Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende pegcetacoplan til behandling af paroksystisk natlig hæmoglobinuri

Til patienter med hæmolytisk anæmi (1. linjebehandling)

Vers. 1.0

Bilagsoversigt

1. Forhandlingsnotat fra Amgros vedr. pegcetacoplan
2. Ansøgers endelige ansøgning vedr. pegcetacoplan

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08.07.2024

DBS/MGK

Forhandlingsnotat

Dato for behandling i Medicinrådet	28.08.2024
Leverandør	SOBI
Lægemiddel	Aspaveli (pegcetacoplan)
Ansøgt indikation	Aspaveli (pegcetacoplan) er indiceret til behandling af voksne patienter med paroksystisk natlig hæmoglobinuri (PNH).
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har følgende pris på Aspaveli (pegcetacoplan):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Nuværende SAIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Aspaveli	1080 mg	1 stk.	25.704,75	[redacted]	[redacted]	[redacted]
Aspaveli	1080 mg	8 stk.	205.638,00	[redacted]	[redacted]	[redacted]

Aftaleforhold

[redacted]

Konkurrencesituationen

Leverandøren har ansøgt om ibrugtagning af Aspaveli til 1. linje behandling af PNH. Amgros er orienteret om at Medicinrådet vil udarbejde en behandlingsvejledning for PNH i nærmeste fremtid.
Der er flere lægemidler, som har indikation til PNH: biosimilære eculizumab, Ultomiris (ravulizumab) og Aspaveli (pegcetacoplan).

Tabel 2 viser lægemiddeludgifter på udvalgte sammenlignelige lægemidler.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. 01.06.2024 pr. år (SAIP, DKK)
Aspaveli	1080 mg	1 stk.	1080 mg 2 gange om ugen/SC	[redacted]	[redacted]
Ultomiris (ravulizumab)	1100mg	1 stk.	3.300 mg hver 8. uge /IV	[redacted]	[redacted]
Bekemv biosimilær (eculizumab)	300mg	1 stk.	900 mg hver 14. dg/IV	[redacted]	[redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Kommentarer	Link
Norge	Clock stop		Link til vurdering
Sverige	Ingen data	Godkendt til 2. linje behandling. Ingen data for 1. linje behandling.	
England	Ingen data	Godkendt til 2. linje behandling. Ingen data for 1. linje behandling	

Konklusion

[redacted]

Application for the assessment of Aspaveli (pegcetacoplan) as monotherapy in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information
[Other]	[Definition of color-code]

Contact information

Contact information	
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Table of contents

Tables and Figures

Abbreviations

Acronym	Definition
AA	Aplastic anaemia
AIC	Akaike information criterion
AP	Anchored protein
ARC	Absolute reticulocyte count
ATC	Anatomical therapeutic chemical
BIC	Bayesian information criterion
BMF	Bone marrow failure
BMI	Body mass index
BMT	Bone marrow transplant
BSC	Best supportive care
BTH	Breakthrough haemolysis
CEM	Cost-effectiveness model
CI	Confidence Interval
COVID	Coronavirus disease
CSR	Clinical Study report
CTCAE	Common Terminology Criteria for Adverse Events
DK	Denmark
DKK	Danska kronor
DMC	Danish Medicines Council
DRG	Diagnostic-related groups
DSU	Decision support unit
EBMT	European Society for Blood and Marrow Transplantation
EC	European Commission
ECG	Electrocardiogram
ECRD	European conference on rare disease and orphan products
ECU	Eculizumab
EHA	European Hematology Association
EMA	European Medicines Agency
EMBASE	Biomedical research database
EORTC	European Organisation for Research, Treatment of Cancer
EQ	EQ-5D-5L was introduced by the EuroQol Group
ESS	Effective sample size
EVH	Extravascular haemolysis
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	Food and drug administration
FL	Florida
GHS	Global health status
GPI	Glycosylphosphatidylinositol
Hb	Haemoglobin
HR	Hazard ratio
HSCT	Haematopoietic stem cell transplantation
HSUV	Health state utility values
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
IPIG	International PNH Interest Group
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intent-to-treat

Acronym	Definition
IV	Intravenous
IVH	Intravascular haemolysis
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
LDPRC	Leukocyte-depleted red blood cells
LLN	Lower Limit of Normal
LPB	Leukocyte poor blood
LPRC	Leukocyte poor packed red blood cell
LS	Least square
MAC	Membrane attack complex
MAIC	Matching adjusted indirect treatment comparison
MASP	Mannose-Binding Lectin -Associated Serine Proteases
MAVE	Major adverse vascular event
MBL	Mannose-Binding Lectin
NA	Not available
NCT	National clinical trial
NICE	National Institute for Health and Care Excellence
NO	Nitric oxide
OLE	Open-label extension
OR	Odds ratio
OS	Overall survival
OVID	Medical information search database
PDF	Portable document format
PESG	Paroxysmal nocturnal haemoglobinuria Education Study Group
PFS	Progression free survival
PNH	Paroxysmal nocturnal haemoglobinuria
PRBC	Packed red blood cells
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life-year
QLQ	Quality-of-Life Questionnaire
QoL	Quality-of-Life
RBC	Red blood cell
RBCT	Red blood cell transfusion
RCP	Randomised controlled period
RCT	Randomised controlled trial
RDI	Relative dose intensity
REF	Reference
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
TCC	Terminal complement complex
TE	Thromboembolism
UK	United Kingdom
ULN	Upper limit of normal
US	United States

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Aspaveli
Generic name	Pegcetacoplan
Therapeutic indication as defined by the European Medicines Agency (EMA)	Expected indication: Aspaveli is indicated as monotherapy in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia
Marketing authorization holder in Denmark	Swedish Orphan Biovitrum AB (Sobi)
ATC code	L04AJ03
Combination therapy and/or co-medication	No
(Expected) Date of EC approval	May/June 2024
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the EMA	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	Aspaveli is indicated in the treatment of adult patients with PNH who are anaemic after treatment with a C5 inhibitor for at least 3 months.
Other indications that have been evaluated by the DMC (yes/no)	Yes. DMC has evaluated Aspaveli for the treatment of adult patients with PNH who are anaemic after treatment with a C5 inhibitor for at least 3 months.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	1080 mg, 20 mL single-dose vial, 1-unit pack and 8-unit pack Strength: 54 mg/mL

Source: EMA (2024)

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	Expected indication: Aspaveli is indicated as monotherapy in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia
Dosage regiment and administration	Solution for infusion. 1,080 mg subcutaneous infusion, twice weekly.
Choice of comparator	Eculizumab, concentrate for solution for infusion.
Prognosis with current treatment (comparator)	Despite treatment with C5 inhibitors PNH patients may suffer from residual intravascular haemolysis (IVH) due to suboptimal C5 inhibition leading to persistent anaemia, as well as extravascular haemolysis (EVH) which is associated with residual anaemia and increased biomarkers of haemolysis (Risitano et al. 2009). Residual anaemia contributes to fatigue, following reduced quality of life, therefore anaemia has emerged as an unmet clinical need in PNH (Risitano et al. 2009). Patients with suboptimal response to treatment with C5 inhibitors and anaemia are receiving blood transfusions (Risitano and Peffault de Latour 2022). A study by Hansen and colleagues included 5,868 Danish patients with acquired haemolytic disorders, whereof 116 PNH patients. The median survival after diagnosis of acquired haemolysis was 23.2 years (Hansen et al. 2020).
Type of evidence for the clinical evaluation	Matching adjusted indirect treatment comparison (MAIC).
Most important efficacy endpoints (Difference/gain compared to comparator)	After weighting in the matching adjusted indirect comparison (MAIC) of pegcetacoplan versus eculizumab, treatment with pegcetacoplan was associated with statistically significant improvements in most clinical and haematologic endpoints compared with eculizumab treatment. A larger proportion of patients treated with pegcetacoplan achieved haemoglobin (Hb) stabilization than patients who received eculizumab (92.23% vs. 64.50%, diff.: 27.73%, p = 0.0001). Pegcetacoplan also showed a greater absolute and percent reduction in LDH level from baseline compared with eculizumab (-2,086.67 U/l, -88.44% vs.-1,199.82 U/l, -76.02%, diff.: - 886.85 U/l and – 12.42%, respectively, both p=0.0001). Additionally, more patients who received pegcetacoplan avoided transfusion during the randomised controlled period than patients who received eculizumab (92.23% vs. 66.10%, diff.: 26.13%, p = 0.0002) (Wong et al. 2023a).

Summary	
Most important serious adverse events for the intervention and comparator	PRINCE: The SAEs in the pegcetacoplan group included anaemia (2.2%), haemolysis (2.2%), thrombocytopenia (2.2%), bone marrow failure (2.2%) and febrile neutropenia (2.2%) and in the supportive care group anaemia (5.6%), thrombocytopenia (5.6%), bone marrow failure (5.6%), febrile neutropenia (5.6%), acute kidney injury (5.6%) and respiratory failure (5.6%). None (0%) of the SAEs were deemed related to pegcetacoplan treatment. There were 2 AEs leading to death, 1 each in the pegcetacoplan (2.2%) and the supportive care (5.6%) group, and both were deemed unrelated to treatment. Study 301: The SAEs in the eculizumab group included ileus (0.8%), pyrexia (1.7%), pneumonia (0.8%), lung adenocarcinoma and adenocarcinoma (0.8%) of the colon (0.8%) and in the ravulizumab group anaemia (0.8%), thrombocytopenia (0.8%), neutropenia (0.8%), myocardial ischemia (0.8%), pyrexia (0.8%) and renal colic (0.8%).
Impact on health-related quality of life	After weighting in the MAIC, pegcetacoplan was associated with a greater increase in EORTC QLQ-C30 general health status compared with eculizumab (25.42 vs 12.90, difference 12.52, p=0.0133) (Wong et al. 2023a).
Type of economic analysis that is submitted	Cost-utility analysis Markov model
Data sources used to model the clinical effects	PRINCE trial data and MAIC
Data sources used to model the health-related quality of life	PRINCE trial data
Life years gained	[redacted]
QALYs gained	[redacted]
Incremental costs	[redacted]
ICER (DKK/QALY)	[redacted]
Uncertainty associated with the ICER estimate	[redacted]
Number of eligible patients in Denmark	The incidence rate per 100,000 person-years in the period 2008 – 2016 was estimated at 0.08 for PNH, which gives an

Summary	
	estimated total PNH incidence of four patients per year based on a population of 5.9 million people (Hansen et al. 2020). Of these, approximately 50% have a clone in need of complement treatment which gives an estimate of two eligible patients in Denmark per year (Svensk förening för hematologi 2021). In the DMC recommendation of pegcetacoplan in second line there was an incidence estimate of 3-4 patients (Medicinrådet 2023). The prevalence per 100,000 persons was estimated at 1.04 for PNH (Hansen et al. 2020), which results in a prevalence of 62 patients in Denmark. The slightly lower figure of 50 prevalent cases was estimated by the DMC in the recommendation of pegcetacoplan in second line (Medicinrådet 2023).
Budget impact (in year 5)	[redacted]

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare and potentially life-threatening disease characterized by the complement-mediated destruction of red blood cells (RBCs), known as haemolysis. PNH results in anaemia, thrombosis, bone marrow dysfunction and a variety of other symptoms and complications (Parker et al. 2005, Kanakura and Kinoshita 2017, Besa 2021).

3.1.1 The complement system and the pathophysiology of PNH

The complement system is a central part of the immune system involved in defence against pathogens, host and cellular homeostasis, and regulation of the immune response (Merle et al. 2015).

It is activated in a stepwise fashion and can be divided into four stages: initiation; C3 convertase formation; C5 convertase formation and terminal complement complex (TCC) or membrane attack complex (MAC) formation, as shown in Figure 1 (Janeway Jr et al. 2001). Complement proteins and receptors work together or separately to mediate different functions in the body and is tightly regulated to avoid damaging own cells and tissues.

In PNH the protective regulators are lacking and consequently the RBCs are unable to protect themselves and are haemolysed (Merle et al. 2015). The cause of this deficiency is an acquired somatic mutation in the phosphatidylinositol glycan anchor biosynthesis class A (PIG-A) gene in the haematopoietic stem cells (HSC). The PIG-A gene is essential for the synthesis of the glycosyl phosphatidylinositol (GPI) anchor required to attach proteins to the cell membrane (Hill et al. 2017). Because stem cells are precursors for different blood cell types, such as erythrocytes, leukocytes, and platelets, the loss of the GPI anchor leads to the under-expression of various cell surface proteins on these cells (Devalet et al. 2015).

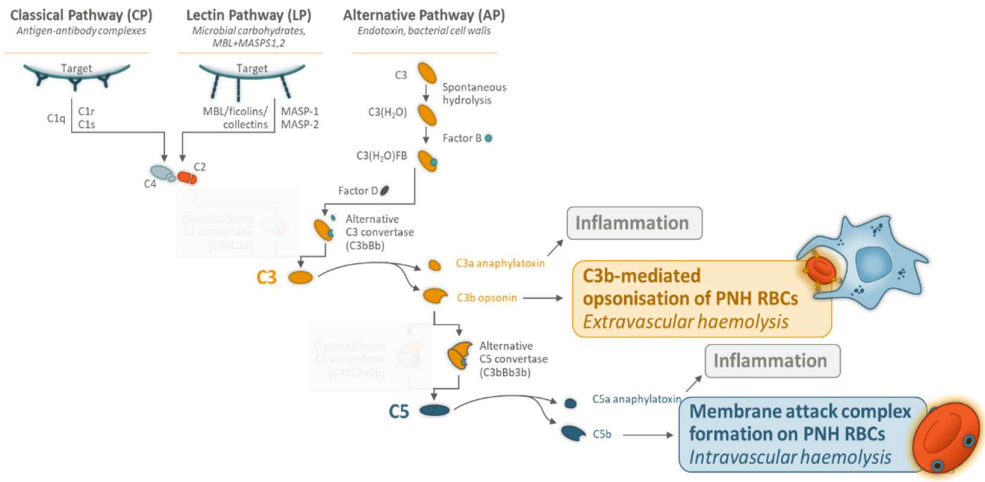
Although GPI anchors more than 150 proteins, two cell surface proteins are of significance for the pathology of PNH: CD55 and CD59. Both CD55 and CD59, when expressed on the cell surface of blood cells, are protective against the complement system, and conversely, in PNH, the loss of CD55 and CD59 on the cell surface of blood cells leads to complement activation that will result in complement-mediated rupturing of RBCs (haemolysis) (Brodsky 2014, Hill et al. 2017).

3.1.2 Haemolysis

There are two types of haemolysis:

- Intravascular haemolysis (IVH) is the destruction RBCs within the circulatory system due to MAC formation on PNH RBCs leading to direct lysis (Figure 1) (Risitano et al. 2019).
- Extravascular haemolysis (EVH) is the destruction of RBCs within the spleen or liver due to C3b-mediated opsonisation and phagocytosis (Figure 1) (Risitano et al. 2019).

Figure 1 The complement system in PNH



MASP = MBL-Associated Serine Proteases; MBL = Mannose-Binding Lectin; PNH = Paroxysmal Nocturnal Haemoglobinuria; RBC = Red Blood Cell.

Source: (Risitano et al. 2019).

Haemolysis results in anaemia and increased levels of free haemoglobin (Hb) in plasma.

- The level of serum Hb is a direct marker of the severity of the haemolysis and a predictor of therapy outcome. It also correlates with the risk of death (Barcellini and Fattizzo 2015, Brodsky 2014, Risitano and Rotoli 2008).
- Increased levels of free Hb can lead to nitric oxide (NO) depletion. NO reduction may contribute to the development of more serious complications such as pulmonary embolism, renal failure, and most commonly thrombosis, given that NO deficiency increases platelet aggregation and accelerates clot formation.
- Released Hb is eventually excreted via urine (haemoglobinuria) (Van Bijnen et al. 2012, Rother et al. 2005).

Haemolysis also leads to the release of other compounds, including lactate dehydrogenase (LDH) and bilirubin. LDH is only released upon cell or tissue damage, and RBCs contain LDH; therefore, an elevated serum LDH level is a sensitive measure of RBC injury, and the level correlates with the extent of RBC damage (haemolysis). As a result of IVH, the circulating levels of the enzyme LDH will be increased. LDH is used both as a diagnostic tool and to monitor the severity of haemolysis.

IVH and EVH can have distinct clinical and lab parameter correlates, depending upon which type of haemolysis is dominant in a patient at a particular time over the course of their disease (Janeway Jr et al. 2001, Brodsky 2014, Barcellini and Fattizzo 2015, Risitano and Rotoli 2008, Zwarthoff et al. 2018, Hill et al. 2017, Kanakura and Kinoshita 2017).

Reticulocytosis in the presence of greatly elevated LDH and, to a lesser extent, elevated bilirubin levels suggest IVH. Reticulocytosis in the absence of elevated LDH, or with slightly elevated LDH, and increased bilirubin levels suggests EVH. Signs of EVH can be inconspicuous in untreated PNH because signs of IVH dominate (Barcellini and Fattizzo 2015, Brodsky 2014).

3.1.3 Clinical manifestations

Due to the complement-mediated haemolysis, patients with PNH may present with multiple clinical symptoms like fatigue, dyspnoea, haemoglobinuria, thrombosis, anaemia, renal dysfunction or damage and smooth muscle dystonia (abdominal pain, erectile dysfunction, and dysphagia). The specific symptoms, progression, and severity vary from one person to another (Mitchell et al. 2017, Parker et al. 2005, Nishimura et al. 2014, Hill et al. 2013, Devalet et al. 2014, Hill et al. 2017, Hillmen et al. 1995).

3.1.3.1 Anaemia

As a result of the haemolysis, patients often present with anaemia. Anaemia in patients with PNH in the context of other primary marrow disorders, such as aplastic anaemia (AA), is characterized by a low level of granulocytes and thrombocytes, low reticulocyte counts, and a modest or no increase in LDH levels (Brodsky 2014) .

3.1.3.2 Fatigue

Fatigue is the leading symptom among patients with PNH (experienced by ≥79% of PNH patients) and is most pronounced during a haemolytic episode but may be experienced regardless of disease severity (clone size and disease activity) (Schrezenmeier et al. 2020). Fatigue may worsen during infections, exercise, pregnancy, or after excessive alcohol consumption and is associated with lower quality of life (QoL) (Hill et al. 2017).

3.1.3.3 Thrombosis

Thrombosis is one of the most severe complications of PNH and is the major cause of death, followed by infectious complications and haemorrhage (Hill et al. 2013, Risitano and Rotoli 2008). In untreated patients with PNH, thrombosis accounts for up to 50% of mortality (Hill et al. 2017). Thrombosis occurs in about 40% of patients with untreated PNH. Most common are venous thrombosis of the liver, abdomen, and the brain. In addition, deep vein thrombosis, pulmonary emboli, and dermal thrombosis are common. The risk of developing thrombosis is correlated with the proportion of PNH clones and the severity of IVH that causes the release of Hb and depletion of NO, which in turn activates platelets (Berentsen et al. 2019, Young et al. 2009, Hill et al. 2013, Devalet et al. 2014, Hillmen et al. 1995).

3.1.3.4 Haemoglobinuria

As a result of the haemolysis, free Hb is released in the serum and eventually excreted via the urine (haemoglobinuria) leading to dark coloured urine. However, not every

patient with PNH has dark urine: haemoglobinuria is cited by almost 50% of patients (Hill et al. 2017).

3.1.3.5 Renal dysfunction or damage

Free Hb is toxic to the kidneys. Hence, kidney failure is a source of morbidity and mortality in patients with PNH. Renal dysfunction or damage present in up to 65% of PNH patients (Hillmen et al. 2010).

3.1.3.6 Smooth muscle dystonia

Another downstream effect of free Hb is the depletion of NO, which is important for smooth muscle cell regulation. Absence or lower amounts of NO can have, consequently, gastrointestinal spasms, abdominal pain, difficulty swallowing, vasoconstriction, pulmonary and systemic hypertension, and erectile dysfunction (Berentsen et al. 2019). Depletion of NO can also precipitate thrombosis as it can activate and, thus, cause aggregation of platelets.

3.1.4 Classification of PNH

The International PNH Interest Group (IPIG) developed a classification scheme for PNH. Depending on the clinical manifestation of the disease (clone size, haemolysis and bone marrow disorder) there are three different subcategories: classic PNH, PNH in the setting of an associated bone marrow disorder, and subclinical (asymptomatic) PNH (Parker et al. 2005, Hill et al. 2017). The only known risk factor for PNH is AA. In patients with AA, the risk of developing clinical PNH is 15%-25% (Schubert et al. 2012).

3.1.5 Patient journey and diagnosis method

On average, it takes close to 2 years and often multiple providers to correctly diagnose PNH due to its rarity and the nature of its diverse symptoms (Mitchell et al. 2017). More than one-third of patients reported to have received a diagnosis more than 2 years after onset of symptoms; in some cases, it took more than 5 years (Mitchell et al. 2017, Shammo et al. 2015).

Patients most often seek medical help from their primary care physician for fatigue, excessive weakness, or dark urine. Other often reported patient complaints are difficulty breathing (dyspnoea) and abdominal or back pain. Although the majority of patients (54%) consulted a primary care physician, a significant number (about 15%) went to the emergency department to receive care (Mitchell et al. 2017). Only one-third of these patients seeking help for their symptoms were later referred to a haematologist. A significant delay in diagnosis can therefore contribute to patient mortality (Mitchell et al. 2017).

Given its rarity and ambiguous symptoms, a PNH diagnosis is typically sought after a patient presents in the clinic with a combination of particular symptoms and clinical manifestations (Mitchell et al. 2017).

If PNH is suspected, the physician may order different blood tests (Brodsky 2009). The most sensitive and reliable diagnostic test that confirms the presence of PNH clone is flow cytometric evaluation of GPI-AP. Determining PNH clone size is important for

determining the severity of the disease, risk for thrombosis, classifying PNH and deciding on appropriate management for the disease (Kanakura and Kinoshita 2017, Moyo et al. 2004, Gupta et al. 2010, Chan et al. 2018).

3.1.6 Patient prognosis and quality of life

Before specific therapy was available, PNH resulted in the death of approximately half of all patients, mainly through thrombotic complications (Hillmen et al. 1995), 10-year mortality rates of 24%-29% for patients with PNH who had no active treatment (de Latour et al. 2008, Fujioka and Asai 1989, Fu et al. 2020). Overall, in patients with PNH with known cause of death, thromboembolism (TE) is the primary source of mortality responsible for between 40% and 67% of deaths (Schrezenmeier et al. 2014). Renal failure is another significant source of mortality in patients with PNH accounting for 8% to 18% of deaths (Kokoris et al. 2018).

The current therapy with C5 inhibitors (eculizumab and ravulizumab) has shown to reduce the thromboembolic risk, thereby impacting on the disease course, morbidity, and long-term survival (Hillmen et al. 2007). However, a large proportion of patients treated with C5 inhibitors remain anaemic, with evidence of EVH (Kelly et al. 2023). In a European cross-sectional survey of adults with PNH treated with eculizumab, total Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue and European Organisation for Research, Treatment of Cancer Quality-of-Life Questionnaire (EORTC QLQ-C30) scores were substantially lower than European general population references (Panse et al. 2022). Similar results were found in a cross-sectional study from the USA (Dingli et al. 2022).

3.2 Patient population

Hansen et al. (2020) collected data regarding all patients with acquired haemolytic disorder diagnoses in 1977 – 2016 from the Danish National Patient Register. The analysis included 116 patients with PNH, and the incidence rate per 100,000 person-years in the period 2008 – 2016 was estimated at 0.08 for PNH. The prevalence proportion per 100,000 persons was estimated at 1.04 for PNH (Hansen et al. 2020). The population size of Denmark was 5,962,689 in February 2024 (Statistics Denmark 2024). Applying the figures from Hansen et al. on this figure gives us a prevalence of 62 patients, and an incidence of approximately four patients per year. The slightly lower figures of 50 prevalent and 3-4 incident patients with PNH were estimated by the Medicines Council in the recommendation of pegcetacoplan in second line (Medicinrådet 2023).

In the PNH population studied by Hansen et al., the median age at diagnosis was 48.4 years (IQR: 31.7, 67.0) and the median age at death was 71.5 years (IQR: 56.5, 79.6) in a PNH population studied in Denmark (Hansen et al. 2020).

Table 1 Incidence and prevalence in the past 5 years

Year	2019	2020	2021	2022	2023
Incidence in Denmark	4	4	4	4	4
Prevalence in Denmark	50-62	50-62	50-62	50-62	50-62
Global prevalence *	N/A	N/A	N/A	N/A	N/A

* For small patient groups, also describe the worldwide prevalence.

Of the four incident patients per year, approximately 50% have a clone in need of complement treatment which gives an estimate of 2 new eligible patients in Denmark each year, and about 25-30 prevalent patients on treatment with complement inhibitors (Medicinrådet 2023, Svensk förening för hematologi 2021).

Table 2 Estimated number of patients eligible for 1L treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	2	4	6	8	10

3.3 Current treatment options

Danish treatment guidelines for PNH have been published by the Danish Haematological Society (Dansk Haematologisk Selskab 2013). Treatment alternatives include blood transfusion, oral iron and folic acid supplementation, bone marrow transplantation, and pharmacotherapy targeting the complement system. Current Danish treatment guidelines are based on the treatment algorithm outlined by the PNH Education Study Group (PESG) founded on the three treatment categories (Sahin et al. 2016):

- Supportive/immunosuppressive treatments
- Treatments changing the course of disease
- Potential curative treatment

3.3.1 Curative treatment

Currently, the only cure for PNH is allogeneic haematopoietic stem cell transplantation (HSCT) . Because of the considerable challenges and risks involved, a bone marrow transplant (BMT) is not a therapeutic option for most patients and is typically

recommended for patients with severe bone marrow failure (BMF), reoccurring life-threatening thromboembolic incidences, and refractory transfusion-dependent haemolytic anaemia (Sahin et al. 2016, Young et al. 2009). In a retrospective study of 26 patients with PNH who received haematopoietic stem cell transplants between 1988 and 2006, the transplant-related mortality rate was 42% (Santarone et al. 2010).

3.3.2 Noncurative treatments

PNH therapy is oriented toward the prevention or treatment of specific symptoms and includes a variety of different therapeutic approaches. The current standard of care (SoC) for PNH in most regions are C5 inhibitors: eculizumab and ravulizumab (EMA 2023b, EMA 2023d).

3.3.2.1 Best supportive care

A number of treatments are currently available to manage the symptoms for patients with PNH.

