase in the haemoglobin level of at least 2 g/dl. Both groups also maintain LDH control below 1.5xupper limit of normal (achieved in 95% of patients). The response also improves patient reported outcomes with increase in FACIT fatigue scores by 8-10 points (clinically significant change). The response translates to an improved patient quality of life, with a rise in FACIT fatigue scores, a reduction in blood transfusion requirements (including

	the small risk of transfusion related complications including iron overload) and reduced hospital attendances.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Iptacopan is an oral treatment, it will therefore be easier for patients. For healthcare professionals, a homecare nursing team will not be required as the treatments are oral rather than IV. Standard monitoring of bloods when starting a new treatment will be undertaken: Full blood count and LDH levels 2-3 weeks after treatment is initiated. Monitoring of lipids and urine protein will be required which are additional tests but will be undertaken with routine testing
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Starting treatment will depend on approved indications Stopping treatment: If patients have remitted their PNH clone to <10% treatment will be stopped (5-10% of patents over several years). Other situations would be a change of treatment rather than stopping complement inhibition and would be due to developing side effects or non-compliance
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some	PNH is an ultra-rare disorder, with patients treated by an NHSE commissioned service. The treatment is oral, and thus easier to administer. Pegcetacoplan, the only other approved proximal complement inhibitor is a subcutaneous infusion twice a week. When on holiday patients are required to

been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	take drug, infusion equipment with them, as well as requiring a fridge for storage which is quite inconvenient. Fatigue is experienced by a large proportion of patients with PNH, either due to anaemia, or due to extravascular haemolysis. This is often difficult to quantify in the current quality of life measures. Fatigue also reduce productivity of patients.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Technology: the advent of oral treatments for PNH increases options for patients, to have a treatment that fits their preference and lifestyle. Iptacopan is the first oral treatment and thus is a significant step change to disease management. Unmet needs: Iptacopan is a proximal complement inhibitor, and thus addresses both intravascular haemolysis, and prevents extravascular haemolysis. Haemoglobin increases to near normal/normal enables patients to improve their quality of life and productivity. There are currently over 12 - 20 patients within a managed access programme to address needs not met by current available treatments. As it is oral, patients with poor venous access and needle aversion are also treated. For patients with limited hand dexterity, pegcetacoplan is also challenging to administer.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Iptacopan side effect: Possible increase in lipids and urine protein– this requires monitoring with the standard PNH blood sampling. Other reported AEs were mild such as headache, diarrhoea, thrombocytopaenia (low plt), arthralgia

	Breakthrough haemolysis (BTH): this is when patients have a loss of complement inhibition and a recurrence of PNH symptoms. Patient education is essential to avoid missed doses of Iptacopan. Patients have 24 hour access to an oncall consultant with the PNH service, for advice in the event of becoming unwell/having BTH. BTH events within the phase three clinical trials were lower than with C5 inhibition. If patients develop BTH, a sudden Hb drop and LDH rise may occur, with which patients would feel unwell. This is manageable by experienced clinicians and can occur with all complement inhibitors.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The PNH service (Leeds and Kings) have participated in Iptacopan clinical trials, with patients experiencing a good response. The general population of treated and untreated patients is reflected similar to trial entry criteria, and thus responses would be similar. Currently there are 12-20 patients treated within a managed access scheme (patients who are unsuitable for or not responding to pegcetacoplan). Treatment is well tolerated, with 3 patients experiencing Hb improvement and 3 patients with stable Hb (from pegcetacoplan), the remainder have 3 month responses awaited.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA778; TA698]?	No
23. How do data on real-world experience compare with the trial data?	As above, we have 12-20 patients within a managed access scheme. These patients do not necessarily reflect the trial population as they are intolerant of or unsuitable for pegcetacoplan. The patients are responding similarly to the trial cohort. This is a small number of patients which are not yet publicly reported.

24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	All patients with PNH are treated within the NHSE commissioned service equally. Iptacopan clinical trials are for patient over the age of 18 and thus the paediatric cohort is not served by the current evidence. Approximately 14% of patients with PNH are below the age of 18, and are currently treated with ravulizumab or within a clinical trial for pegcetacoplan. Pregnancy: Patients who are pregnant are currently not advised to take Iptacopan, due to limited toxicology data. Patients are currently and will continue to be managed with eculizumab.

Topic-specific questions:

1. In the economic model, the annual probability of treatment discontinuation for the complement inhibitor-experienced population with residual anaemia, is informed by treatment-specific all-cause discontinuation rates in the APPLY-PNH trial for iptacopan, and the PEGASUS trial for pegcetacoplan (see row 1 in the table below).

