Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende pegcetacoplan til behandling af paroksystisk natlig hæmoglobinuri (PNH)

Vers. 3.0

Bilagsoversigt

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

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11-08-2023

MGK

Forhandlingsnotat

Dato for behandling i Medicinrådet	Genforhandling
Leverandør	SOBI
Lægemiddel	Aspaveli (pegcetacoplan)
Ansøgt indikation	Aspaveli (pegcetacoplan) er indiceret til behandling af voksne patienter med paroksystisk natlig hæmoglobinuri (PNH), som er anæmiske efter behandling med en C5-hæmmer i mindst 3 måneder.
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet 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]

Prisen er betinget af Medicinrådets anbefaling.

[redacted]

Aftaleforhold

[redacted]

Konkurrencesituationen

På nuværende tidspunkt anvendes primært Ultomiris (ravulizumab) og i mindre udstrækning Soliris (eculizumab) til behandling af PNH i Danmark.

[redacted]

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. 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]
Biosimilær (eculizumab)	300mg	1 stk.	900 mg hver 14. dag/IV	[redacted]	[redacted]

[redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Ikke anbefalet	Link til anbefaling
Sverige	Delvis anbefalet	Link til anbefaling
England	Anbefalet	Link til anbefaling

Konklusion

[redacted]

Medicinrådet

Application for the assessment of pegcetacoplan for treatment of paroxysmal nocturnal hemoglobinuria (PNH)

March 2022

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

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1. Basic information

Contact information	
Name	**Karin Sennfält**
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Overview of the pharmaceutical	
Proprietary name	Aspaveli
Generic name	Pegcetacoplan
Marketing authorization holder in Denmark	Swedish Orphan Biovitrum AB (Sobi)
ATC code	L04AA54
Pharmacotherapeutic group	Selective immunosuppressants
Active substance(s)	Pegcetacoplan
Pharmaceutical form(s)	Subcutaneous infusion
Mechanism of action	Pegcetacoplan is a compstatin derivative that binds C3 and C3b of the complement system, thereby regulating the C3 and the generation of downstream effectors of complement activation. By targeting the complement cascade improvements in hematological parameters, such as hemoglobin, bilirubin, reticulocytes, and LDH, can be achieved. In PNH, extravascular hemolysis is facilitated by C3b opsonisation (labelling of the RBC) while intravascular hemolysis is mediated by the downstream membrane attack complex (MAC). Pegcetacoplan addresses both intravascular and extravascular hemolysis (which cause anemia in patients with PNH) by regulating the complement at the C3 level
Dosage regimen	1080 mg by subcutaneous infusion twice weekly via a commercially available infusion pump with a reservoir of at least 20 mL
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Pegcetacoplan is indicated in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who are anaemic after treatment with a C5 inhibitor for at least 3 months.

Overview of the pharmaceutical	
Other approved therapeutic indications	No
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	No
Packaging – types, sizes/number of units, and concentrations	Pack size: 1080 mg, 20 mL single-dose vial, 1 unit pack and 8 unit pack Strength: 54 mg/mL
Orphan drug designation	Yes

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2. Abbreviations

Abbreviation	Description of abbreviation
AA	Aplastic anemia
AE	Adverse event
AEEA	amino(ethoxyethoxy)acetic acid
ALDVMM	Adjusted limited dependent variable mixture model
AP	Anchored protein
APAC	Asia-Pacific
ARC	Absolute reticulocyte count
ATC	Anatomical therapeutic chemical
BMF	Bone marrow failure
BMI	Body mass index
BMT	Bone marrow transplant
BNP	B-type natriuretic peptide
BTH	Breakthrough hemolysis
CAC	Complement-amplifying conditions
CEM	Cost effectiveness model
CFB	Change from baseline
CI	Confidence interval
CSR	Clinical study report
DAT	Direct antiglobulin test
DGHO	Society for Diagnosis and Therapy of Hematological and Oncological Diseases
DOAC	Direct oral anticoagulant
DKK	Danish krona
ECG	Electrocardiogram
EHA	European Hematology Association
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire—Core 30 Scale
EQ	EuroQol
FACIT	Functional Assessment of Chronic Illness Therapy–Fatigue Subscale
FDA	Food and Drug Administration
GHS	Global health status
GPI	Glycolipid glycosylphosphatidylinositol

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HAD	High disease activity
HR	Hazard ratio
HRQoL	Health-related quality-of-life
HSC	Hematopoietic stem cells
HTA	Health-technology assessment
ICD	International Classification of Diseases
ICE	Intercurrent event
ICER	Incremental cost-effectiveness ratio
ISR	Injection-site reactions
ITT	Intention to treat
IV	Intravenous
KOL	Key opinion leader
LASA	Linear Analog Assessment Scale
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LLN	Lower limit of normal
LPK	Liver pyruvate kinase
LS	Least square
MAC	Membrane attack complex
MASP	Mannose-binding lectin-associated serine protease
MAVE	Major adverse vascular event
MBL	Mannose-binding lectin
MDKK	Million danish krona
MDS	Myelodysplastic syndrome
MMRM	Mixed-effect model for repeated measures
NI	Noninferiority
NICE	National institute for health and care excellence
NO	Nitric oxide
OLP	Open-label period
OR	Odds ratio
PESG	PNH Education Study Group
PI	Prescribing information
PIGA	Phosphatidylinositol glycan anchor biosynthesis class A
PNH	Paroxysmal nocturnal hemoglobinuria

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PRBC	Packed red blood cell
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life-year
QOL	Quality-of-life
RBC	Red blood cell
RCP	Randomized controlled period
RMSE	Root mean square
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SOC	Standard of care
TA	Transfusion avoidance
TE	Thromboembolism
TEAE	Treatment-emergent adverse event
TIBC	Ferritin, transferrin, and iron-binding capacity
TMA	Thrombotic microangiopathy
UK	United Kingdom
ULN	Upper limit of normal
US	United States
USD	United States Dollar

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3. Tables and Figures

3.1 Tables

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3.2 Figures

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4. Summary

Population

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired, hematologic disorder characterized by intravascular and extravascular hemolysis that can result in life-threatening complications, including anemia and venous thrombosis. Depending on the clinical manifestation of the disease there are three different subcategories: classic PNH, PNH in the setting of an associated bone marrow disorder, and subclinical PNH. The focus of this submission is on classic PNH, which constitutes to a prevalence of approximately 51 patients in Denmark.

The current standard of care, consisting of the complement protein C5 inhibitors eculizumab and ravulizumab, addresses the intravascular but not the extravascular hemolysis. Despite improvements with C5 inhibitor treatment, many patients with PNH continue to experience ongoing hemolysis, with the majority still having chronic low hemoglobin levels which impacts the amount of oxygen carried to tissues and vital organs. Long term, the chronic low levels of hemoglobin can lead to an enlarged heart or heart failure. Studies show that 36% of patients treated with C5 inhibitors continued to receive at least two transfusions within 12 months. Many PNH patients experience persistently low hemoglobin which also have a large negative impact on health-related quality of life. Real-world evidence studies have shown that 72% of patients have hemoglobin levels below 12 g/dL (7.44 mmol/l) and 79% of PNH patients continue to experience fatigue despite treatment with C5 inhibitors. Despite PNH patients not reaching optimal response from C5 inhibitor treatment, discontinuation is rare as effective treatment options are missing.

Intervention

Pegcetacoplan is the first and only therapy addressing both intravascular and extravascular hemolysis by regulating the complement at the C3 level. Pegcetacoplan is a compstatin derivative that inhibits C3 and C3b of the complement system. By targeting the complement cascade earlier than eculizumab or ravulizumab (which act at C5), improvements in hematological parameters, such as hemoglobin, bilirubin, reticulocytes, and lactate dehydrogenase (LDH), can be achieved.

Pegcetacoplan is indicated in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who are anaemic after treatment with a C5 inhibitor for at least 3 months.

Comparator

Ravulizumab (Ultomiris) is considered the most relevant comparator to pegcetacoplan, as the majority of patients in Denmark is treated with ravulizumab. Ravulizumab is a humanized monoclonal antibody specifically designed to target the complement protein C5. Ravulizumab is administered in the hospital setting every eight weeks by intravenous infusion.

Currently the only treatment available to PNH patients is C5 inhibitors. However, not all patients respond to this treatment and can remain transfusion dependent, anemic, and fatigued. There are also patients that, although not transfusion dependent, can remain severely anemic and fatigued, which subsequently has a major impact on quality-of-life and productivity. A recent study into the burden of illness for patients with PNH has demonstrated that anemia and breakthrough hemolysis were occurring, and patients treated with C5 inhibitors reported a median hemoglobin level of 10g/dL (6.21 mmol/L). In addition, neither ravulizumab nor eculizumab, as C5 inhibitors, addresses extravascular hemolysis. Thus, there is an unmet need for patients currently on C5 inhibitors.

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Outcomes

No head-to-head data between ravulizumab and pegcetacoplan is available. However, ravulizumab has been shown, in two clinical studies, to be noninferior to eculizumab in terms of clinical efficacy and safety profile. Therefore, data from the pivotal PEGASUS trial, where pegcetcoplan was compared with eculizumab, is presented in this submission.

PEGASUS was a prospective, randomized, multicenter, open-label, active-comparator controlled study in patients with PNH who were receiving eculizumab but continue to have hemoglobin levels < 10.5 g/dL (6.52 mmol/l). Patients were randomized to receive either pegcetacoplan or eculizumab. The treatment period of the study consisted of three parts: (1) a 4-week run-in period, (2) a 16-week randomized control period, and (3) a 32-week open-label pegcetacoplan-only period.

The primary objective was to establish the efficacy and safety of pegcetacoplan compared with eculizumab in patients with PNH who continued to have hemoglobin levels < 10.5 g/dL (6.52 mmol/L) despite treatment with eculizumab. Pegcetacoplan demonstrated head-to-head, statistically superior increase in mean hemoglobin of 3.8 g/dL (2.36 mmol/L) vs. eculizumab in the PEGASUS trial, an improvement that is clinically meaningful.

The first of the key secondary endpoints was transfusion avoidance (yes/no), defined as the proportion of patients who did not require a transfusion during the randomized control period of the study. Pegcetacoplan provided a significant improvement in transfusion avoidance, with 85.4% of patients' transfusion free in the pegcetacoplan arm and 15% in the eculizumab arm. Pegcetacoplan also showed significant improvements in fatigue vs eculizumab, the difference being 11.58 points as measured by the FACIT fatigue score. This improvement is three times higher than the threshold considered clinically meaningful.

In terms of safety, data from PEGASUS showed that pegcetacoplan was well tolerated, with a safety profile similar to eculizumab.

Health economic evaluation

A de novo cost-effectiveness model was developed to estimate the long-term cost-effectiveness of pegcetacoplan compared with the current standard of care ravulizumab. The model uses a Markov model structure and is based on outcomes and patient characteristics in the PEGASUS clinical trial.

The model estimated the long-term costs and outcomes (e.g., quality-adjusted life-year [QALY]) incurred in the expected licensed population for pegcetacoplan in the treatment of PNH.

The base-case analysis was conducted from a Danish limited social perspective as defined in the Danish medicine councils' methods guide section 6.7. From this perspective, the analysis accounted for direct medical costs, including drug costs, administration costs, health-state costs, adverse event (AE) costs, and patient costs. The base-case analysis employed a lifetime (51.2 years) time horizon, starting with patients switching to pegcetacoplan.

[redacted]

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5. The patient population, the intervention and choice of comparator

5.1 The medical condition and patient population

5.1.1 Overview

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired, hematologic disorder that manifests with episodic hemolysis that can result in life-threatening complications, including anemia and venous thrombosis (Hill 2017). PNH derives its name from its sudden, episodic (= paroxysmal), night- occurring (= nocturnal) blood in the urine (= hemoglobinuria, passing of breakdown product of red blood cells [RBCs] into urine) (AAMDS 2020). However, not every patient with PNH has dark urine. The episodic passing of blood into urine does not happen only at night, but it is often most visible in the morning because of concentrated urine (AAMDS 2020).

5.1.2 Disease description

Clinically, PNH is characterized as bone marrow failure, hemolytic anemia, and thrombocytosis (elevated number of platelets) (Parker 2016). Blood cells—specifically, hematopoietic stem cells (HSC)—from patients with PNH lack various cell surface proteins because the anchor that binds and holds them on the surface, the glycolipid glycosylphosphatidylinositol (GPI), is either missing or dysfunctional (Lee 2014, Mon Pere 2018). The cause of this is somatic loss-of-function mutations in the gene phosphatidylinositol glycan anchor biosynthesis class A (PIGA) in clonal blood cells of patients with PNH. PIGA codes for a protein that is crucial for the synthesis of GPI anchors (Hill 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 2015). Although GPI anchors to 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, their loss leads to complement activation that results in the destruction of RBCs (Brodsky 2014).

The complement system is part of the innate immune response and is composed of a large number of plasma and membrane bound proteins. The complement system has three main functions: to opsonize foreign cells, such as pathogens (i.e., mark pathogens for destruction), to induce inflammatory responses to fight infection, and direct destruction of the foreign cells (Janeway 2001). Upon triggering of the complement system, a complement protein is cleaved into its active form, which then cleaves other proteins into their active forms in a cascade-like manner (Figure 1) (Berentsen 2019). Once fully activated, the complement system culminates in proteolytic, inflammatory, and lytic processes.

In normal blood cells, CD59 and CD55 are part of the host's self-recognition mechanism and protects the cells from being destroyed if the complement system is activated to fight an infection (Parker 2016). Since a patient with PNH lacks, or has defective CD59 and CD55, own cells are destroyed through a complement-initiated membrane attack complex (MAC) that forms pores into the cell membrane. The MAC is assembled through the association of several complement proteins. The presence of CD59 on the cell surface prevents the aggregation of the complement factor C9 and, hence, the lytic pores (Brodsky 2014). In addition, CD55 disassembles the enzyme C3-convertase, hindering the activation of complement factors C3 and C5; which are necessary for the functional formation of MAC. Specifically, RBCs are sensitive to lysis as they do not have a nucleus (Hill 2017).