Depending on the symptoms of anaemia, patients may receive RBC transfusions. Transfusions temporarily improve haemolysis and elevate Hb levels, as the transfused cells express CD59 and CD55 on their cell surface and are resistant to complement-initiated lysis (Dansk Haematologisk Selskab 2013, Sahin et al. 2016).

Supplementation with folate, iron, and vitamin B12 can support increased erythropoiesis in the bone marrow (Dansk Haematologisk Selskab 2013, Sahin et al. 2016).

Corticosteroids, though controversial due to their significant side effects, are sometimes used in short-term regimens to address symptomatic EVH (Dansk Haematologisk Selskab 2013, Sahin et al. 2016).

For managing thrombotic risk, prophylactic anticoagulant therapy with coumarin derivatives or heparin may be considered. In cases of acute thrombosis, heparin is typically employed (Dansk Haematologisk Selskab 2013, Sahin et al. 2016). Despite preventive measures, the risk of thrombohaemolysis remains considerable, although eculizumab therapy has shown a marked reduction in thrombotic events (Schrezenmeier et al. 2014).

3.3.2.2 Complement inhibitors targeting C5

To date, the European Medicines Agency (EMA) have approved two complement-inhibitory drugs targeting C5 for patients with PNH: eculizumab (Soliris®) and ravulizumab (Ultomiris®) (EMA 2023b, EMA 2023d). Two biosimilars of eculizumab, Bekemv® and Epysqli®, were recently approved by EMA (EMA 2023a, EMA 2023c). C5 inhibitors inhibit the formation of the MAC and in doing so compensates for the CD59 deficiency of patients with PNH. C5 inhibitors are effective in handling the IVH in PNH.

Eculizumab is a humanized monoclonal antibody administered as an intravenous (IV) infusion specifically designed to target the complement protein C5, thereby preventing its cleavage and the formation of the terminal attack complex. This averts the

complement-mediated lysis of blood cells and haemolysis (McKeage 2011, Young et al. 2009). Eculizumab was granted EMA approval in June 2007 based on the results of the TRIUMPH study and the prespecified interim 26-week analysis of the SHEPHERD study. According to the current EMA label, eculizumab is indicated in adults and children for the treatment of PNH (EMA 2023b).

Ravulizumab is an eculizumab-like monoclonal antibody that is administered with longer intervals than eculizumab. The IV formulation of ravulizumab was approved by the EMA on July 3, 2019, for the treatment of patients with PNH. The subcutaneous (SC) formulation of ravulizumab was approved by the EMA in May 2023 (EMA 2023d).

3.3.2.3 Complement inhibitors targeting C3

Pegcetacoplan is the first and only self-administered SC C3-targeted therapy for PNH patients, which gives an opportunity for self-administration (Hillmen et al. 2021). Pegcetacoplan was first approved by the EMA in December 2021, in complement-inhibitor-experienced adult PNH patients (EMA 2024), and it was recommended for this indication by the Medicines Council in November 2023 (Medicinrådet 2023). Pegcetacoplan exerts broad regulation of the complement cascade by binding to C3 and C3b, thereby controlling the mechanisms that lead to both EVH and IVH.

3.3.3 Unmet need

3.3.3.1 Unmet need despite treatment with supportive care

In patients with PNH, haemolysis contributes significantly to anaemia, and treatment is indicated for several reasons: (1) patients with chronic haemolysis complain of lethargy, malaise, fatigue, and loss of sense of well-being that significantly diminishes QoL; (2) there is evidence that chronic haemolysis has a negative effect on renal function; (3) the dysphagia and male impotence of PNH appears to be related to haemolysis; and (4) a correlation between thrombosis and haemolysis may exist (Parker et al. 2005, Hill et al. 2013, Hill et al. 2017, Risitano and Rotoli 2008).

Treatment with supportive care, such as corticosteroids, supplements, and RBC transfusions, is limited by inconsistent response rates and unfavourable toxicity profiles. There are no experimental data that provide a plausible explanation for why steroids should ameliorate the haemolysis of PNH. Folate supplementation is recommended to compensate for increased utilisation associated with heightened erythropoiesis that is a consequence of haemolysis but is not used to treat the underlying condition (Parker et al. 2005).

Anaemia is most often treated with RBC transfusions. IV administration of RBC transfusions require invasive procedures and results in high use of health care resources (Bittner et al. 2018). Transfusion dependence has a negative impact on a patient's QoL and requires substantial resources, including hospital admissions. Iron overload is a consequence of chronic transfusions and is associated with an elevated risk of morbidity and mortality (Platzbecker et al. 2012). After transfusion of 10-20 units of RBCs, a majority of people develop iron overload because the body cannot effectively excrete

excess iron (Gao et al. 2014). Iron is, therefore, deposited in parenchymal tissues and in reticuloendothelial cells, and, without a chelating therapy, can cause progressive damage to the liver, heart, endocrine system, brain, and joints (Gao et al. 2014, Takatoku et al. 2013). Transfusion-dependent patients may progress to secondary iron overload with organ impairment, which may be fatal in those who are heavily iron-overloaded (Gao et al. 2014).

For PNH patients treated with supportive care alone, the unmet need is thus very high.

3.3.3.2 Unmet need despite treatment with C5 inhibitors

The availability of C5 inhibitors therapies has significantly improved clinical outcomes and overall survival in PNH patients by lowering the risk of IVH and thrombosis. However, there are limitations to treatment with C5 inhibitors and unmet clinical needs remain for patients with PNH.

Even if C5 inhibitors have shown to be effective at targeting the IVH in PNH, most patients with PNH on C5 inhibition will experience mild to moderate C3-mediated EVH as well as residual IVH (Bittner et al. 2018, Stoner et al. 2014). As C5 inhibitors do not compensate for the CD55 deficiency, the C3d (a split product of C3b) deposition on the PNH red cells in patients treated with C5 inhibitors leads to the emergence of EVH (in 25-50% of patients treated with eculizumab) (McKinley et al. 2017, Brodsky 2014, Risitano et al. 2019, Hill et al. 2017). Further, PNH patients display elevated LDH levels, absolute reticulocyte count (ARC) and bilirubin levels during C5 inhibitor therapy, indicating ongoing haemolysis (Fishman et al. 2023, Versmold et al. 2023).

The majority of PNH patients experience a suboptimal response to C5 inhibitors and remain anaemic (Dingli et al. 2022, Panse et al. 2022, Sicre de Fontbrune et al. 2022, Hillmen et al. 2013, Risitano et al. 2019). Chronic anaemia may be associated with various complications such as cognitive impairment, heart complications, pulmonary hypertension, kidney failure, decreasing QoL and increasing fatigue. Cognitive problems included memory loss, confusion, brain fog, problems concentrating, and difficulty focusing on tasks (Schneider et al. 2016, Shah and Agarwal 2013, Badireddy and Baradhi 2020). As a result, patients treated with C5 inhibitors continue to experience persistent PNH symptoms, the most common being anaemia-related fatigue, with a considerable negative impact on QoL measures as documented by mean FACIT-Fatigue, global health status (GHS) and Physical Functioning scores (Dingli et al. 2022, Panse et al. 2022, Sicre de Fontbrune et al. 2022, Muus et al. 2017). In Denmark, it is estimated that 8-10 out of 25-30 patients with PNH on treatment with C5 inhibitors have an unsatisfactory response to treatment (Medicinrådet 2023).

Accordingly, despite C5 inhibitor treatment, many PNH-patients still require transfusions (Dingli et al. 2022, Sicre de Fontbrune et al. 2022, Fishman et al. 2023, Kelly et al. 2022, McKinley et al. 2017, Versmold et al. 2023). In a German long-term study of 76 patients treated with eculizumab over a mean follow-up of 5.6 years, 43% experienced breakthrough haemolysis (BTH) and 63% transfusion dependence during follow-up (Versmold et al. 2023). In the Netherlands, out of 33 PNH patients who started eculizumab because of transfusion dependency, only 2 (6.1%) had reached a complete

haematological response after 12 months of therapy (Schaap et al. 2023). In Denmark, [redacted]

3.4 The intervention

Pegcetacoplan is a selective immunosuppressant (L04AJ03). Pegcetacoplan binds to complement protein C3 and its activation fragment C3b with high affinity, thereby inhibiting the cleavage of C3 and the generation of downstream effectors of complement activation. In PNH, EVH is facilitated by C3b opsonization while IVH is mediated by the downstream MAC. Pegcetacoplan exerts broad regulation of the complement cascade by acting proximal to both C3b and MAC formation, thereby controlling the mechanisms that lead to EVH and IVH. Pegcetacoplan is currently recommended by the Danish Medicines Council (DMC) for PNH in C5 experienced patients (Medicinrådet 2023).

An overview of pegcetacoplan is found in Table 3.

Table 3 Overview of pegcetacoplan

Overview of pegcetacoplan	
Therapeutic indication relevant for the assessment	Expected indication: monotherapy in the treatment of adult patients with PNH who have haemolytic anaemia
Method of administration	Solution for infusion
Dosing	1,080 mg subcutaneous infusion, twice weekly.
Dosing in the health economic model (including relative dose intensity)	1,080 mg subcutaneous infusion, twice weekly.
Should the medicine be administered with other medicines?	No
Treatment duration / criteria for end of treatment	Lifelong treatment, or until spontaneous remission occurs
Necessary monitoring, both during administration and during the treatment period	Vaccination of patients against encapsulated bacteria, including *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type B at least 2 weeks prior to initiation of pegcetacoplan. If immediate therapy is indicated, the required vaccines should be administered as soon as possible, and the patient treated with appropriate antibiotics until 2 weeks after vaccination.

Overview of pegcetacoplan	
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	No
Package size(s)	1,080 mg, 20 mL single-dose vial, 1-unit pack and 8-unit pack Strength: 54 mg/mL

3.4.1 The intervention in relation to Danish clinical practice

Pegcetacoplan is since December 2021 indicated in the treatment of adult patients with PNH who are anaemic after treatment with a C5 inhibitor for at least 3 months (EMA 2024), and for this indication it received a positive recommendation from the DMC in November 2023 (Medicinrådet 2023). Compared with continued C5 inhibitor therapy, pegcetacoplan reduces anaemia and the need for blood transfusions, improving patients' quality of life. The DMC states that pegcetacoplan is priced at the same level as the cheapest C5 inhibitor therapy, and because patients can be treated at home and need fewer blood transfusions, pegcetacoplan is associated with lower costs overall than the current C5 inhibitors (Medicinrådet 2023).

3.5 Choice of comparator(s)

The C5 inhibitors eculizumab and ravulizumab are indicated for treatment of PNH and are considered equivalent in second line by the DMC (Medicinrådet 2023). As a result of the introduction of eculizumab biosimilars in 2023, there has been a significant price reduction for eculizumab. This has resulted in that the majority of patients that have previously received ravulizumab have switched to, or are expected to switch to, eculizumab. An overview of the comparator – eculizumab – is found in Table 4.

Table 4 Overview of eculizumab

Overview of comparator	
Generic name	Eculizumab
ATC code	L04AJ01

Overview of comparator	
Mechanism of action	Eculizumab is a terminal complement inhibitor that specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex C5b-9. (In PNH patients, uncontrolled terminal complement activation and the resulting complement-mediated IVH are blocked with eculizumab treatment. In most PNH patients, eculizumab serum concentrations of approximately 35 microgram/mL are sufficient for essentially complete inhibition of terminal complement-mediated IVH. In PNH, chronic administration of eculizumab resulted in a rapid and sustained reduction in complement mediated haemolytic activity.
Method of administration	Concentrate for solution for infusion.
Dosing	The PNH dosing regimen for adult patients (≥18 years of age) consists of a 4-week initial phase followed by a maintenance phase. Initial phase: 600 mg of eculizumab administered via intravenous infusion every week for the first 4 weeks. Maintenance phase: 900 mg of eculizumab administered the fifth week, followed by 900 mg of Soliris administered every 14 ± 2 days.
Dosing in the health economic model (including relative dose intensity)	900 mg intravenously every 2 weeks (Loading dose: 600 mg intravenously every week for 4 weeks) RDI: 100%
Should the medicine be administered with other medicines?	No
Treatment duration/ criteria for end of treatment	Lifelong treatment, or until spontaneous remission occurs
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	300 mg, 30 mL single-dose vial, 1-unit pack. Strength: 10 mg/mL per vial

3.6 Cost-effectiveness of the comparator(s)

C5-inhibitors are since many years used in clinical practice but have not been formally assessed by the DMC. However, in their recent assessment of pegcetacoplan in the

treatment of patients with PNH in second line, C5-inhibitors were deemed to be the most relevant comparators. Since the introduction of eculizumab biosimilars in Denmark, eculizumab is expected to be the most cost-effective out of the available C5 inhibitors.

The DMC states in the recommendation from 23rd of November 2023 that pegcetacoplan is priced at the same level as the cheapest C5 inhibitor therapy, and because patients can be treated at home and need fewer blood transfusions, pegcetacoplan is associated with lower costs overall than the current C5 inhibitors (Medicinrådet 2023).

Based on the above there is no need to develop additional analyses versus alternative comparators such as ravulizumab or no treatment.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

In Table 5 the efficacy outcome measures relevant for the application are listed. The outcomes are chosen based on feasibility of inclusion in an indirect treatment comparison between pegcetacoplan and eculizumab.

Table 5 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Proportion of subjects who achieved Hb stabilization PRINCE	Baseline through week 26	Avoidance of a >1 g/dL decrease in Hb concentrations in the absence of transfusion	Hb was measured by the investigator at every study visit
Proportion of patients with stabilized Hb Study 301	Baseline through week 26 (day 183)	Avoidance of a ≥2 g/dL decrease in Hb level in the absence of transfusion	Hb was measured by the investigator at every study visit
Change in LDH levels PRINCE	Baseline through week 26	Change in LDH levels	LDH was measured by the investigator at every study visit
Change in LDH levels 301	Baseline through week 26 (day 183)	Change in LDH levels	LDH was measured by the investigator at every study visit
LDH normalization PRINCE	Baseline through week 26	Normalization of LDH concentrations (≤1 × the	LDH was measured by the investigator at every study visit

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
		ULN) in the absence of transfusions	
Proportion of participants with normalization of (LDH) levels Study 301	Day 29 through week 26 (day 183)	Haemolysis as measured by LDH normalization	LDH was measured by the investigator at every study visit
Proportion of subjects who received transfusion or had decrease of Hb > 2 g/dL PRINCE	Baseline through week 26	Transfusion refers to any transfusion of packed red blood cells (PRBC), leukocyte-depleted red blood cells (LDPRC), leukocyte poor packed red blood cell (LPRC), leukocyte poor blood (LPB) or whole blood	Hb, LDH and reticulocyte count were measured and evaluated by the investigator at every study visit. A PRBC transfusion was to be administered if Hb concentration was <7 g/dL or ≥7 and <9 g/dL with signs or symptoms of sufficient severity to warrant a transfusion
Transfusion avoidance PRINCE	Baseline through week 26	The proportion of subjects who did not require a transfusion during the randomised controlled period (RCP).	Red blood cell (RBC) transfusions were administered when patients had a Hb level ≤9 g/dL with anaemia-related signs or symptoms of sufficient severity to warrant transfusion or a Hb level ≤7 g/dL regardless of the presence of clinical signs or symptoms
Transfusion avoidance Study 301	Baseline through week 26 day 183)	The proportion of patients who remain transfusion-free and do not require a transfusion as per protocol-specified guidelines.	RBC transfusions were administered when patients had a Hb level ≤9 g/dL with anaemia-related signs or symptoms of sufficient severity to warrant transfusion or a Hb level ≤7 g/dL regardless of the presence of clinical signs or symptoms
Breakthrough haemolysis (BTH) PRINCE	Baseline through week 26	≥1 new or worsening sign or symptom of IVH (fatigue; haemoglobinuria; abdominal pain; dyspnoea; anaemia [Hb\10 g/dl], or MAVEs including thrombosis, dysphagia, or erectile dysfunction) in the	Patients were trained to contact study center if signs or symptoms appeared. BTH was reported as an AE and assessed and up to the PI to report.

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
		presence of LDH C 2 9 ULN after prior reduction to\1.5 9 ULN with treatment	
BTH Study 301	Baseline through week 26 day 183)	≥1 new or worsening sign or symptom of IVH (fatigue; haemoglobinuria; abdominal pain; dyspnoea; anaemia [Hb\10 g/dl], or MAVEs including thrombosis, dysphagia, or erectile dysfunction) in the presence of LDH C 2 9 ULN after prior reduction to\1.5 9 ULN with treatment	BTH was reported as an AE and assessed and up to the PI to report.
MAVEs PRINCE	Baseline through week 26	Proportion of patients experiencing MAVEs (including thrombosis)	AEs were assessed by the investigator at every study visit. Subjects were instructed to notify the PI or other study personnel in the event of an AE.
MAVEs Study 301	Baseline through week 26 (day 183)	Proportion of patients experiencing MAVEs (including thrombosis)	AEs were assessed by the investigator at every study visit. Subjects were instructed to notify the PI or other study personnel in the event of an AE.
FACIT-Fatigue PRINCE	Baseline through week 26	Change in FACIT-Fatigue score	The questionnaire was answered at every other study visit (with 4 weeks intervals).
FACIT-Fatigue Study 301	Baseline through week 26 (day 183)	Change in FACIT-Fatigue score	The questionnaire was answered at every other study visit (with 4 weeks intervals).
EORTC QLQ C30 PRINCE	Baseline through week 26	Change in QLQ-C30 score	The questionnaire was answered at every other study visit (with 4 weeks intervals).
EORTC QLQ C30 Study 301	Baseline through week 26 (day 183)	Change in QLQ-C30 score	The questionnaire was answered at every other study visit (with 4 weeks intervals).

* Time point for data collection used in analysis (follow up time for time-to-event measures)

Validity of outcomes

Transfusion avoidance: Patient relevant endpoint according to DMC assessment of pegcetacoplan as second line treatment (Medicinrådet 2023).

FACIT-Fatigue: The FACIT-Fatigue Scale is a 13-item Likert scaled instrument that is self-administered by the subjects during clinic visits. Subjects were presented with 13 statements and asked to indicate their responses as it applied to the past 7 days. The 5 possible responses are “Not at all” (0), “A little bit” (1), “Somewhat” (2), “Quite a bit” (3), and “Very much” (4). With 13 statements, the total score has a range of 0 to 52. Clinically meaningful, ≥3-point increase (Cella et al. 2002). Patient relevant endpoint according to DMC assessment (Medicinrådet 2023).

EORTC QLQ-C30: The EORTC QLQ-C30 questionnaire (version 3.0) consists of 30 questions comprised of both multi-item scales and single-item measures to assess overall quality of life in subjects. Questions were designated by functional scales, symptom scales, and global subject QoL/overall perceived health status. For the first 28 questions the 4 possible responses are “Not at all’ (1), ‘A little’ (2), ‘Quite a bit’ (3) and ‘Very much’ (4). For the remaining 2 questions the response is requested on a 7-point scale from 1 (‘Very poor’) to 7 (‘Excellent’). Each scale has a range of 0% - 100%. A high scale score represents a higher response level. Baseline is defined as average of measurements prior to first dose of pegcetacoplan or on prior to randomization of supportive care. Post baseline missing values are imputed using multiple imputation method with Markov Chain Mont Carlo method (Aaronson et al. 1993). The norm for the general population is 75.7% (Hinz et al. 2014).

4. Health economic analysis

4.1 Model structure

A de novo cost effectiveness model (CEM) was developed in Microsoft Excel to estimate the long-term cost-effectiveness of pegcetacoplan and eculizumab. The applied Markov model structure is based on [redacted] The long-term costs and outcomes (e.g., quality-adjusted life-years [QALY]) incurred in the target population i.e., treatment-naïve patients, were estimated.

4.1.1 Model type

The Markov model structure can be divided into two subsections, [redacted]

Figure 2 Model structure

[redacted]

[redacted]

4.1.2 Transition probabilities

[redacted]

Figure 3 [redacted]

[redacted]

4.1.3 Mortality

In a study by Kelly et al. 2011 (Kelly et al. 2011), the survival of 79 consecutive patients treated with eculizumab in Leeds between 2002 and 2010 was compared to the survival of 30 patients assessed between 1997 and 2004, who fulfilled the criteria for treatment with eculizumab but were not treated with eculizumab. The results suggested that the survival of patients treated with eculizumab was not different from the age- and sex-matched general population but was significantly better than patients who were not treated with eculizumab (hazard ratio (HR) = 0.21).

In line with this, the Danish age- and sex-matched general population mortality was considered for patients receiving complement inhibitors (DMC 2023).

4.1.4 Adverse events

Two adverse events were included in the model: BTH and major adverse vascular events (MAVEs).

The probability of BTH occurrence for pegcetacoplan patients was based on the PRINCE trial data. There were two BTH events among 35 pegcetacoplan patients during a mean of 244.8 days of follow-up. To inform the input value for the model, the value was adjusted to the cycle length (26 weeks). Furthermore, there were no MAVE events among pegcetacoplan patients in the PRINCE trial.

The probability of BTH for eculizumab was sourced from the matching adjusted indirect treatment comparison (MAIC).

The cost of managing adverse events was based on Sundhetsdatastyrelsen's diagnostic-related groups (DRG) rates, with code 17MA02 being used for BTH and code 26MP16 for MAVE (Sundhetsdatastyrelsen 2024).

QALY loss for BTH and MAVE were calculated based on disutility and duration of event. Duration and disutility of BTH was sourced from O'Connell 2020 (OConnell et al. 2020), describing a cost-utility analysis of ravulizumab compared to eculizumab in PNH. Duration of MAVE was based on mean duration of deep venous thrombosis events from Dasta 2015 (Dasta et al. 2015), describing costs for hospitalization for deep vein thrombosis and pulmonary embolism, while disutility was sourced from Sullivan 2006 (Sullivan and Ghushchyan 2006) for venous thrombosis, describing values of utility loss for various health events. [redacted]

[redacted]

Data concerning adverse events are presented in Table 6.

Table 6 Adverse events

Adverse event	Probability (per cycle)		Cost (per event)	QALY loss (per event)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

4.1.5 Treatment discontinuation

It is assumed in the base case analysis that patients do not discontinue treatment which reflects current treatment practice in Denmark (Sobi 2024).

4.2 Model features

Table 7 Features of the economic model

Model features	Description	Justification
Patient population	Patients with PNH who are naive to complement inhibitors	
Perspective	Limited societal perspective	According to DMC guidelines

Model features	Description	Justification
Time horizon	Lifetime (55.5 years) horizon	To capture all health benefits and costs in line with DMC guidelines
Cycle length	6 months (26 weeks)	In line with the follow-up period in the PRINCE trial, at which the efficacy was assessed
Half-cycle correction	Yes	
Discount rate	3.0 %	The DMC applies a discount rate of 3.0 % for all years
Intervention	Pegcetacoplan	
Comparator(s)	Eculizumab	Patients in Denmark who need active complement inhibiting treatment are currently treated with C5 inhibitors, and have been for many years
Outcomes	Life years, QALYs, BTH events, number of transfusions	To inform outcomes for pegcetacoplan, individual patient data (IPD) from PRINCE was deemed the best available source. Outcomes for eculizumab are based on hazard ratios sourced from the MAIC as well as from the study of Kelly et al, 2011 (Kelly et al. 2011).

5. Overview of literature

5.1 Literature used for the clinical assessment

A systematic literature review (SLR) was conducted to identify randomised controlled trials (RCTs) and phase 3 single-arm trials recruiting patients with PNH, who are naive to complement inhibitors. The search was run in Medline, EMBASE, Cochrane CENTRAL database and ClinicalTrial.gov through the OVID interface using a search strategy constructed based on the inclusion/exclusion criteria presented in Appendix H, as well as on selected conference websites and the Food and drug administration (FDA) and EMA registries. The last search was conducted January 17th, 2024, and identified a total of 52 publications corresponding to 11 unique trials. The SLR is summarized in Appendix H.

Of the included trials, 6 were RCTs (PRINCE, TRIUMPH, Study 301, CLNP023X2204, COMMODORE 2 and SB12-3003). Of these, 1 study (Study 301) investigated eculizumab and ravulizumab, both C5 inhibitors, in complement inhibitor-naïve patients with PNH and was thus suitable for a matching-adjusted indirect comparison (MAIC) vs pegcetacoplan using data from PRINCE. Relevant literature included in the assessment is shown in Table 8.

Table 8 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
CSR, A Phase 3, Randomized, Multicenter, Open Label, Controlled Study to Evaluate The Efficacy And Safety Of Pegcetacoplan In Patients With Paroxysmal Nocturnal Haemoglobinuria (PNH). 2021, Apellis. P. 192. (Apellis Pharmaceuticals data on file 2021) Wong, R.S.M.N.-C, et al. Pegcetacoplan controls hemolysis in complement inhibitor-naive patients with paroxysmal nocturnal Haemoglobinuria. Blood advances, 2023. 7(11): p. 2468-2478. (Wong et al. 2023b)	PRINCE	NCT04085601	Start: 27/08/19 Completion: 23/06/21	Pegcetacoplan vs supportive care for patients with PNH naïve to complement inhibitors
Lee, J.W.d.F., et al. Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: The 301 study. Blood, 2019. 133(6): p. 530-539. (Lee et al. 2019) Schrezenmeier H, et al. Predictors for Improvement in Patient-Reported Outcomes: Post-Hoc Analysis of a Phase 3 Randomized, Open-Label Study of Eculizumab and Ravulizumab in Complement Inhibitor-Naïve Patients with Paroxysmal Nocturnal Haemoglobinuria (PNH). *Ann Hematol*. 2024;103(1): p. 5-15. Doi: 10.1007/s00277-023-05483-0. (Schrezenmeier et al. 2024)	Study 301	NCT 3056040	Start: 20/12/16 Completion: 28/02/23	Ravulizumab vs eculizumab for patients with PNH naïve to complement inhibitors

* If there are several publications connected to a trial, include all publications used.

5.2 Literature used for the assessment of health-related quality of life

In the systematic literature search that was conducted to identify RCTs) and phase 3 single-arm trials recruiting patients with PNH who are naive to complement inhibitors, 4 studies (PRINCE, Study 301, TRIUMPH, COMMODORE 2) assessed health-related quality of life data. All of these addressed fatigue using the FACIT-Fatigue tool and the QOL using the EORTC QLQ-30. However, patient level EORTC-QLQ30 data was used for mapping to EQ-5D-5L. Relevant literature included in the assessment is shown in Table 9. The publications in Table 9 were identified in a database search. The publications were selected based on relevance to this model. OConnell et al. (2020) was selected as source for BTH since a cost-effectiveness analysis of ravulizumab and eculizumab was considered to be relevant, due to same disease and consistency between models. Dasta et al. (2015) and Sullivan and Ghushchyan (2006) were considered as relevant sources for MAVE due to large sample size, reported utility loss due to various events and using the same questionnaire.