Annual discontinuation rate in complement-inhibitor experienced population with residual anaemia			
	Iptacopan (24-week data), APPLY-PNH	**Iptacopan (48-week data), APPLY-PNH**	**Pegcetacoplan**
1	3.43%	2.72%	16.13% (PEGASUS trial)
2	3.43%	2.72%	Same as iptacopan
3	3.43%	2.72%	5%
4	3.43%	2.72%	10%

The EAG have considered alternative assumptions for the annual discontinuation rates, outlined in the table. Please could you advise which discontinuation rate for pegcetacoplan aligns most with your clinical expertise? Are the differences in discontinuation rates between iptacopan and pegcetacoplan similar to what you would expect in NHS clinical practice?

Comment: discontinuation rates are similar to current practice. Reasons for discontinuation include intolerance due t needle aversion, or recurrent breakthrough events. This is anticipated to be lower in Iptacopan but there is fewer patient years usage to date of Iptacopan compared to pegcetacoplan.

2. Please could you estimate the current proportion of people who have eculizumab and the proportion of people that have ravulizumab in the complement inhibitor-naïve and complement inhibitor-experienced populations in NHS clinical practice? Are there any considerations for using eculizumab rather than ravulizumab or vice versa?

Comment:

Complement naïve: Ravulizumab is therefore the main first treatment option for all patients except for indication of pregnancy. 40 patients were commenced on treatment (2022-2023) across Leeds and Kings service for England, one patient started eculizumab for the indication of pregnancy.

Complement experienced populations: There are a small number of women each year who change from ravulizumab to eculizumab for management through pregnancy, and a very small number of patients who have changed from ravulizumab to eculizumab for patient preference. In total there are approximately 30-35 patients on eculizumab and 271 patients on ravulizumab (2022-2023 data)

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

PNH is now a chronic disease once diagnosed in the UK, as C5 inhibition has near normalised life expectancy

Unmet needs in PNH remain, in particular with extravascular haemolysis with fatigue. Whilst addressed with pegcetacoplan it is not suitable for all patients

Iptacopan is the first oral treatment option available, with improved outcomes for complement treated and complement naïve patients with PNH

Increasing treatment options empowers patients in their disease ownership and management.

Thank you for your time.

Your privacy

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Iptacopan for treating paroxysmal nocturnal haemoglobinuria [ID6176]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with or caring for a patient with paroxysmal nocturnal haemoglobinuria. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

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NICE National Institute for Health and Care Excellence

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **4 April.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

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NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with paroxysmal nocturnal haemoglobinuria

Table 1 About you, paroxysmal nocturnal haemoglobinuria, current treatments and equality

1. Your name	Louise Peacock
2. Are you (please tick all that apply)	☒ A patient with paroxysmal nocturnal haemoglobinuria ? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with paroxysmal nocturnal haemoglobinuria ? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	PNH Support UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience

Patient expert statement

Iptacopan for treating paroxysmal nocturnal haemoglobinuria [ID6176]

	☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with PNH? **If you are a carer (for someone with PNH) please share your experience of caring for them**	Living with chronic illness is hard. There are the physical challenges that come with the illness itself – in the case of Aplastic Anaemia and PNH, this is extreme exhaustion, infection, breathlessness dysphagia haemolysis, regular hospital admissions and blood transfusions – and the psychological symptoms are equally gruelling. Permanent exhaustion can lead to depression, constant fear of infection breeds anxiety and we patients are often lonely and isolated. It's harder still when you have rare illnesses that only a small handful of individuals truly understand. Imagine the stress when you visit A&E at an unfamiliar hospital and the doctor googles your illness and then asks, "what treatment do you think you need?". I'm lucky. I have a voice and can champion my health and my needs, but I worry about those who don't. I hope my involvement here today will have a positive impact for others. PNH and Aplastic Anaemia are uncurable illnesses, but they are manageable. However, "management" is a very loaded term. The daily experience of living with chronic illness often feels like bare-knuckled survival. I was first diagnosed with severe Aplastic Anaemia in 2005 when I was three months pregnant. I was 28 and it was an extremely traumatic time. I was