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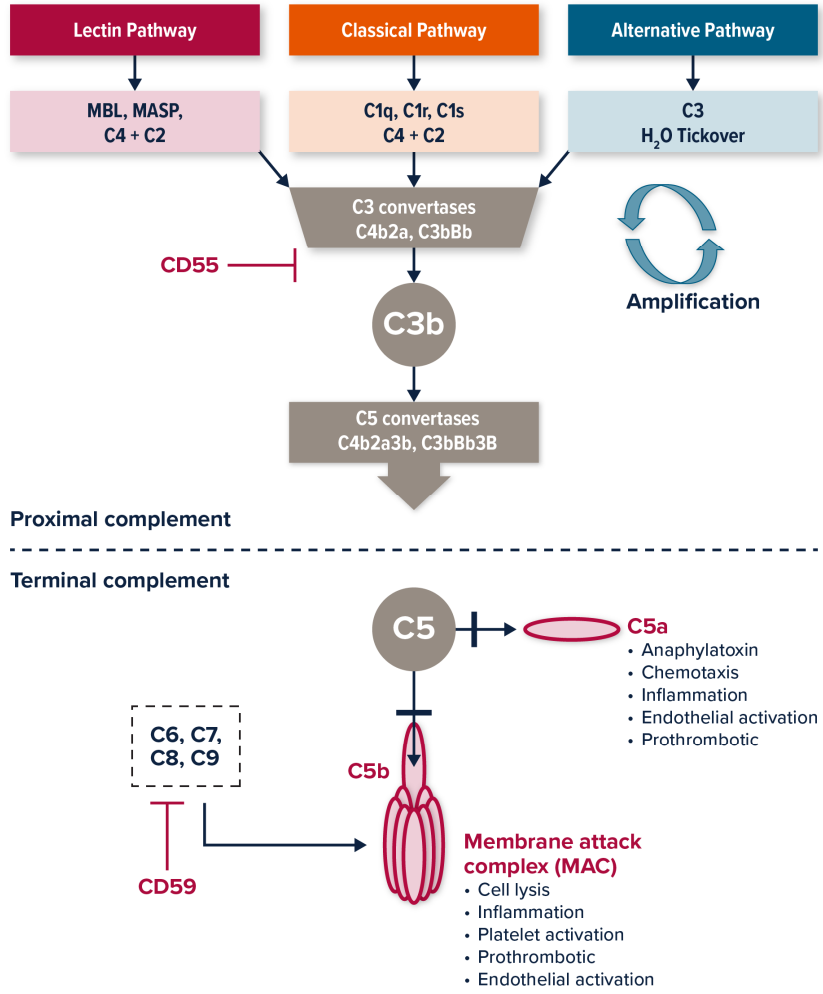
Figure 1: Complement system



MASP = mannose-binding lectin-associated serine protease; MBL = mannose-binding lectin.

Note: The lectin, classical, and alternative pathways converge at the point of C3 activation. In PNH, hemolysis is usually chronic, because the alternative pathway is always in a low-level activation state. CD55 inhibits proximal complement activation by blocking the formation of C3 convertases; CD59 inhibits terminal complement activation by preventing the incorporation of C9 in the MAC. The absence of CD55 and CD59 on PNH cells leads to hemolysis, inflammation, platelet activation, and thrombosis.

Note on C3 vs. C5 on intravascular and extravascular hemolysis: By regulating the complement at the C3 level, both intravascular and extravascular hemolysis (which cause anemia in patients with PNH) is addressed. Regulating C5 addresses intravascular hemolysis in PNH, therefore most patients with PNH on eculizumab continue to experience mild to moderate extravascular hemolysis.

Source: Adapted from Brodsky (2014).

In general, complement regulators such as CD55 and CD59 are important to protect red blood cells against destruction, following hemolysis, inflammation and platelet activation

Although more than one HSC cell can carry a mutation in PIGA, clinical symptoms of PNH occur if the growth of mutant HSC cells is faster than normal non-PIGA mutant cells and the population of PIGA mutant cells reaches a certain proportion (Parker 2016, Hill 2017). It is not yet clear how the mutant clone(s) gain a growth advantage over normal cells. Therefore, it has been postulated that a deleterious mutation in PIGA is crucial for PNH, but is not the only determinant, indicating that additional factors or mutations are necessary (Hill 2017).

How the disease develops is not clear yet. The primary risk factor for PNH is aplastic anemia (AA) as about 10% of patients with AA develop PNH (AAMDS 2020).

Pegcetacoplan is indicated for patients who are anemic after treatment with a C5 inhibitor. The PNH disease types other than classic PNH are different forms of the disease, which would not have been treated with C5 inhibitors. Hence, the other PNH types fall outside the indication of pegcetacoplan.

5.1.3 Classification of PNH

Depending on the clinical manifestation of the disease there are three different subcategories (Parker 2005): classic PNH, PNH in the setting of an associated bone marrow disorder, and subclinical PNH.

The focus of this submission is on classic PNH.

5.1.3.1 Classic PNH

Patients with classic PNH have disease manifestations indicating intravascular hemolysis, such as elevated reticulocyte (immature RBC) count, abnormally high concentration of serum LDH and indirect bilirubin, and abnormally low concentration of serum haptoglobin. These patients do not have associated bone marrow failure disorder. The cellular composition of the marrow shows abnormally high numbers of immature RBCs (erythroid hyperplasia) and normal or near-normal morphology, but without chromosomal abnormalities. Patients with classic PNH typically have > 50% of GPI-anchored protein (GPI-AP) deficient granulocytes (Parker 2016).

5.1.3.2 PNH in the setting of an associated bone marrow disorder

In this subcategory, patients have a history of associated bone marrow disease. Tests to analyze the bone marrow and chromosomal changes are used to identify if PNH occurred in association with AA, myelodysplastic syndrome (MDS), or other myelopathy (i.e., myelofibrosis). Identifying karyotypic abnormalities that are typical of a specific bone marrow disorder contributes further to the diagnosis (i.e., abnormalities of chromosomes 5q, 7, and 20q are associated with MDS). The clone size of GPI-AP–deficient granulocytes is typically < 50% (Parker 2016).

5.1.3.3 Subclinical PNH

Subclinical PNH (PNH-sc) patients have no clinical or laboratory evidence of hemolysis (Parker 2016). Small PNH clones, as determined by populations of GPI-AP–deficient hematopoietic cells (peripheral blood erythrocytes, granulocytes, or both), are detected by very sensitive flow cytometric analysis. Subclinical PNH is observed in association with bone marrow failure syndromes, particularly AA and refractory anemia-MDS. The clone size of GPI-AP–deficient granulocytes in these patients is < 10% (Parker 2016).

5.1.4 Incidence and prevalence of PNH

As a rare disease, there is limited information on the precise incidence and prevalence of PNH. According to Orphanet the global prevalence of PNH is between 1 to 9 per 100,000 persons(Orphanet 2017). In addition, a 2019 retrospective study on the US population estimated the prevalence of PNH to be around 1.3 per 100,000 (Jalbert 2019).

In a study by Lund Hansen and colleagues (Hansen 2020), data were collected on all patients with acquired hemolytic disorder diagnoses in 1977 to 2016 from the Danish National Patient Register linked with information from the Danish Civil Registration System. Inclusion of patients from the Patient Register was based on previously validated diagnosis

codes for specific acquired hemolytic disorders. Data on PNH clone size is not available, but a post hoc defined sensitivity model excluded all patients with a diagnosis of MDS and/or AA before or within six months after the diagnosis of PNH.

The analysis included 5,868 patients with acquired hemolytic disorders, whereof 116 PNH patients. During the period 1980 to 2016 the proportion of women was 50.0% and 41.6% of patients were deceased. The median age at diagnosis was 48.4 years, median age at death 71.5 years, and the median survival after diagnosis of acquired hemolysis was 23.2 years. The incidence rates per 100 000 person-years in 1980 to 1993 and 2008 to 2016 were 0.04 and 0.08 for PNH, respectively. The prevalence proportion per 100 000 persons in 1980 and 2015 was 0.18 and 1.04 respectively for PNH (Hansen 2020).

An epidemiology study was conducted over a period of 6 years to describe PNH clones detected by flow cytometry in Denmark, Finland, Norway, and Sweden. The study population included all patient samples referred for PNH testing between 2001 and 2016. The total population of the study regions was 13.2 million. The mean incidence of newly detected PNH clones was 2.33 per million; Denmark, 2.05 per million; Finland = 2.98 per million; Norway, 2.53 per million; and Sweden, 1.74 per million (Korkama 2018) – this study included clone size from 0.1-100%. Nevertheless, since not all PNH patients with small clone size are in need of treatment, the aforementioned incidence should be seen as an estimation.

Table 1: Number of PNH patients in Denmark

[redacted]

Table 2 presents the number of patients in Denmark who are expected to use pegcetacoplan in the coming years, broken down from the 51 prevalent patients as explained above.

Table 2: Estimated number of patients eligible for treatment

[redacted]

5.1.4.1 Age groups for pegcetacoplan

As presented above in section 5.1.4, the median age at diagnosis was 48.4 years and the median age at death was 71.5 years in a PNH population studied in Denmark (Hansen 2020). Additionally, in a study covering a population of 13.2 million in the Nordics (Korkama 2018) the mean age of patients diagnosed with PNH was 52 years, with an age range of 6 to 90 years.

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There are no subgroups where pegcetacoplan is expected to have a different efficacy and/or safety than anticipated for the entire population. In addition, there are no studies on patients under 18 years of age.

5.1.5 Patient populations relevant for this application

Pegcetacoplan's position in the current treatment algorithm is for treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who are anaemic after treatment with a C5 inhibitor for at least 3 months. C5 inhibitors, such as eculizumab and ravulizumab, reduces intravascular hemolysis, but most patients on eculizumab continue to experience extravascular hemolysis and anemia. Therefore, there is an unmet need for these patients.

Pegcetacoplan is targeting the C3 molecule, which is upstream of C5 (Figure 1), thereby controlling both intravascular and extravascular hemolysis. Pegcetacoplan provides an important additional treatment option for patients with PNH, as it addresses both intravascular and extravascular hemolysis, leading to increased hemoglobin levels, and a major reduction in blood transfusions in PNH patients.

5.2 Current treatment options and choice of comparator

5.2.1 Current treatment options

Patients with suspected PNH should undergo an initial clinical workup, including complete blood count, reticulocyte count, Coombs assay, and LDH level testing. For patients with anemia, all other potential causes of anemia should be ruled out prior to cytometric testing for PNH testing for PNH (Dezern 2018). These diagnostic studies aid in the classification of patients with PNH into groups outlined by the International PNH Interest Group. Treatment options vary based on group classification (Parker 2016).

Guidelines for the diagnosis, treatment, and management of PNH have been described by several PNH organizations. The PNH Education Study Group (PESG), established in 2013, outlines a treatment algorithm for PNH that groups treatments into three categories: supportive/immunosuppressive treatments, treatments changing the course of disease, and potential curative treatment (Sahin 2016). Guidelines on the therapeutic treatment for PNH have also been outlined by the International PNH Interest Group (Parker 2005, Parker 2016). Treatment of PNH with eculizumab is recommended with benefit for classic PNH and PNH in the setting of another bone marrow failure syndrome (AA or low-risk MDS) if patients have large clones and clinically significant hemolysis.

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: supportive/immunosuppressive treatments, treatments changing the course of disease, and potential curative treatment. These international treatment guidelines are based on the publication 'Diagnosis and management of paroxysmal nocturnal hemoglobinuria' by Parker et al. 2005, and the year 2016 update on the diagnosis and management of paroxysmal nocturnal hemoglobinuria (Parker 2016).

Currently, the only cure for PNH is allogeneic hematopoietic stem cell transplantation (Mitchell 2017). Because of the considerable challenges and risks involved, a bone marrow transplant is not a therapeutic option for most patients. No alternative curative drug treatment exists.

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5.2.2 Choice of comparator

Clinical experts consulted in Denmark confirm that most patients on C5 have switched to ravulizumab. Pegcetacoplan is indicated in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who are anaemic after treatment with a C5 inhibitor for at least 3 months. It should also be mentioned that, due to the lack of alternative treatments and the severity of the disease, patients on C5 inhibitors remain on this treatment, even if the treatment does not sufficiently control their disease (Interviews with clinical experts 2021). Hence, ravulizumab remains the most relevant comparator to pegcetacoplan in the Danish setting.

5.2.3 Description of the comparator(s)

An overview of ravulizumab is presented in Table 3 below.

Table 3: Product description of ravulizumab

Product description	
Name of preparation/pharmaceutical	Ultomiris
Active ingredient	Ravulizumab
ATC code	L04AA43
Pharmaceutical form	Concentrate for solution for infusion
Strength Packaging	• 300 mg/30 ml • 1100mg/11 ml • 300mg/3 ml
Recommended daily dose	The recommended dosing regimen consists of a loading dose followed by maintenance dosing, administered by intravenous infusion, based on the patient's body weight
Should the intervention be used with other drugs?	No
Treatment length/criteria for termination of treatment	Lifetime treatment
Required monitoring, under administration or during treatment period	All patients should be monitored for early signs of meningococcal infection and sepsis, evaluated immediately if infection is suspected, and treated with appropriate antibiotics
Requirements of diagnostics or other tests	To reduce this risk of infection, all patients must be vaccinated against meningococcal infections at least two weeks prior to initiating ravulizumab
Medically approved indication	Ultomiris is indicated in the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH): - in patients with hemolysis with clinical symptom(s) indicative of high disease activity -in patients who are clinically stable after having been treated with eculizumab for at least the past 6 months

5.3 The intervention

An overview of pegcetacoplan is presented in Table 4 below.

Table 4: Product description of pegcetacoplan

Product description	
Name of preparation/pharmaceutical	Aspaveli
Active ingredient	Pegcetacoplan
ATC code	L04AA54
Pharmaceutical form	Subcutaneous infusion
Strength	1080 mg/20 mL (54 mg/mL) in a single-dose vial
Recommended daily dose	1080 mg by subcutaneous infusion twice weekly via a commercially available infusion pump with a reservoir of at least 20 mL
Should the intervention be used with other drugs?	No
Treatment length/criteria for termination of treatment	Lifelong treatment
Required monitoring, under administration or during 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
Requirements of diagnostics or other tests	No
Medically approved indication	Pegcetacoplan is indicated in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who are anaemic after treatment with a C5 inhibitor for at least 3 months.

5.3.1 Pack size and price

The strength, pack size, and pharmacy purchase price (*Apotekets indkøbspris, AIP*) per pack for pegcetacoplan are included in Table 5 below.