Table 9 Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
OConnell, et al., Cost-Utility Analysis of Ravulizumab Compared with Eculizumab in Adult Patients with Paroxysmal Nocturnal Hemoglobinuria. PharmacoEconomics, 2020. 38(9): p. 981-994. (OConnell et al. 2020)	Disutility and duration of BTH	10.2.2
Dasta, J. F., Pilon, D., Mody, S. H., Lopatto, J., Laliberte, F., Germain, G., Bookhart, B. K., Lefebvre, P. & Nutescu, E. A. 2015. Daily hospitalization costs in patients with deep vein thrombosis or pulmonary embolism treated with anticoagulant therapy. Thromb Res, 135, 303-10. (Dasta et al. 2015)	Duration of MAVE	10.2.2
Sullivan, P. W. & Ghushchyan, V. 2006. Preference-Based EQ-5D index scores for chronic conditions in the United States. Med Decis Making, 26, 410-20. (Sullivan and Ghushchyan 2006)	Disutility of MAVE	10.2.2

5.3 Literature used for inputs for the health economic model

All but one of the inputs used in the model were derived from the studies included in the MAIC. The hazard ratio for risk of death with eculizumab was however sourced from Kelly et al., 2011, which is presented in Table 10

[redacted]

Table 10 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Kelly, R.J., et al., Long-term treatment with eculizumab in paroxysmal nocturnal Haemoglobinuria: sustained efficacy and improved survival. Blood, 2011. 117(25): p. 6786-92. (Kelly et al. 2011)	Hazard ratio, risk of death, eculizumab	Targeted literature review on mortality with PNH	Table 4.1.3

6. Efficacy

6.1 Efficacy of pegcetacoplan compared to eculizumab for PNH

6.1.1 Relevant studies

6.1.1.1 PRINCE (NCT04085601)

PRINCE is a randomized multicentre, open-label, interventional, controlled study in complement inhibitor-naive patients with PNH. Patients were randomized to receive either pegcetacoplan or supportive care only. The treatment period of the study consisted of two parts (Figure 4):

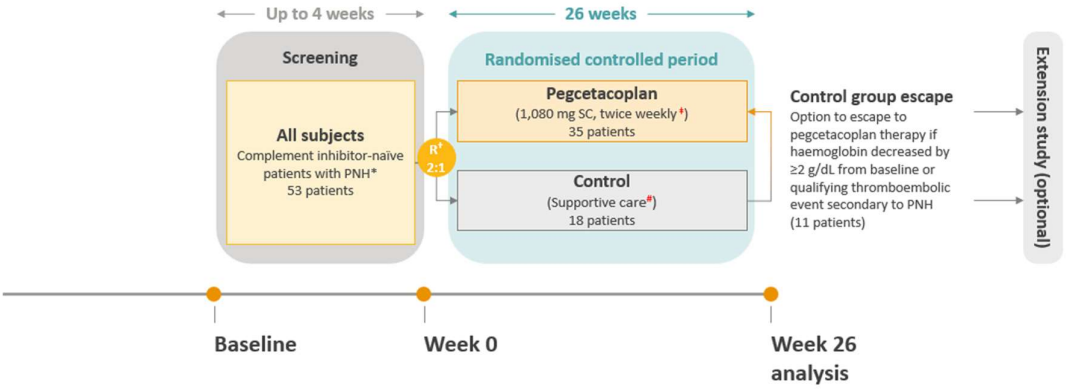
- ≤ 4-week screening period
- 26-week randomized controlled period.

Patients randomized to the pegcetacoplan group self-administered SC of pegcetacoplan 1,080 mg twice weekly. Patients randomized to the control group continued supportive care (including transfusions, anticoagulants, corticosteroids and supplements [iron, folate, and vitamin B12]), but could escape to pegcetacoplan treatment if their Hb level decreased ≥ 2 g/dL below their baseline measurement or if they had a qualifying thromboembolic event secondary to PNH. During the 26-week randomized controlled period, patients visited the study clinic every 2 weeks for efficacy and safety assessments (Wong et al. 2023b).

Following completion of the randomised controlled period (RCP), all subjects (including those on supportive care) were offered entry into a separate open-label extension (OLE) study (Study APL2-307; (NCT03531255)) to receive treatment with pegcetacoplan (Wong et al. 2023a).

The randomisation was stratified by the number of packed red blood cells (PRBC) transfusions (< 4, ≥ 4) received within the 12 months before screening.

Figure 4 PRINCE Study Design



* No C5 inhibitor within 3 months of screening.
† Randomisation was stratified by the number of packed RBC transfusions (< 4, ≥ 4) within 12 months before screening.

‡ After 4 weeks of pegcetacoplan treatment and reaching a steady state, any patient receiving pegcetacoplan with LDH concentrations > 2x ULN on 1 occasion could be considered for dose adjustments to pegcetacoplan 1080 mg every third day.

#Including transfusions, anticoagulants, corticosteroids, and supplements (iron, folate, and vitamin B12).
PNH = Paroxysmal Nocturnal Haemoglobinuria; R = Randomisation; SC = Subcutaneous.

Source: (Wong et al. 2023b).

6.1.1.2 ALXN1210-PNH-301 (NCT03056040)

The Study 301 (ALXN1210-PNH-301) is an open-label, active-controlled study conducted in complement inhibitor-naive patients with PNH. Patients were stratified into six groups based on transfusion history (0, 1-14, or > 14 units of packed RBC in the 1 year before the first dose of study drug) and LDH screening level (1.5 to < 3 times the upper limit of normal [ULN] or ≥ 3 × ULN). Enrolment of patients without a history of transfusion in the past year was capped at 20%. Hb levels were evaluated before randomisation and within 5 days before study drug initiation; patients were transfused, if necessary, to reach the protocol-specified Hb level. Patients within each of the six groups were randomly assigned in a 1:1 ratio to receive ravulizumab or eculizumab. The ravulizumab IV group received a loading dose (2,400 mg for patients weighing ≥ 40 to < 60 kg, 2,700 mg for patients ≥ 60 kg to < 100 kg, and 3,000 mg for patients ≥ 100 kg) on Day 1, followed by maintenance doses of ravulizumab (3,000 mg for patients ≥ 40 to < 60 kg, 3,300 mg for patients ≥ 60 to < 100 kg, and 3,600 mg for patients ≥ 100 kg) on Day 15 and every 8 weeks thereafter. Patients assigned to eculizumab received induction doses of 600 mg on days 1, 8, 15, and 22, followed by maintenance dosing of 900 mg on Day 29 and every 2 weeks thereafter per the approved PNH dosing regimen.

The study was conducted in 123 centres in 25 countries and consisted of a 4-week screening period and a 26-week randomized treatment period and up to 2 years OLE period.

Table 11 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
PRINCE, NCT04085601 (Wong et al. 2023a)	Phase 3, randomised multicentre, interventional, open-label, controlled study of pegcetacoplan vs supportive care.	≤ 4-week screening period followed by 26-week randomized controlled period Patients who were randomised to supportive care could escape to pegcetacoplan treatment if their haemoglobin (Hb) level decreased ≥ 2 g/dL below their baseline measurement or if they had a qualifying thromboembolic event secondary to PNH.	Complement inhibitor naïve patients with PNH. The study was conducted in 22 centres (Hong Kong, Malaysia, Philippines, Singapore, Thailand, Colombia, Mexico, and Peru) where complement inhibitors were not approved or widely available (i.e., patients were receiving supportive care only for PNH treatment).	Self-administered SC of pegcetacoplan 1080 mg twice weekly	Supportive care (excluding C5 inhibitors, including transfusions, anticoagulants, corticosteroids and supplements [iron, folate, and vitamin B12]),	***Primary endpoints:*** Hb stabilisation defined as avoidance of a > 1 g/dL decrease in Hb concentrations from baseline in the absence of transfusion through Week 26 (yes/no) Change from baseline in LDH concentration to Week 26 ***Secondary endpoints:*** Hb response (yes/no) in the absence of transfusions (Hb response is defined as ≥ 1 g/dL increase in Hb from baseline at Week 26) Change from baseline to Week 26 in ARC Change from baseline through Week 26 in Hb concentration Proportion of subjects who received transfusion and/or had decrease of Hb > 2 g/dL from baseline (yes/no) Transfusion avoidance (yes/no), defined as the proportion of subjects who did not require a transfusion during the RCP Number of PRBC units transfused from baseline to Week 26 Change from baseline to Week 26 in FACIT–Fatigue Scale score Normalisation of Hb concentrations (≥ 1x LLN) from Baseline to Week 26 in the absence of transfusions (yes/no) Normalisation of LDH concentrations (≤ 1 × the ULN) from Week 4 through Week 26 in the absence of transfusions (yes/no) Change from baseline to Week 26 in European Organisation for Research and Treatment of Cancer 30-item QLQ C30 scores Change from baseline through Week 26 in Linear Analog Scale Assessment scores

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
						ARC normalisation (< 1 × the ULN) at Week 26 (yes/no) Time to failure of Hb stabilisation Time to first transfusion ***Additional endpoints:*** Number and percentage of subjects achieved Hb concentration ≥ 11 g/dL and ≥ 12 g/dL at Week 26 Number and percentage of subjects without PRBC transfusion during the RCP Total and indirect bilirubin normalisation levels (defined as ≤ 1× the ULN) at Week 26 in the absence of transfusion (yes/no) Number and percentage of subjects achieving ≥ 3 points improvement in FACIT-Fatigue Scale score from baseline through Week 26 Normalisation of Hb concentrations (defined as ≥ 1x the LLN) from baseline at Week 26 in the absence of transfusions (yes/no) Normalisation of LDH concentrations ≤ 1× ULN at Week 26 in the absence of transfusions (yes/no) ARC normalisation (< 1× ULN) from baseline through Week 26 in the absence of transfusion (yes/no) Normalisation of LDH concentrations (yes/no) of ≤ 1 × the ULN from baseline through Week 26 in the absence of transfusions (yes/no) Normalisation of Hb concentrations (defined as ≥ 1xLLN) from Week 4 through Week 26 in the absence of transfusions (yes/no) ARC normalisation (< 1× the ULN) from Week 4 through Week 26 in the absence of transfusion (yes/no) ***Safety endpoints:***

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
						Incidence and severity of TEAEs Incidence of thromboembolic events Changes from baseline in laboratory parameters Changes from baseline in electrocardiogram (ECG parameters Incidence of anti–pegcetacoplan peptide antibodies
Study 301, NCT 3056040 **(Lee et al. 2019)**	Phase 3, multi-center, randomised, active-controlled, open-label study of ravulizumab versus eculizumab.	26-week randomised treatment period, followed by an extension of up to 2 years, during which all patients received ravulizumab.	Complement inhibitor naïve patients with PNH.	Ravulizumab Weight based dosing regimen consisting of a loading dose followed by a maintenance dose that should be administered once every 8-weeks, starting 2 weeks after loading dose administration. (Loading dose 2,400 mg for ≥ 40 to < 60 kg, 2,700 mg for ≥ 60 kg to < 100 kg, and 3,000 mg for ≥ 100 kg)	Eculizumab Initial phase: 600 mg of eculizumab administered via a 25–45 minute (35 minutes ± 10 minutes) IV infusion every week for the first 4 weeks. Maintenance phase: 900 mg of eculizumab administered via a 25–45 minute (35 minutes ± 10 minutes) IV infusion for the fifth week,	***Primary endpoints:*** Change in LDH level % change in LDH level LDH normalization Change in Hb level % change in Hb level Hb stabilization Transfusion avoidance ***Secondary endpoints:*** Time to first LDH normalization Transfusion requirements ***Safety endpoints:*** Breakthrough haemolysis Major adverse vascular events (MAVEs) ***Quality of Life:*** Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
				(Maintenance doses 3,000 mg for ≥ 40 to < 60 kg, 3,300 mg for ≥ 60 to < 100 kg, and 3,600 mg for ≥ 100 kg)	followed by 900 mg of eculizumab administered via a 25–45 minute (35 minutes ± 10 minutes) IV infusion every 14 ± 2 days	

Abbreviations: ARC = absolute reticulocyte count; LDH = lactate dehydrogenase; LLN = lower limit of normal; PNH = paroxysmal nocturnal haemoglobinuria; PRBC = packed red blood cell; RCP = randomised controlled period; ULN = upper limit of normal

6.1.2 Comparability of studies

As no comparative clinical trial data are available for pegcetacoplan vs. C5 inhibitors in treatment naive patients (the PRINCE trial was conducted vs. supportive care), a matching-adjusted indirect comparison (MAIC) based on the PRINCE and 301 Studies (vs. eculizumab and ravulizumab) was conducted in this population (Wong et al. 2023a).

6.1.2.1 Comparability of patients across studies

Before weighting, there were significant differences at baseline for white race, American Indian or Alaska Native race and mean LDH level between the pegcetacoplan and eculizumab groups. The same parameters, with the addition of EORTC QLQ-C30 overall health score, varied at baseline between the ravulizumab and the pegcetacoplan arm (Table 12).

For a comparison of the baseline demographics and clinical characteristics after weighting, see Table 60.

Table 12 Baseline demographic and clinical characteristics of the study population (before weighting)[1]

	PRINCE trial	Study 301 trial			
	Pegcetacoplan (N=346)	Ravulizumab (N=125)	Eculizumab (N=121)	p value[1]	
Characteristic	[A]	[B]	[C]	[A] vs. [B]	[A] vs. [C]
Sex					
Male	19 (55.9)	65 (52.0)	69 (57.0)	0.8350	1
Female	15 (44.1)	60 (48.0)	52 (43.0)	0.8350	1
Age at first infusion of study drug, years	42.7 ± 12.5	44.8 ± 15.2	46.2 ± 16.2	0.4166	0.1833
Race					
Asian	23 (67.6)	72 (57.6)	57 (47.1)	0.3887	0.0544
White	0 (0.0)	43 (34.4)	51 (42.1)	<0.0001*	<0.0001*
Black or African American	2 (5.9)	2 (1.6)	4 (3.1)	0.2006	0.613
American Indian or Alaska Native	8 (23.5)	1 (0.8)	1 (0.8)	<0.0001*	<0.0001*
Other[2]	1 (2.9)	4 (3.2)	4 (3.3)	1	1
Not reported/unknown	0 (0.0)	3 (2.4)	4 (3.3)	1	0.5767
Weight, kg	65.3 ± 13.4	68.2 ± 15.6	69.2 ± 14.9	0.2731	0.1393
Height, cm	164.6 ± 7.7	166.3 ± 9.0	166.2 ± 10.7	0.2717	0.3291
Time from PNH diagnosis to consent, years[3] (mean ± SD or median [range])	5.8 ± 5.96	3.8 [0, 41]	3.9 [0, 34]	-	-
No PRBC transfusions received within 1 year before study entry	5 (14.7)	23 (18.4)	21 (17.4)	0.8045	0.9111
LDH, U/L[4]	2,092.4 ± 902.3	1,633.5 ± 778.8	1,578.3 ± 727.1	0.0069*	0.0009*
Haemoglobin, g/dl[5]	9.6 ± 1.4	9.4 ± NR	9.60 ± NR	0.3909	1
EORTC QLQ-C30 score at baseline					

General health status	64.5 ± 18.8	56.1 ± 20.3	57.5 ± 20.3	0.0241 *	0.0614
Physical functioning	81.6 ± 14.6	76.6 ± 17.1	76.4 ± 17.6	0.0903	0.0819
Fatigue symptoms	36.3 ± 20.0	39.3 ± 22.7	37.3 ± 23.4	0.4473	0.7992

Data are presented at n (%) or mean ± standard deviation unless otherwise indicated.

Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; LDH, lactate dehydrogenase; NR, not reported; PNH, paroxysmal nocturnal haemoglobinuria; PRBC, packed red blood cell.

Notes:

1. P values for continuous and categorical variables were calculated with the Wald test (i.e., z and chi-squared tests, respectively).
2. Subjects in the Study 301 trial who identified as being of multiple races were included in this category.
3. The Study 301 trial reported range and the PRINCE trial reported standard deviation; the p value was not calculated because the measures of variability did not match.
4. Normal range, 120–246 U/L.
5. Normal range, 12.3–15.3 g/dL for women and 14.0–17.5 g/dL for men. The p value was not calculated because standard deviations were not calculated because standard deviations were not reported in the Study 301 trial.
6. There were 35 patients who received Pegcetacoplan in PRINCE. Of these, 34 were included in the current analysis, whereas one was excluded because of a lack of LDH and haemoglobin data after baseline.

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

The PRINCE study aimed to evaluate the efficacy and safety of pegcetacoplan compared to best supportive care (BSC) in treatment of C5 inhibitor naive PNH patients.

The patients included in the PRINCE study were between 20 and 74 years of age, with a mean age of 44.5 years. The proportion of females in PRINCE was 45.28%, which is somewhat smaller than what has been estimated among Danish PNH patients eligible for treatment (Hansen et al. 2020). Regarding patient weight, the mean among patients in PRINCE was 63.72 kg, which is likely to differ quite substantially from the average weight among Danish patients eligible for treatment; the median weight of Danish adults (25-44 years) has been estimated at 75.19 kg(SDU DK 2024). This difference can probably be explained by 67.6% of the patients in PRINCE being of Asian race (Wong et al. 2023b). Due to this difference, the mean patient weight in the PEGASUS trial, instead of PRINCE, was used in the base case. The mean patient weight in PEGASUS was 75.30 kg and was used in the Aspaveli 2nd line application (Medicinrådet 2023). However, the mean patient weight in PRINCE is used as a scenario analysis.

Table 13 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (reference)	Value used in health economic model (reference if relevant)
Age	48.4 (median age at diagnosis) (Hansen et al. 2020)	[redacted]
Gender	50% female (Hansen et al. 2020)	[redacted]
Patient weight	75.19 kg (SDU DK 2024)	[redacted]

6.1.4 Efficacy – results per PRINCE

The coprimary efficacy endpoints in PRINCE were

- Hb stabilisation (defined as avoidance of a > 1 g/dL decrease in Hb concentration from baseline in the absence of transfusion through Week 26 [yes/no])
- change in LDH concentration from baseline to Week 26

Efficacy was analysed in a hierarchical fashion, starting with the coprimary endpoints and then progressing stepwise through the secondary endpoints after statistical significance was reached for the coprimary endpoints (Wong et al. 2023a).

Discontinuations for any reasons and AEs are described in Appendix B Table 33.

6.1.4.1 Key efficacy endpoints – PRINCE

6.1.4.1.1 Hb stabilisation from baseline through week 26

The first coprimary endpoint was Hb stabilisation defined as avoidance of a > 1 g/dL decrease in Hb concentration from baseline in the absence of transfusion. Table 14 shows the results of the first coprimary endpoint analysis. In the pegcetacoplan group, 85.7% patients achieved Hb stabilisation, compared to 0 patients in the supportive care group. The adjusted difference between two groups of 73.1% was statistically significant (95% CI 0.572-0.890; P < 0.0001), showing the superiority of pegcetacoplan treatment over supportive care in stabilising Hb concentration over 26 weeks (Wong et al. 2023b).

Table 14 Primary analysis: Hb stabilisation in the absence of transfusion from baseline through week 26—PRINCE

	Pegcetacoplan (N = 35)	Supportive Care (N = 18)	Difference (95% CI)	*P* Value
Hb stabilisation* n (%)	30 (85.7)	0	73.1% (95% CI 57.2%-89.0%)	< 0.0001

CI = Confidence Interval; Hb = Haemoglobin; N = Number of Subjects in Treatment Groups; n = Number of Subjects with Event.

*Patients who received a transfusion, escaped from the control arm to pegcetacoplan treatment, withdrew from the study before week 26, or were lost to follow-up were categorised as failing to achieve Hb stabilisation.

Source: (Wong et al. 2023b).

6.1.4.1.2 Change from baseline in LDH concentration at week 26

The second coprimary endpoint was change from baseline in LDH concentration at week 26. Table 15 shows the results of the second coprimary endpoint analysis. The least square (LS) mean change from baseline in LDH concentration was –1,870.5 U/L for patients in the pegcetacoplan group compared with –400.1 U/L in supportive care group, with a statistically significant adjusted difference of –1,470.4 U/L (95% CI, –2,113.4 to –827.3; *P* < 0.0001). These data prove the superiority of pegcetacoplan over supportive care in decreasing LDH concentrations (Wong et al. 2023b).

Table 15 Primary analysis: Change From baseline in LDH concentration at week 26—PRINCE

	Pegcetacoplan (N = 35)	Supportive Care (N = 18)	Difference (95% CI)	*P* Value

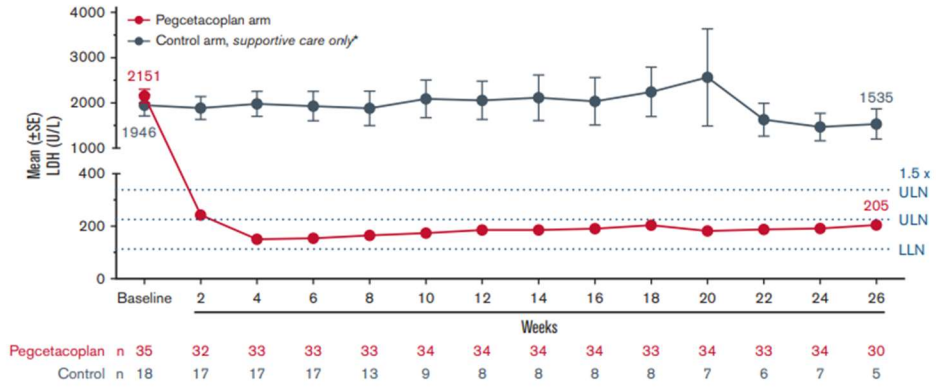
Change from baseline in LDH concentration, LS mean (SE) U/L	–1,870.5 (101.0)	–400.1 (313.0)	–1,470.4 (–2,113.4, –827.3)	< 0.0001

LDH = Lactate Dehydrogenase; LS = Least Square; N = Number of Subjects in Treatment Groups; SE = Standard Error.

Source: (Wong et al. 2023b)

Figure 5 shows the mean LDH concentration observed in both treatment groups during the RCP. By Week 2, mean LDH levels in the pegcetacoplan group were reduced by ~90% from baseline; in most cases, the new LDH level was sustained through Week 26. LDH concentrations remained elevated in the supportive care group (Wong et al. 2023a).

Figure 5 Mean (SE) LDH concentration (U/L) over time by treatment group during the RCP—PRINCE



*Control group patients received supportive care (e.g., transfusions, corticosteroids, and supplements [iron, folate, vitamin B12]). LDH = Lactate Dehydrogenase; LLN = Lower Limit of Normal; SE = Standard Error; ULN = Upper Limit of Normal.

Source: (Wong et al. 2023b)

6.1.5 Efficacy – results per Study 301

6.1.5.1 Key efficacy endpoints – Study 301

Ravulizumab met the objective of noninferiority compared with eculizumab on both coprimary endpoints and point estimates for both coprimary endpoints favoured ravulizumab. Ninety-two of 125 patients (73.6%) receiving ravulizumab and 80 of 121 patients (66.1%) receiving eculizumab avoided transfusion, with a between-group difference of 6.8% (95% CI, -4.66 to 18.14; $P_{inf} < 0.0001$). The adjusted prevalence of LDH normalisation was 53.6% for the ravulizumab group and 49.4% for the eculizumab group; the adjusted odds ratio (OR) for comparison of ravulizumab vs. eculizumab was 1.19 (95% CI, 0.80-1.77; $P_{inf} < 0.0001$).

Ravulizumab was noninferior to eculizumab on the four key secondary endpoints (Table 16) with all point estimates consistently favouring ravulizumab. The between-group difference in least squares mean percentage change in LDH levels was -0.83% (95% CI, −5.21 to 3.56; $P_{inf} < 0.0001$). Proportions of patients with BTH were 4.0% (5 of 125 patients had one event each) in the ravulizumab group vs. 10.7% (13 of 121 patients had a total of 15 events) in the eculizumab group (difference, −6.7% [95% CI, −14.21 to 0.18]; $P_{inf} < 0.0001$).

The mean (SD) total number of PRBC units transfused during the treatment period was comparable in the ravulizumab (4.8 [5.1]) and eculizumab (5.6 [5.9]) groups. Three patients experienced MAVEs, two in the

ravulizumab group and one in the eculizumab group. Patients in both treatment groups reported improvements from baseline in clinical manifestations of PNH (Table 16).

Table 16 Coprimary and key secondary efficacy outcomes at day 183— Study 301

	Ravulizumab (N = 125)	Eculizumab (N = 121)	Statistics for Comparison	Treatment Effect	Noninferiority Margin	Conclusion
Coprimary endpoints						
Transfusion avoidance rate, % (95% CI)	73.6 (65.87-81.33)	66.1 (57.68-74.55)	Difference in rate	6.8 **(−4.66** to 18.14)	−20%	Noninferior
LDH normalisation, % (95% CI)	53.6 (45.9-61.2)	49.4 (41.7-57.0)	OR	1.19 (**0.80**-1.77)	0.39	Noninferior
Key secondary efficacy endpoints						
LDH, least squares mean % change (95% CI)	-76.84 (-79.96 to -73.73)	−76.02 (−79.20 to −72.83)	Difference in % change from baseline	−0.83 (−5.21 to **3.56**)	20%	Noninferior
FACIT-Fatigue score, least squares mean change (95% CI)	7.07 (5.55-8.60)	6.40 (4.85-7.96)	Difference in change from baseline	0.67 **(−1.21** to 2.55)	−5.0	Noninferior
BTH rate, % (95% CI)	4.0 (0.56-7.44)	10.7 (5.23-16.26)	Difference in rate	−6.7 (−14.21 to **0.18**)	20%	Noninferior
Hb stabilisation rate, % (95% CI)	68.0 (59.82-76.18)	64.5 (55.93-72.99)	Difference in rate	2.9 **(−8.80** to 14.64)	−20%	Noninferior

BTH = Breakthrough Haemolysis; CI = Confidence Interval; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy–Fatigue Subscale; Hb = Haemoglobin; LDH = Lactate Dehydrogenase; OR = Odds Ratio.