	supported with red blood and platelet transfusions every one to two weeks for approx. five months and was isolated at home to avoid infection. My son was born a few weeks early and even at only one week old, his blood counts were better than mine! I slowly recovered and was no longer transfusion dependent. I was treated with Cycolsporin, iron and folic acid and my blood counts gradually stabilised though remaining low. Around about this time, I was told about another illness called PNH. This was an illness that was even rarer than Aplastic Anaemia that often developed in patients with bone marrow illness. My clone at the time was very small but grew over the following five years until I became increasingly symptomatic in 2011/2012. I was exhausted, struggled to swallow, was frequently breathless and suffered with chest and abdominal pain, plus severe headaches. I often had episodes of haemolysis with black urine and was frequently jaundiced. My LDH count was usually between 1500-2000 and I was treated with Warfarin to ameliorate the risk of clots.
7a. What do you think of the current treatments and care available for PNH on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	Eventually, I was treated with Eculizumab with regular fortnightly infusions in hospital. The first six months were brutal – I had severe side effects with nausea and dizziness but my LDH count dropped and the headaches eased. I was still at great risk from infection and frequently had severe haemolysis episodes where I would need to be admitted to hospital for treatment and blood transfusions. The fortnightly treatment also meant that I often felt on a roller-coaster of symptoms as the positive impact of the infusion would begin to wane relatively swiftly and struggled with venous access.

	In 2017, I started treatment with Ravelizumab. The change from fortnightly to two-monthly infusions was a positive step. I felt less medicalised and had a little more control of my life again. However, my HB count remained stubbornly low and so the exhaustion and fatigue continued as did the hospital admissions and transfusions. Sometimes a simple cold or sore throat was enough to trigger a severe haemolysis crisis. In the worst instance, my HB dropped to 59. I was also treated with IPO injections every week to try and boost my HB levels (usually around an average of 90-95). At this time, I was also really struggling with the severe pain of Endometriosis, knowing that I needed a hysterectomy but the instability of my PNH made this too dangerous.
8. If there are disadvantages for patients of current NHS treatments for PNH (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Throughout this period, I tried to live as normal a life as I could. I raised my son, kept hold of my career in publishing and am very grateful to my wonderful husband and family who helped me navigate it all. I tried to manage my daily ration of energy and consider how to spend it best. I tried not to mind that the options open to others were stubbornly out of my reach. Chronic illness makes life decisions for you and the layers of loss begin to accumulate like silt in a river. Beneath the surface, an undertow of sadness tugged at me, and I was referred to the psychological therapist in the haematology team. There are small losses that you try not to mind, such as missing parties or not being able to travel for work, but the larger losses are devastating. We could have only one child, not the large family we planned, and the need for isolation during the pandemic meant I was cut off from my father as he rapidly deteriorated with early onset dementia.

	These losses aren't counted on a blood count chart. Life marches on, regardless of illness, and being left behind is lonely.
9a. If there are advantages of Iptacopan for treating paroxysmal nocturnal haemoglobinuria over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does Iptacopan for treating paroxysmal nocturnal haemoglobinuria help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	And then in July 2021, I was lucky enough to be included on the trial for Iptacopan. Within a couple of weeks, my blood count shot up to over 120 – I was in the normal range for the first time in 17 years. The exhaustion lifted, the abdominal and chest pain disappeared, and I am now transfusion independent. My complexion turned from yellow/grey to pinkish white and my arms and veins began to heal. Sometimes, I can manage a short hike, I can climb stairs easily and, most importantly, some of the anxiety has lifted. I no longer live in fear of the possible consequences of a cold or fever, however mild. Iptacopan isn't a cure, though I wish it was. I have side effects to manage, I have little stamina and frequently need to sleep during the day. And, of course, living on strong immunosuppressants is tricky. Since then, I have had two severe infections – Covid and Pneumococcal Cellulitis (the latter requiring five days in hospital) – but these did not trigger haemolysis episodes or require any transfusions. In March 2023 I had the long-awaited hysterectomy and, again, did not suffer any episodes or require blood transfusions. I now live without the chronic pain of endometriosis and so my overall health has improved too. But am I less of a burden on the NHS (in terms of transfusions and hospital admissions) and I am more present in the workplace. I am more present to

	myself and to my family. Iptocapan has given me options and opened some doors, and all we want is options because options give us hope.
10. If there are disadvantages of Iptacopan for treating paroxysmal nocturnal haemoglobinuria over current treatments on the NHS please describe these. For example, are there any risks with this treatment? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from Iptacopan for treating paroxysmal nocturnal haemoglobinuria or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering PNH and Iptacopan for treating paroxysmal nocturnal haemoglobinuria? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or	

belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

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NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with paroxysmal nocturnal haemoglobinuria

Table 1 About you, paroxysmal nocturnal haemoglobinuria, current treatments and equality