Table 5: The strength, pack size, and pharmacy purchase price per pack

[redacted]

5.3.2 Mechanism of action

Pegcetacoplan is a compstatin derivative that inhibits C3 and C3b of the complement system, thereby regulating the C3 and the generation of downstream effectors of complement activation. By targeting the complement cascade improvements in hematological parameters, such as hemoglobin, bilirubin, reticulocytes, and LDH, can be achieved. In PNH, extravascular hemolysis is facilitated by C3b opsonisation (labelling of the RBC) while intravascular hemolysis is mediated by the downstream membrane attack complex (MAC). Pegcetacoplan addresses both intravascular and extravascular hemolysis (which cause anemia in patients with PNH) by regulating the complement at the C3 level.

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Pegcetacoplan is a symmetrical molecule comprised of two identical pentadecapeptides covalently bound to the ends of a linear 40-kiloDalton (kDa) PEG molecule. The peptide portions of pegcetacoplan contain 1-methyl-L-tryptophan (Trp(Me)) in position 4 and amino(ethoxyethoxy)acetic acid (AEEA) in position 14.

The importance of targeting C3 inhibition is demonstrated in Figure 1 in the disease description section 5.1.2 above.

6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

A systematic literature review (SLR) was performed to identify published evidence from randomized controlled trials (RCTs) and observational studies regarding the efficacy and safety of treatments given to patients with paroxysmal nocturnal hemoglobinuria (PNH). The methods and full results are outlined here.

6.2 Search strategy

The following electronic databases were searched on July 30, 2020 and updated on March 11, 2021: MEDLINE, MEDLINE In-Process, Embase, the Cochrane Library (comprising the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews and the Database of Abstracts of Reviews of Effectiveness) and BioSciences Information Services (BIOSIS). BIOSIS was not searched in the SLR update, as searches in this database were captured via the MEDLINE and Embase searches. These searches were supplemented by a grey literature search, which included the search of the websites of the American Society of Hematology (ASH), European Hematology Association (EHA) and the International Society for Pharmacoeconomic and Outcomes Research (ISPOR) to identify conference abstracts not yet indexed in Embase. Grey literature searches were conducted using free terms, which are given Appendix A. To identify ongoing clinical trials, the following websites were searched:

- ClinicalTrials.gov: http://www.clinicaltrials.gov
- International Clinical Trials Registry Platform Search Portal (Search Portal from the World Health Organization): http://apps.who.int/trialsearch/

Reference lists of relevant studies, recent systematic reviews, and meta-analyses also were searched to identify further relevant studies because these are typically good sources of additional material that can supplement the articles retrieved from the standard medical databases.

Search terms included combinations of free text and Medical Subject Headings or Emtree subject headings. The following concepts were included in the search strategy:

- Search terms relating to the population of interest (PNH)
- Search terms relating to study type (RCTs, observational studies [including cohort, longitudinal, cross-sectional, prospective, and retrospective studies])
- Exclusionary terms: unwanted publication types (e.g., comments, editorials, letters, and case reports) and studies in animals but not in humans.

For full details on the literature search, inclusion and exclusion criteria, search strings used, and list of identified studies, please refer to Appendix A.

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6.3 List of relevant studies

Details of the studies identified in the SLR can be found in Appendix A. Of the identified studies, only one study was a clinical trial that provided data for pegcetacoplan in patients with PNH, this was the PEGASUS trial that is described in detail in section 7 (see also Appendices B and C). With regards to ravulizumab, two clinical trials were identified, Study 301 (NCT02946463) and Study 302 (NCT03056040). Both studies are described in section 7, as well as in Appendices B and C.

Table 6 Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of
Hillmen, P., Szer, J., Weitz, I., Röth, A., Höchsmann, B., et al. (2021a). Pegcetacoplan versus eculizumab in paroxysmal nocturnal hemoglobinuria. New England Journal of Medicine 384(11): 1028-1037	PEGASUS	NCT03500549	Actual Study Start Date: June 14, 2018 Actual Primary Completion Date: November 14, 2019 Actual Study Completion Date: August 13, 2020	pegcetacoplan vs. ravulizumab[a]
Lee, J. W., Sicre de Fontbrune, F., Wong Lee, L., Pessoa, V., Gualandro, S., et al. (2019b). Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study. Blood 133(6): 530-539.	ALXN1210-PNH-301	NCT02946463	Actual Study Start Date: December 20, 2016 Actual Primary Completion Date : January 25, 2018 Estimated Study Completion Date : January 31, 2023	pegcetacoplan vs. ravulizumab[a]
Kulasekararaj, A. G., Hill, A., Rottinghaus, S. T., Langemeijer, S., Wells, R., et al. (2019b). Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor-experienced adult patients with PNH: the 302 study. Blood 133(6): 540-549.	ALXN1210-PNH-302	NCT03056040	Actual Study Start Date: June 5, 2017 Actual Primary Completion Date: March 8, 2018 Estimated Study Completion Date: March 2021	pegcetacoplan vs. ravulizumab[a]

[a]PEGASUS is used as a proxy in comparison with ravulizumab

Studies not included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of
Study protocol https://clinicaltrials.gov/ProvidedDocs/39/NCT02264639/Prot_000.pdf	PHARAOH	NCT02264639	Actual Study Start Date: February 23, 2015 Actual Primary Completion Date: October 22, 2018	*Not used for this application*

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of
Statistical analysis plan https://clinicaltrials.gov/ProvidedDocs/39/NCT02264639/SAP_001.pdf			Actual Study Completion Date : October 22, 2018	
Del Pozo Martín Y. 2021 ASH annual meeting. Lancet Haematol. 2022 Feb;9(2):e92-e93. doi: 10.1016/S2352-3026(21)00384-7. Epub 2021 Dec 16.	PRINCE	NCT04085601	Actual Study Start Date: August 15, 2019 Actual Primary Completion Date: June 23, 2021 Actual Study Completion Date: June 23, 2021	*Not used for this application*
Study protocol https://clinicaltrials.gov/ProvidedDocs/33/NCT02588833/Prot_000.pdf Statistical analysis plan https://clinicaltrials.gov/ProvidedDocs/33/NCT02588833/SAP_001.pdf	PALOMINO	NCT03593200	Actual Study Start Date: August 16, 2018 Actual Primary Completion Date: October 22, 2019 Actual Study Completion Date: October 22, 2019	*Not used for this application*
Study protocol https://clinicaltrials.gov/ProvidedDocs/00/NCT03593200/Prot_000.pdf Statistical analysis plan https://clinicaltrials.gov/ProvidedDocs/00/NCT03593200/SAP_001.pdf	PADDOCK	NCT02588833	Actual Study Start Date: December 1, 2015 Actual Primary Completion Date: August 26, 2019 Actual Study Completion Date: August 26, 2019	*Not used for this application*

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7. Efficacy and safety

The pivotal study of pegcetacoplan is a head-to-head clinical trial with eculizumab (PEGASUS). There is no head-to-head trial of pegcetacoplan versus ravulizumab.

The clinical efficacy of ravulizumab in comparison with eculizumab, the other C5 inhibitor, has been investigated in two Phase III clinical trials, Study 301, and Study 302. In both studies, ravulizumab achieved noninferiority to eculizumab for all endpoints (see section 7.1.4). In addition, it showed a similar safety profile. Details of both studies, including study design and patient characteristics, can be found in Appendix B and C.

7.1 Efficacy and safety of pegcetacoplan compared to eculizumab for PNH

7.1.1 Relevant studies

7.1.1.1 PEGASUS

The PEGASUS (APL2-302) trial is a completed prospective, randomized, multicenter, open-label, active-comparator controlled study in patients with PNH receiving eculizumab but continued to have hemoglobin levels < 10.5 g/dL. Patients were randomized to receive either pegcetacoplan or eculizumab.

Table 7: Overview of PEGASUS

PEGASUS (APL2-302)	Study number ClinicalTrials.gov NCT03500549
Study design	Prospective, randomized, multicenter, open-label, active-comparator controlled study in patients with PNH who are receiving eculizumab but continue to have hemoglobin levels < 10.5 g/dL
Study size	A total of 80 patients were enrolled in the study (10 more than planned): 41 in the pegcetacoplan group and 39 in the eculizumab group
Patient population	Adult patients (≥ 18) with PNH who are receiving eculizumab therapy, but continue to have hemoglobin levels < 10.5 g/dL
Intervention	Pegcetacoplan
Comparator	Eculizumab
Follow-up	After completion of the randomized controlled period (end of Week 16), patients continued into a 32-week open-label period
Is the study used in the HE-model?	Yes
Reason for including/excluding from HE-model	Head-to-head pivotal Phase 3 trial
Reported primary end-points (definition)	Change from baseline to Week 16 hemoglobin level, excluding data before the randomized controlled period
Other reported end-points (definition)	Key secondary endpoints: • Transfusion avoidance (yes/no), defined as the proportion of patients who do not require a transfusion during the 16-week randomized controlled period

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PEGASUS (APL2-302)	Study number ClinicalTrials.gov NCT03500549
	• Change from baseline to Week 16 reticulocyte count, excluding data before the randomized controlled period • Change from baseline to Week 16 LDH level, excluding data before the randomized controlled period • Change from baseline to Week 16 in the FACIT-Fatigue scale total score version 4, excluding data before the randomized controlled period

Reference: CSR SOBI data on file, ClinicalTrials.gov NCT03500549

7.1.1.1.1 Study design and treatment

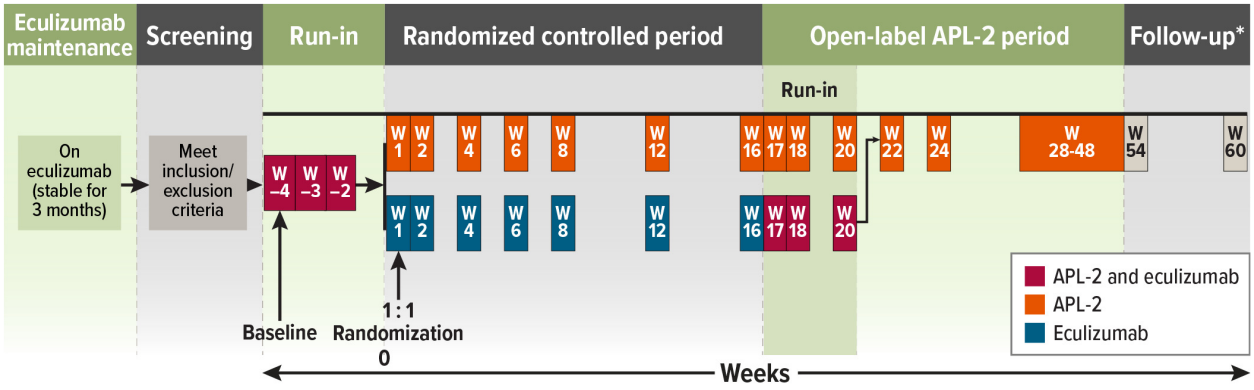
The treatment period of the study consisted of three parts: (1) a 4-week run-in period, (2) a 16-week randomized control period, and (3) a 32-week open-label pegcetacoplan-only period (Figure 2) (Peffault de Latour 2021).

During the 4-week run-in period (Week −4 to Day 1), patients received self-administered twice-weekly SC doses of pegcetacoplan (1,080 mg) in addition to the current prescribed dose of eculizumab. The run-in period was for safety purposes to avoid switching patients abruptly to pegcetacoplan and was not intended to evaluate combination therapy. On Day 1, patients were randomized to receive either pegcetacoplan monotherapy or eculizumab for the 16-week randomized controlled period. During the 16-week randomized controlled period, patients had clinical site visits at Weeks 1, 2, 4, 6, 8, 12, and 16 for efficacy and safety assessments (Hillmen 2021b).

After completion of the randomized controlled period (end of Week 16), patients continued into a 32-week open-label period as follows (Hillmen 2021b, Peffault de Latour 2021):

- Patients randomized to pegcetacoplan continued to receive twice-weekly doses of pegcetacoplan (1,080 mg). During the 32-week period, patients had clinical site visits at Weeks 17, 18, 20, 22, and 24 and every 4 weeks thereafter until Week 48 for efficacy and safety assessment.
- Patients who received eculizumab in the randomized controlled period could subsequently receive pegcetacoplan monotherapy. Similar to the initial 4-week run-in period, patients received twice-weekly doses of pegcetacoplan (1,080 mg) in addition to eculizumab for 4 weeks as a run-in period (Weeks 16-20). After the run-in period, patients could continue receiving pegcetacoplan monotherapy until Week 48.
- After completion of the entire 52-week treatment period at Week 48 (4-week run-in period + 16-week randomized controlled period + 32-week open-label pegcetacoplan period), patients were offered entry into an open-label extension study (NCT03531255). If the patient selected not to continue in the long-term safety extension study, they returned to the site for two additional safety visits 6 weeks apart and completed their exit visit at Week 60 (see also Figure 2) (Apellis Pharmaceuticals data on file 2019).

Figure 2: PEGASUS study design



APL-2 = pegcetacoplan, W = week.

Source: Hillmen (2021b), (Peffault de Latour 2021)

The randomization was stratified by the following:

- Number of transfusions before screening, i.e. in practice before baseline of the study
- Platelet count at screening (< 100 000 vs. ≥ 100 000)

7.1.1.1.2 PEGASUS participants

The study was conducted in 54 sites across 11 countries in the Asia-Pacific region, North America, and Europe (Australia, Belgium, Canada, France, Germany, Japan, Russia, South Korea, Spain, UK, and US).

Key inclusion criteria in PEGASUS included:

- Hemoglobin was < 10.5 g/dL at the screening visit
- Absolute reticulocyte count was > 1.0 times ULN at the screening visit
- Platelet count was > 50 000/mm3 at the screening visit

See Appendix B for a full list of PEGASUS patient inclusion and exclusion criteria.

7.1.1.1.3 PEGASUS objectives and endpoints

Study objectives

The primary objective was to establish the efficacy and safety of pegcetacoplan compared with eculizumab in patients with PNH who continue to have hemoglobin levels < 10.5 g/dL despite treatment with eculizumab (Hillmen 2021b).
Primary endpoint:

- Change from baseline to Week 16 hemoglobin level, excluding data before the randomized controlled period

Key secondary endpoints:

- Transfusion avoidance (yes/no), defined as the proportion of patients who do not require a transfusion during the 16-week randomized controlled period
- Change from baseline to Week 16 reticulocyte count, excluding data before the randomized controlled period
- Change from baseline to Week 16 LDH level, excluding data before the randomized controlled period

- Change from baseline to Week 16 in the FACIT-Fatigue scale total score version 4, excluding data before the randomized controlled period

7.1.1.1.4 PEGASUS planned efficacy analyses

The primary endpoint was conducted on the ITT data set, which included all patients who were randomized, censored for transfusion (Hillmen 2021b).