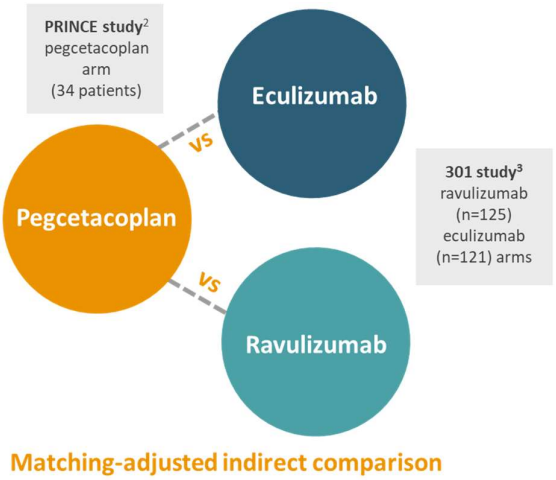
Note: For the transfusion avoidance endpoint, treatment differences (95% Cis) are based on estimated differences in percent with 95% CI. For the LDH normalisation endpoint, the adjusted prevalence within each treatment is displayed. Testing of the noninferiority hypothesis is assessed by comparing the bolded limit of the 95% CI to the noninferiority margin.

Source: Lee et al. (2019).

7. Comparative analyses of efficacy

To assess the relative efficacy of pegcetacoplan vs. eculizumab, a matching-adjusted indirect comparison (MAIC) was conducted using individual patient data (IPD) from PRINCE (pegcetacoplan, n = 34) and aggregated data from Study 301, in which eculizumab (n=121) was compared to ravulizumab (n=125) (Figure 6).

Figure 6 Matching-adjusted comparison design



Source: Wong et al. (2023a)

7.1.1 Differences in definitions of outcomes between studies

Endpoints were compared between the PRINCE and Study 301 trials before and after matching using 26-week data from the PRINCE trial. Before matching, the Wald test and 95% Cis were used to compare categorical and continuous endpoints (i.e., chi-squared and z tests, respectively). After matching, endpoints were compared between balanced treatment groups using statistical tests that incorporated weights generated during matching (i.e., weighted chi-squared tests for categorical endpoints, and weighted z tests for continuous endpoints). By incorporating weights developed during the matching process, any observed differences in efficacy outcomes could not be attributed to differences in baseline characteristics of patients in the PRINCE and Study 301 trials (Wong et al. 2023c, Lee et al. 2019).

Regarding the Hb stabilization endpoint, patient level data was used to estimate the number of patients using a threshold of 2 g/dl to be comparable to the population in Study 301.

Table 17 Comparison of endpoint definitions

Endpoint	PRINCE definition	Study 301 definition
Change in LDH level	Change in LDH levels from baseline to week 26	Change in LDH levels from baseline to week 26 (day 183)
LDH normalization	LDH normalization at week 26 in the absence of transfusions	Haemolysis as measured by LDH normalization from days 29 through 183
Time to first LDH normalization	Time to first occurrence of LDH normalization	Time to first occurrence of LDH normalization

Hb stabilisation	Avoidance of a ≥1 g/dl decrease in Haemoglobin (Hb) level in the absence of transfusion	Avoidance of a ≥2 g/dl decrease in Hb level in the absence of transfusion
Transfusion avoidance	Proportion of patients with transfusion avoidance through week 26 Study guidelines: transfusions will be administered if Hb is < 7 g/dl without symptoms, or ≥7 to<9 g/dl with symptoms	Proportion of participants who remained transfusion free and did not require a transfusion per protocol-specified guidelines through week 26 (day 183) Study guidelines: Hb value ≤ 9 g/dl with signs or symptoms of sufficient severity to warrant a transfusion, or a Hb value ≤ 7 g/dl regardless of presence of clinical signs/symptoms
Transfusion requirements	Total number of units of PRBC transfused from week 4 to week 26	Total number of units of PRBC transfused from baseline to week 26 (day 183)
BTH	≥1 New or worsening sign or symptom of intravascular haemolysis (IVH) (fatigue; haemoglobinuria; abdominal pain; dyspnoea; anaemia [Hb < 10 g/dl], or MAVEs including thrombosis, dysphagia, or erectile dysfunction) in the presence of LDH ≥ 2 × ULN after prior reduction to < 1.5 × ULN with treatment	≥1 New or worsening sign or symptom of IVH (fatigue; haemoglobinuria; abdominal pain; dyspnoea; anaemia [Hb < 10 g/dl]; or MAVEs including thrombosis, dysphagia, or erectile dysfunction) in the presence of LDH ≥ 2 × ULN after prior reduction to < 1.5 × ULN with treatment
MAVEs	Proportion of patients experiencing MAVEs (including thrombosis)	Proportion of patients experiencing MAVEs (including thrombosis)
FACIT-Fatigue	Week 26 change from baseline in FACIT-Fatigue score	Week 26 (day 183) change from baseline in FACIT-Fatigue score
General health status (EORTC QLQ-C30)	Week 26 change from baseline in general health status EORTC QLQ-C30 score	Week 26 (day 183) change from baseline in general health status EORTC QLQ-C30 score
Physical functioning (EORTC QLQ-C30)	Week 26 change from baseline in physical functioning EORTC QLQ-C30 score	Week 26 (day 183) change from baseline in physical functioning EORTC QLQ-C30 score
Fatigue symptoms (EORTC QLQ-C30)	Week 26 change from baseline in fatigue symptom EORTC QLQ-C30 score	Week 26 (day 183) change from baseline in fatigue symptom EORTC QLQ-C30 score

EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; FACIT = Functional Assessment of Chronic Illness Therapy; LDH = lactate dehydrogenase; MAVE = major adverse vascular event; PNH = paroxysmal nocturnal haemoglobinuria; ULN = upper limit of normal

Source: (Wong et al. 2023a)

7.1.2 Method of synthesis

In the PRINCE trial, weights were assigned to each patient using a propensity score model based on logistic regression. The weighted averages and percentage of baseline attributes were matched to those of the Study 301 aggregated data.

To estimate the likelihood of enrolment in the Study 301 versus in the PRINCE study, a propensity score model based on logistic regression was used to assign weights to each patient in the

PRINCE IPD. Matching was performed such that the weighted means and proportions of baseline characteristics in the PRINCE study IPD matched those of the Study 301 aggregate data. The weight applied to each patient in the PRINCE IPD was equal to the inverse odds of their enrolment in the Study 301 versus in the PRINCE study. Separate sets of weights were generated to compare pegcetacoplan to ravulizumab and pegcetacoplan to eculizumab. Model adequacy was assessed by considering effective sample size (ESS) and through visual inspection of histograms of patient weights. Adequate models were required to have an ESS of at least 50% of the initial PRINCE study population. Because of sample size limitations, it was not possible to adjust for all effect modifiers. Patients from the PRINCE study were weighted on Asian race, age at first infusion, female sex, and baseline EORTC general health score. The effective sample sizes of the pegcetacoplan arm were 24 and 22, matched to 125 patients from the ravulizumab arm and 121 from the eculizumab arm, respectively.

In Figure 7, the propensity scores for pecgcetacoplan versus ravulizumab and eculizumab are presented. As can be seen, there are few near-zero weights and no extreme values. Hence, the weight distributions appear stable.

A bias factor analysis was conducted to quantify the extent of residual bias from unmeasured confounders, which provided a set of adjusted results of the unanchored MAIC. A set of potential confounders that were binary baseline variables (e.g., age ≥65 years, overweight/ obese, history of AA) was selected, and a bias factor was calculated for each. Unanchored indirect comparisons were separately adjusted for each bias factor by subtracting the factor from the effect estimate and 95% CI (Wong et al. 2023a).

Figure 7 [redacted]

7.1.3 Results from the comparative analysis

Table 18 Results from the comparative analysis of pegcetacoplan vs. eculizumab for patients with PNH who have haemolytic anaemia

	Pegcetacoplan (n=22) matched to eculizumab	Eculizumab (n=121)	Pegcetacoplan vs. eculizumab unanchored indirect comparison	p value[1]
Endpoint[2]	**[A]**	**[B]**	**[A–B]**	**[A] vs. [B]**
Primary endpoints				

LDH level (change from baseline), U/L (mean [95% CI])	-2,086.67 [-2,477.13, -1,696.21]	-1,199.82 [-1,202.71, -1,196.93]	-886.85 [-1,277.32, -496.38]	<0.0001*
LDH level (percentage change from baseline) (mean [95% CI])	-88.44 [-92.05, -84.84]	-76.02 [-76.20, -75.84]	-12.42 [-16.03, -8.81]	<0.0001*
LDH normalization[3] (percent [95% CI])	71.56 [49.02, 86.81]	45.00 [35.59, 53.94]	26.56 [5.07, 48.05]	0.0154*
Hb level (change from baseline), g/dL (mean [95% CI])	2.37 [1.40, 3.34]	0.59 [-0.68, 1.85]	1.78 [0.18, 3.37]	0.0289*
Hb level (percentage change from baseline) (mean [95% CI])	25.62 [14.11, 37.13]	6.13 [-7.07, 19.33]	19.49 [1.98, 37.00]	0.0291*
Hb stabilization[4] (percent [95% CI])	92.23 [72.32, 98.18]	64.50 [55.25, 72.95]	27.73 [13.93, 41.53]	0.0001*
Transfusion avoidance[5] (percent [95% CI])	92.23 [72.32, 98.18]	66.10 [56.95, 74.47]	26.13 [12.39, 39.87]	0.0002*
Secondary endpoints				
Transfusion requirement (total number of PRBC units transfused) (mean [95% CI])	0.98 [-0.80, 2.76]	5.60 [4.55, 6.65]	-4.62 [-6.69, -2.55]	<0.0001*
Time to first LDH normalization[6], days (mean [95% CI])	15.93 [13.65, 18.22]	29.00 [19.40, 38.60]	-13.07 [-22.94, -3.20]	0.0095*
BTH[7] (percent [95% CI])	0.00 [0.00, 0.00]	10.70 [5.85, 17.67]	-10.70 [-16.21, -5.19]	0.0001*
MAVEs (percent [95% CI])				
	0.00 [0.00, 0.00]	0.83 [0.02, 4.52]	-0.83 [-2.44, 0.79]	0.3153
FACIT-Fatigue score (change from baseline) (mean [95% CI])	10.00 [5.14, 14.85]	6.40 [4.85, 7.95]	3.60 [-1.50, 8.69]	0.1667
EORTC QLQ-C30 (change from baseline) (mean [95% CI])				
General health status	25.42 [16.30, 34.55]	12.90 [9.02, 16.78]	12.52 [2.60, 22.44]	0.0133*
Physical functioning	7.68 [2.41, 12.95]	11.50 [8.36, 14.64]	-3.82 [-9.96, 2.31]	0.2218
Fatigue symptoms	-25.93 [-38.66, -13.20]	-18.60 [-22.97, -14.23]	-7.33 [-20.79, 6.13]	0.2860

Abbreviations: CI, confidence interval; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FACIT, Functional Assessment of Chronic Illness Therapy; Hb = Haemoglobin; LDH, lactate dehydrogenase; MAVE, major adverse vascular event; PRBC, packed red blood cell; ULN, upper limit of normal.

1. P values for the unanchored comparisons before and after weighting were calculated with the Wald test and weighted Wald test, respectively (i.e., chi-squared test for categorical endpoints and z test for continuous endpoints).

2. The following baseline characteristics were used for weighting: Asian race, age at first infusion, female sex, and baseline EORTC general health score.

3. LDH normalization was defined as LDH level <1× ULN (246 U/L) in the absence of transfusions during the randomised controlled period.

4. Hb stabilization was defined as avoidance of a ≥2 g/dL decrease in Hb level in the absence of transfusions during the randomised controlled period.

5. Transfusions received during the randomised controlled period.

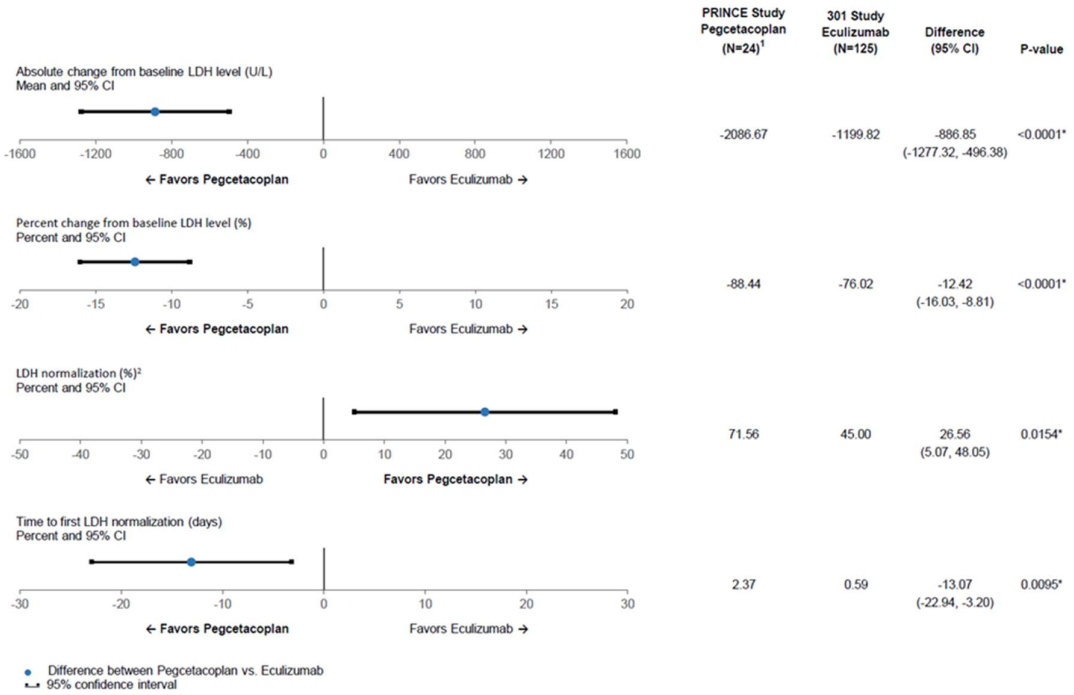
6. Time (in days) to first LDH normalization in the Study 301 trial was reported as a median value.

7. The reporting requirements for breakthrough haemolysis differed between the PRINCE and Study 301 trials, where PRINCE required reports from both scheduled and unscheduled visits and the Study 301 trial required reports only from scheduled visits.

7.1.4 Efficacy – results per LDH endpoints

Pegcetacoplan demonstrated greater absolute and percent decreases in LDH level from baseline compared to eculizumab (difference, −886.85 U/L; difference, −12.42%; *P* < 0.0001 for both) (Figure 8). The proportion of patients who achieved LDH normalisation with pegcetacoplan was higher than with eculizumab (difference, 26.56%; *P* = 0.0154). Furthermore, time to first LDH normalisation was shorter in patients receiving pegcetacoplan than in those who were treated with eculizumab (difference, −13.07 days; *P* = 0.0095).

Figure 8 Unanchored comparisons between pegcetacoplan and eculizumab – LDH Endpoints



CI = Confidence Interval; LDH = Lactate Dehydrogenase.

The following baseline characteristics were used for weighting: Asian race, age at first infusion, female sex, and baseline EORTC general health score. *Significant *P* values.

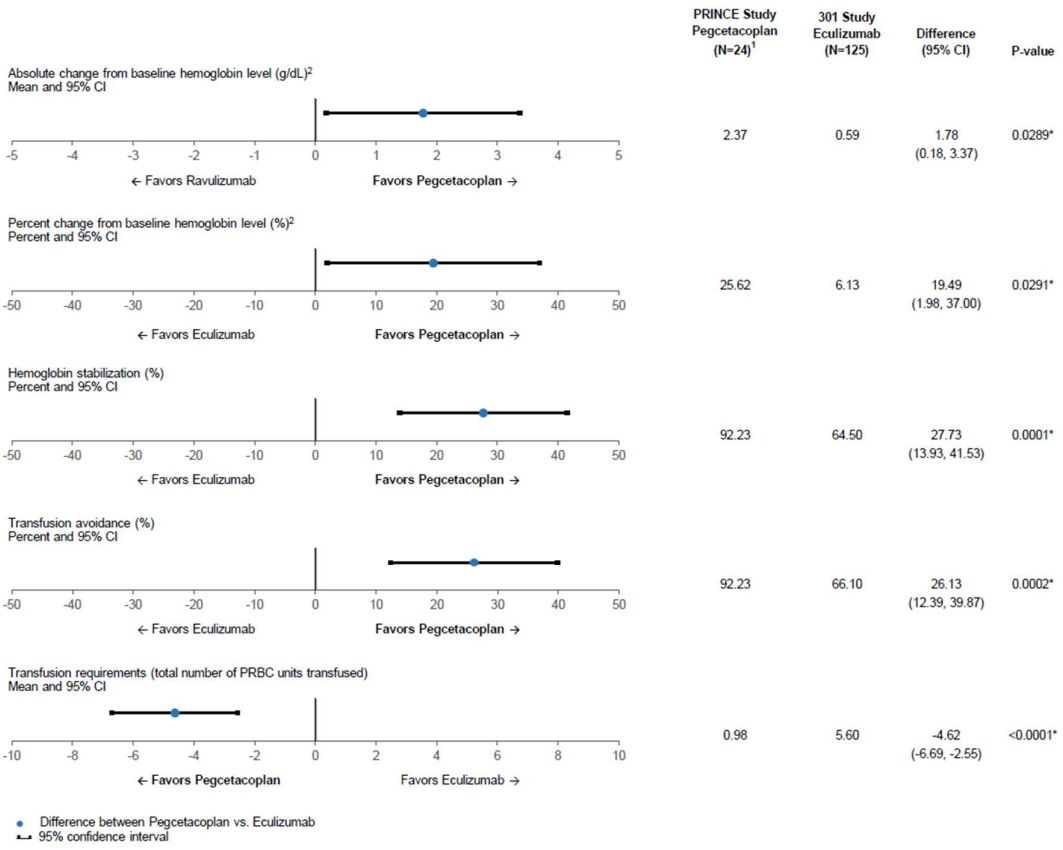
Source: Wong et al. (2023a).

7.1.5 Efficacy – results per haematologic endpoints

Pegcetacoplan was also associated with greater absolute and percent increases in Hb levels from baseline after weighting compared to eculizumab (difference, 1.78 g/dL; *P* = 0.0289, and difference, 19.49%; *P* = 0.0291, respectively; Figure 9). Patients treated with pegcetacoplan had a higher rate of Hb stabilisation than those treated with eculizumab (difference, 27.73%; *P* = 0.0001).

After weighting, more patients who received pegcetacoplan achieved transfusion avoidance compared to patients who received eculizumab (difference, 26.13%; *P* = 0.0002). Treatment with pegcetacoplan resulted in fewer PRBC units transfused than eculizumab (difference, −4.62 units; *P* < 0.0001) during the RCT period.

Figure 9 Unanchored comparisons between pegcetacoplan and eculizumab – haematologic endpoints



CI = Confidence Interval.

1.The following baseline characteristics were used for weighting: Asian race, age at first infusion, female sex, and baseline EORTC general health score. 2. Change in Hb level in the Study 301 was estimated from values for percent Hb stabilisation and mean Hb levels reported by Lee et al. and Schrezenmeier et al. *Significant *P* values.

Source: Wong et al. (2023a).

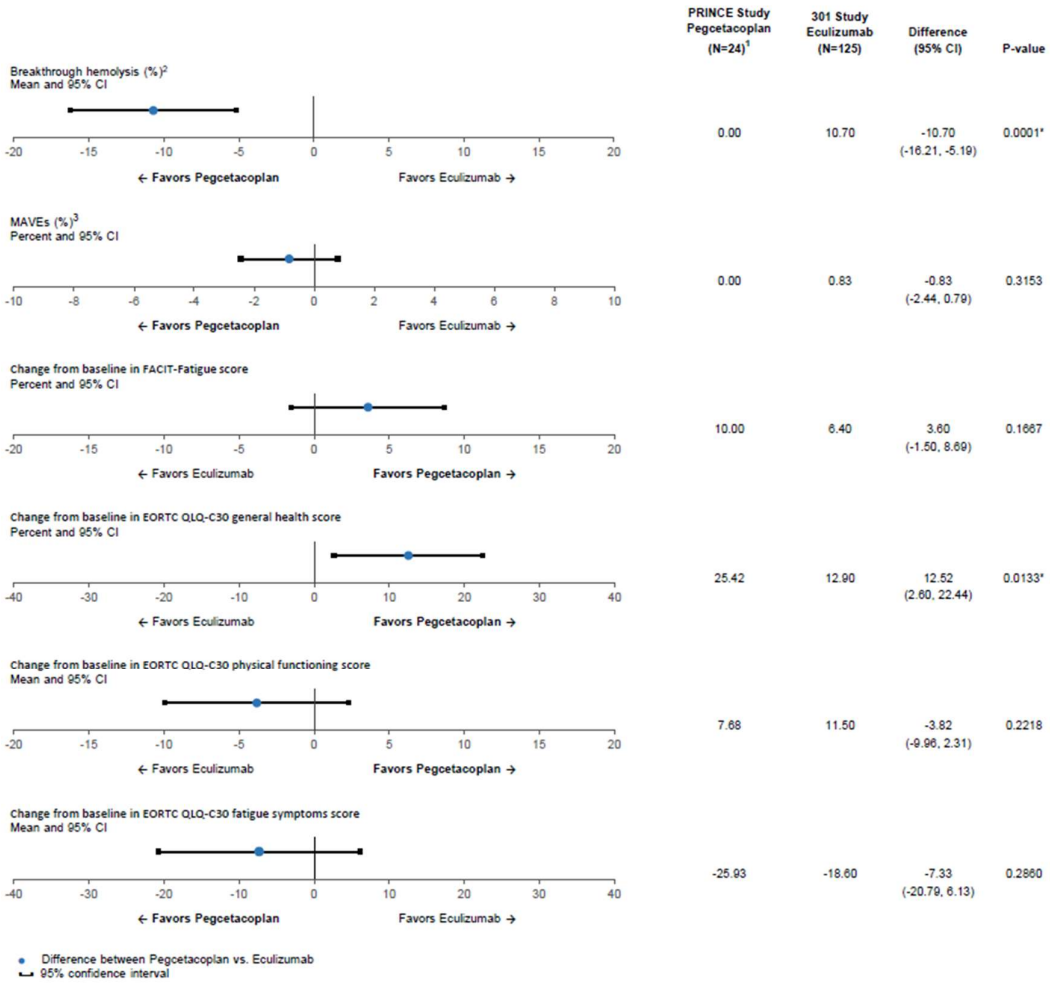
7.1.6 Safety and quality-of-life results

After weighting, a smaller proportion of patients experienced BTH when treated with pegcetacoplan than with eculizumab (difference, −10.70%; *P* = 0.0001; Figure 10).

However, no significant difference in the proportion of patients who experience MAVEs with pegcetacoplan vs. eculizumab (*P* = 0.3153) was reported.

The EORTC QLQ-C30 general health status score increased more with pegcetacoplan than with eculizumab (difference, 12.52; *P* = 0.0133; Figure 10). There were no significant differences between pegcetacoplan and or eculizumab in the other QOL outcomes. Changes in the FACIT-Fatigue score, EORTC QLQ-C30 physical functioning score, and EORTC QLQ-C30 fatigue symptoms score were comparable for pegcetacoplan vs. eculizumab (*P* = 0.1667, 0.2218, and 0.2860, respectively).

Figure 10 Unanchored comparisons between pegcetacoplan and eculizumab – safety and QOL endpoints



CI = Confidence Interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire–Core Module, version 3; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy–Fatigue Subscale; MAVE = Major Adverse Vascular Events.

1. The following baseline characteristics were used for weighting: Asian race, age at first infusion, female sex, and baseline EORTC general health score. 2. Breakthrough haemolysis was defined as ≥ 1 new or worsening sign or symptom of IVH (fatigue, haemoglobinuria, abdominal pain, dyspnoea, anaemia [Hb < 10 g/dL], or MAVEs) in the presence of LDH ≥ 2 x ULN after prior reduction to < 1.5 x ULN with treatment. 3. MAVEs were defined as: thrombophlebitis/deep vein thrombosis; pulmonary embolus; myocardial infarction; transient ischemic attack; unstable angina; renal vein thrombosis; acute peripheral vascular occlusion; mesenteric/visceral vein thrombosis or infarction; mesenteric/visceral arterial thrombosis or infarction; hepatic/portal vein thrombosis (Budd–Chiari syndrome); cerebral arterial occlusion/cerebrovascular accident; cerebral venous occlusion; renal arterial thrombosis; gangrene (non-traumatic; nondiabetic); amputation (non-traumatic; nondiabetic); and dermal thrombosis. *Significant *P* values.
Source: Wong et al. (2023a)

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

8.1.1 Baseline patient distribution

Baseline patient distribution was based on patient-level data from the PRINCE trial. [redacted]

[redacted] (Table 19).

Table 19. Baseline patient distribution

Health state	Endpoint definition		
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

8.1.2 Patient distribution during the randomised controlled period

Patient distribution was based on patient-level data from the PRINCE trial. Patients were categorized according to the following principles:

[redacted]

[redacted]

8.1.3 Transition probabilities

The modelled health states differ depending on the key endpoints included in the model. The following are available in the model:

[redacted]

The values used in the model are presented also in graphical form in Section 8.1.3.3.

8.1.3.1 Pegcetacoplan

Transition probabilities for pegcetacoplan were calculated based on patient-level data from the PRINCE trial.

Data concerning the number of patients achieving stabilization and requiring transfusion at the end of 26 weeks of the PRINCE trial are presented in Table 20. Data are presented separately for pegcetacoplan and pooled (pegcetacoplan + placebo) arms. Of note, 53 patients participated in the PRINCE trial, but data on transfusion requirement was not available for one patient.

Table 20 Patient level data from PRINCE trial – Hb stabilization (≥2 g/dL) and transfusions

From To (after 26 weeks)	Initial state (pegcetacoplan patients)		Initial state (pooled arms)	
	Transfusion Required	Transfusion not Required	Transfusion Required	Transfusion not Required
Transfusion not Required and Haemoglobin Stabilized	22/24 (91.67%)	10/10 (100.00%)	24/37 (64.86%)	11/15 (73.33%)
Transfusion not Required and Haemogloin NOT Stabilized	0/24 (0.00%)	0/10 (0.00%)	0/37 (0.00%)	1/15 (6.67%)
Transfusion Required	2/24 (8.33%)	0/10 (0.00%)	13/37 (35.14%)	3/15 (20.00%)

[redacted]

Table 21 [redacted]

From To (after 26 weeks)	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]The transition probability to the Haemoglobin NOT Stabilized state was set to 0% since all patients not requiring transfusion achieved Hb stabilization.