1. Your name	Alex Naylor
2. Are you (please tick all that apply)	☐ **A patient with paroxysmal nocturnal haemoglobinuria? X** ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with paroxysmal nocturnal haemoglobinuria**?** ☐ **A patient organisation employee or volunteer? X** ☐ Other (please specify):
3. Name of your nominating organisation	PNH Support
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ **Yes, my nominating organisation has provided a submission X** ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ **Yes, I authored / was a contributor to my nominating organisations submission X** ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing X
5. How did you gather the information included in your statement? (please tick all that apply)	☐ **I am drawing from personal experience X**

Patient expert statement

Iptacopan for treating paroxysmal nocturnal haemoglobinuria [ID6176]

	☐ **I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: X** I am a Trustee of PNH Support and am involved in patient support activities that allow me to see a broader perspective of our patient population's needs across the country. ☐ I **have completed part 2 of the statement after attending the expert engagement teleconference X** ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with PNH? **If you are a carer (for someone with PNH) please share your experience of caring for them**	I was diagnosed in 2017, after a routine blood test flagged further investigation. It took six months of tests before being diagnosed. Within days of meeting the PNH Team at King's College Hospital I started on eculizumab at the standard dose (900mg IV). After three or four months I was still suffering from anaemia, fatigue and tests showed that the dose wasn't high enough to have a suitable effect on my disease. My prescription was increased to 1200mg and shortly afterwards I became pregnant. Before I was 12 weeks into my pregnancy I decided that I was too fatigued to work and gave up employment as a high-level Executive Assistant. My pregnancy was closely managed as it is considered high risk due to the heightened risk of thrombosis in a PNH patient; during this time my eculizumab dose was increased twice more (1500mg in second trimester and 1800mg in third trimester). I had one blood transfusion and treated for suspected meningitis during my pregnancy. After the birth of my child (July 2018) my eculizumab dose was brought down to 900mg but was again increased to 1200mg after a number of infections which brought about breakthrough haemolysis. During these infections I would be treated with additional eculizumab and antibiotics. The chronic symptoms of anaemia, fatigue, cognitive issues (language processing, memory loss), insomnia and breathlessness were always present. Having a small infant and these

	symptoms meant that I wasn't in a position to return to work. In autumn of 2019 I noticed that I had worsening abdominal bloating and pain, and issues with my digestion; along with further regular infections that were treated with additional eculizumab and antibiotics. In spring 2020 my regular dose of eculizumab was increased to 1500mg in an effort to boost my energy levels and alleviate the symptoms mentioned above and to help stave off further infections. This was then amended to 1200mg on a 12 day cycle, instead of the standard 14 day cycle, in an effort to 'tweak' the dose to my benefit. The increased management of my condition and physical health meant that I regularly suffered from anxiety and at times became depressed. Investigative hospital visits left me mentally and physically exhausted. The frequent IVs and blood tests left me with scarring in multiple places in my veins. It was standard to have 3-4 pricks before a suitable vein was found and this happened every 12 days. I had chronic fatigue, anaemia and cognitive issues, insomnia and joint pain as well as abdominal issues which were thought to be linked to low nitric oxide levels and smooth muscle dystonia. At best I was able to work 2-5 hrs per week, in order to manage my homecare nurse visits (to administer eculizumab), frequent hospital visits and maintain a steady state of health and energy that was required with a young family. I sorely missed my ability to work as it had previously given me my identity, a sense of self-worth and independence. In 2020 I was screened and invited to join a Phase 1 trial for a tablet – not Iptacopan. Within the first four weeks I had gained a significant amount of haemoglobin and my LDH levels had dropped to within normal levels. After six months I was taken off of eculizumab and have been in good health. This has been sustained for the past four years, with no hospitalisations and only minor infections. Importantly, my PNH doesn't flare up when I do suffer with a cold or everyday virus and the sustained improvements to my cognitive health have meant that I have navigated the multiple lockdowns over the past two years as well as studying and changing career. I have also been able to travel to the US and successfully manage my medication timings so that I have had no ill effects or PNH flare-ups.