Key secondary endpoints were tested in a hierarchical manner, after statistical significance was reached for the primary endpoint. The testing was conducted on the ITT data set. If one hypothesis tested was not significant, all subsequent tests would not be assessed for statistical significance.

The key secondary endpoint hierarchy was as follows:

1. Proportion of patients with transfusion avoidance (TA) in both treatment groups
2. Change from baseline to Week 16 in absolute reticulocyte count
3. Change from baseline to Week 16 in LDH
4. Change from baseline to Week 16 in FACIT-Fatigue total score

7.1.1.1.5 PEGASUS patient disposition

A total of 80 patients were enrolled in the study (10 more than planned): 41 in the pegcetacoplan group and 39 in the eculizumab group. At Week 16, 38 patients in the pegcetacoplan group and 39 patients in the eculizumab group remained on study drug. Three patients, all in the pegcetacoplan group, were withdrawn from study treatment during the randomized controlled period (RCP) (Day 1 to Week 16) because of an AE (Hillmen 2021a).

7.1.1.1.6 PEGASUS baseline demographics and characteristics

Please refer to Appendix C for details on PEGASUS baseline demographics and characteristics.

7.1.2 Efficacy and safety – results per study

7.1.2.1 PEGASUS primary efficacy analysis

7.1.2.1.1 Changes in hemoglobin from baseline to Week 16

The primary efficacy endpoint was the change from baseline in hemoglobin level at Week 16 of the RCP, censored for transfusion. The primary endpoint analysis was a between-treatment-group comparison using a mixed-effect model for repeated measures (MMRM). The difference between pegcetacoplan and eculizumab least square (LS) mean hemoglobin changes from baseline at Week 16 was calculated along with its two-sided 95% CI and associated *P* value from the MMRM model for the ITT set, censored for transfusions.

Table 8 shows the results of the primary endpoint analysis. With this analysis, the LS mean change from baseline at Week 16 in the pegcetacoplan and eculizumab groups was 2.37 g/dL and −1.47 g/dL, respectively. The difference in LS mean change from baseline in hemoglobin between the two groups of 3.84 g/dL was statistically significant (95% CI, 2.33-5.34; $P < 0.0001$).

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Table 8: Primary analysis: change from baseline in hemoglobin during randomized controlled period using MMRM model, censored for transfusion (Intent-to-Treat set) – PEGASUS

	Pegcetacoplan (N = 41) LS Mean (SE) g/dL	Eculizumab (N = 39) LS Mean (SE) g/dL	Difference (95% CI)	*P* Value
Week 2	3.07 (0.289)	0.83 (0.306)	2.24 (1.45-3.03)	< 0.0001[a]
Week 4	2.78 (0.249)	−1.50 (0.295)	4.28 (3.56-5.00)	< 0.0001[a]
Week 6	2.68 (0.285)	−1.51 (0.411)	4.19 (3.23-5.14)	< 0.0001[a]
Week 8	2.38 (0.303)	−1.74 (0.451)	4.12 (3.07-5.18)	< 0.0001[a]
Week 12	2.75 (0.285)	−1.57 (0.422)	4.33 (3.34-5.31)	< 0.0001[a]
Week 16	2.37 (0.363)	−1.47 (0.666)	3.84 (2.33-5.34)	< 0.0001[a]

CI = confidence interval; ITT = intent-to-treat; LS = least square; MMRM = mixed-model repeated measures.

a Significant at the 0.05 α level.

Note: Baseline is the average of measurements recorded before taking the first dose of pegcetacoplan, which will include local and central laboratory values during the screening period. Model includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of stratification factors number of transfusions and platelet count at screening. Data excluded from the absence of transfusions model. All values after intercurrent events were set to missing.

Source: Hillmen (2021b)

Table 9 displays the observed and change from baseline (CFB) hemoglobin data for the ITT set (censored for transfusion) during the RCP. As in the primary analysis, the results are consistent with increased mean hemoglobin levels in the pegcetacoplan group by Week 2, and through Week 16, with an increase in mean CFB of 2.79 g/dL at the Week 16 time point. Table 10 shows descriptive data for the intent-to-treat set using all available data.

Table 9: Descriptive summary: observed values and changes from baseline in hemoglobin during randomized controlled period, censored for transfusion (Intent-to-Treat)

Visit	Pegcetacoplan (N = 41)			Eculizumab (N = 39)		
	n	Mean (SD) g/dL	CFB g/dL	n	Mean (SD) g/dL	CFB g/dL
Baseline	41	8.69 (1.075)	NA	39	8.68 (0.886)	NA
Week 2	40	11.91 (1.630)	3.18 (1.440)	38	9.49 (2.274)	0.76 (2.076)
Week 4	40	11.55 (1.619)	2.82 (1.376)	26	8.03 (1.264)	−0.82 (1.338)
Week 6	38	11.45 (2.008)	2.72 (1.650)	12	8.61 (1.391)	−0.32 (1.310)
Week 8	36	11.48 (1.863)	2.74 (1.701)	12	8.71 (0.763)	−0.37 (0.633)
Week 12	36	11.91 (1.538)	3.06 (1.513)	9	8.84 (1.228)	−0.39 (1.125)
Week 16	36	11.65 (1.885)	2.79 (2.030)	6	9.27 (0.841)	0.03 (0.437)

CFB = change from baseline; ITT = intent-to-treat; NA = not applicable; RCP = randomized controlled period; SD = standard deviation.

Notes: Baseline is the average of measurements recorded before taking the first dose of pegcetacoplan, which will include local and central laboratory values during the screening period. All values after the intercurrent events during RCP were set to missing. This table summarizes data as observed with no imputation of missing data.

Source: Hillmen (2021b)

Table 10: Descriptive summary: mean change in hemoglobin levels at Weeks 16, using all available data (Intent-to-Treat Set)

	Change From Baseline at Week 16 in Hemoglobin Levels	
	Pegcetacoplan (N = 41)	Eculizumab (N = 39)
Baseline hemoglobin, mean (SD) g/dL	8.8 (1.0)	8.7 (0.9)
Change at Week 16, mean (SD) g/dL	+2.73 (2.0)	−0.15 (0.9)

SD = standard deviation.

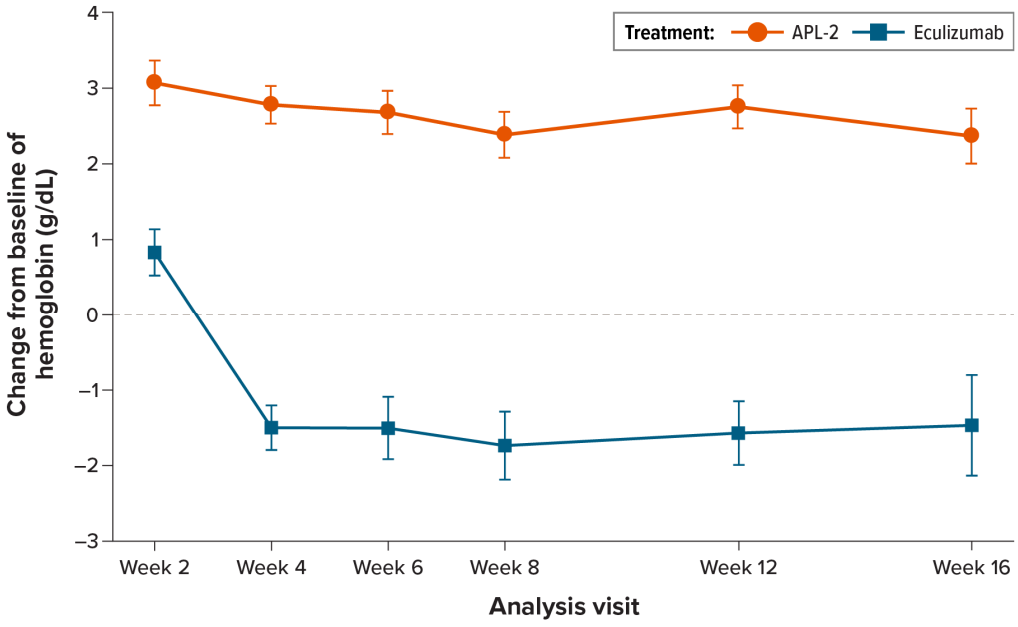
Note: Baseline is the average of measurements recorded prior to taking the first dose of investigational product APL-2, which included local and central lab values during the screening period.

This table summarizes data as observed with no imputation of missing data.

Source: Hillmen (2021b)

A plot of LS mean CFB in hemoglobin over time in the RCP using the MMRM model censored for transfusion is shown in Figure 3. Essentially, pegcetacoplan maintained the efficacy on hemoglobin outcome through Week 16. In the eculizumab group, the LS mean CFB decreased from Week 2 to Week 4, then remained relatively constant through Week 16. The difference in LS mean CFB in hemoglobin between groups started at Week 2 and was maintained through Week 16.

Figure 3: Least square mean (± SE) change from baseline in hemoglobin using MMRM Over time, censored for transfusion in the randomized controlled period (Intent-to-Treat Set)

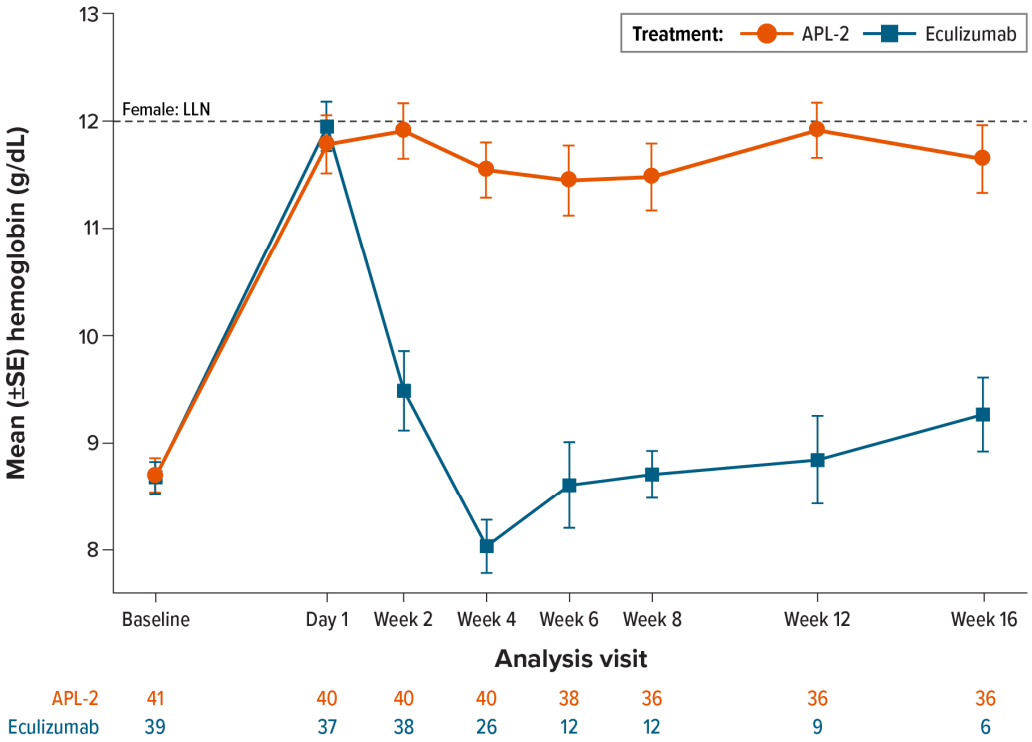


APL-2 = pegcetacoplan, MMRM = mixed-model repeated measures; SE = standard error.

Source: Hillmen (2021b)

Figure 4 shows a plot of the observed mean hemoglobin levels over time censored for transfusion in the RCP for the ITT set. By Week 2, hemoglobin levels had decreased from Day 1 values in the eculizumab group but remained stable in the pegcetacoplan group. The hemoglobin levels were consistently higher in the pegcetacoplan group than in the eculizumab group from Week 2 through Week 16. The results are consistent with the primary analysis.

Figure 4: Mean (± SE) plot of hemoglobin over time, censored for transfusion, randomized controlled period, Intent-to-Treat Set



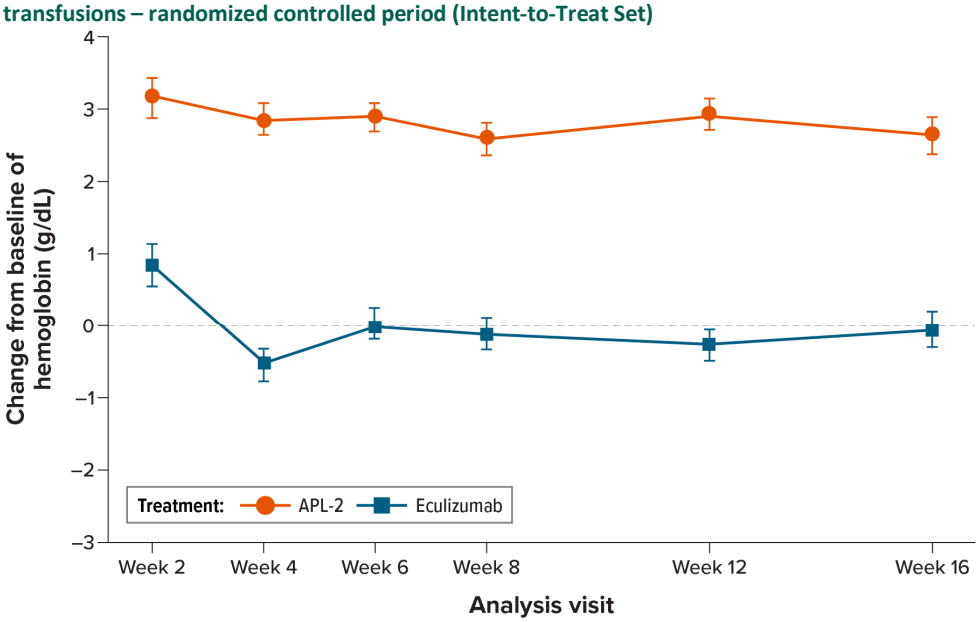
APL-2 = pegcetacoplan, ICE = intercurrent event; ITT = intent-to-treat; LLN = lower limit of normal; MMRM = mixed-effect model for repeated measures; PRBC = packed red blood cell; SE = standard error.

Note: Baseline is the average of measurements recorded before taking the first dose of pegcetacoplan, which will include local and central laboratory values during the screening period. For PRBC transfusion and withdrawal from the study, all measurements after the ICE events were be set to missing. The normal range of central hemoglobin (g/dL) for female is [12, 16]. The normal range of central hemoglobin (g/dL) for male is [13.6, 18]. The normal range of local hemoglobin (g/dL) is [11.2, 18].