The results of the calculations are presented in Table 22.

Table 22 [redacted]

Probabilities after 26 weeks	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]		[redacted]

[redacted]

[redacted]

Calculated intervals are presented in Table 23.

Table 23 [redacted]

To From	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Table 24.

Table 24 [redacted]

To From	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

8.1.3.2 Eculizumab

Transition probabilities for eculizumab were calculated based on transition probabilities for pegcetacoplan and ORs between eculizumab and pegcetacoplan. OR for eculizumab were calculated based on MAIC using the following formula:

$$OR = \frac{Prob_{ecu} * (1 - Prob_{peg})}{Prob_{peg} * (1 - Prob_{ecu})}$$

Where $Prob_{peg}$ and $Prob_{ecu}$ are probabilities of transition for pegcetacoplan and eculizumab respectively.

Results of OR calculations are presented in Table 25.

[redacted] Table 25 [redacted] Transition probabilities for eculizumab calculated based on transition probabilities for pegcetacoplan and ORs between eculizumab and pegcetacoplan are presented in Table 26.

Table 25 [redacted]

Outcome	Probability		Odds ratio (comparator vs pegcetacoplan)
	Pegcetacoplan	Eculizumab	
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Table 26 [redacted]

From	To		
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

8.1.3.3 Transition probability diagrams

In this section the transition probabilities diagrams are presented. The probabilities are marked on each branch, for each drug separately. The inputs indicate the probability of transition in every cycle (so after every 6 months). The transitions are constant with time.

Furthermore, the patients flow, in the time horizon of the analysis is presented in the Appendix B.

Figure 11 [redacted]

Figure 12 [redacted]

Figure 13 [redacted]

8.1.4 Extrapolation of efficacy data

Not applicable.

8.1.4.1 Extrapolation of [effect measure 1]

Not applicable.

Table 27 Summary of assumptions associated with extrapolation of [effect measure]

Method/approach	Description/assumption
Data input	N/A
Model	N/A
Assumption of proportional hazards between intervention and comparator	N/A
Function with best AIC fit	N/A
Function with best BIC fit	N/A
Function with best visual fit	N/A
Function with best fit according to evaluation of smoothed hazard assumptions	N/A
Validation of selected extrapolated curves (external evidence)	N/A
Function with the best fit according to external evidence	N/A
Selected parametric function in base case analysis	N/A
Adjustment of background mortality with data from Statistics Denmark	N/A
Adjustment for treatment switching/cross-over	N/A
Assumptions of waning effect	N/A
Assumptions of cure point	N/A

8.1.4.2 Extrapolation of [effect measure 2]

Not applicable.

8.1.5 Calculation of transition probabilities

Please see Section 8.1.3.

Table 28 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
N/A			

8.2 Presentation of efficacy data from [additional documentation]

Not applicable.

8.3 Modelling effects of subsequent treatments

No subsequent treatment included in the model.

8.4 Other assumptions regarding efficacy in the model

Estimation of the probability of adverse events is described in Section 11.5.

8.5 Overview of modelled average treatment length and time in model health state

Table 29, Table 30, and Table 31 are not applicable for the Markov model used. In Section 8.1.3, the transition probabilities used are compared to clinical data.

Table 29 [Outcome measure] estimates in the model

	Modelled average [Outcome measure] (reference in Excel)	Modelled median [Outcome measure] (reference in Excel)	Observed median from relevant study
N/A			

Table 30 [Outcome measure] estimates in the model

	Modelled average [Outcome measure] (reference in Excel)	Modelled median [Outcome measure] (reference in Excel)	Observed median from relevant study
N/A			

Table 31 [Outcome measure] estimates in the model

	Modelled average [Outcome measure] (reference in Excel)	Modelled median [Outcome measure] (reference in Excel)	Observed median from relevant study
N/A			

Below, the average treatment length for pegcetacoplan and eculizumab is presented. Since treatment is given continuously over the patient's lifetime and no treatment discontinuation is assumed in the base case analysis, the modelled mean treatment length corresponds to the undiscounted average number of life years in the model with the respective treatments. Moreover, the mean number of months in the respective health states are presented for the two respective treatments.

Table 32 [redacted]

Treatment	Treatment length (months)	[redacted]	[redacted]	[redacted]	Death (months)
Pegcetacoplan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eculizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

9. Safety

9.1 Safety data from the clinical documentation

The safety of pegcetacoplan was evaluated in the PRINCE study by analysis of incidence and severity of treatment-emergent adverse events (TEAEs), incidence of thromboembolic events, changes from baseline in laboratory parameters, changes from baseline in electrocardiogram (ECG) parameters and incidence of anti–pegcetacoplan peptide antibodies. The TEAEs in Study 301, regarding the safety of eculizumab, were recorded and reported during the primary evaluation period, which was defined as events that started during or after the first infusion of study treatment up to before dosing on Day 183. Adverse events that occurred during or after dosing on Day 183 were considered as part of the Extension Period and were not reported.

Table 33 Overview of safety events. In Study 301 the adverse events were recorded over a period of 183 days and in PRINCE over a mean duration of 226.5 days of treatment

	Pegcetacoplan (N=46)	Supportive care (N=18)	Ravulizumab (N=125)	Eculizumab (N=121)	Difference (pegcetacoplan vs. eculizumab), % (95 % CI)
Number of adverse events, n	[redacted]	32	178	170	[redacted]
Number and proportion of patients with ≥1 adverse events, n (%)	[redacted]	12 (66.7)	109 (87.2)	104 (86.0)	[redacted]
Number of serious adverse events*, n	[redacted]	5	14	12	[redacted]
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	[redacted]	3 (16.7))	11 (8.8)	9 (7.4)	[redacted]
Number of CTCAE grade ≥ 3 events, n	N/A	N/A	N/A	N/A	N/A
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	N/A	N/A	N/A	N/A	N/A
Number of adverse reactions, n	[redacted]	N/A	N/A	N/A	N/A

	Pegcetacoplan (N=46)	Supportive care (N=18)	Ravulizumab (N=125)	Eculizumab (N=121)	Difference (pegcetacoplan vs. eculizumab), % (95 % CI)
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	[redacted]	N/A	N/A	N/A	N/A
Number and proportion of patients who had a dose reduction, n (%)	[redacted]	1 (5.6)	N/A	N/A	N/A
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	[redacted]	0	0	2 (1.7)	[redacted]
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	[redacted]	0	0	1 (0.8)	[redacted]

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

§ CTCAE v. 5.0 must be used if available.

Source: (Apellis Pharmaceuticals data on file 2021, Lee et al. 2019)

In Study 301 there were no SAEs for eculizumab recorded that had a frequency of ≥ 5%.

Table 34 Serious adverse events in PRINCE over a mean duration of 226.5 days of systemic treatment

Adverse events	Pegcetacoplan (N=46)		Supportive care (N=18)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Death, n (%)	1 (2.2)	1	1 (5.6)	1
Anaemia, n (%)	3 (6.5)	N/A	1 (5.6)	N/A
Haemolysis, n (%)	3 (6.5)	N/A	0	0

Adverse events	Pegcetacoplan (N=46)		Supportive care (N=18)	
Thrombocytopenia, n (%)	3 (6.5)	N/A	1 (5.6)	N/A
Bone marrow failure, n (%)	1 (2.2)	N/A	1 (5.6)	N/A
Febrile neutropenia, n (%)	1 (2.2)	N/A	1 (5.6)	N/A
Acute kidney injury, n (%)	0	0	1 (5.6)	N/A
Respiratory failure, n (%)	0	0	1 (5.6)	N/A

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

Source: (Wong et al. 2023b)

Please see Section 4.1.4.

Probability of BTH occurrence for pegcetacoplan patients was based on the PRINCE trial data. There were two BTH events among 35 pegcetacoplan patients during mean 244.8 days of follow-up. To inform input value for model, value was adjusted to cycle length (26 weeks). Furthemore, there were no MAVE events among pegcetacoplan patients in the PRINCE trial. The MAIC data associated with the values in Table 35 are presented in Table 36.

Table 35 [redacted]

Adverse events	Pegcetacoplan	Eculizumab		
Adverse event, n (%)	**Frequency used in economic model for intervention**	**Frequency used in economic model for comparator**	**Source**	**Justification**
BTH	[redacted]	[redacted]	[redacted]	[redacted]
MAVE	[redacted]	[redacted]	[redacted]	[redacted]

Adverse events	Pegcetacoplan	Eculizumab	[redacted]

9.2 Safety data from external literature applied in the health economic model

Table 36 presents the estimated shares of patients experiencing BTHs and MAVEs among patients treated with pegcetacoplan and eculizumab respectively from the published MAIC (Wong et al. 2023a). The reason for the difference between the observed share of patients who experienced BTH and the frequency used in the model is that in the matching procedure of the MAIC, a number of patients were excluded. Hence, after weighting, there were no BTH events in the pegcetacoplan arm. However, in entire PRINCE trail population, there were 2 cases of BTH in pegcetacoplan arm.

Table 36 Adverse events in the MAIC

Adverse events	Pegcetacoplan (N=22)			Eculizumab (N=121)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
BTH	0%		4.3%	10.7%		10.7%	-10.7% (-16.2%, -5.2%)	
MAVE	0%		0.0%	0.8%		0.8%	-0.8% (-2.4%, 0.8%)	

10. Documentation of health-related quality of life (HRQoL)

All health-related quality of life (HRQoL) data were based on data from the European Organization for Research and Treatment of Cancer (EORTC) QLQC30 questionnaire in the PRINCE trial.

Table 37 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
European Organization for Research and Treatment of Cancer (EORTC) QLQC30 questionnaire	PRINCE trial	Instrument used to elicit clinical effectiveness and health state utility values

10.1 Presentation of the health-related quality of life

10.1.1 Study design and measuring instrument

The study design of PRINCE is described in section 6.1.1.1. In the PRINCE trial, patients' QoL was measured using the European Organization for Research and Treatment of Cancer (EORTC) QLQC30 questionnaire. Since the EQ-5D-5L questionnaire was not used in the trial, the EQ-5D-5L values were mapped from the EORTC responses. The mapping procedure is presented in Section 10.2.1.1.

10.1.2 Data collection

In PRINCE, HRQoL data were collected at baseline, week 4, week, 8, week 12, week 16, week 20 and week 26. Table 38 shows the pattern of missing HRQoL data.

Table 38 Pattern of missing data and completion

Assumptions that were used:

[redacted]

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

10.1.3 HRQoL results

EORTC QLC-C30 scores in subjects treated with pegcetacoplan demonstrated improvements in scores during the course of treatment. At Week 26, the LS mean (SE) changes (improvements) from baseline in EORTC QLC-C30 scores for pegcetacoplan (N=35) was 18.90 (2.909) (Apellis Pharmaceuticals data on file 2021). Figure 14 plots the mean observed EORTC QLC-C30 scores over time by PRINCE treatment arm during the study period.

Figure 14 [redacted]

[redacted]

In Table 39 below, the number of patients and mean values are based on planned arm code, describing the assignment to study arm for the EORTC outcome. The 95% CI was estimated assuming normal distribution.

Table 39 HRQoL EORTC QLC-C30 summary statistics

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
[redacted]					

10.2 Health state utility values (HSUVs) used in the health economic model

10.2.1 HSUV calculation

The HSUVs are based on EQ-5D-5L mapped from EORTC and the Danish tariff described by Jensen et al was applied (Jensen et al. 2021).

A linear regression model was used to estimate values related to the respective health states:

*Utility = α*Baseline utility + β*Transfusion avoidance + γ*Haemoglobin outcome + SUBJID (random intercept)*

The independent variables are defined as:

- Utility at baseline (a continuous variable in the model), since it is considered a strong predictor of utility during the trial.
- Transfusion avoidance (a categorical variable in the model) was defined as a lack of RBCT during the randomised part of the trial. Otherwise, patients who required transfusions were classified 'Transfusion Required'. For simplicity, the status of transfusion avoidance or requirement was assigned to all visits.
- Hb response (categorical variable) was used to estimate the disutility associated with not meeting the response of the Hb level. Hb response was assessed separately for each visit based on the values of change from baseline in Hb level or value of Hb measurement. Three different definitions of Hb response were tested, with the assessment carried out at each visit separately:
    - Avoidance of Hb drops by >1 g/dL. Patients whose Hb level did not drop by more than 1 g/dL from baseline were considered responders at respective visits.
    - Avoidance of Hb drops by >2 g/dL. Patients whose Hb level did not drop by more than 2 g/dL from baseline were considered responders at respective visits.
    - Hb level ≥12 g/dL. Patients whose Hb level was at least 12 g/dL were considered responders at respective visits.

[redacted]

A linear regression model was used to calculate the required utility values based on data collected across all visits with available EORTC results and Hb measurements. Additionally, patient ID was used as a random effect to account for a correlation between the measurements from the same patient.

The HSUVs associated with respective health states and Hb responses were predicted from the models, accounting for random intercepts representing variability across the participants of the PRINCE trial.

To include variability of HSUVs in time due to patients' age health state, adjustments were performed using general population utilities data provided by the DMC. Utility values were adjusted to each age using following methodology (Danish Medicines Council 2021). The incremental reduction each year were calculated for each interval based on those values using formula $RedByYear = \frac{Utility_{n+1} - Utility_n}{NumberOfYears_n}$, where $Utility_n$ is utility value in age group n (e.g. 30-39), and $NumberOfYears_n$ is number of years in age group (e.g. 10 years in mentioned 30-39 age group).

10.2.1.1 Mapping

In the PRINCE trial, patients' QoL was measured using the EORTC QLQC30 questionnaire. Since a 5-level version of the EQ-5D questionnaire was not used in this trial, the EQ-5D-5L values were mapped from the EORTC responses. As there is no mapping algorithm available specifically for patients with PNH, the response mapping algorithm developed by Hagiwara et al., 2020 was used (Hagiwara et al. 2020). The coefficients from Hagiwara et al., 2020 were used to calculate the probabilities of being at the respective levels of each EQ-5D-5L domain. The EQ-5D-5L utilities were then calculated for each patient at each visit using the Danish tariff, i.e., by substituting the probability of being in each response level to the following ordinal logistic regression model:

$$EQ5D = 1 - 0.041*PRMOB2 - 0.054*PRMOB3 - 0.157*PRMOB4 - 0.220*PRMOB5 - 0.035*PRSC2 - 0.050*PRSC3 - 0.144*PRSC4 - 0.209*PRSC5 - 0.033*PRUA2 - 0.040*PRUA3 - 0.139*PRUA4 - 0.174*PRUA5 - 0.048*PRPAIN2 - 0.094*PRPAIN3 - 0.381*PRPAIN4 - 0.537*PRPAIN5 - 0.072*PRAD2 - 0.191*PRAD3 - 0.430*PRAD4 - 0.618*PRAD5$$

where PR represents the probability of level 2, 3, 4, or 5 in a specific dimension described by the letter code: MOB – mobility, SC – self-care, UA – usual activities, PAIN – pain/discomfort, AD – anxiety/depression.

10.2.2 Disutility calculation

The utility decrease for BTH and MAVE was included in the model as a utility decrease per event in each cycle. The sizes of the QALY losses for BTH and MAVE per event were calculated based on disutility and duration of eventusing the following equation:

[redacted]

O'Connell 2020 describes a cost-utility analysis of ravulizumab compared to eculizumab in PNH, it was therefore considered as a relevant source for data concerning BTH. Sullivan 2006 describes values of utility loss for various chronic health events. In Dasta 2015, costs for hospitalization for deep vein thrombosis and pulmonary embolism were described.

Moreover, a QALY loss per blood transfusion was included, which was calculated as the difference in utility between individuals achieving Hb stabilization and those that received transfusion during the last month, divided by 12 since the disutility is assumed to last for one month.

10.2.3 HSUV results

Table 40 Overview of HSUVs [and disutilities]

HSUVs	Results [95% CI]	Instrument	Tariff (value set) used	Comments
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				

HSUVs	Results [95% CI]	Instrument	Tariff (value set) used	Comments
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				

10.3 HSUVs measured in other trials than the clinical trials forming the basis for relative efficacy

Not applicable.

10.3.1 Study design

Not applicable

10.3.2 Data collection

Not applicable

10.3.3 HRQoL Results

Not applicable

10.3.4 HSUV and disutility results

Not applicable

Table 41 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
N/A				

Table 42 Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
N/A				

11. Resource use and associated costs

11.1 Medicine costs - intervention and comparator

Patients on pegcetacoplan were assumed to receive a dose of 1,080 mg SC twice per week. The pharmacy purchase price per package (1,080 mg) is DKK 25,705 (Danish Medicines Agency 2024a). Since the recommended treatment dose (1,080 mg) is identical to the package size, waste and vial sharing is not relevant. Patients receiving eculizumab were assumed to receive a dose of 900 mg IV every second week, except for the first 4 weeks on treatment during which the patient receives 600 mg every week as loading doses. The pharmacy purchase price per package (300 mg) is DKK 33,745 (Danish Medicines Agency 2024b). The recommended treatment dose (900 mg) is equivale to three packages (two for loading doses). Hence waste and vial sharing is not of relevance.

Patients receiving pegcetacoplan and eculizumab may be given increased doses if they do not respond sufficiently to the labelled dose. In the base case, eculizumab and pegcetacoplan recommended dosing levels were derived from the summary of product characteristics for each drug (EMA 2024, EMA 2023b).

Table 43 Medicine costs used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Pegcetacoplan (SC)	1,080 mg	100 %	Twice weekly	No
Eculizumab (IV)	900 mg (loading doses: 600 mg for 4 weeks)	100 %	Every second week (loading dose: every week)	No

11.2 Medicine costs – co-administration

Supportive treatments are used to manage PNH-related disease symptoms as concomitant medications for patients receiving pegcetacoplan or eculizumab. Drugs used and proportion of patients using each supportive drug was based on PRINCE trial concomitant medication data. Drug costs were sourced from medicinpriser.dk and standard doses for each drug were used. Moreover, vaccinations against *Neisseria meningitidis* types A, C, W, Y, and B are required for all patients receiving complement inhibitors. Additionally, for pegcetacoplan vaccination for pneumococcal disease was necessary, therefore PCV13 and PPSV23 cost was added. Costs of vaccinations and antibiotics were sourced from medicinpriser.dk. [redacted]

[redacted]

11.3 Administration costs

The base-case analysis assumed patients on pegcetacoplan had their first administration in a clinic and received training on self-administration. Patients self-administered subsequent doses at home. The unit cost for SC administration training was estimated to be [redacted] for pegcetacoplan. Administration cost was based on Sundhetsdatastyrelsen's DRG tariffs for 2024 using code 17MA98 (MDC17 1-dagsgruppe, pat. mindst 7 år) (Sundhetsdatastyrelsen 2024). A one-off pump cost for pegcetacoplan in-home infusion was also included in the base case to a cost of [redacted] Moreover, a one-time transportation cost of [redacted] and a cost for patient time was included in the base case. [redacted] (Danish Medicines Council 2024, Danmarks statistik 2024).

Eculizumab IV infusion was estimated to last [redacted]. Administration cost was based on Sundhetsdatastyrelsen's DRG tariffs for 2024 using code 17MA98 (MDC17 1-dagsgruppe, pat. mindst 7 år) (Sundhetsdatastyrelsen 2024). In addition, the transportation cost and patient time cost employed for pegcetaocplan was also included for eculizumab. No preparation time for IV administration was included in the model, which may be seen as a conservative assumption.

Table 44 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
IV administration	Each IV administration	[redacted]	17MA98	17MA98 DRG 2024 MDC17 1-dagsgruppe, pat. mindst 7 år
SC administration	If "Self-administered" option is chosen (base case), one-time administration cost is applied representing the cost associated with a one training session for patients. If pegcetacoplan is administered by medical personnel, the cost applies for each administration	[redacted]	17MA98	17MA98 DRG 2024 MDC17 1-dagsgruppe, pat. mindst 7 år

11.4 Disease management costs

Health state costs were estimated through costs of managing complications, costs of blood transfusion and other resource use costs.

11.4.1 Costs of blood transfusion

Costs of blood transfusion were incurred by patients in the [redacted], consisting of a blood transfusion cost and costs for treating severe acute reactions of blood transfusion.

Blood transfusion costs were estimated based on unit cost per transfusion and transfusion frequency per cycle. The unit cost per transfusion was sourced from Sundhetsdatastyrelsen (Transfusion af blod, øvrig, DRG tariff 16PR02). In terms of the transfusion frequency, the model assumed patients in [redacted] health state undergo number of transfusions corresponding with treatment, estimated based on patient level data from the PRINCE trial. There was large discrepancy between average and maximum number of transfusions in one cycle, so it was assumed that patient's state is worsening when untreated. It was assumed that with each cycle patients stay in the [redacted] health state, the number of transfusions is increased by [redacted] A conservative scenario was explored in which the number of transfusions did not increase.

Table 45. [redacted]

Initial	Increment per cycle	Maximum number in one cycle
[redacted]	[redacted]	[redacted]

11.4.2 Other resource use costs

Apart from the costs mentioned above, other health care resource use such as haematologist visits and blood tests are expected to differ by health states. In the [redacted]

Costs for transportation and patient time [redacted] are added to the cost of each haematology visit and blood transfusion.

Table 46 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Haematology visit	[redacted]	[redacted]	17MA98	DRG 2024
	[redacted]			

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
	[redacted]			
Blood transfusion	[redacted]	[redacted]	16PR02	DRG2024

11.5 Costs associated with management of adverse events

Two adverse events were included in the model: BTH and MAVEs.

Probability of BTH occurrence for pegcetacoplan patients was based on the PRINCE trial data. There were two BTH events among 35 pegcetacoplan patients during mean 244.8 days of follow-up. To inform the input value for model, the value was adjusted to cycle length (26 weeks). Furthermore, there were no MAVE events among pegcetacoplan patients in the PRINCE trial. Probability of BTH for eculizumab was sourced from MAIC.

The cost of managing adverse events was based data from Sundhetsdatastyrelsen, with DRG code 17MA02 being used for BTH and code 26MP16 for MAVE (Sundhetsdatastyrelsen 2024).

QALY loss for BTH and MAVE were calculated based on disutility and duration of event. Duration and disutility of BTH was sourced from O'Connell 2020 (OConnell et al. 2020). Duration of MAVE was based on mean duration of deep venous thrombosis event from Dasta 2015, while disutility was sourced from Sullivan 2006 for venous thrombosis (Dasta et al. 2015, Sullivan and Ghushchyan 2006). Risk per cycle and QALY loss per event concerning adverse events are presented in Table 6. In Table 48, the associated costs are presented.

[redacted]

Table 47 Adverse events

Adverse event	Probability (per cycle)		QALY loss (per event)
	PEG	ECU	
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Table 48 Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff
BTH	17MA02	55,859
MAVE	26MP16	208,658

11.6 Subsequent treatment costs

No subsequent treatments are included.

Table 49 Medicine costs of subsequent treatments

Medicine	Strength	Package size	Pharmacy purchase price [DKK]	Relative dose intensity	Average duration of treatment
N/A					

11.7 Patient costs

Patient costs were estimated by the time spent per procedure and the transportation cost. Patient costs were sourced from the DMC guidance document with a cost of DKK 140 for transportation (round trip) and DKK 203 per hour for patient time (Danish Medicines Council 2024). [redacted]

Table 50 Patient costs used in the model

Activity	Time spent (minutes)
Training session for administration of pegcetacoplan	[redacted]
Home administration of pegcetacoplan	[redacted]
Hospital administration of pegcetacoplan	[redacted]
Administration of eculizumab	[redacted]
Haematologist visit	[redacted]
Blood transfusion	[redacted]
BTH	[redacted]

Activity	Time spent (minutes)
MAVE	[redacted]
Transportation	[redacted]

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

No other costs are included.

12. Results

12.1 Base case overview

Table 51 presents an overview of the base case.

Table 51 Base case overview

Feature	Description
Comparator	Eculizumab
Type of model	Markov model
Time horizon	[redacted]
Treatment line	1st line. Subsequent treatment lines not included.
Measurement and valuation of health effects	In the PRINCE trial, patients' QoL was measured using the European Organization for Research and Treatment of Cancer (EORTC) QLQC30 questionnaire. Since the EQ-5D-5L questionnaire was not used in the trial, the EQ-5D-5L values were mapped from the EORTC responses. Danish population weights were used to estimate health-state utility values
Costs included	[redacted]
Dosage of medicine	Pegcetacoplan: 1080 mg twice weekly Eculizumab: 900 mg every 2 weeks (Loading dose: 600 mg every week for 4 weeks)
Average time on treatment	[redacted]
Parametric function for PFS	Not applicable
Parametric function for OS	Not applicable
Inclusion of waste	Not applicable

Feature	Description
Average time in model health state	[redacted]

12.1.1 Base case results

Table 52 presents further information on the base case results. As can be seen, pegcetacoplan on average generates [redacted] which can be compared to [redacted] with eculizumab. [redacted]

Since the price and effect of ravulizumab is similar to eculizumab, similar results would have been expected if pegcetacoplan would have been compared to ravulizumab instead.

Table 52 Base case results, discounted estimates

	Pegcetacoplan	Eculizumab	Difference
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

	Pegcetacoplan	Eculizumab	Difference
[redacted]			

Incremental costs per life year gained	**Pegcetacoplan cost saving vs eculizumab**
Incremental cost per QALY gained (ICER)	**Pegcetacoplan dominates eculizumab**

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

Table 53 presents the results of the performed one-way sensitivity analyses. As can be seen, [redacted] has the greatest effect on the results. However, note that in all scenario analyses [redacted]

Table 53 One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
[redacted]					

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
[redacted]					[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

12.2.2 Probabilistic sensitivity analyses

To account for the joint uncertainty of the underlying parameter estimates, a stochastic sensitivity analysis was performed. The probabilistic sensitivity analysis (PSA) shows the overall uncertainty of the incremental cost-effectiveness results for pegcetacoplan compared to eculizumab.

[redacted]

In Table 61, the point estimates, and lower and upper bound used to form the basis for the selected probability distributions used in the probabilistic analysis are presented.

Table 54. PSA results

Treatment	Mean Incr. QALYs (SD)	Mean Incr. Costs (SD)	ICER
[redacted]	[redacted]	[redacted]	[redacted]

Figure 15 [redacted]

Figure 15. The cost-effectiveness plane

13. Budget impact analysis

The numbers presented in Table 55 represent the number of patients expected to be treated in a scenario when pegcetacoplan is introduced and one scenario when pegcetacoplan is not introduced. For full details on the market share for the specific PC regimens, please refer to the BIM inputs sheet in the CEM. The expected budget impact is presented in Table 56.