	To help to quantify the massive changes in my life that a tablet delivery system has brought: I have since requalified and am now a Personal Trainer, specialising in Outdoors work; my son is 6 years old and I easily keep up with his high energy levels; I no longer experience problems when needing a blood test and am confident in taking my medication at its set times and travelling with it.
7a. What do you think of the current treatments and care available for PNH on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	**7a** My previous experience and knowledge of the population show me that the current standard of care does not cover or fully treat all patients; such as patients with extravascular haemolysis or those who do not feel able to undertake or maintain self-administered sub-cutaneous infusions. For some patients the current delivery methods (infusions and sub-cutaneous injections) can damage their physical and mental health. Family life, emotional wellbeing and ability to work or study are hindered by the associated management of infusion and sub-cut delivery methods. **7b** PNH Support undertook an online survey (comprising primarily multi-choice questions) in September 2023 of PNH patients and carers across England and Wales. 94 patients and carers provided completed survey responses. 90 responses were received from England: and 4 from Wales. 75 patients and 19 carers responded. I am aware from the responses to this survey that over half of patients surveyed stated they would like there to be more treatment options with different delivery methods e.g. injections, tablets etc. One patient commented "*Tablet form if effective would be brilliant. Saving cannulation*"; 45% of patients chose the response option "I would like there to be more treatment options which provide me with better quality of life (less symptoms etc)".

8. If there are disadvantages for patients of current NHS treatments for PNH (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Eculizumab/Ravulizmab: navigating and managing homecare arrangements impact both work and family life (including length and timing of holidays). The stress surrounding homecare arrangements also has a psychological impact. Repeated cannulation of veins leads to vein damage making infusions physically and psychologically difficult. Some patients on these treatments experience clinically significant extra-vascular haemolysis and a reduced quality of life and currently their only alternative treatment option is pegcetacopan. Pegcetacopan: Not all patients feel able to self-administer this sub-cutaneous delivery treatment for various reasons including confidence. Arrangements also need to be managed for the drugs and associated equipment to be delivered and stored in patients' homes.
9a. If there are advantages of Iptacopan for treating paroxysmal nocturnal haemoglobinuria over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does Iptacopan for treating paroxysmal nocturnal haemoglobinuria help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	**9a** – It's my understanding that Iptacopan benefits the entire UK PNH patient population in many aspects including quality of life, ability to work, study, provide caregiving and care for oneself. **9b** – In my opinion the most important advantage to Iptacopan is its delivery method, as this then positively impacts the other advantages listed above at 9a. **9c** – Treatment with Iptacopan negates all issues to do with homecare, vascular scarring, reduced qualtiy of life as a result of extravascular haemolysis and removes the need for patients to keep sharps and medical equipment in their homes.
10. If there are disadvantages of Iptacopan for treating paroxysmal nocturnal haemoglobinuria over current treatments on the NHS please describe these.	The 6 patients we surveyed in September 2023 who were treated with iptacopan were asked what they thought the disadvantages of the treatment were and half said there were none. However, named disadvantages were: concern about long term side effects; the number of times the iptacopan tablets needed to be taken per

For example, are there any risks with this treatment? If you are concerned about any potential side effects you have heard about, please describe them and explain why	day; and the need for the tablets to be stored in the fridge which impacts long distance travel. One patient stated that it had not eased his erectile dysfunction symptoms. I would also add that forgetting a treatment dose can lead to the return of symptoms in a short amount of time, which makes adherence very important. Clearly patient education around tablet adherence is a key factor that needs to be considered and planned for.
11. Are there any groups of patients who might benefit more from Iptacopan for treating paroxysmal nocturnal haemoglobinuria or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	In my opinion iptacopan has the capacity to benefit all groups of patients who qualify for treatment.
12. Are there any potential equality issues that should be taken into account when considering PNH and Iptacopan for treating paroxysmal nocturnal haemoglobinuria? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics	I am not aware of any equality issues.

More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	PNH Support's 2023 survey results revealed that over half of surveyed patients treated with iptacopan could now work full or part time since being treated with this drug. The independence, autonomy and improved quality of life experienced by patients on this treatment means they can be contributing members of society (through employment and other ways) which impacts their psychological wellbeing. All these factors also positively impact their carers/family and their wellbeing.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- From my perspective of having experienced 2 different treatment delivery methods (intravenous infusions and tablets) I believe all PNH patients needing treatment would benefit from being treated with iptacopan. The independence and autonomy provided by a tablet delivery method can contribute to improved mental health and wellbeing.
- Treatment with a tablet (as the least invasive delivery method) will allow patients (and their carers) to be contributing members of society including through working, studying or caregiving. Employment means patients can contribute more fully to society and can rely less on the State and their families leading to increased independence and quality of life.
- There are a number of disadvantages to treatment with intravenous infusion with the most significant being the damage to veins from repeated cannulation and the burden of managing the arrangements for the infusions which also has a psychological impact.
- There are disadvantages to treatment with a sub-cutaneous injection including dealing with self-administration and managing the delivery of the drug and associated equipment.
- I am aware that the majority of patients and carers would like there to be more treatment options available. The individual nature of PNH means that having a variety of treatment options means that more patients (and therefore their families) have the possibility of a better quality of life.

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