Source: Hillmen (2021b).

Figure 5 is a plot of LS mean CFB in hemoglobin over time in the RCP using the MMRM model uncensored for transfusion. Results for both treatment groups were similar to those seen when examining data censored for transfusion.

Figure 5: Least square mean (± SE) change from baseline in hemoglobin level using MMRM over time, uncensored for transfusions – randomized controlled period (Intent-to-Treat Set)



APL-2 = pegcetacoplan, MMRM = mixed-effect model for repeated measures; SE = standard error.

Source: PEGASUS CSR (SOBI 2020a)

Table 11 shows the MMRM that was generated using observed data from the ITT set, censored for transfusion. By this analysis, LS mean for CFB in hemoglobin in those with ≥ 4 transfusions was 2.11 g/dL and −4.02 g/dL for the pegcetacoplan and eculizumab groups, respectively, with a difference of 6.13 g/dL. For those in the < 4 transfusion stratum, at Week 16 the LS mean for CFB in hemoglobin was 2.97 g/dL and −0.01 g/dL for the pegcetacoplan and eculizumab groups, respectively, with a difference of 2.98 g/dL. However, the ≥ 4 transfusion stratum had only one subject in the eculizumab group who avoided transfusions during the RCP. Therefore, the MMRM analysis was repeated by strata for the ITT set using data uncensored for transfusion. In this analysis, the Week 16 LS mean for CFB in hemoglobin in those with ≥ 4 transfusions/year was 2.42 g/dL and −0.15 g/dL for the pegcetacoplan and eculizumab groups, respectively, with a difference of 2.56 g/dL. For those in the < 4 transfusion stratum, the Week 16 LS mean for CFB in hemoglobin was 2.90 g/dL and −0.09 g/dL for the pegcetacoplan and eculizumab groups, respectively, with a difference of 2.99 g/dL. These data indicate that the improvements seen in hemoglobin level with pegcetacoplan over the hemoglobin level with eculizumab, as demonstrated with the primary endpoint analysis, is a benefit observed regardless of baseline transfusion status.

Table 11: Primary analysis: change from baseline in hemoglobin (g/dL) during randomized controlled period using MMRM by PRBC transfusion, censored by transfusion (Intent-to-Treat Set) - PEGASUS

	Pegcetacoplan LS Mean (SE) g/dL	Eculizumab LS Mean (SE) g/dL	Difference (95% CI) g/dL	*P* Value
Number of PRBC transfusions < 4				
n	20	16	NA	NA
Week 16	2.97 (0.364)	—0.01 (0.493)	2.98 (1.73-4.23)	< 0.0001 [a]
Number of PRBC transfusions ≥ 4				
n	21	23	NA	NA
Week 16	2.11 (0.598)	—4.02 (2.395)	6.13 (0.79-11.48)	0.0278 [a]

CI = confidence interval; LS = least square; NA = not applicable; PRBC = packed red blood cell; SE = standard error.

Notes: Baseline is the average of measurements recorded before taking the first dose of pegcetacoplan, which will include local and central laboratory values during the screening period.

Model includes treatment + baseline value + analysis visit + analysis visit × treatment. Data excluded from the model: All values after intercurrent events were set to missing.

a Significant at the 0.05 α level.

Source: Hillmen (2021b)

Table 12 presents, by transfusion strata, the mean observed and CFB hemoglobin values during the RCP for the ITT set, censored for transfusion. Regardless of transfusion strata, the mean hemoglobin increased by at least 2.4 g/dL in the pegcetacoplan group at all time points from Week 4 to Week 16, while in the eculizumab group the mean hemoglobin was stable or decreased at these same time points. Therefore, at least a 2 g/dL increase in hemoglobin was observed with pegcetacoplan, even among subjects requiring frequent transfusions prior to study entry.

Table 12: Descriptive summary: observed values and changes from baseline in hemoglobin during randomized controlled period by number of packed red blood cell transfusions, censored for transfusion (Intent-to-Treat Set)—PEGASUS

Visit	Pegcetacoplan (N = 20)			Eculizumab (N = 16)		
	n	Mean (SD) g/dL	CFB g/dL	n	Mean (SD) g/dL	CFB g/dL
Stratification: Number of PRBC transfusions < 4						
Baseline	20	8.93 (1.098)	NA	16	8.90 (0.896)	NA
Week 2	19	12.43 (1.610)	3.42 (1.197)	16	10.51 (1.676)	1.62 (1.458)
Week 4	19	11.83 (1.756)	2.82 (1.147)	15	8.06 (1.012)	-0.88 (0.690)
Week 6	18	11.79 (1.961)	2.80 (1.522)	7	8.77 (0.840)	-0.51 (0.673)
Week 8	18	11.74 (2.327)	2.77 (1.957)	8	8.86 (0.548)	-0.52 (0.462)
Week 12	17	12.39 (1.617)	3.26 (1.510)	7	9.01 (0.847)	-0.29 (0.500)
Week 16	17	12.35 (1.797)	3.22 (1.581)	5	9.38 (0.887)	0.06 (0.480)
	Pegcetacoplan (N = 21)			**Eculizumab (N = 23)**		
Stratification: Number of PRBC transfusions ≥ 4						
Baseline	21	8.47 (1.030)	NA	23	8.53 (0.868)	NA
Week 2	21	11.43 (1.534)	2.96 (1.627)	22	8.74 (2.392)	0.14 (2.261)
Week 4	21	11.29 (1.482)	2.82 (1.584)	11	8.00 (1.600)	−0.75 (1.949)
Week 6	20	11.14 (2.047)	2.64 (1.766)	5	8.38 (2.036)	−0.05 (1.972)
Week 8	18	11.22 (1.262)	2.71 (1.457)	4	8.40 (1.117)	−0.06 (0.883)
Week 12	19	11.49 (1.369)	2.88 (1.535)	2	8.25 (2.616)	−0.77 (2.876)
Week 16	19	11.02 (1.779)	2.41 (2.339)	1	8.70 (-)	−0.13 (-)

CFB = change from baseline; NA = not applicable; PRBC = packed red blood cell; SD = standard deviation.

Notes: Baseline is the average of measurements recorded before taking the first dose of pegcetacoplan, which will include local and central laboratory values during the screening period.

All values after the intercurrent events during randomized controlled period were set to missing. This table summarizes data as observed with no imputation of missing data.

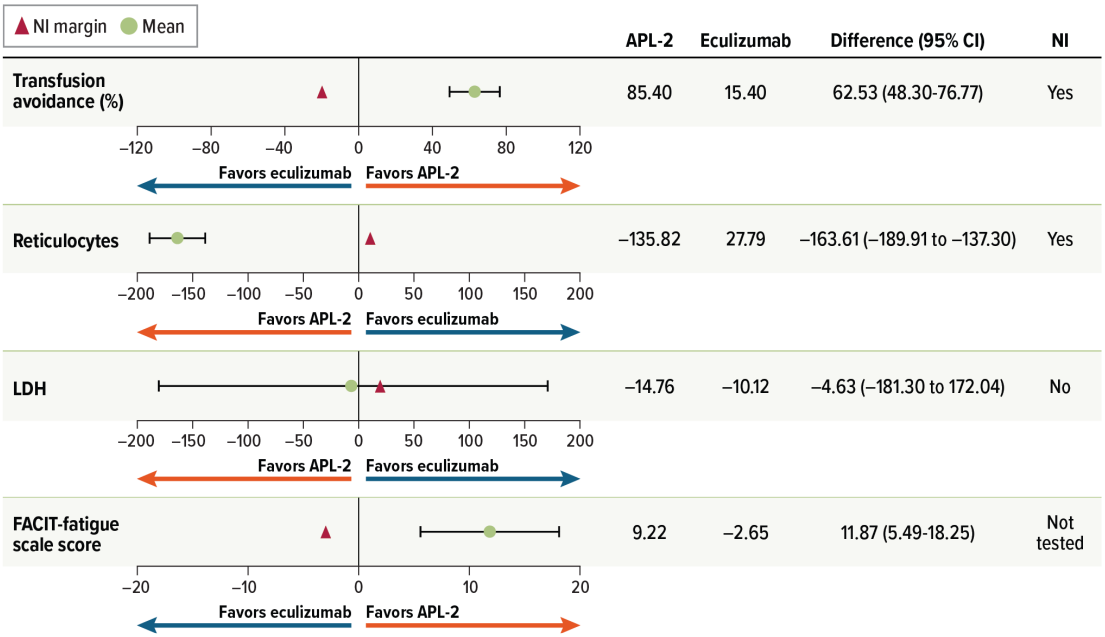
Source: Hillmen (2021b).

7.1.2.2 PEGASUS key secondary efficacy analysis

Key secondary endpoints were tested in a hierarchical manner after statistical significance was reached for the primary endpoint. Key secondary endpoints were tested first for noninferiority and, if all were met, then superiority was tested sequentially for TA, absolute reticulocyte count (ARC), LDH, and FACIT-Fatigue score using a closed-testing procedure at a significance level of 0.05. Noninferiority was concluded if the appropriate limit of the 95% two-sided CI indicated that pegcetacoplan was not inferior to eculizumab by the defined noninferiority margin for each key secondary efficacy endpoint. Once one hypothesis was tested as not significant, all subsequent tests were not assessed statistically.

Figure 6 provides an overview of the results for the key secondary endpoints using a plot to display noninferiority margins and statistics. Pegcetacoplan was noninferior to eculizumab for TA, for CFB in reticulocytes.
For LDH, the LS mean CFB at Week 16 was −14.76 for pegcetacoplan and −10.12 for eculizumab, with a difference of −4.63 (95% CI, −181.30 to 172.04). The upper bound of the 95% CI of the adjusted treatment difference was not less than the prespecified noninferiority margin of 20; thus, noninferiority was not met.
Although the noninferiority for the FACIT-Fatigue score was not assessed because of the prespecified hierarchical testing, the difference between pegcetacoplan and eculizumab was 11.87 points (95% CI, 5.49-18.25).

Figure 6: Plot of Noninferiority Margins and Statistics for Transfusion Avoidance, Reticulocyte Count, Lactate Dehydrogenase, and FACIT-Fatigue Scores During Randomized Controlled Period (Intent-to-Treat Set)



APL-2 = pegcetacoplan, CI = confidence interval; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy–Fatigue Subscale; LDH = lactate dehydrogenase; LS mean = least squares mean; NI = noninferiority.

Notes: Red triangle represents NI margin; black square represents mean.

Transfusion avoidance—NI test (2.5% level) using a NI margin of -20% for the difference between proportions.

Change from baseline to Week 16 in ARC—NI test (2.5% level) using a NI margin of +10.

Change from baseline to Week 16 in LDH—NI test (2.5% level) using a NI margin of +20.

Change from baseline to Week 16 in FACIT-Fatigue score—NI test (2.5% level) using a NI margin of −3.

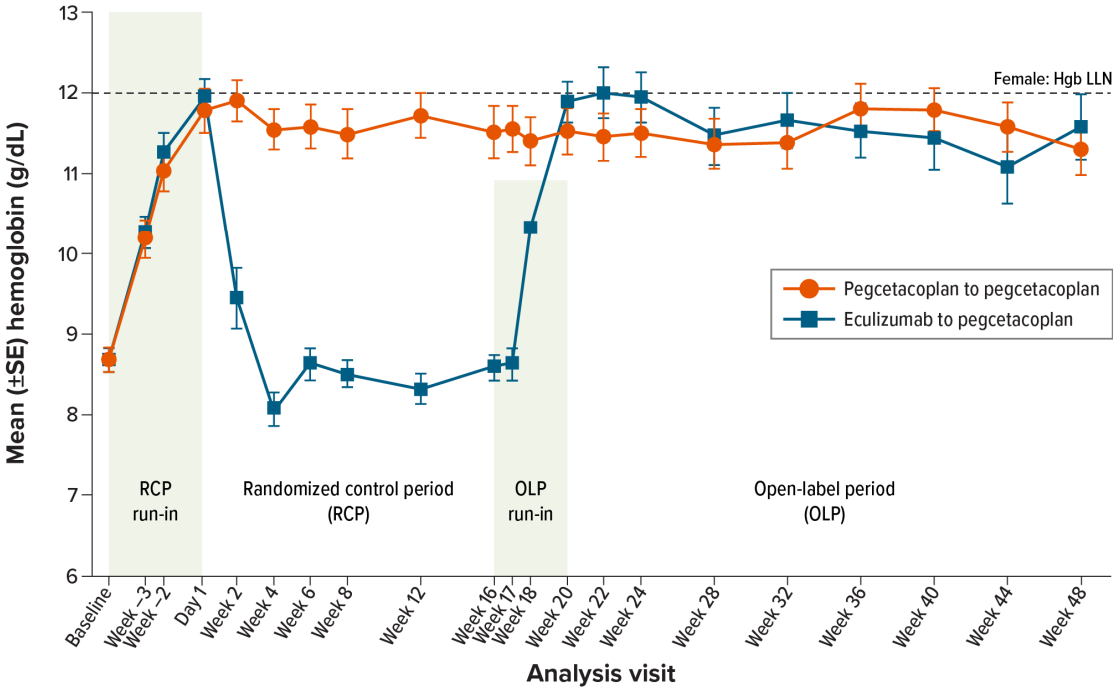
Source: Hillmen (2021b).

For detailed results for the key secondary endpoints and additional secondary endpoints, please refer to Appendix K.

7.1.2.3 PEGASUS Top-line results from Week 48

All patients (n = 77) who completed the 16-week RCP of the PEGASUS study, which evaluated pegcetacoplan compared with eculizumab, entered the open-label period, and received pegcetacoplan from Week 17 to Week 48. Top-line results from Week 48 demonstrated sustained hematological and clinical improvements in patients with PNH who were treated with pegcetacoplan. At Week 48, hemoglobin increases were sustained in pegcetacoplan-treated patients with a mean improvement from baseline of 2.7 g/dL, which is equal to the 2.7 g/dL mean increase seen at Week 16 with pegcetacoplan-treated patients. Additionally, eculizumab-treated patients who switched to pegcetacoplan during the open-label period experienced sustained improvements in hemoglobin and other hematological and clinical measures, similar to patients treated with pegcetacoplan monotherapy during the RCP (Figure 7).

Figure 7: PEGASUS: Sustained hemoglobin improvement over 48 Weeks of treatment with pegcetacoplan



LLN = lower limit of normal; OLP = open-label period; RCP = randomized controlled period; SE = standard error.