Number of patients (including assumptions of market share)

Table 55 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

Budget impact

Table 56 Expected budget impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
[redacted]					
[redacted]					
[redacted]					

14. List of experts

[redacted]

[redacted]

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Appendix A. Main characteristics of studies included

Table 57 Main characteristic of studies included

Trial name: PRINCE	**NCT number: NCT04085601**
Objective	The primary objective of this study was to evaluate the efficacy and safety of pegcetacoplan compared to supportive care (SC), (excluding complement inhibitors), in subjects with PNH.
Publications – title, author, journal, year	**Pegcetacoplan controls hemolysis in complement inhibitor-naive patients with paroxysmal nocturnal hemoglobinuria,** R. S. M. Wong, J. R. Navarro-Cabrera, N. S. Comia, Y. T. Goh, H. Idrobo, D. Kongkabpan, et al., Blood Adv 2023 Vol. 7 Issue 11 Pages 2468-2478
Study type and design	A phase 3, randomised, multicenter, open-label, controlled study, completed 29th December 2019. The study consisted of a screening period of up to 4 weeks, followed by a randomised controlled period (RCP) of 26 weeks. A total of 53 patients with PNH who met all of the inclusion criteria and none of the exclusion criteria were randomised (2:1 ratio) to receive either pegcetacoplan or to remain on their current supportive care (excluding complement inhibitors) from Visit 2 (Day 1) to Visit 15 (Week 26). All subjects on supportive care or pegcetacoplan who completed Visit 15 (Week 26) were eligible to roll over into a separate open-label, long-term extension study, during which all subjects received pegcetacoplan treatment. Subjects had the option to enter the long-term extension study or complete the safety follow-up period (Visit 16 [Week 28], Visit 17 [Week 30], and Visit 18 [Week 34]). Randomization was stratified by the number of packed red blood cell (PRBC) transfusions within the 12 months prior to screening (<4;≥4) (i.e. number of transfusion events regardless of PRBC units transfused). If, at any point during the study, any subject assigned to the supportive care treatment arm had Hb concentrations ≥2 g/dL below the baseline value or presented with a qualifying thromboembolic event secondary to PNH, they were offered early escape therapy with pegcetacoplan. An external, independent, data monitoring committee assessed the safety/tolerability data of the study periodically. Subjects who failed the screening procedures were not rescreened for the study unless this was agreed upon in advance and documented in writing by the sponsor.
Sample size (n)	53 • Pegcetacoplan: 35 (+11 from roll over extension study) • Supportive care, excluding complement inhibitors: 18

Trial name: PRINCE		NCT number: NCT04085601
Main inclusion criteria	• Age at least 18 years old • PNH diagnosis confirmed by high-sensitivity flow cytometry (granulocyte or monocyte clone > 10%) • Haemoglobin (Hb) levels below the lower limits of normal (LLN) (male: < 13.6 g/dL; female: < 12.0 g/dL) • LDH levels ≥ 1.5 times the upper limit of normal (1.5x ULN; ≥ 339 U/L) • Vaccination against Streptococcus pneumoniae, Neisseria meningitidis (types A, C, W, Y, and B), and Haemophilus influenzae (type B) within 2 years prior to day 1 of pegcetacoplan dosing or agree to vaccination 14 days following initiation of pegcetacoplan treatment with prophylactic antibiotic therapy for ≥ 14 days before and after vaccination • Ferritin levels ≥LLN (≥ 13 ng/mL) or total iron binding capacity ≤ ULN (≤ 155 µg/dL). If a patient was receiving iron supplements at screening, the investigator must have ensured that the patient's dosage was stable for 4 weeks prior to screening, and it must have been maintained throughout the study. Patients not receiving iron at screening must not have started iron supplementation during the course of the study • Body mass index (BMI) ≤ 35 kg/m^2 • A platelet count of > 50,000/mm^3 • An absolute neutrophil count > 500/mm^3	
Main exclusion criteria	• Receiving treatment with any complement inhibitor (i.e., eculizumab, ravulizumab) within 3 months prior to screening • A hereditary complement deficiency • History of BMT • Concomitant use of any of the following medications if the patient was not on a stable regimen for the specified period prior to screening: erythropoietin, immunosuppressants (for ≥ 8 weeks), systemic corticosteroids, vitamin K antagonists (i.e., warfarin) with a stable international normalized ratio, iron supplements, vitamin B12, folic acid, or low-molecular-weight heparin (for ≥ 4 weeks) • History or presence of hypersensitivity or idiosyncratic reaction to compounds related to the investigational product or SC administration • Participated in any other investigational drug trial or exposure to other investigational agent/device/procedure within 30 days or 5 half-lives • Plan to become pregnant or were currently a breastfeeding woman • History of meningococcal disease	

Trial name: PRINCE	NCT number: NCT04085601
	• Any comorbidity or condition (such as malignancy) that, in the opinion of the investigator, could put the patient at increased risk or potentially confound study data.
Intervention	46 patients received the investigational product: pegcetacoplan Doses: – 1,080 mg twice weekly, or – 1,080 mg every 3 days (ie, a dose on every third day) Route of administration: subcutaneous (SC) infusion Dose adjustment was considered on the basis of clinical response.
Comparator(s)	Current supportive care (excluding complement inhibitors)
Follow-up time	The mean duration of exposure was 226.5 days
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** **Primary endpoints:** • Hb stabilization defined as avoidance of a >1 g/dL decrease in Hb concentrations from baseline in the absence of transfusion through Week 26 • Reduction in LDH concentration from baseline to Week 26 **Secondary endpoints:** • Hb response in the absence of transfusions (Hb response is defined as ≥1 g/dL increase in Hb from baseline at Week 26) • change from baseline to Week 26 in ARC • change from baseline through Week 26 in Hb concentration • proportion of subjects who received transfusion or had decrease of Hb > 2 g/dL from baseline • transfusion avoidance, defined as the proportion of subjects who did not require a transfusion during the RCP. • number of packed red blood cells (PRBC) units transfused from baseline to Week 26 • change from baseline to Week 26 in Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue Scale score • normalization of Hb concentrations (≥1xLLN) from Baseline to Week 26 in the absence of transfusions

- normalization of LDH concentrations (≤1 × the ULN) from Week 4 through Week 26 in the absence of transfusions
- change from baseline to Week 26 in European Organisation for Research and Treatment of Cancer 30-item QLQ C30 scores
- change from baseline through Week 26 in Linear Analog Scale Assessment scores
- ARC normalization (<1 x the ULN) at Week 26
- time to failure of Hb stabilization
- time to first transfusion

Additional secondary endpoints:

- number and percentage of subjects achieved Hb concentration ≥11 g/dL and ≥12 g/dL at Week 26
- number and percentage of subjects without PRBC transfusion during the RCP
- total and indirect bilirubin normalization levels (defined as ≤1× the ULN) at Week 26 in the absence of transfusion
- number and percentage of subjects achieving ≥3 points improvement in FACIT-Fatigue Scale score from baseline through Week 26
- normalization of Hb concentrations (defined as ≥1x the LLN) from baseline at Week 26 in the absence of transfusions
- normalization of LDH concentrations ≤1× ULN at Week 26 in the absence of transfusions
- ARC normalization from Week 4 through Week 26 in the absence of transfusion

Exploratory endpoints:

- The proportion of patients with breakthrough haemolysis, defined as at least 1 new or worsening symptom or sign of intravascular haemolysis (fatigue; haemoglobinuria; abdominal pain; shortness of breath [dyspnea]; anaemia [Hb <10 g/dL]; major adverse vascular events (MAVEs), including thrombosis; dysphagia; or erectile dysfunction) in the presence of elevated LDH ≥2 × the ULN, after prior LDH reduction to <1.5 x the ULN on therapy
- Transfusion avoidance: the proportion of subjects who did not require a transfusion during the RCP. Subjects who did not have a transfusion but withdrew before Week 26 or escaped from supportive care to pegcetacoplan were considered as a failure in transfusion avoidance.

Trial name: PRINCE	NCT number: NCT04085601

Method of analysis

The efficacy endpoints were primarily evaluated with the intent-to-treat (ITT) set. All statistical testing was at the 5% level of significance (2-sided) and all point estimates for the comparison between treatment groups was accompanied by 2-sided 95% CIs. All possible efforts were made to ensure that subjects completed all the required assessments. Endpoints were summarized and, where appropriate, plotted over time for each treatment group. Baseline assessments were performed on Day 1 prior to the start of study treatment for subjects randomised to pegcetacoplan and at Day 1 for subjects randomised to supportive care.

The coprimary efficacy endpoints were analysed using the ITT set. The coprimary efficacy endpoints are:

- Hb stabilization defined as decrease of ≤1 g/dL in Hb concentrations from baseline to Week 26 in the absence of transfusions
- Reduction in LDH concentration from baseline to Week 26

For the first coprimary endpoint, the number and percentage of subjects who achieve Hb stabilization was computed for treatment groups and compared between treatment groups using a stratified Cochran-Mantel-Haenszel χ-square test. The treatment difference in percentages and 95% CI for the difference is presented using the stratified Miettinen-Nurminen method.
Subjects who received a transfusion through Week 26, escaped from supportive care to pegcetacoplan, or withdrew from the study before providing primary efficacy assessments were categorized as failing to achieve Hb stabilization. The second coprimary endpoint, change from baseline to Week 26 in LDH, was analysed using an analysis of covariance (ANCOVA) model (ITT set) with a multiple imputation approach for handling missing data. The ANCOVA model included terms for treatment, stratification factor, and baseline LDH concentration. The difference between treatment groups was estimated, along with its 95% CI and P value. All LDH concentrations obtained prior to transfusion, withdrawal from the study or treatment, and/or switch to pegcetacoplan were included in the model.

As missing data may potentially bias the outcome of the statistical analyses and the subsequent estimation of the magnitude of the treatment effect, the following sensitivity and supportive analyses were performed to evaluate the robustness of the results from the primary analysis methods:

- The first coprimary efficacy endpoint was also analysed using a logistic regression with the effects of treatment group and stratification factor included. The odds ratio of being an Hb stabilization achiever for the pegcetacoplan versus supportive care group and associated 95% CI was estimated.
- The second coprimary endpoint was analysed using a mixed-effects model for repeated measures with the fixed effects of treatment, stratification factor, visit, visit by treatment

interaction, and baseline LDH concentration using an unstructured covariance matrix.

- The second coprimary endpoint was analyzed using an analysis of covariance (ANCOVA) model (ITT set) with a last observation carried forward approach for handling missing data. The ANCOVA model included terms for treatment, stratification factor, and baseline LDH concentration.
- The second coprimary endpoint was analyzed using an ANCOVA model (ITT set) with a baseline best observation carried forward (BOCF) approach for handling missing data. The ANCOVA model included terms for treatment, stratification factor, and baseline LDH concentration.

The secondary endpoints were analyzed using the ITT set and were repeated using the per-protocol set. To preserve the Type 1 error rate, the key secondary endpoints were tested in a hierarchical manner after statistical significance was reached for the 2 coprimary endpoints. Once one hypothesis was tested not significant, all subsequent tests were not assessed. Estimates were computed for all key secondary and secondary endpoints regardless of whether a hypothesis was tested not significant preventing assessment of subsequent tests.

Summary statistics by randomization strata and by treatment groups are presented at each assessment visit during the 26-week randomised treatment period.

Continuous endpoints were analyzed using ANCOVA model (ITT set) with a multiple imputation approach for handling missing data. The ANCOVA model included terms for treatment, stratification factors, and baseline variable level. The difference between treatment groups was estimated, along with its 95% CI and P value. If a subject received a transfusion during his/her treatment period, the pretransfusion Hb values, reticulocyte values, and FACIT-Fatigue Scale score were used in the model.

For categorical endpoints, the number and percentage of subjects was tabulated by treatment group and compared between treatment groups using a stratified Cochran-Mantel-Haenszel χ-square test.

Kaplan-Meier plots were presented for time-to-event endpoints for each treatment group, and survival estimates were provided.

The number of units of PRBCs transfused was compared between the treatment groups using a Wilcoxon rank sum test. The difference between the medians was estimated along with its 95% CI (stratified). Subjects who withdrew before Week 26 had the number of units estimated from the duration that they were in the study (ie, number per week × 12). This equates to an analysis of the frequency of transfusions.

Trial name: PRINCE		NCT number: NCT04085601
Subgroup analyses	N/A	
Other relevant information	N/A	

Trial name: Study 301		NCT number: NCT 3056040
Objective	The primary purpose of this study was to assess the noninferiority of ravulizumab compared to eculizumab in adult participants with PNH who had never been treated with a complement inhibitor (treatment-naïve).	
Publications – title, author, journal, year	Brodsky, R.A.P.d.L., et al., Characterization of breakthrough hemolysis events observed in the phase 3 randomized studies of ravulizumab versus eculizumab in adults with paroxysmal nocturnal Haemoglobinuria. Haematologica, 2021. 106(1): p. 230-237. Ishiyama, K.N., et al., Results from multinational phase 3 studies of ravulizumab (ALXN1210) versus eculizumab in adults with paroxysmal nocturnal Haemoglobinuria: subgroup analysis of Japanese patients. International Journal of Hematology, 2020. 112(4): p. 466-476. Lee, J:W., et al., Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study. Blood 2019. 133(6) p. 530-539 Schrezenmeier, H.K., et al., One-year efficacy and safety of ravulizumab in adults with paroxysmal nocturnal Haemoglobinuria naïve to complement inhibitor therapy: open-label extension of a randomized study. Therapeutic advances in hematology, 2020. 11. Kulasekararaj, A.G.G., et al., Long-term safety and efficacy of ravulizumab in patients with paroxysmal nocturnal Haemoglobinuria: 2-year results from two pivotal phase 3 studies. European Journal of Haematology, 2022. 109(3): p. 205-214. Schrezenmeier, H.K., et al., Predictors for improvement in patient-reported outcomes: post hoc analysis of a phase 3 randomized, open-label study of eculizumab and ravulizumab in complement inhibitor-naive patients with paroxysmal nocturnal Haemoglobinuria. Annals of Hematology, 2024. 103(1): p. 5-15. Schrezenmeier, H.K., et al., One-year efficacy and safety of ravulizumab in adults with paroxysmal nocturnal Haemoglobinuria naive to complement inhibitor therapy: open-label extension of a randomized study. Therapeutic Advances in Hematology, 2020. 11(no pagination). Schwartz CE, et al., Norm-based comparison of the quality-of-life impact of ravulizumab and eculizumab in paroxysmal nocturnal Haemoglobinuria. Orphanet J Rare Dis. 2021 Sep 15;16(1):389.	

Trial name: Study 301	NCT number: NCT 3056040
Study type and design	A Phase 3, Randomised, Open-Label, Active-Controlled, Multicenter study. Patients were randomly assigned in a 1:1 ratio. The study consisted of a 4-week screening period and a 26-week randomised treatment period, the Primary Evaluation Period was completed 25th January 2018. After completion of the 26-week Primary Evaluation Period, all participants had the opportunity to enter the Extension Period, wherein participants will receive ravulizumab for up to 5 years. This study is ongoing. The data presented is for the Primary Evaluation Period.
Sample size (n)	246 • ravulizumab: 125 • eculizumab: 121
Main inclusion criteria	• Male or female ≥18 years of age. • PNH diagnosis confirmed by documented by high-sensitivity flow cytometry. • Presence of 1 or more of the following PNH-related signs or symptoms within 3 months of screening: fatigue, Haemoglobinuria, abdominal pain, shortness of breath (dyspnea), anaemia (Hb <10 g/dL), history of a major adverse vascular event (MAVE) (including thrombosis), dysphagia, or erectile dysfunction; or history of PRBC transfusion due to PNH. • Lactate dehydrogenase (LDH) level ≥1.5 times the upper limit of normal at screening. • Documented meningococcal vaccination not more than 3 years prior to, or at the time of, initiating study treatment. • Female participants of childbearing potential must use highly effective contraception starting at screening and continuing until at least 8 months after the last dose of ravulizumab. • Willing and able to give written informed consent and comply with study visit schedule.
Main exclusion criteria	• Treatment with a complement inhibitor at any time. • History of bone marrow transplantation. • Body weight <40 kg. • Females who are pregnant, breastfeeding, or who have a positive pregnancy test at screening or Day 1. • Participation in another interventional clinical study or use of any experimental therapy within 30 days before initiation of study drug on Day 1 in this study or within 5 half-lives of that investigational product, whichever is greater.

Trial name: Study 301	NCT number: NCT 3056040
	• History of or ongoing major cardiac, pulmonary, renal, endocrine, or hepatic disease that, in the opinion of the investigator or sponsor, would preclude participation. • Unstable medical conditions (for example, myocardial ischemia, active gastrointestinal bleed, severe congestive heart failure, anticipated need for major surgery within 6 months of randomization, coexisting chronic anaemia unrelated to PNH). • Any comorbidity or condition (such as malignancy) that, in the opinion of the investigator, could put the patient at increased risk or potentially confound study data.
Intervention	125 patients received the investigational product: ravulizumab • loading dose on Day 1 and maintenance doses on Day 15 and every 8 weeks thereafter, administered by intravenous (IV) infusion. Dosages are based on the patient's body weight. • All treatments were given as IV infusions. For participants weighing ≥40 to <60 kilogram (kg): 2,400 mg was given as a single loading dose, followed by 3,000 mg as maintenance dose. For participants weighing ≥60 to <100 kg: 2,700 mg was given as a loading dose, followed by 3,300 mg as maintenance dose. For participants weighing ≥100 kg: 3000 mg was given as a loading dose, followed by 3,600 mg as maintenance dose • After completion of the Primary Evaluation Period, all participants had the opportunity to enter the Extension Period, wherein participants will receive weight-based doses of ravulizumab for up to 5 years.
Comparator(s)	121 patients received the active comparator: eculizumab • Participants received 600 mg of eculizumab on Days 1, 8, 15, and 22, followed by 900 mg of eculizumab on Day 29 and every 2 weeks thereafter for 26 weeks • After completion of the Primary Evaluation Period, all participants had the opportunity to enter the Extension Period, wherein participants will receive weight-based doses of ravulizumab for up to 5 years.
Follow-up time	183 days for the primary evaluation period
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Primary endpoints:** • Transfusion avoidance, defined as the proportion of patients who remain transfusion-free and do not require a transfusion

Trial name: Study 301	NCT number: NCT 3056040
	as per protocol-specified guidelines through Day 183 (Week 26) • Haemolysis as directly measured by the normalization of LDH levels (LDH-N) from Day 29 (first scheduled evaluation status post initiation of maintenance dosing) through Day 183 **Secondary endpoints:** • Percentage change in LDH from Baseline to Day 183 • Change in quality of life (QoL) assessed via the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale, Version 4, from Baseline to Day 183 • Proportion of patients with breakthrough haemolysis, defined as at least one new or worsening symptom or sign of intravascular haemolysis (IVH) (fatigue, Haemoglobinuria, abdominal pain, shortness of breath [dyspnea], anaemia [Hb < 10 g/dL], MAVE, including thrombosis, dysphagia, or erectile dysfunction) in the presence of elevated LDH≥2 × ULN, after prior LDH reduction to < 1.5 × ULN on therapy • Proportion of patients with stabilized Hb, defined as avoidance of a ≥2 g/dL decrease in Hb level from baseline in the absence of transfusion through Day 183 **Additional secondary endpoints:** • Change in the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 Scale (QLQ-C30), Version 3.0, from Baseline to Day 183 • Time to first occurrence of LDH-N • Total number of units of PRBCs transfused through Day 183 • Change in clinical manifestations of PNH (fatigue, Haemoglobinuria, abdominal pain, shortness of breath, chest pain, dysphagia, and erectile dysfunction) from Baseline to Day 183 • Proportion of patients experiencing MAVEs through Day 183
Method of analysis	Efficacy analyses were performed on the Full Analysis Set (FAS). The coprimary efficacy endpoint analyses, as well as key secondary endpoint analyses were also performed on the Per Protocol (PP) set. A difference in the percentage of patients achieving TA in the 2 treatment groups was calculated between treatment groups, along with a 95% CI for the difference. The difference between treatment groups was computed as a weighted combination of the differences between the treatment groups within stratification groups (using Mantel-Haenszel). The 95% CI for the difference between treatment groups was calculated

Trial name: Study 301	NCT number: NCT 3056040
	using the stratified Newcombe confidence interval method. Results from the model were presented as odds ratios with 95% CIs.
Subgroup analyses	N/A
Other relevant information	N/A

Appendix B. Efficacy results per study

Results per study

Table 58 Results per study

Results of PRINCE (NCT04085601)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Hb stabilisation defined as avoidance of a > 1 g/dL decrease in hb concentration from baseline in the absence of transfusion, n (%)	Pegcetacoplan	35	85.7% (69.7, 95.2)	73.1%	57.2, 89.0	< 0.0001	N/A	N/A	N/A	The number and percentage of subjects who achieve Hb stabilization was computed for treatment groups and compared between treatment groups using a stratified Cochran-Mantel-Haenszel χ-square test. The treatment difference in percentages and 95% CI for the difference is presented using the stratified Miettinen-Nurminen method.	Wong, Navarro-Cabrera, et al. (2023a)
	Supportive care	18	0% (0.0, 18.5)								

Results of PRINCE (NCT04085601)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Change from baseline in LDH concentration, LS mean (SE) U/L	Pegcetacoplan	35	–1,870.5 (-2,066.7, -1674.3)	–1,470.4	–2,113.4, –827.3	<.0001	N/A	N/A	N/A	Analysis of covariance (ANCOVA) model (ITT set) with a multiple imputation approach for handling missing data. The ANCOVA model included terms for treatment, stratification factor, and baseline LDH concentration. The difference between treatment groups was estimated, along with its 95% CI and P value. All LDH concentrations obtained prior to transfusion, withdrawal from the study or treatment, and/or switch to pegcetacoplan were included in the model. 2 types of sensitivity analyses were performed: MMRM (Mixed-effects Model for Repeated Measures) and the tipping point imputation approach	(Wong et al. 2023b)
	Supportive care	18	–400.1 (-1,013.6, 213.4)								

Results of PRINCE (NCT04085601)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Hb response (yes/no) in the absence of transfusions (from baseline at Week 26)	Pegcetacoplan	35	71.4% (53.7, 85.4)	54.1%	33.9, 74.3	< 0.0001	N/A	N/A	N/A	The secondary endpoints were analyzed using the ITT set and were repeated using the per-protocol set. For **categorical endpoints**, the number and percentage of subjects was tabulated by treatment group and compared between treatment groups using a stratified Cochran-Mantel-Haenszel χ-square test	(Wong et al. 2023b)
	Supportive care	18	5.6% (0.1, 27.3)								
ARC change from baseline, LS mean (SD) Cells×10^9/L	Pegcetacoplan	35	–123.3 (-126.3, -120.3)	–103.8	–158.9, –48.7	0.0002	N/A	N/A	N/A	**Continuous endpoints** were analyzed Using an ANCOVA model (ITT set) with a multiple imputation approach for handling missing data. The ANCOVA model included terms for treatment, stratification factors, and baseline variable level	(Wong et al. 2023b)
	Supportive care	18	–19.4 (-31.0, -7.8)								
Hb change from	Pegcetacoplan	35	2.9	2.7	1.0, 4.4	0.0019	N/A	N/A	N/A	Continuous endpoint see above	(Wong et al. 2023b)

Results of PRINCE (NCT04085601)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
baseline, LS mean (SE) [g/dL]			(2.1, 3.7)								
	Supportive care	18	0.3 (-1.3, 1.9)								
Transfusion or decrease of Hb >2 g/dL, n (%)	Pegcetacoplan	35	11.4% (3.2, 26.7)	-75.1%	–90.4, 0.60	< 0.0001	N/A	N/A	N/A	Categorical endpoint see above	(Wong et al. 2023c)
	Supportive care	18	100% (81.5, 100)								
Transfusion avoidance, n (%)	Pegcetacoplan	35	91.4% (76.9, 98.2)	72.4%	55.8, 89.0	<.0001	N/A	N/A	N/A	Categorical endpoint see above	(Wong et al. 2023b)
	Supportive care	18	5.6% (0.1, 27.3)								
Total number of PRBC	Pegcetacoplan	35	21 (0.0) (0-19)	3.0	2.0, 4.0	< 0.0001	N/A	N/A	N/A	Continous endpoint see above	(ClinicalTrials.gov 2019)

Results of PRINCE (NCT04085601)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
transfusion units n (median) (range)	Supportive care	18	59 (3.0) (0-13)								
Change from baseline in FACIT–Fatigue Scale score, LS mean (SE)	Pegcetacoplan	35	7.8 (5.4, 10.2)	4.5	-0.2 to 9.2	0.0610	N/A	N/A	N/A	Continous endpoint see above	(Wong et al. 2023b)
	Supportive care	18	3.3 (-0.8, 7.4)								
ARC normalisation at week 26 in the absence of transfusions, n (%)	Pegcetacoplan	35	60.0% (42.1, 76.1)	46.4%	25.3, 67.5	0.0002 (nominal)	N/A	N/A	N/A	Categorical endpoint see above	(Wong et al. 2023b)
	Supportive care	18	5.6% (0.1, 27.3)								

Results of PRINCE (NCT04085601)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Change from baseline in EORTC QLQ-C30 scores, LS mean (SE)	Pegcetacoplan	35	18.9 (13.2, 24.6)	21.8	9.4, 34.2	0.0006 (nominal)	N/A	N/A	N/A	Continuous endpoint, see above	(Wong et al. 2023b)
	Supportive care	18	-2.9 (-14.1, 8.3)								

ARC = Absolute Reticulocyte Count; CI = Confidence Interval; Hb = Haemoglobin; LDH = Lactate Dehydrogenase; LS = Least Square; N = Number of Subjects in Treatment Groups; PRBC = Packed Red Blood Cells; SD = Standard Deviation; SE = Standard Error

Results of Study 301 (NCT 3056040)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Transfusion	Ravulizumab	125	73.6 (65.9-81.3)	6.8	-4.7, 18.1	N/A	N/A	N/A	N/A	.	Lee JW, et al., Ravulizumab (ALXN1210) vs eculizumab

Results of Study 301 (NCT 3056040)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
avoidance rate, %											in adult patients with PNH naive to complement inhibitors: the 301 study. Blood. 2019 Feb 7;133(6):530-539.
	Eculizumab	121	66.1 (57,7, 74.6)								
LDH normalization, %	Ravulizumab	125	53.6 (45.9-61.2)	1.2	0.8, 1.8	N/A	N/A	N/A	N/A		Lee, 2019
	Eculizumab	121	49.4 (41.7-57.0)								
	Ravulizumab	125	-76.8 (-80.0, -73.7)	-0.8	−5.21, 3.56	N/A	N/A	N/A	N/A		Lee, 2019

Results of Study 301 (NCT 3056040)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
LDH, LS mean % change	Eculizumab	121	−76.0 (−79.2 −72.8)								
FACIT-Fatigue score, LS mean change	Ravulizumab	125	7.07 (5.6-8.6)	-0.7	−1.21, 2.55	N/A	N/A	N/A	N/A		Lee, 2019
	Eculizumab	121	6.40 (4.9-8.0)								
Breakthrough Haemolysis rate, %	Ravulizumab	125	4.0 (0.6-7.4)	-6.7	−14.21, 0.18	N/A	N/A	N/A	N/A		Lee, 2019
	Eculizumab	121	10.7 (5.2-16.3)								
Hb stabilization rate, %	Ravulizumab	125	68.0 (59.8-76.2)			N/A	N/A	N/A	N/A		Lee, 2019
	Eculizumab	121	64.5								

Results of Study 301 (NCT 3056040)												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
			(55.9-73.0)								

* Ravulizumab was noninferior to eculizumab for both coprimary and all key secondary end points (P_{inf} < .0001)

CI = Confidence Interval; Hb = Haemoglobin; LDH = Lactate Dehydrogenase; LS = Least Square; N = Number of Subjects in Treatment Groups

Appendix C. Comparative analysis of efficacy

In the PRINCE trial, weights were assigned to each patient using a propensity score model based on logistic regression. The weighted averages and percentage of baseline attributes were matched to those of the Study 301 aggregated data.