Source: Peffault de Latour (2021).

Patients treated with pegcetacoplan maintained improvements across key secondary endpoints, including TA. Throughout the 48-week study, 73% of patients treated with pegcetacoplan remained transfusion free. For comparison, 25% of patients were transfusion free over the year prior to entering the PEGASUS study while being treated with eculizumab. Additionally, among patients treated with eculizumab who switched to pegcetacoplan during the open-label period, 72% remained transfusion free. Improvements across additional markers of disease, such as reticulocyte count, LDH levels, and the FACIT-Fatigue scores, were maintained.

7.1.3 Safety results – PEGASUS

7.1.3.1 Run-in period

Co-administration of pegcetacoplan and eculizumab in the run-in period of 28 days was well tolerated with no discontinuations due to treatment-emergent adverse events (TEAEs). One SAE related to pegcetacoplan and eculizumab resolved despite continuing both drugs (Hillmen 2021b).

7.1.3.2 Randomized controlled period

Table 13 shows the results of TEAEs during RCP.

Table 13: Overview of treatment-emergent adverse events during randomized controlled period (Safety Set)—PEGASUS

	Statistics	Pegcetacoplan + Eculizumab[a] (N = 79)	Pegcetacoplan (N = 41)	Eculizumab (N = 39)
Any TEAEs	n (%)	12 (15.2)	36 (87.8)	34 (87.2)
Treatment-related TEAEs, related to pegcetacoplan	n (%)	2 (2.5)	16 (39.0)	NA
Treatment-related TEAEs, related to eculizumab	n (%)	1 (1.3)	NA	7 (17.9)
Treatment-related TEAEs, related to infusion	n (%)	0	9 (22.0)	0
Serious TEAEs	n (%)	2 (2.5)	7 (17.1)	6 (15.4)
Serious TEAEs, related to pegcetacoplan	n (%)	0	1 (2.4)	NA
Serious TEAEs, related to eculizumab	n (%)	0	NA	1 (2.6)
Serious TEAEs, related to infusion	n (%)	0	0	0
Injection-site reaction	n (%)	0	15 (36.6)	1 (2.6)
TEAEs leading to study drug discontinuation	n (%)	0	3 (7.3)	0

AE = adverse event; NA = not applicable; TEAE = treatment-emergent adverse event.

Notes: A TEAE is an AE that commenced on or after the time of first study drug administration or an AE with increase in severity from pretreatment.

If a subject has multiple occurrences of a TEAE, the subject is presented only once in the subject count and all occurrences are counted each time in the total events count. All TEAEs are presented only once in the total unique events count.

Definitely related and possibly related AEs are classified as Related AEs while unlikely related and not related AEs are classified as Unrelated AEs. AE with unknown relationship to study drug is counted as Related AE in the table.

a TEAEs that occurred after randomization date but before the first monotherapy are summarized under the pegcetacoplan + eculizumab group.

Source: Hillmen (2021b).

The following safety results were obtained in the RCP:

- Similar percentage of subjects in the pegcetacoplan (87.8%) and eculizumab group (87.2%) reported at least one TEAE.

- The numbers and proportions of subjects with SAEs and treatment-related SAEs in both pegcetacoplan and eculizumab groups were similar, including one subject in each treatment group who had a treatment-related SAE.
- More TEAEs occurred in the pegcetacoplan group than in the eculizumab group, likely due to the greater frequency of injection-site reactions (ISRs) in the pegcetacoplan group, though none were severe, serious, or led to study drug discontinuation.
- Of the subjects who had TEAEs related to study treatment, 39% (16 subjects) were on pegcetacoplan and 17.9% (7 subjects) were in the eculizumab group. Most of these were ISRs (36.6% in the pegcetacoplan group and 2.6% in the eculizumab group).
- Similar proportion of TEAEs in the SOC (system organ class) of Infections and Infestations occurred in both drug groups (29.3% in pegcetacoplan and 25.6% in the eculizumab group). None of the four infections during the study led to study drug discontinuation.
- TEAEs in the SOC of Nervous System Disorders were more frequent in the eculizumab group (30.8%) when compared with the pegcetacoplan group (14.6%) and were attributed to more frequent headache and dizziness TEAEs in the eculizumab cohort none of which led to drug discontinuation:
    - Headache: 23.1% in the eculizumab group versus 7.3% in pegcetacoplan group
    - Dizziness: 10.3% in the eculizumab group versus 2.4% in pegcetacoplan group
- TEAEs related to diarrhea, all rated mild, were more frequent in the pegcetacoplan group (22% vs. 2.6%) and did not lead to study drug discontinuation.
- There were no serious infections in the study known to be caused by an encapsulated organism, which is a potential risk in with all complement therapies.
- No TEAEs of thrombosis or drug hypersensitivity were reported during the study.
- No safety signal as assessed by clinical parameters (labs, electrocardiograms (ECGs), vital signs, and physical examination findings) appeared during study period.

In summary, the data showed that the overall safety of pegcetacoplan is comparable to that of eculizumab through 16 weeks. Some TEAEs, such as ISRs and diarrhea, were more frequent in the pegcetacoplan group, while others, such as hemolysis and headache, were more frequent in the eculizumab group. None of the TEAEs in the pegcetacoplan limited overall tolerability or led to study drug discontinuation.

During the RCP (Table 14), 15 subjects (36.6%) in the pegcetacoplan group reported an injection-related TEAE. The most common reports include injection-site erythema (36.6%), ISR (12.2%), injection-site swelling (9.8%), and injection-site induration (7.3%). In the eculizumab group, there was 1 subject with a TEAE in the category of ISR, and this event was related to vaccination (vaccination site pain). There were no TEAEs of ISR that were serious, severe, or led to study drug discontinuation.

Table 14: Injection-site reaction treatment-emergent adverse events by system organ class and preferred term during randomized controlled period (Safety Set)—PEGASUS

System Organ Class/ Preferred Term	Statistics	Pegcetacoplan + Eculizumab[a] (N = 79)	Pegcetacoplan (N = 41)	Eculizumab (N = 39)
Any TEAEs	n (%)	0	15 (36.6)	1 (2.6)
General disorders and administration site conditions	n (%)	0	15 (36.6)	1 (2.6)
Injection-site erythema	n (%)	0	7 (17.1)	0
Injection-site reaction	n (%)	0	5 (12.2)	0

System Organ Class/ Preferred Term	Statistics	Pegcetacoplan + Eculizumab[a] (N = 79)	Pegcetacoplan (N = 41)	Eculizumab (N = 39)
Injection-site swelling	n (%)	0	4 (9.8)	0
Injection-site induration	n (%)	0	3 (7.3)	0
Injection-site bruising	n (%)	0	2 (4.9)	0
Infusion site swelling	n (%)	0	1 (2.4)	0
Injection-site pain	n (%)	0	1 (2.4)	0
Injection-site pruritus	n (%)	0	1 (2.4)	0
Vaccination site pain	n (%)	0	0	1 (2.6)

TEAE = treatment-emergent adverse event.

Notes: A TEAE is an adverse event that commenced on or after the time of first study drug administration or an adverse event with increase in severity from pretreatment.

Adverse events were coded to System Organ Class and Preferred Term using MedDRA version 20.0.

If a subject has multiple occurrences of a TEAE, the subject is presented only once in the subject count (n) column for a given System Organ Class and Preferred Term.

a TEAEs that occurred after randomization date but before the first monotherapy are summarized under the pegcetacoplan + eculizumab group.

Source: Hillmen, 2021.

Hemolytic TEAEs were evaluated through an analysis in which all TEAEs that included the term "hemolysis" or "hemolytic" were counted (Table 15). By this analysis, hemolytic TEAEs were reported more frequently in the eculizumab group as compared with the pegcetacoplan group. Specifically, there were 11 subjects (28.2%) in the eculizumab group, compared with 4 subjects (9.8%) in the pegcetacoplan group, who had hemolytic TEAEs. In addition, there was 1 subject (1.3%) in the pegcetacoplan + eculizumab group with a hemolytic TEAE.

Table 15: Post hoc analysis: hemolytic events during randomized controlled period by treatment group (Safety Set)—PEGASUS

System Organ Class Preferred Term	Pegcetacoplan + Eculizumab n (%)	Pegcetacoplan n (%)	Eculizumab n (%)
All subjects	79	41	39
Subjects with at least one hemolytic TEAE	1 (1.3%)	4 (9.8%)	11 (28.2%)
Blood and lymphatic system disorders	1 (1.3%)	4 (9.8%)	11 (28.2%)
Hemolysis	0	4 (9.8%)	9 (23.1%)
Extravascular hemolysis	0	0	1 (2.6%)
Hemolytic anemia	1 (1.3%)	0	1 (2.6%)

TEAE = treatment-emergent adverse event.

Notes: Subjects who were randomly assigned but not treated are excluded.

Adverse events were coded to System Organ Class and Preferred Term using MedDRA version 20.0.

If a subject has multiple occurrences of a TEAE, the subject is presented only once in the subject count (n) column for a given System Organ Class and Preferred Term.

Events are sorted by descending frequency count in the pegcetacoplan column.

Source: Hillmen, 2021

7.1.3.3 Top-line results from Week 48

The safety profile of pegcetacoplan was consistent with previously reported data, and no new safety signals were identified during the 48-week period. Twenty-four of 80 pegcetacoplan monotherapy-treated patients (30%) experienced an SAE; five of the SAEs (6%) were assessed to be possibly related to study treatment. No cases of meningitis were reported. One death was reported due to COVID-19[1] and was unrelated to study treatment. The most common AEs reported throughout the study were ISRs (36%), hemolysis (24%), and diarrhea (21%). Twelve out of 80 patients (15%) discontinued because of AEs, with five discontinuations due to hemolysis. Sixty-four of the 67 patients (96%) who completed the open-label period opted to enter the extension study.

7.1.4 Comparative analyses of efficacy and safety

As described above, the PEGASUS trial is a direct comparison between pegcetacoplan and the C5 inhibitor eculizumab in PNH patients that remain anemic despite treatment with eculizumab.

The efficacy of ravulizumab vs eculizumab has been studied in two randomized controlled trials (RCTs), Study 301 (Lee 2019) and Study 302 (Kulasekararaj 2019b). In both studies, ravulizumab demonstrated noninferiority against eculizumab.

Study 301 included adult patients with PNH naive to complement inhibitors. The two primary endpoints were transfusion avoidance , and hemolysis as measured by LDH normalization. Key secondary endpoints included percentage change from baseline in LDH and change from baseline in QoL. Ravulizumab met the objective of noninferiority compared with eculizumab on both coprimary endpoints. Ravulizumab was also noninferior to eculizumab on the key secondary endpoints.

Study 302 included adult patients previously treated with eculizumab. The primary efficacy endpoint was hemolysis, as directly measured by percentage change in LDH levels from baseline. The key secondary efficacy endpoint was proportion of patients with breakthrough hemolysis. Ravulizumab achieved noninferiority compared with eculizumab for the primary endpoint of percentage change in LDH, with the point estimate for treatment difference favoring ravulizumab. Treatment with ravulizumab also achieved noninferiority compared with eculizumab for all secondary endpoints.

As the ravulizumab Study 302 included patients previously treated with eculizumab, it would be relevant to conduct an indirect comparison with the PEGASUS study for pegcetacoplan which was also conducted in eculizumab pre-treated patients. However, there are significant differences between the trials in some important parameters. Most notably, history of transfusions within one year before first dose was considerably higher in the PEGASUS trial than in Study 302 (~70% vs ~13%) whereas the hemoglobin levels were lower (~8.6 vs ~11 g/dL) (Appendix C). These differences are likely due to the inclusion of patients in the PEGASUS trial with Hb levels <10.5 g/dL at screening, and the fact that PEGASUS specifically included patients that were anemic despite C5 inhibition whereas this was not the case in Study 302 (Appendix B). These differences would violate the basic assumption of transitivity in an indirect comparison, i.e., that the two sets of trials do not differ with respect to the distribution of effect modifiers. Moreover, there is a difference in trial duration, 16 weeks in the PEGASUS trial and 26 weeks in Study 302. For these reasons, any attempt at conducting an indirect comparison of pegcetacoplan and ravulizumab via eculizumab is likely to result in skewed results.

[1] Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Thus, due to the above-mentioned differences in study designs, it was deemed not feasible to conduct an indirect comparison between pegcetacoplan and ravulizumab. However, as ravulizumab and eculizumab were shown to be of equal efficacy in C5 inhibitor naïve (study 301) as well as C5 inhibitor experienced populations (study 302), eculizumab was for the purpose of this comparison used as a proxy for ravulizumab. In other words, it is assumed that the outcomes from the comparison with eculizumab in the PEGASUS trial can be applied also for a comparison with ravulizumab.

Method of synthesis
Non applicable.

Results from the comparative analysis
Based on reasoning above, it is assumed that the outcomes from the comparison with eculizumab in the PEGASUS trial can be applied also for the comparison with ravulizumab.

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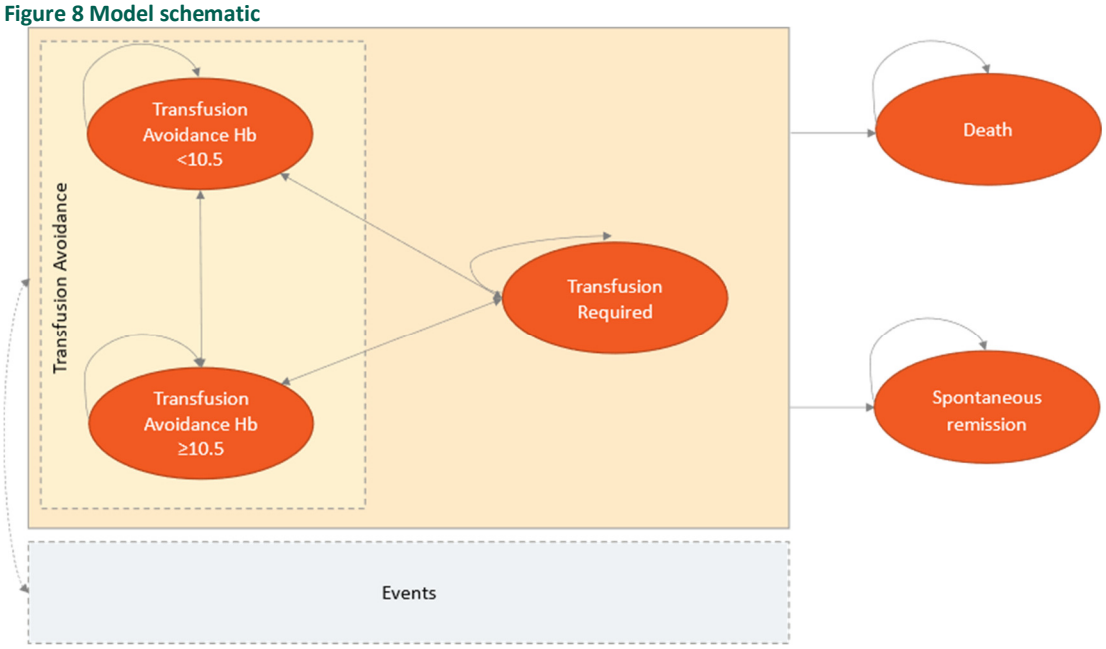
8. Health economic analysis

8.1 Model

A systematic literature review (SLR) was conducted in order to identify studies assessing the cost-effectiveness of treatments in PNH (further described in Appendix H – Literature search for HRQoL data). Based on the findings in the SLR, a de novo cost-effectiveness model (CEM) was developed to estimate the long-term cost-effectiveness of pegcetacoplan and its comparator, which uses a Markov model structure. The model estimates the long-term costs and outcomes (e.g., quality-adjusted life-year [QALY]) incurred in the target population. The model structure is outlined in Figure 8.

Figure 8 Model schematic



The model consists of three health states – Transfusion Avoidance AND Hb <10.5g/dL, Transfusion Avoidance AND Hb≥10.5g/dL and Transfusion Required. Hemoglobin cut-off at 10.5g/dL is consistent with the inclusion criteria in the PEGASUS clinical trial.

Patients who have not received a blood transfusion stay in the Transfusion Avoidance health state. They can stay in the same health state or move to the other Transfusion Avoidance health state with a different Hb range. Once patients require a blood transfusion, they move to the Transfusion Required health state and stay there for one cycle. After that, patients can move back to one of the Transfusion Avoidance health states or remain in the Transfusion Required health state if subsequent transfusion is needed.

The average number of transfusions for patients in the Transfusion Required health state was estimated based on the patient level data from PEGASUS clinical trial.

In the base-case, Spontaneous Remission is not considered because there is no evidence to indicate Spontaneous Remission rates will differ by treatment option.

A summary of the core elements of the economic model is shown in Table 16.

Table 16 Technical description of the economic model

Aspect	Details	Comment
Analytical method	Markov model structure	Commonly used model structure in CE analysis employing transition probabilities between health states
Time horizon	Lifetime (51.2 years)	To capture the costs and outcomes over the patient's lifetime.
Cycle length	4 weeks	Weekly cycles until week 28 to accommodate differing administration cycles for chemotherapies
Half-cycle correction	Yes	The model calculated mid-cycle estimates in each health state by taking the average of patients present at the beginning and at the end of each cycle.
Discounting options	Costs and health outcomes	Both costs and outcomes are subject to annual discounting in the evaluation
Treatment arms	Pegcetacoplan Ravulizumab (Ultomiris) Eculizumab (Soliris)	In line with clinical practice in Denmark, ravulizumab is considered to be the most relevant comparator for the main analysis. Eculizumab is included in scenario analyses considering the treatment option is available in Denmark.
Software used	Microsoft Excel (Office 365)	Excel is an accessible and widely available platform
Input		
Clinical efficacy and safety	PEGASUS clinical trial	The PEGASUS trial is the key registrational trial for pegcetacoplan. See section 0 for further information on clinical efficacy and safety
Treatment duration	Life-time	Pegcetacoplan is expected to be used according to the approved label continuously throughout a patient's life.
Costs	A review of published studies and previous HTA submissions reporting the economic burden in patients with PNH	Costs are sourced from official Danish sources as per guidance (Medicinrådet 2021)
Utilities	PEGASUS EORTC QLQC30 mapped to Danish EQ-5D-5L A review of previous HTA submissions within advanced PNH	In the PEGASUS trial, patients' quality of life (QOL) was measured based on EORTC QLQC30, then mapped to Danish EQ-5D-5L.
Output		
Cost-effectiveness ratios	Incremental cost effectiveness ratio (ICER)	ICER: Incremental cost per effect (e.g. life years gained, QALYs)
Costs	Disaggregated, total and incremental	-
QALYs	Disaggregated, total and incremental	-
Life years (LY)	Disaggregated, total and incremental	-
Cost-efficiency frontier	Yes	-

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Incremental cost-effectiveness plane	Yes	-
Cost-effectiveness acceptability curve and frontiers	Yes	-
Automated PSA and DSA	Yes	-

AE: Adverse events DSA: Deterministic sensitivity analysis; EQ-5D: EuroQol-5 dimensions; HTA: Health technology assessment; ICER: Incremental cost-effectiveness ratio;; PSA: Probabilistic sensitivity analysis; QALY: Quality adjusted life year; SEER: Surveillance, Epidemiology, and End Results program; US: United States

8.1.1 Key assumptions for Danish adaptation

8.1.1.1 Perspective

As stated in the "Medicinrådets metodevejledning for vurdering af nye lægemidler" (Medicinrådet 2021) from DMC a "limited societal perspective" is applied where the indirect costs of carers accompanying patients at every physician visits in terms of loss of leisure time, and transportation costs of the patients will be included. Productivity changes as a result of the intervention is not considered.

8.1.1.2 Time horizon, cycle length and discounting

The base-case analysis employs a 4-week cycle length and uses a lifetime (51.2 years) horizon, starting with patients switching to pegcetacoplan. The lifetime horizon aims to capture the potential impact on costs and outcomes over a patient's lifetime, in line with the guidelines from the DMC (Medicinrådet 2021). Alternative shorter time horizons (40, 20 and 10 years) are explored in scenario analyses.

The model applies a discount rate of 3.5% between years 0-35 and 2.5% from year 36 onwards for costs and health effects in the base case (FM 2021).

8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

8.2.1 Presentation of input data used in the model and how they were obtained

Table 17 summarizes and presents the estimates that inform the base case health economic model. The input data that informs the model include clinical effect, health state, disease management, monitoring, administration, QALY, AEs, and costs.

Table 17 Input data used in the model

Variable	Value	Measurement of Uncertainty (Distribution)	Reference and Corresponding Section in This Report
Perspective	Limited societal perspective	NA	(Medicinrådet 2021)
Discount rate: costs Discount rate: outcomes	3.5% years 0-35, 2.5% years 36-51.2	Lower bound:1.5% Upper bound: 5.0%	(FM 2021, Medicinrådet 2021)
Mean age (years)	48.8	SE=1.79 (normal)	PEGASUS CSR (SOBI 2020a)
Percentage female	61.3%	n/N=49/80 (beta)	
Mean weight (kg)	75.25	SE=1.97 (normal)	
Time since diagnosis (years)	10.18	SE=0.96 (normal)	

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Variable	Value	Measurement of Uncertainty (Distribution)	Reference and Corresponding Section in This Report
[redacted]		Fixed	SOBI
Ravulizumab pack price PPP (per 300 mg) (DKK)	37,388.73	Fixed	(Laegemiddelstyrelsen 2021e)
Eculizumab pack price PPP (per 300 mg) (DKK)	34,273,00	Fixed	(Laegemiddelstyrelsen 2021e)
Drug price discount: pegcetacoplan, eculizumab, ravulizumab	0%	Fixed	Assumption
Dosing level for patients on pegcetacoplan	Patients assumed to receive dose as per label See Table 30	Dirichlet Distribution based on the approach from Briggs et al. (2003)	Table 30
Supportive treatment costs	See Section 8.5.1.2	Gamma	Section 8.5.1.2
Transition probabilities	See Table 19 and Table 20	Dirichlet Distribution based on the approach from Briggs et al. (2003)	Table 19 and Table 20
Probability of developing complications per cycle	See Table 21	Beta	Table 21
Pegcetacoplan arm HR for death: PNH vs. general population	1.0	Fixed	Assumption: patients receiving complement inhibitors have comparable mortality to age- and sex-matched general population
Eculizumab arm HR for death: PNH vs. general population	1.0	Fixed	
Ravulizumab arm HR for death: PNH vs. general population	1.0	Fixed	
Utility: TA Hb < 10.5	0.788	SE = 0.08 (beta)	Recalculated based on the patients' level data from PEGASUS clinical trial (Tobit regression model) Assumption: Complication disutility was already accounted for within the mapped EQ-5D utility Table 25
Utility: TA Hb ≥ 10.5	0.845	SE = 0.08 (beta)	
Utility: Transfusion Required	0.751	SE = 0.08 (beta)	Recalculated based on the patients' level data from PEGASUS clinical trial (Tobit regression model) Assumption: Complication disutility was already accounted for within the mapped EQ-5D utility Table 25
Disutility associated with AEs	Excluded		Assumption: Complication disutility was already accounted

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Variable	Value	Measurement of Uncertainty (Distribution)	Reference and Corresponding Section in This Report
			for within the mapped EQ-5D utility
Disutility associated with complications	See Table 29	Beta	Assumption: Complication disutility was already accounted for within the mapped EQ-5D utility Table 29
Duration of complications		Normal	Recalculated based on the patients' level data from PEGASUS clinical trial (Tobit regression model) Assumption: Complication disutility was already accounted for within the mapped EQ-5D utility Table 29 Table 28 Assumption based on Lloyd et al. (2019) and Stoner et al. (2015) Assumption
Disutility due to eculizumab IV infusion	-0.057	SE = 0.006[a] (normal)	
Disutility due to ravulizumab IV infusion	0.000	Fixed	
Probability of developing AEs	See Table 29		Table 29
Pegcetacoplan SC administration unit cost for the first dose (DKK)	3,203	Fixed	Assuming one subcutaneous administration visit (Sundhedsdatastyrelsen 2021a)
Pegcetacoplan SC administration unit cost for subsequent doses (DKK)	0	Fixed	Assumption: patients self-administer subsequent doses at home
Pegcetacoplan pump cost for in-home infusion (DKK)	4,500		Assumption
Administration cost for eculizumab and ravulizumab (DKK)	3,203	Fixed	(Sundhedsdatastyrelsen 2021b)
Unit costs of managing complications	See Table 34		Table 34
Unit cost of blood transfusion (DKK)	4,628.00	SE = 731[a] (Gamma)	(Sundhedsdatastyrelsen 2021p)
Mean number of transfusions for patients in Transfusion Required health state - pegcetacoplan	1.00	Fixed	Based on the patients' level data from PEGASUS clinical trial
Mean number of transfusions for patients in Transfusion Required health state - eculizumab	1.36	Fixed	Based on the patients' level data from PEGASUS clinical trial Table 37

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Variable	Value	Measurement of Uncertainty (Distribution)	Reference and Corresponding Section in This Report
Mean number of transfusions for patients in Transfusion Required health state – ravulizumab	1.36	Fixed	Based on the patients' level data from PEGASUS clinical trial Table 37
Probability of developing severe acute reactions of blood transfusion		Beta	Based on the patients' level data from PEGASUS clinical trial Table 37 Table 38
Unit costs of managing severe acute reactions	Excluded	Gamma	Based on the patients' level data from PEGASUS clinical trial Table 37
Health care resource use frequency by health state	Table 38		Based on the patients' level data from PEGASUS clinical trial Table 37 Table 38 In order to capture the limited societal perspective in the health economic model, the unit costs in Table 39 includes transportation cost of 100 DKK and time spent at hospital (assumed time is 1 hour) at a cost of 179 DKK. Table 39 Table 40
Health care resource use unit costs	Table 39 Table 40		
AE unit costs	Table 34		
Indirect costs (Productivity losses)	Excluded		(Medicinrådet 2021)
Patient cost for travelling	100 DKK	Fixed	(Medicinrådet 2021)
Patient cost for time spent on treatment (1h)	179 DKK	Fixed	(Medicinrådet 2021)

8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice

8.2.2.1 Patient population

According to Danish PNH experts mean age varies, but most patients with classic PNH are diagnosed between 30-50 years of age (Danish PNH experts 2021).

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The patient population in this health economic analysis is representative of the licensed population for pegcetacoplan, adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who are anaemic after treatment with a C5 inhibitor for at least 3 months (referred as treatment-switch patients hereafter). The patient characteristics were based on the treatment-switch, intention-to-treat (ITT), patient population included in the PEGASUS trial. Patient characteristics are presented in Table 18.

Table 18 Patient population

Patient population Important baseline characteristics	Clinical documentation	Used in the model (number/value including source)	Danish clinical practice (including source)
Mean age (years)	PEGASUS	48.8	30-50 years of age (KOL 1 2021)
Female (%)	PEGASUS	61.3%	Assumption (derived from PEGASUS)
Mean weight (kg)	PEGASUS	75.3	Assumption (derived from PEGASUS)
Time since diagnosis (years)	PEGASUS	10.2	Assumption (derived from PEGASUS)

8.2.2.2 Intervention

Pegcetacoplan is a compstatin derivative that inhibits C3 and C3b of the complement system. By targeting the complement cascade earlier than eculizumab or ravulizumab (which act at C5), improvements in hematological parameters, such as hemoglobin, bilirubin, reticulocytes, and LDH, can be achieved. Pegcetacoplan addresses both intravascular and extravascular hemolysis (which cause anemia in patients with PNH) by regulating the complement at the C3 level. Pegcetacoplan is expected to be used in Danish clinical practice according to the expected label.

8.2.2.3 Comparators

Currently, the only cure for PNH is an allogeneic hematopoietic stem cell transplantation (Mitchell R 2017). Because of the considerable challenges and risks involved, a bone marrow transplant is not a therapeutic option for most patients and is typically recommended for patients with severe bone marrow failure, re-occurring life-threatening thromboembolic incidences, and refractory transfusion-dependent hemolytic anemia (Young NS 2009 , Sahin F 2016). The current strategy of the treatment is to manage the symptoms therefore its non-curative. To date, the only approved therapies for PNH are the C5-inhibitory drugs eculizumab and ravulizumab (Hill 2010, Stern RM 2019).

Based on interviews with PNH experts almost all patients in Denmark in need of C5 treatment are treated with Ultomiris (ravulizumab) (Danish PNH experts 2021).

There is no head-to-head trial between pegcetacoplan and ravulizumab. As mentioned in section 0, due to differences in recruited study populations in the relevant trials, any indirect comparison between pegcetacoplan and ravulizumab would have been biased. Therefore, no such attempt was made. Instead, given the noninferiority of ravulizumab to eculizumab in C5 inhibitor naïve (study 301) and experienced (study 302) PNH patients, comparative data vs eculizumab from the PEGASUS trial was used as a proxy for ravulizumab in the present model.