To estimate the likelihood of enrolment in the Study 301 versus in the PRINCE study, a propensity score model based on logistic regression was used to assign weights to each patient in the PRINCE IPD. Matching was performed such that the weighted means and proportions of baseline characteristics in the PRINCE study IPD matched those of the Study 301 aggregate data. The weight applied to each patient in the PRINCE IPD was equal to the inverse odds of their enrolment in the Study 301 versus in the PRINCE study. Separate sets of weights were generated to compare pegcetacoplan to ravulizumab and pegcetacoplan to eculizumab. Model adequacy was assessed by considering effective sample size and through visual inspection of histograms of patient weights. Adequate models were required to have an ESS of at least 50% of the initial PRINCE study population. Because of sample size limitations, it was not possible to adjust for all effect modifiers. Patients from the PRINCE study were weighted on Asian race, age at first infusion, female sex, and baseline EORTC general health score.

A bias factor analysis was conducted to quantify the extent of residual bias from unmeasured confounders, which provided a set of adjusted results of the unanchored MAIC. A set of potential confounders that were binary baseline variables (e.g., age ≥65 years, overweight/ obese, history of AA) was selected, and a bias factor was calculated for each. Unanchored indirect comparisons were separately adjusted for each bias factor by subtracting the factor from the effect estimate and 95% CI (Wong et al. 2023a).

Table 59 Comparative analysis of studies comparing pegcetacoplan to eculizumab for patients with PNH

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
LDH level (mean change from baseline), U/L	PRINCE and Study 301	-886.85	-1,277.32, -496.38	<0.0001*	NA	NA	NA		[redacted]

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
LDH level (mean percentage change from baseline)	PRINCE and Study 301	N/A	N/A	N/A	-12.42	-16.03, -8.81	<0.0001*		[redacted]
LDH normalization[3] (percent)	PRINCE and Study 301	N/A	N/A	N/A	26.56	5.07, 48.05	0.0154*		[redacted]
Haemoglobin (Hb) level (mean change from baseline), g/dL	PRINCE and Study 301	1.78	0.18, 3.37	0.0289*	N/A	N/A	N/A		[redacted]
Hb level (mean percentage change from baseline)	PRINCE and Study 301	N/A	N/A	N/A	19.49	1.98, 37.00	0.0291*		[redacted]
Hb stabilization[4] (percent)	PRINCE and Study 301	N/A	N/A	N/A	27.73	13.93, 41.53	0.0001*		[redacted]
Transfusion avoidance[5] (percent)	PRINCE and Study 301	N/A	N/A	N/A	26.13	12.39, 39.87	0.0002*		[redacted]
Transfusion requirement (mean total number of PRBC units transfused	PRINCE and Study 301	-4.62	-6.69, -2.55	<0.0001*	N/A	N/A	N/A		[redacted]
Time to first LDH normalization[6], (mean days)	PRINCE and Study 301	-13.07	-22.94, -3.20	0.0095*	N/A	N/A	N/A		[redacted]

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
Breakthrough haemolysis[7] (percent)	PRINCE and Study 301	N/A	N/A	N/A	-10.70	-16.21, -5.19	0.0001*		[redacted]
MAVEs (percent)	PRINCE and Study 301	N/A	N/A	N/A	-0.83	-2.44, 0.79	0.3153		[redacted]
FACIT-Fatigue score (mean change from baseline)	PRINCE and Study 301	3.60	-1.50, 8.69	0.1667	N/A	N/A	N/A		[redacted]
EORTC QLQ-C30 (mean change from baseline)									[redacted]
General health status	PRINCE and Study 301	12.52	2.60, 22.44	0.0133*	N/A	N/A	N/A		[redacted]
Physical functioning	PRINCE and Study 301	-3.82	-9.96, 2.31	0.2218	N/A	N/A	N/A		[redacted]
Fatigue symptoms	PRINCE and Study 301	-7.33	-20.79, 6.13	0.2860	N/A	N/A	N/A		[redacted]

*Before matching, the Wald test with 95% confidence interval (CI) was used to compare categorical and continuous variables (i.e., chi squared and z tests, respectively). After matching, outcomes were compared between balanced treatment groups using statistical tests that incorporated weights generated during matching. The weighted Wald test with 95% CI was used for comparisons of categorical and continuous variables (i.e., weighted chi-squared and z tests, respectively).

C.1 Baseline clinical and demographic characteristics

After weighting the pegcetacoplan arm separately to match the ravulizumab and eculizumab arms (on Asian race, age at first infusion, female sex, and EORTC QLQ-C30 general health score), there was a higher proportion of patients who were American Indian or Alaska Native in the pegcetacoplan arm than in the ravulizumab (30.4% vs. 0.8%, P = 0.0026) or eculizumab(36.7% vs. 0.8%, P = 0.0008) arms. Patients who received pegcetacoplan had greater mean baseline LDH levels than those who received ravulizumab (2,220.27 U/L vs. 1,633.50 U/L, P = 0.0004) or eculizumab (2,291.04 U/L vs. 1,578.30 U/L, P = 0.0001). No additional baseline variables varied substantially between patients treated with pegcetacoplan vs. ravulizumab or eculizumab (Table 60).

Table 60 Baseline demographic and clinical characteristics of the study population (after weighting)[1]

	PRINCE trial		Study 301 trial			
Analysis sample, n Effective sample, n	Pegcetacoplan 34 [9] 24		Ravulizumab 125 -	Eculizumab 121 -	SMD	
Characteristic	[A]	[A`]	[B]	[C]	[A] vs. [B]	[A`] vs. [C]
Sex, %						
Male	52.0	57.0	52.0	57.0	0	0
Female	48.0	43.0	48.0	43.0	0	0
Age at first infusion of study drug, mean ± SD, y	44.80 ± 13.39	46.20 ± 13.60	44.80 ± 15.20	46.20 ± 16.20	0	0
Race, %						
Asian	57.6	47.1	57.6	47.1	–	–
White	0.0	0.0	34.4	42.1	–	–

Black or African American	7.6	10.7	1.6	3.1	–	–
American Indian or Alaska Native	30.4	36.7	0.8	0.8	–	–
Other[5]	4.4	5.4	3.2	3.3	–	–
Not reported/unknown	0.0	0.0	2.4	3.3	–	–
Weight, kg	66.84 ± 14.34	66.89 ± 14.49	68.20 ± 15.60	69.20 ± 14.90	-0.08826	-0.15566
Height, cm	165.00 ± 6.84	165.52 ± 6.62	166.30 ± 9.00	166.20 ± 10.70	-0.14947	-0.06669
Time from PNH diagnosis to consent, years[6] **(mean ± SD or median [range])**	6.58 ± 5.95	6.20 ± 5.84	3.80 [0, 41]	3.90 [0, 34]	–	–
No packed PRBC transfusions received within 1 year before study entry, %	13.8	12.1	18.4	17.4	–	–
LDH, U/L[7]	2,220.27 ± 883.67	2,291.04 ± 967.38	1,633.50 ± 778.80	1,578.30 ± 16.22	0.73704	1.90759
Hb, g/dl[8]	9.67 ± 1.40	9.61 ± 1.43	9.40 ± 0.00	9.60 ± 0.00	0.48756	–
EORTC QLQ-C30 score at baseline						
General health status	56.1 ± 18.0	57.5 ± 18.2	56.1 ± 20.3	57.5 ± 20.3	0	0
Physical functioning	80.0 ± 14.7	80.6 ± 15.0	76.6 ± 17.1	76.4 ± 17.6	0.20302	0.24365
Fatigue symptoms	42.1 ± 20.6	42.4 ± 21.7	39.3 ± 22.7	37.3 ± 23.4	0.12509	0.22026

Data are presented at n (%) or mean ± standard deviation unless otherwise indicated.

Abbreviations: EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; LDH, lactate dehydrogenase; NR, not reported; PNH, paroxysmal nocturnal haemoglobinuria; PRBC, packed red blood cell.

Notes:

1. The following baseline characteristics were used for weighting: Asian race, age at first infusion, female sex, and baseline EORTC QLQ-C30 general health score.
2. Weighted for comparison with the ravulizumab cohort.
3. Weighted for comparison with the eculizumab cohort.
4. P values for continuous and categorical variables were calculated with the Wald test (i.e., z and chi-squared tests, respectively), but were not calculated for variables used for matching subjects (shown as "~").
5. Subjects in the Study 301 trial who identified as being of multiple races were included in this category.
6. The Study 301 trial reported range and the PRINCE trial reported standard deviation; the p value was not calculated because the measures of variability did not match.
7. Normal range, 120–246 U/L.
8. Normal range, 12.3–15.3 g/dL for women and 14.0–17.5 g/dL for men. The p value was not calculated because standard deviations were not reported in the Study 301 trial.
9. There were 35 patients who received Pegcetacoplan in PRINCE. Of these, 34 were included in the current analysis, whereas one was excluded because of a lack of LDH and haemoglobin data after baseline.

Appendix D. Extrapolation

Not applicable.

D.1 Extrapolation of [effect measure 1]

D.1.1 Data input

D.1.2 Model

D.1.3 Proportional hazards

D.1.4 Evaluation of statistical fit (AIC and BIC)

D.1.5 Evaluation of visual fit

D.1.6 Evaluation of hazard functions

D.1.7 Validation and discussion of extrapolated curves

D.1.8 Adjustment of background mortality

D.1.9 Adjustment for treatment switching/cross-over

D.1.10 Waning effect

D.1.11 Cure-point

D.2 Extrapolation of [effect measure 2]

Appendix E. Serious adverse events

Table 50 Serious adverse advents observed during the full study periods in the trials used for the health economic analysis

PRINCE Pegcetacoplan (N=46) (Apellis Pharmaceuticals data on file 2021)	PRINCE Supportive care (N=18) (Apellis Pharmaceuticals data on file 2021)	Study 301 Ravulizumab (N=125) (ClinicalTrials.gov 2023)	Study 301 Eculizumab (N=121) (ClinicalTrials.gov 2023)
[redacted]	[redacted]	[redacted]	[redacted]

Appendix F. Health-related quality of life

Not applicable.

Appendix G. Probabilistic sensitivity analyses

Below, in Table 61, the point estimates, and lower and upper bound used to form the basis for the selected probability distributions used in the probabilistic analysis are presented. The results of the probabilistic sensitivity analysis are presented in Section 12.2.2.

Table 61 Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

The objective of the SLR is to collect the evidence available for the efficacy and safety of pegcetacoplan, eculizumab, ravulizumab, iptacopan, danicopan, and crovalimab for the treatment of patients with PNH naïve to complement inhibitors. The results of this SLR are to be used in assessing the clinical value of pegcetacoplan compared to other drugs used in the management of patients with PNH naïve to complement inhibitors.

Table 62 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Ovid interface	No timeframe restriction	17.01.2024
Medline	Ovid interface	No timeframe restriction	08.02.2024
CENTRAL	Cochrane Library	No timeframe restriction	17.01.2024
ClinicalTrials	ClinicalTrials.gov	No timeframe restriction	17.01.2024

Abbreviations:

Table 63 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
FDA website	www.fda.gov		17.01.2024
EMA website	www.ema.europa.eu		17.01.2024

Abbreviations:

Table 64 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
European conference on rare disease and orphan products (ECRD)	conference website	Manual search	List individual terms used to search in the conference material:	17.01.2024
European Society for Blood and Marrow	conference website	Manual search		17.01.2024

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Transplantation (EBMT)				
American Society of Haematology (ASH)	conference website	Manual search		17.01.2024
European Hematology Association (EHA)	conference website	Manual search		17.01.2024
International Society for Pharmacoeconomics and Outcomes Research (ISPOR)	conference website	Manual search		17.01.2024

H.1.1 Search strategies

The searches were conducted in the MEDLINE and Embase (access via the OVID interface) and the Cochrane CENTRAL database on 7th February 2022, and updated on 23rd June 2023 and on 17th of January 2024. Selected conference websites were searched manually to make sure that all important data, even those published as abstracts only, were identified. The searches were performed also for any additional medical reports on the drugs of interest on the EMA and FDA websites.

Table 65 Search strategy table for MEDLINE and Embase

No.	Query	Results
#1	Nocturnal Paroxysmal H?emoglobinuria/ or Paroxysmal H?emoglobinuria, Nocturnal/ or H?emoglobinuria, Nocturnal Paroxysmal/ or Paroxysmal Nocturnal H?emoglobinuria/ or H?emoglobinuria, Paroxysmal Nocturnal/	9,502
#2	H?emoglobinuria, Paroxysmal/ or Paroxysmal H?emoglobinuria/	9,543
#3	Paroxysmal Cold H?emoglobinuria/ or H?emoglobinuria, Paroxysmal Cold/ or Paroxysmal H?emoglobinuria, Cold/ or Cold Paroxysmal H?emoglobinuria/ or H?emoglobinuria, Cold Paroxysmal/	3,702
#4	Marchiafava?Micheli Syndrome/ or Syndrome, Marchiafava?Micheli/	0
#5	or/1-4	9,566
#6	(Nocturnal Paroxysmal H?emoglobinuria or Paroxysmal H?emoglobinuria, Nocturnal or H?emoglobinuria, Nocturnal Paroxysmal or Paroxysmal Nocturnal H?emoglobinuria or H?emoglobinuria, Paroxysmal Nocturnal or PNH or H?emoglobinuria, Paroxysmal or Paroxysmal H?emoglobinuria	11,918

No.	Query	Results
	or Paroxysmal Cold H?emoglobinuria or H?emoglobinuria, Paroxysmal Cold or Paroxysmal H?emoglobinuria, Cold or Cold Paroxysmal H?emoglobinuria or H?emoglobinuria, Cold Paroxysmal or Marchiafava?Micheli Syndrome or Syndrome, Marchiafava?Micheli).mp.	
#7	or/5-6	11,918
#8	Randomized controlled trials as Topic/	308,790
#9	Randomized controlled trial/	1,252,639
#10	Random allocation/	195,671
#11	Double blind method/	337,554
#12	Single blind method/	74,636
#13	clinical trial/	1,560,563
#14	clinical trial, phase i.pt.	23,142
#15	clinical trial, phase ii.pt.	37,016
#16	clinical trial, phase iii.pt.	19,906
#17	clinical trial, phase iv.pt.	2,267
#18	controlled clinical trial.pt.	94,685
#19	randomized controlled trial.pt.	558,117
#20	multicenter study.pt.	314,757
#21	clinical trial.pt.	533,697
#22	exp Clinical Trials as topic/	750,962
#23	(clinical adj trial$).tw.	1,034,525
#24	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	445,987
#25	PLACEBOS/	356,680
#26	placebo$.tw.	570,912
#27	randomly allocated.tw.	73,271
#28	Randomization/	199,490
#29	Single blind procedure/	45,069

No.	Query	Results
#30	Double blind procedure/	192,029
#31	Crossover procedure/	69,365
#32	Placebo/	376,559
#33	Randomi?ed controlled trial$.tw.	491,150
#34	Rct.tw.	71,860
#35	Random allocation.tw.	4,142
#36	Allocated randomly.tw.	5,152
#37	(allocated adj2 random$).tw.	81,029
#38	Prospective study/	49,185
#39	Double blind$.tw.	388,792
#40	((treble or triple) adj blind$).tw.	2,709
#41	Prospective study/	1,357,764
#42	or/8-41	5,251,211
#43	case report.tw.	830,307
#44	Case study/	2,329,416
#45	letter/	2,306,324
#46	historical article/	367,551
#47	Abstract report/	89,538
#48	or/43-47	5,380,292
#49	42 not 48	5,105,486
#50	7 and 49	1,113
#51	remove duplicates from 50	948
#52	51	948
#53	limit 52 to English language	908

The search strategy updates for this query resulted in further 180 results on June 23rd, 2023 and further 98 results on January 17th, 2024.

Table 66 Search strategy table for Cochrane CENTRAL

No.	Query	Results
#1	MeSH descriptor: [Haemoglobinuria, Paroxysmal] explode all trees	53
#2	PNH or (Marchiafava?Micheli Syndrome) or (Syndrome, Marchiafava?Micheli)	213
#3	Nocturnal next/3 h?emoglobinuria	234
#4	#1 or #2 or #3 in Trials	**264**

Table 67 Search strategy table for clinicaltrials.gov

No.	Query	Results
#1	Paroxysmal nocturnal haemoglobinuria or PNH	102

Table 68 Search strategy table for MEDLINE and Embase for single arm trials

No.	Query	Results
#1	Nocturnal Paroxysmal H?emoglobinuria/ or Paroxysmal H?emoglobinuria, Nocturnal/ or H?emoglobinuria, Nocturnal Paroxysmal/ or Paroxysmal Nocturnal H?emoglobinuria/ or H?emoglobinuria, Paroxysmal Nocturnal/	10,478
#2	H?emoglobinuria, Paroxysmal/ or Paroxysmal H?emoglobinuria/	10,519
#3	Paroxysmal Cold H?emoglobinuria/ or H?emoglobinuria, Paroxysmal Cold/ or Paroxysmal H?emoglobinuria, Cold/ or Cold Paroxysmal H?emoglobinuria/ or H?emoglobinuria, Cold Paroxysmal/	3,914
#4	Marchiafava?Micheli Syndrome/ or Syndrome, Marchiafava?Micheli/	0
#5	or/1-4	10,554
#6	(Nocturnal Paroxysmal H?emoglobinuria or Paroxysmal H?emoglobinuria, Nocturnal or H?emoglobinuria, Nocturnal Paroxysmal or Paroxysmal Nocturnal H?emoglobinuria or H?emoglobinuria, Paroxysmal Nocturnal or PNH or H?emoglobinuria, Paroxysmal or Paroxysmal H?emoglobinuria or Paroxysmal Cold H?emoglobinuria or H?emoglobinuria, Paroxysmal Cold or Paroxysmal H?emoglobinuria, Cold or Cold Paroxysmal H?emoglobinuria or H?emoglobinuria, Cold	13,243

No.	Query	Results
	Paroxysmal or Marchiafava?Micheli Syndrome or Syndrome, Marchiafava?Micheli).mp.	
#7	or/5-6	13,243
#8	(single arm or single arm trial?).mp.	44,543
#9	extension?.mp.	507,699
#10	open label?.mp.	170,781
#11	(ole or sat).ti,ab.	29,170
#12	8 or 9 or 10 or 11	721,904
#13	7 and 12	353
#14	remove duplicates from 13	274

H.1.2 Systematic selection of studies

The list of titles and abstracts were screened by two independent reviewers according to the defined inclusion and exclusion criteria, in order to select relevant articles pertaining to the topic of interest. The decisions from the two reviewers were combined and discrepancies were resolved by consensus or by a third reviewer. All references and analysts' decisions were saved.

Table 69 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Patients with PNH, who are naïve to complement inhibitors	• Not relevant population • Not human
Intervention	• Pegcetacoplan • Eculizumab • Ravulizumab • Iptacopan • Danicopan • Crovalimab	
Comparators	Not restricted	
Outcomes	**Clinical efficacy**: • Haemoglobin (Hb) response (proportion of patients with Hb stabilisation, proportion of patients with Hb improvement, mean change in Hb level from baseline) • Hb normalisation	Not relevant outcome

	• Haemolysis (including change from baseline in LDH, decrease in LDH level) • Breakthrough haemolysis • Thromboembolic events • Transfusion requirements • Transfusion independence or avoidance • LDH normalisation • Serum bilirubin • Absolute reticulocyte count normalisation **Clinical safety:** • Total SAEs • Treatment-emergent adverse events • Major adverse vascular events **Patient-reported outcomes (PROs):** • Fatigue • QoL measures	
Study design/publication type	RCTs, phase 3 single-arm trials	Not relevant study design/duplicate
Language restrictions	English	Not relevant language

Figure 16 PRISMA flow diagram of the records for the existing SLR

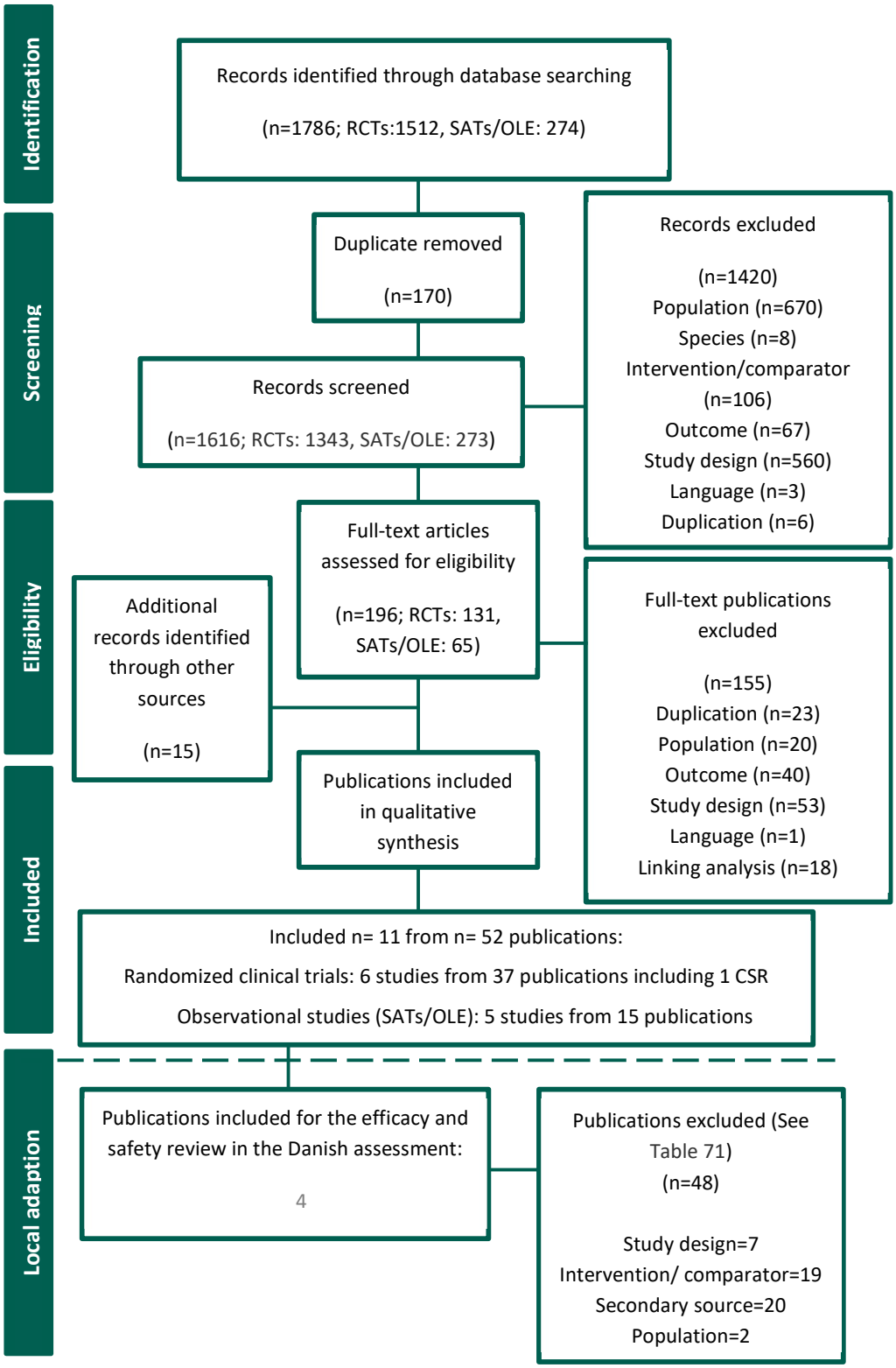

Table 70 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
PRINCE/ NCT04085601 CSR, *A PHASE 3, RANDOMIZED, MULTICENTER, OPEN LABEL, CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF PEGCETACOPLAN IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)*. 2021, Apellis. p. 192. Wong, R.S.M.N.-C., J. R. Comia, N. S. Goh, Y. T. Idrobo, H. Kongkabpan, D. Gomez-Almaguer, D. Al-Adhami, M. Ajayi, T. Alvarenga, P. Savage, J.	Evaluation of the Efficacy and Safety of Pegcetacoplan in Patients with Paroxysmal Nocturnal Haemoglobinuria (PNH)	A Phase 3, Randomised, Multicenter, Open-Label, Controlled Study	Patients With PNH	Pegcetacoplan (46) and Supportive care (18)	Hb stabilization defined as avoidance of a >1 g/dL decrease in Hb concentrations from baseline in the absence of transfusion and reduction in LDH concentration from baseline to Week 26, follow-up time 26 weeks	Hb response (yes/no) in the absence of transfusions (Hb response is defined as ≥1 g/dL increase in Hb from baseline, change from baseline in absolute reticulocyte count (ARC), and Hb concentration, proportion of subjects who received transfusion or had decrease of Hb > 2 g/dL, transfusion avoidance (yes/no), defined as the proportion of subjects who did not require a transfusion during the RCP, number of packed red blood cells (PRBC) units

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Deschatelets, P. Francois, C. Grossi, F. Dumagay, T., *Pegcetacoplan controls hemolysis in complement inhibitor-naive patients with paroxysmal nocturnal hemoglobinuria.* Blood advances, 2023. **7(11)**: p. 2468-2478.						transfused, change in Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue Scale score, normalization of Hb concentrations (≥1xLLN) in the absence of transfusions (yes/no), normalization of LDH concentrations (≤1 × the ULN) in the absence of transfusions (yes/no), change in n European Organisation for Research and Treatment of Cancer 30-item QLQ C30 scores, change in Linear Analog Scale Assessment scores, ARC normalization, time to failure of Hb

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
						stabilization and to first transfusion, follow-up for 26 weeks
Study 301/ NCT 3056040 Lee, J.W.d.F., F. S. Lee, L. W. L. Pessoa, V. Gualandro, S. Fureder, W. Ptushkin, V. Rottinghaus, S. T. Volles, L. Shafner, L. Aguzzi, R. Pradhan, R. Schrezenmeier, H. Hill, A., *Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: The 301 study.* Blood, 2019. **133**(6): p. 530-539.	To assess the noninferiority of ravulizumab compared to eculizumab in adult participants with PNH who had never been treated with a complement inhibitor (treatment-naïve).	A Phase 3, Randomised, Open-Label, Active-Controlled Study	Complement Inhibitor-Naïve Adult Patients With (PNH)	Ravulizumab (125) and eculizumab (121)	Proportion Of Participants With Normalization Of Lactate Dehydrogenase (LDH) Levels and Percentage Of Participants Who Achieved Transfusion Avoidance, follow-up for 183 days	Percentage Of Participants With Breakthrough Haemolysis (BTH), Percent Change From Baseline In LDH Levels, Change From Baseline In Quality Of Life As Assessed By The Functional Assessment Of Chronic Illness Therapy (FACIT)-Fatigue and Percentage Of Participants With Stabilized Hb Levels, follow-up for 183 days

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Schrezenmeier, H.K., A. Mitchell, L. de Latour, R. P. Devos, T. Okamoto, S. Wells, R. Popoff, E. Cheung, A. Wang, A. Tomazos, I. Patel, Y. Lee, J. W., *Predictors for improvement in patient-reported outcomes: post hoc analysis of a phase 3 randomized, open-label study of eculizumab and ravulizumab in complement inhibitor-naive patients with paroxysmal nocturnal hemoglobinuria.* Annals of Hematology, 2024. **103(1)**: p. 5-15.						

H.1.3 Quality assessment

Once full publications were collected, full texts were evaluated by two independent reviewers to verify if they meet the inclusion criteria. Differences were resolved by consensus or by a third reviewer. Analysts' decisions and reasons were saved. Once the articles list was finalized, all references were checked for any possible linking (i.e. to check if different articles originate from the same study).
Data from studies included in the review were extracted using extraction templates created in Excel. One analyst extracted the data, while another senior analyst validated the accuracy of the extracted data. The quality of the included studies was assessed only for RCTs and appraised according to the Cochrane risk of bias tool v.2 (RoB2).

H.1.4 Unpublished data

N/A

Table 71 Studies and publications excluded in the Danish application

Study	Publication	Publication type (primary/secondary source)	Reason for exclusion in DMC dossier
PRINCE (NCT04085601) Pegcetacoplan vs SoC	Bogdanovic, A., Tse, E., Yeh M., and J. Szamosi, Wong, R. *Evaluation of pegcetacoplan in paroxysmal nocturnal hemoglobinuria patients with aplastic anemia in the PRINCE study*. in *EHA 2023 Congress*. 2023	Secondary (abstract)	Poster abstract, sub group analysis on patients with AA/PNH Secondary source
	Desai, D.W., R. Al-Adhami, M. Savage, J. Horneff, R. Yeh, M. Dumagay, T. Gomez-Almaguer, D., *MDS-113 Pegcetacoplan Rapidly Stabilizes Complement-Inhibitor Naive Patients With Paroxysmal Nocturnal Hemoglobinuria Experiencing Hemolysis With Acute Hemoglobin Decreases: A Post Hoc Analysis from the Phase 3 PRINCE Trial.* Clinical Lymphoma, Myeloma and Leukemia, 2022. **22(Supplement 2)**: p. S305-S306.	Secondary (abstract)	Conference abstract, post hoc analysis on Hb normalisation Secondary source
	Mulherin, B.Y., M. Al-Adhami, M. Savage, J. Dingli, D., *Hemoglobin, lactate dehydrogenase, and facit-fatigue normalization rates in patients treated with pegcetacoplan: Results from the pegasus and prince phase 3 clinical trials.* Bone Marrow Transplantation, 2022. **57(Supplement 1)**: p. 246-247.	Secondary (abstract)	Conference abstract: LDH and FACIT-fatigue results from PRINCE and PEGASUS studies. Secondary source
	Panse, J.D., N. Okuyama Sasaki, S. Peffault De Latour, R. Schafhausen, P. Straetmans, N. Al-Adhami, M. Ajayi, T. Chen, C. Yeh, M. Wong, R. S., *Post Hoc Analysis of the Effect of Pegcetacoplan Treatment of Patients with Paroxysmal Nocturnal Hemoglobinuria and Baseline*	Secondary (manuscript)	Post hoc analysis of PNH patients with baseline Hb>10 g/dl Secondary source

	Hemoglobin Levels Greater Than 10 Grams per Deciliter. Blood, 2021. **138**(Supplement 1): p. 2194.		
	Wong, R.S.N., J. R. Comia, N. S. Goh, Y. T. Idrobo, H. Kongkabpan, D. Gomez-Almaguer, D. Al-Adhami, M. Ajayi, T. Alvarenga, P. Deschatelets, P. Francois, C. Grossi, F. Dumagay, T., *Efficacy and Safety of Pegcetacoplan Treatment in Complement-Inhibitor Naive Patients with Paroxysmal Nocturnal Hemoglobinuria: Results from the Phase 3 Prince Study.* Blood, 2021. **138**(Supplement 1): p. 606.	Secondary (abstract)	Conference abstract, first results from PRINCE Secondary source
	Wong, R.A.-A., M. Savage, J. Horneff, R. Yeh, M. Dumagay, T. Gomez-Almaguer, D., *Pegcetacoplan Rapidly Stabilizes Complement Inhibitor Naive Patients with Paroxysmal Nocturnal Hemoglobinuria Experiencing Hemolysis with Acute Hemoglobin Decreases; Prince Trial Post Hoc Analysis.* HemaSphere, 2022. **6(Supplement 3)**: p. 1397-1398.	Secondary (abstract)	Same as Desai (2022) published at another conference Secondary source
	Brodsky, R.A.P.d.L., Regis Rottinghaus, Scott T. Roth, Alexander Risitano, Antonio M. Weitz, Ilene C. Hillmen, Peter Maciejewski, Jaroslaw P. Szer, Jeff Lee, Jong Wook Kulasekararaj, Austin G. Volles, Lori Damokosh, Andrew I. Ortiz, Stephan Shafner, Lori Liu, Peng Hill, Anita Schrezenmeier, Hubert, *Characterization of breakthrough hemolysis events observed in the phase 3 randomized studies of ravulizumab versus eculizumab in adults with paroxysmal nocturnal hemoglobinuria.* Haematologica, 2021. **106**(1): p. 230-237.	Secondary (manuscript)	Characterisation of breakthrough hemolysis on ecu and ravu Secondary source
Study 301 (NCT02946463) Ravulizumab vs eculizumab	EMA, *Assessment report EMA/CHMP/220699/2019.* EMA report, 2019.	Secondary	Assessment report Secondary source
	FDA, *BLA Multi-Disciplinary Review and Evaluation BLA 761108 Ultomiris (ravulizumab).* 2018.	Secondary (report)	Review and evaluation BLA Secondary source
	Ishiyama, K.N., S. Usuki, K. Yonemura, Y. Ikezoe, T. Uchiyama, M. Mori, Y. Fukuda, T. Okada, M. Fujiwara, S. I. Noji, H. Rottinghaus, S. Aguzzi, R. Yokosawa, J. Nishimura, J. I. Kanakura, Y. Okamoto, S., *Results from multinational phase 3 studies of ravulizumab (ALXN1210) versus eculizumab in adults with paroxysmal nocturnal hemoglobinuria: subgroup analysis of Japanese patients.* International Journal of Hematology, 2020. **112**(4): p. 466-476.	Secondary (manuscript)	Subgroup analysis of Japanese patients Secondary source
	Kulasekararaj, A.G.G., M. Langemeijer, S. Kulagin, A. Ogawa, M. Yu, J. Mujeebuddin, A. Nishimura, J. I. Peffault de Latour, R. Latypova, A. Barcellini, W. Barraco, F. Beam, D. Bettelheim, P. Borisenkova, E. Brodsky, A. Carnley, B. Cermak, J. Chen, T. Y. Chew, L. P. Chew, T. K. Choi, C. W. Choi, Y. Chung, J. S. De Guibert, S. Devos, T. Dunaev, Y. Dwilewicz-Trojaczek, J. Edahiro, Y. Elykomov, I. Engelberger, M. I. Pomponi, F. Fuereder, W. Fujii, N. Fujiwara, S. Galieni, P. Gaya Valls, A. Girault, S. Gomez	Secondary (manuscript)	Extension: 2-year results from 2 pivotal studies Secondary source

Almaguer, D. Gonzalez Fernandez, F. A. Gritsaev, S. Gunduz, E. Hantaweepant, C. Harada, H. Hoglund, M. Huang, W. H. Husin, A. Ikezoe, T. Ishiyama, K. Ito, Y. Jang, J. H. Jo, D. Y. Kang, K. W. Kennedy, J. Kim, H. J. Kim, J. A. Kim, J. S. Kimura, F. Kobune, M. Kosugi, H. Kulasekararaj, A. Lai, K. M. Larratt, L. Lee, G. W. Lee, J. H. Lee, J. H. Lee, J. W. Lin, C. C. Lukina, E. Martynova, E. Matsumura, I. Meike, G. Menosi Gualandro, S. F. Minaeva, N. Mori, Y. Morita, K. Morselli Ramalho, F. M. Mun, Y. C. Muus, P. Myasnikov, A. Naito, K. Ninomiya, H. Nogami, A. Notaro, R. Ojeda Gutierrez, E. Okada, M. Okamoto, S. Olkhovik, T. Pane, F. Paquette, R. Park, J. S. Peffault de la Tour, R. Piatek, C. Piekarska, A. Pontes Reis, M. L. Pospelova, T. Ptushkin, V. Roeth, A. Rojnuckarin, P. Rosa Pessoa, V. D. L. Rossi, B. Salleh, S. Salvino de Araujo, M. A. Samuel, D. Saraeva, N. Schrezenmeier, H. Shatokhin, Y. Shelekhova, T. Sohn, S. K. Steinerova, K. Sunami, K. Syed Abdul Kadir, S. S. Tamura, S. Theunissen, K. Toh, S. G. Tomita, A. Torregrosa Diaz, J. M. Ueda, Y. Usuki, K. Vannucchi, A. M. Viboonjuntra, P. Viigimaa, I. Volkova, S. Wang, M. C. Won, J. H. Wong, L. L. L. Wong, V. F. Yap, E. S. Yeh, S. P. Yhim, H. Y. Yonemura, Y. Yoon, S. S. Zhuravkov, A., *Long-term safety and efficacy of ravulizumab in patients with paroxysmal nocturnal hemoglobinuria: 2-year results from two pivotal phase 3 studies.* European Journal of Haematology, 2022. **109(3)**: p. 205-214.		
Peffault De Latour, R.S., J. Kulasekararaj, A. Kim, J. S. Piatek, C. I. Kulagin, A. D. Hill, A. Wang, J. Yu, J. Ogawa, M. Schrezenmeier, H. Lee, J. W., *Efficacy and Safety of Ravulizumab in Older Patients Aged >65 Years with Paroxysmal Nocturnal Hemoglobinuria in the 301 and 302 Phase 3 Extension Studies.* Blood, 2020. **136(Supplement 1)**: p. 42-43.	Secondary (abstract)	Subgroup analysis, safety of ravulizumab in older patients aged >65 years Secondary source
Risitano, A.J., J. H. Gyeong-Won, L. Wanachiwanawin, W. Schrezenmeier, H. Yonemura, Y. Munir, T. Pavani, R. Wang, J. Kulagin, A. D. Kulasekararaj, A. Sicre de Fontbrune, F. Roth, A., *Transfusion Requirements in Adult Patients with Paroxysmal Nocturnal Hemoglobinuria with or without a History of Bone Marrow Disorder Receiving Ravulizumab and Eculizumab: Results from a Phase 3 Non-Inferiority Study Extension.* Blood, 2020. **136**(Supplement 1): p. 31-33.	Secondary (abstract)	Extension study, transfusion requirement Secondary source
Roth, A.R., A. Jang, J. H. Lee, G. W. Wanachiwanawin, W. Schrezenmeier, H. Yonemura, Y. Munir, T. Pavani, R. Aguzzi, R. Shafner, L. Kulagin, A. Sicre de Fontbrune, F., *Transfusion requirements in adult patients with paroxysmal nocturnal hemoglobinuria naive to complement inhibitors receiving Ravulizumab or Eculizumab: results from a phase 3 non-inferiority study.* Oncology Research and Treatment, 2019. **42(Supplement 4)**: p. 97.	Secondary (abstract)	Transfusion requirements in ecu and ravu Secondary source
Schrezenmeier, H.L., J. W. Rottinghaus, S. T. Lee Lee, L. W. Pessoa, V. Gualandro, S. Fureder, W. Ptushkin, V. Sicre De Fontbrune, F. Volles, L. Shafner, L. Damokosh, A. Aguzzi, R. Pradhan, R. Ortis, S. Hill, A., *Results from a phase 3, multicenter, noninferiority study of ravulizumab (ALXN1210) versus eculizumab (ECU) in adult patients (pts) with paroxysmal nocturnal hemoglubinuria (PNH) naive to*	Secondary (abstract)	First results from the non-inferior study ecu vs ravu Secondary source

	complement inhibitors (CI). Hamostaseologie, 2019. **39**(Supplement 1).		
	Schrezenmeier, H.K., A. Mitchell, L. Sicre de Fontbrune, F. Devos, T. Okamoto, S. Wells, R. Rottinghaus, S. Liu, P. Ortiz, S. Shafner, L. Lee, J. W. Socie, G., *One-Year Efficacy of Ravulizumab (ALXN1210) in adult patients with paroxysmal Nocturnal hemoglobinuria naive to complement inhibitors.* Oncology Research and Treatment, 2019. **42(Supplement 4)**: p. 297.	Secondary (abstract)	Abstract presentation: 1-year results from ravu Secondary source
	Schrezenmeier, H.K., A. Mitchell, L. Sicre de Fontbrune, F. Devos, T. Okamoto, S. Wells, R. Rottinghaus, S. T. Liu, P. Ortiz, S. et al.,, *One-year efficacy and safety of ravulizumab in adults with paroxysmal nocturnal hemoglobinuria naïve to complement inhibitor therapy: open-label extension of a randomized study.* Therapeutic advances in hematology, 2020. **11**.	Secondary (manuscript)	Extension study of of ravulizumab Secondary source
	Schrezenmeier, H.H., A. Piatek, C. I. Pefault De La Tour, R. Wong Lee Lee, L. Wells, R. Brodsky, R. Seok Kim, J. Nishimura, J. Kuriakose, P. Pavani, R. Liu, P. Ortiz, S. Lee, J. W. Kulasekararaj, A., *Breakthrough hemolysis in adult patients with paroxysmal nocturnal hemoglobinuria treated with Ravulizumab: Results of a 52-week extension from two phase 3 studies.* Oncology Research and Treatment, 2020. **43(Supplement 4)**: p. 177-178.	Secondary (abstract)	Conference anstract: BTH on ravulizumab Secondary source
	Schrezenmeier, H.L., J. W. Hill, A. Ptushkin, V. V. Pessoa, V. Notaro, R. Wang, J. Ogawa, M. Okamoto, S. Wong, L. L. Peffault De Latour, R. Kulasekararaj, A., *Efficacy and Safety of Concomitant Use of Ravulizumab and IST in Patients with Paroxysmal Nocturnal Hemoglobinuria up to 52 Weeks.* Blood, 2020. **136(Supplement 1)**: p. 37-38. (extension period)	Secondary (abstract)	Abstract on efficiacy and safety of ravulizumab Secondary source
	Schrezenmeier, H.K., A. Mitchell, L. Sicre de Fontbrune, F. Devos, T. Okamoto, S. Wells, R. Rottinghaus, S. T. Liu, P. Ortiz, S. Lee, J. W. Socie, G., *One-year efficacy and safety of ravulizumab in adults with paroxysmal nocturnal hemoglobinuria naive to complement inhibitor therapy: open-label extension of a randomized study.* Therapeutic Advances in Hematology, 2020. **11**(no pagination). (extension period)	Secondary (manuscript)	OLE on ravulizumab Secondary source
TRIUMPH (NCT00122330) Eculizumab vs placebo	Brodsky, R.A.M., P. DÑŒhrsen, U. Hill, A. Bessler, M. Coutre, S. De Paz, R. Moskovits, T. Nakamura, R. Van Den Neste, E., *Effect of the terminal complement inhibitor eculizumab on patient reported outcomes in paroxysmal nocturnal hemoglobinuria (PNH): phase III triumph study results.* Blood, 2006. **108**(11 Part 2): p. 16-17.	Secondary (manuscript)	Study design
	Dmytrijuk, A.R.-S., K. Cohen, M. H. Rieves, D. Weiss, K. Pazdur, R., *FDA report: Eculizumab (Soliris) for the treatment of patients with paroxysmal nocturnal hemoglobinuria.* Oncologist, 2008. **13**(9): p. 993-1000.	Secondary (manuscript)	Study design
	Euctr, S.E., *A Hemoglobin Stabilization and Transfusion Reduction Efficacy and Safety Clinical Investigation, Randomized, Multi-Center, Double-Blind, Placebo-Controlled, Using Eculizumab in Paroxysmal Nocturnal Hemoglobinuria Patients - TRIUMPH.*	Secondary (abstract)	Study design

	https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2004-000646-20-SE, 2004.		
	FDA, *BLA STN 125166/0 Eculizumab (Soliris).* 2006.	Secondary (report)	Study design
	Hillmen, P.Y., N. S. Schubert, J. Brodsky, R. A. Socie, G. Muus, P. Roth, A. Szer, J. Elebute, M. O. Nakamura, R. Browne, P. Risitano, A. M. Hill, A. Schrezenmeier, H. Fu, C. L. Maciejewski, J. Rollins, S. A. Mojcik, C. F. Rother, R. P. Luzzatto, L., *The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria.* New England Journal of Medicine, 2006. **355**(12): p. 1233-1243	Primary (manuscript)	Study design
	Schubert, J.H., P. Dührsen, U. Young, N. S. Elebute, M. Szer, J., *Treatment with the terminal complement inhibitor eculizumab improves anemia in patients with paroxysmal nocturnal hemoglobinuria: phase III Triumph study results.* Blood (ASH annual meeting abstracts), 2006. **108**: p. 124.	Secondary (abstract)	Study design
	Schubert, J.H., P. Roth, A. Young, N. S. Elebute, M. O. Szer, J. Gianfaldoni, G. Socie, G. Browne, P. Geller, R. Rother, R. P. Muus, P., *Eculizumab, a terminal complement inhibitor, improves anaemia in patients with paroxysmal nocturnal haemoglobinuria.* British Journal of Haematology, 2008. **142**(2): p. 263-272.	Secondary (clinical registry)	Study design
CLNP023X2204 (NCT03896152) Iptacopan 25mg vs 50mg	Jang, J.H.W., L. L. Ko, B. S. Yoon, S. S. Li, K. Rozenberg, I. Nidamarthy, P. K. Chawla, R. Junge, G. Yap, E. S., *12-Month Analysis of a Phase 2 Study of Iptacopan (LNP023) Monotherapy for Paroxysmal Nocturnal Hemoglobinuria.* Blood, 2021. **138**(Supplement 1): p. 2173.	Secondary (abstract)	Intervention/ comparator
	Jang, J.H.W., L. Ko, B. S. Yoon, S. S. Li, K. Baltcheva, I. Nidamarthy, P. K. Chawla, R. Junge, G. Yap, E. S., *Iptacopan monotherapy in patients with paroxysmal nocturnal hemoglobinuria: a 2-cohort open-label proof-of-concept study.* Blood Advances, 2022. **6(15)**: p. 4450-4460.	Primary (manuscript)	Intervention/ comparator
	NCT. *Efficacy, Safety, Pharmacokinetics and Pharmacodynamics Study, Assessing Multiple LNP023 Doses in Adult Patients With Paroxysmal Nocturnal Hemoglobinuria*. 2023 24.01.2024]; Available from: https://clinicaltrials.gov/study/NCT03896152.	Secondary (clinical registry)	Intervention/ comparator
COMMODORE 2 (NCT04434092) Crovalimab vs eculizumab	Röth, A.G.H., A. Brodsky, Chatree Chatree Chai-Adisaksopha, Teresita Dumagay, Roberta Demichelis, Martin Höglund, Richard Kelly, Je-Hwan LEE, Jun-ichi Nishimura, Naoshi Obara, Antonio Maria Risitano, Anna Gaya, Anita Appius, Brittany Gentile, Raluca Negricea, Zilu Zhang, Simon Buatois, Bing Han. *The phase III, randomized COMMODORE 2 trial: results from a multicenter study of crovlimab vs eculizumab in paroxysmal nocturnal hemoglobinuria (PNH) patients naive to complement inhibitors*. in *EHA 2023 Congress*. 2023.	Secondary (abstract)	Intervention/ comparator
	Lundberg, P.d.l.I., Silvia Kelly, Richard J. Kulasekararaj, Austin Nishimura, Jun-Ichi Risitano, Antonio M. Roeth, Alexander Buatois, Simon Chebon, Sammy Patel, Himika Kiialainen, Anna, *Biomarker Analyses in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) Treated with*	Secondary (abstract)	Intervention/ comparator

	Crovalimab and Eculizumab: Results from the Phase III Randomized COMMODORE 2 Trial. Blood, 2023. **142**(Supplement 1): p. 4088-4088.		
	Panse, J.C., Jaroslav Kyselova, Olena Gotoh, Akihiko Sahin, Fahri Schrezenmeier, Hubert Chang, Alice C. Gentile, Brittany Uguen, Marianne Han, Bing, *Patient-Reported Outcomes (PROs) in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) Treated with Crovalimab and Eculizumab: Results from the Phase III Randomized COMMODORE 2 and COMMODORE 1 Trials.* Blood, 2023. **142**(Supplement 1): p. 4090-4090.	Secondary (abstract)	Intervention/ comparator
SB12-3003 (NCT04058158) Eculizumab vs eculizumab biosimilar SB12	Jang, J.H.G., R. D. Bumbea, H. Nogaieva, L. Wong, L. L. L. Lim, S. M. Kim, Y. Park, J., *A phase III, randomised, double-blind, multi-national clinical trial comparing SB12 (proposed eculizumab biosimilar) and reference eculizumab in patients with paroxysmal nocturnal haemoglobinuria.* eJHaem, 2023. **4(1)**: p. 26-36.	Primary (manuscript)	Intervention/ comparator
	Jang, J.H.L., Soo Min Tomuleasa, Ciprian Oliynyk, Hanna Lanamtieng, Theerin Park, Jihye Kim, Younsoo Jung, Jinah Russo, Paola, *Efficacy of SB12 (Eculizumab Biosimilar) in Asian and Non-Asian Patients with Paroxysmal Nocturnal Hemoglobinuria: Subgroup Analysis of a Global Phase III Randomized Controlled Trial.* Blood, 2023. **142**(Supplement 1): p. 2727-2727.	Secondary (abstract)	Intervention/ comparator
	Jang, J.H.D., R. Nogaieva, L. Wong, L. L. Lim, S. M. Kim, Y. Park, J., *Sensitivity Analysis on the Primary Efficacy Results of SB12 (Eculizumab Biosimilar) Phase III Study in Paroxysmal Nocturnal Hemoglobinuria Patients.* Blood, 2022. **140(Supplement 1)**: p. 8658-8659.	Secondary (abstract)	Intervention/ comparator

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

The objective and search strategy of the literature searches for health-related quality of life does not deviate from the literature searches for the clinical assessment and all parameters can be found within appendix H.

Table 72 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Embase.com		dd.mm.yyyy
Medline	Ovid		dd.mm.yyyy
Specific health economics databases[1]			dd.mm.yyyy

Abbreviations:

[1] Papaioannou D, Brazier J, Paisley S. Systematic searching and selection of health state utility values from the literature. Value Health. 2013;16(4):686-95.

Table 73 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
e.g. NICE	www.nice.org.uk		dd.mm.yyyy
ScHARRHUD	www.scharrhud.org		dd.mm.yyyy

Table 74 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	e.g. conference website	Electronic search	List individual terms used to search in the congress material:	dd.mm.yyyy
	Journal supplement [insert reference]	Skimming through abstract collection		dd.mm.yyyy

I.1.1 Search strategies

N/A

Table 75 Search strategy for [name of database]

No.	Query	Results
#1		88244
#2		85778
#3		115048
#4		7011
#5		10053
#6		12332
#7		206348
#8		211070
#9	#7 OR #8	272517
#10	#3 AND #6 AND #9	37

Literature search results included in the model/analysis:

N/A

I.1.2 Quality assessment and generalizability of estimates

N/A

I.1.3 Unpublished data

N/A

Appendix J. Literature searches for input to the health economic model

J.1 External literature for input to the health economic model

The literature used for input in the health economic model was not identified through a systematic or targeted review.

J.1.1 Ex. Systematic search for […]

Table 76 Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	e.g. Embase.com	e.g. 1970 until today	dd.mm.yyyy
Medline			dd.mm. yyyy
CENTRAL	Wiley platform		dd.mm. yyyy

Abbreviations:

N/A

J.1.2 Ex. Targeted literature search for [estimates]

N/A

Table 77 Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search
e.g. NICE	www.nice.org.uk		dd.mm.yyyy
			dd.mm.yyyy

Abbreviations:

[Describe the selection process and criteria for inclusion or exclusion.]

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