8.2.2.4 Relative efficacy outcomes

Pegcetacoplan was studied in the PEGASUS trial. The primary objective was to establish the efficacy and safety of pegcetacoplan compared with eculizumab in patients with PNH who continue to have hemoglobin levels < 10.5 g/dL despite treatment with eculizumab.

Primary endpoints in PEGASUS:

- Change from baseline to Week 16 hemoglobin level, excluding data before the randomized controlled period

Key secondary endpoints:

- Transfusion avoidance (yes/no), defined as the proportion of patients who do not require a transfusion during the 16-week randomized controlled period
- Change from baseline to Week 16 reticulocyte count, excluding data before the randomized controlled period
- Change from baseline to Week 16 LDH level, excluding data before the randomized controlled period
- Change from baseline to Week 16 in the FACIT-Fatigue scale total score version 4, excluding data before the randomized controlled period

The HE-model utilizes efficacy data from PEGASUS. Specifically, hemoglobin level and transfusion avoidance are important parameters in the model. This aligns with PNH-related clinical practice (including in Denmark), as both variables are important indicators of treatment efficacy and status of disease.

Transition probabilities for patients receiving pegcetacoplan and ravulizumab were estimated from the PEGASUS trial patient level data based on the following approach:

- Patients were classified into appropriate health states depending on their medical characterization on the planned visits during PEGASUS clinical trial period.

- Transition probabilities between health states were estimated using a multinomial logistic regression model, estimated using SAS software, with:

  - The current health state as outcome variable,
  - Health state 4 weeks earlier, treatment (Tx), visit category (Visit) and age as covariates,
  - Random intercept at patient level (i) (ui),
  - Interaction between treatments and visit category.

$$Health\ state_{current} \sim Health\ state_{previous} + Tx + Visit + Tx * Tx * Visit + Age + u_i$$

- Transition probabilities were calculated separately for Week 4, Weeks 8-16, and Open label period, based on the visit's categories during PEGASUS clinical trial.

The transition probabilities for the first cycle were obtained from Week 4 data of the clinical trial, and for the remaining cycles probabilities were based on Week 8-16 data. Transition probabilities for ravulizumab were assumed to be the same as those for eculizumab. Base-case transition probabilities are presented in Table 19 and Table 20.

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Table 19 Transition probabilities applied in the first cycle

From	To		
	TA Hb <10.5g/dL	TA Hb ≥10.5g/dL	Transfusion Required
Transition probabilities for patients receiving pegcetacoplan			
TA Hb <10.5g/dL	23.24%	74.38%	2.38%
TA Hb ≥10.5g/dL	1.19%	98.74%	0.07%
Transfusion Required	12.08%	84.41%	3.51%
Transition probabilities for patients receiving ravulizumab			
TA Hb <10.5g/dL	26.35%	0.01%	73.64%
TA Hb ≥10.5g/dL	39.73%	0.46%	59.81%
Transfusion Required	11.20%	0.01%	88.79%

Hb = hemoglobin; TA = transfusion avoidance.

Table 20 Transition probabilities applied in the subsequent cycles

From	To		
	TA Hb <10.5g/dL	TA Hb ≥10.5g/dL	Transfusion Required
Transition probabilities for patients receiving pegcetacoplan			
TA Hb <10.5g/dL	41.06%	56.01%	2.93%
TA Hb ≥10.5g/dL	2.76%	97.14%	0.11%
Transfusion Required	23.93%	71.23%	4.84%
Transition probabilities for patients receiving ravulizumab			
TA Hb <10.5g/dL	65.20%	0.07%	34.74%
TA Hb ≥10.5g/dL	76.16%	1.98%	21.86%
Transfusion Required	39.78%	0.09%	60.13%

Hb = hemoglobin; TA = transfusion avoidance.

8.2.2.5 Complications

Patients with PNH can develop disease-related complications, such as breakthrough hemolysis, thrombosis, acute kidney damage, chronic kidney disease, pulmonary hypertension, and iron overload. Probabilities of having complications are expected to only differ by health state, except for iron overload. The probability of developing iron

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overload is treatment specific. Disutility of complications that were not observed in the trial are accounted for over the duration of the complication, whereas disutility of complications that were observed in the trial is not included to avoid double counting (Table 21). Health related utility was measured throughout the clinical trial and thus complications are reflected in the overall utility measured. There is an option to include disutility in the model, however, such a scenario would double count the disutility due to complications.

Table 21 Probability of developing complications per cycle

	TA Hb< 10.5g/dL	TA Hb ≥ 10.5g/dL	Transfusion Required	Spontaneous Remission	Source
Breakthrough hemolysis	0.0032	0.0000	0.1334	0.000	SOBI data on file PEGASUS CSR (Sobi Data on file 2021)
Thrombosis	0.0000	0.0000	0.0000	0.0000	SOBI data on file PEGASUS CSR (SOBI 2020a)
Acute kidney damage	0.0000	0.0000	0.0000	0.0000	Assumption
Chronic kidney disease	0.0000	0.0000	0.0000	0.0000	Assumption
Pulmonary hypertension	0.0000	0.0000	0.0000	0.0000	Assumption
Iron overload for patients on pegcetacoplan	NA	NA	NA	NA	SOBI data on file (SOBI 2020a)
Iron overload for patients on eculizumab	NA	NA	NA	NA	SOBI data on file, (SOBI 2020a)
Iron overload for patients on ravulizumab	NA	NA	NA	NA	Ravulizumab study 302, (Kulasekararaj 2019a)

CSR = clinical study report; NA = not applicable; TA = transfusion avoidance.

8.3 Extrapolation of relative efficacy

No extrapolation is applied in the model, the relative efficacy is assumed to be constant over the modelled time horizon.

8.3.1 Treatment discontinuation

Treatment discontinuation is rare. According to our knowledge no patients with PNH have discontinued treatment with C5 inhibitors in Denmark.

In the base-case analysis, no treatment discontinuation was assumed because there is no other effective active treatment available in Denmark and patients would still be better managed with C5 or C3 inhibitor treatment than no treatment.

8.3.2 Mortality

Mortality is included in the model under "Country specific data" Row 337. The source is National Life Tables, Statistics Denmark, Based on data for years 2019-2020 (Statistics Denmark 2021).

In the base-case, treatment-specific mortality data is applied (no difference between treatments), and it is assumed no increased mortality directly associated with health states or complications.

As a scenario analysis, increased mortality rates are applied to patients in relevant health state and/or complications by defining hazard ratio (HR).

8.3.2.1 Mortality for patients receiving complement inhibitors

For patients receiving complement inhibitors, probability of death is estimated based on age- and sex-matched general population mortality due to the following considerations:

- The leading cause of death before eculizumab became available was thrombosis, which has now been proven to be well managed by eculizumab. Published long-term overall survival (OS) data suggest patients receiving eculizumab have comparable OS to the age-adjusted general population (Kelly RJ 2011).
- As pegcetacoplan is expected to reduce both intravascular and extravascular hemolysis, in principle, it can reduce the risk of kidney damage; it is however rare for patients with PNH to develop life-threatening severe kidney disease.
- Published long-term OS data were only stratified by patients with and without eculizumab. No long-term OS data are available for patients receiving other complement inhibitors (ravulizumab and pegcetacoplan).

As a scenario analysis, mortality is modelled through the increased mortality risk due to the following events/health condition:

- Death due to PNH-related complications, such as breakthrough hemolysis, thrombosis, acute kidney damage, chronic kidney disease, pulmonary hypertension, and iron overload.
- Death due to severe acute reaction of blood transfusion.
- Increased mortality for patients in the suboptimal Transfusion Required health state.

Death due to complications and severe acute reaction of blood transfusion were modelled through probability of death per event. Increased mortality for patients in the Transfusion Required health state was modelled by applying HR to age- and sex- matched general population mortality. Assumptions were used wherever data were not available.

8.4 Documentation of health-related quality of life (HRQoL)

8.4.1 Overview of health state utility values (HSUV)

A systematic literature review (SLR) was performed to identify published utility values associated with PNH (SOBI 2020b). The searches of the following electronic databases were performed on November 13, 2020: MEDLINE, MEDLINE In-Process, Embase, EconLit, the Cochrane Library, and BioSciences Information Services. These searches were

supplemented by a targeted desktop research, which included the search of the European Hematology Association's website to identify the 2020 conference abstracts not yet indexed in Embase, the search of the Cost-Effectiveness Analysis Registry to identify relevant utility weights, and the searches to identify relevant health technology assessment (HTA) documents from the International Network of Agencies for Health Technology Assessment (INAHTA), the NICE, the Scottish Medicines Consortium, the Canadian Agency for Drugs and Technologies in Health (CADTH), and the Pharmaceutical Benefits Advisory Committee. Bibliographic lists of included economic analyses and SLRs, as well as the identified HTA documents, were searched for further studies of interest.

The database searches had no language limitations. There was also no date limitation, apart from the searches of conference proceedings, which were limited to abstracts published in the last 2 years. Search terms consisted of combinations of free text and Medical Subject Headings or Emtree subject headings and included terms for the health condition of interest, the interventions of interest, the relevant study types, and outcomes of interest.

Twenty-six studies (24 unique studies) were identified and included in the systematic review: 11 studies from searches for economic evaluations (including HTAs), 13 studies from searches for cost and resource-use data, and 2 studies from searches for utility data. No identified studies were based on the Danish population.

Table 22 presents summary findings from the SLR on identified utility estimates.

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Table 22 Summary Table of Utility Weights Identified in SLR

Author (Year), Country, Ref ID	Study Population	Methods of Elicitation and Valuation	Health-State Description	Utility Estimate	Source
O'Connell et al. (2020) US Ref ID: 133	Cohort 1: PNH patients naive to eculizumab Cohort 2: PNH patients clinically stable on the maintenance dose of eculizumab Cohort 3: PNH patients clinically stable on off-label use of a higher maintenance dose	Health utility estimated by mapping the HRQOL measure collected in the 301 and 302 studies (QLQ-C30 to EQ-5D-3L). Mapping was performed using the methodology reported in McKenzie and van der Pol (2009).	Cohort 1, Cohort 2, Cohort 3		
			No BTH state: eculizumab	0.79, 0.83, 0.83	(O'Connell T 2020)
			No BTH state: ravulizumab	0.80, 0.87, 0.87	
			Decrease in health utility for BTH event: eculizumab or ravulizumab	−0.11, −0.40, −0.40	
			Decrease in health utility for transmission: eculizumab or ravulizumab	−0.11, −0.10, −0.10	
			Increase in health utility associated with reduced health care provider visit frequency: ravulizumab	+0.057	(Lloyd AJ 2019)
Coyle et al. (2014) Canada Ref ID: 24	Patients with MDS	Depending on the complication, different patient populations were used	Transfusion independent	0.84	(Szende A 2009)
			Reduced transfusion requirements	0.77	
			Transfusion dependent	0.60	
	Depending on the complication, different patient populations were used	Utility values for complications were derived from the literature.	Iron overload	0.85	(Delea TE 2007)
			Iron overload–related cardiac disease	0.80	
			Thrombotic event	0.94	(Hind D 2007)

Author (Year), Country, Ref ID	Study Population	Methods of Elicitation and Valuation	Health-State Description	Utility Estimate	Source
			Advanced renal disease	0.88	(Gorodetskaya I 2005)
			Renal dialysis	0.81	
			Cytopenia	0.997	(Gould MK 1999)
			MDS/AML	0.26	(Younis T 2011)
			Spontaneous resolution	0.925	(Canada. 1995)

AML = acute myeloid leukemia; BTH = breakthrough hemolysis; HRQOL = health-related quality of life; MDS = myelodysplastic syndrome; PNH = paroxysmal nocturnal hemoglobinuria; QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; US = United States. Note: HTA documents or published economic evaluations available as abstracts only were excluded from this summary because the model input data are not consistently presented by these publication types

8.4.2 Health state utility values used in the health economic model

In the PEGASUS trial, patients' quality of life (QOL) was measured based on EORTC QLQC30, Table 23 provides a description of the patient-reported outcomes measures used in the PEGASUS clinical trial.

Table 23 Patient-Reported Outcomes Measures Used in the Pegcetacoplan Clinical Trials

Measure	Description	Studies Included
FACIT-Fatigue	• 13-item Likert scale • Total score range 0-52 • A higher score corresponds to higher QOL (lower fatigue) • An increase in score of 3 or more is considered to be clinically meaningful	PEGASUS
LASA for Quality of Life	• 3 item scale asking respondents to rate their perceived level of functioning • Domains include activity level, ability to carry out daily activities, and overall QOL • Scores are analyzed for the individual components and the combined scale	PEGASUS
EORTC QLQ-C30 Questionnaire (version 3.0)	• 30 item questionnaire composed of both multi-item scales and single-item measures to assess overall QOL • Domains are functional scales, symptom scales and global QOL/perceived health status • Scoring followed guidelines provided by the EORTC	PEGASUS

EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire–Core Module; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy–Fatigue Subscale; LASA = Linear Analog Assessment Scale; QOL = quality of life.

The EQ-5D utility weights for each patient at each visit were estimated by mapping EORTC QLQ-C30 QOL data using Danish utility weights. Since no mapping algorithm is available for patients with PNH, one had to be created (See Appendix I Mapping of HRQoL data for more information on the mapping method).

Age adjustment of utility values was applied to account for the increased morbidity and decreased function linked to increasing age. The age adjustment was calculated using the multiplicative method as described in NICE DSU Technical Support Document 12 (Ara 2011). The general population utility values used in the age adjustment calculations are listed in Table 24 (Wittrup-Jensen 2009, Nordjylland 2021).

Table 24: General Danish population utility values

Age group (years)	Mean utility
50-69	0.818
70-79	0.813
80+	0.721

Patient-level data from the PEGASUS trial, specifically responses to the EORTC QLQ-C30 questionnaire, were utilized with the created mapping algorithm to calculate EuroQol five-dimensional (EQ-5D-5L) utility values using Danish preference weights (Jensen CE 2021). The HE-model health-state utilities are presented in Table 25.

Table 25 Health state utility used in the model

	Mean	Source
Transfusion Avoidance Hb < 10.5g/dL	0.749	(Jensen CE 2021, SOBI 2021)
Transfusion Avoidance Hb ≥ 10.5g/dL	0.829	(Longworth 2014, Jensen CE 2021, SOBI 2021)
Transfusion Required	0.734	(Jensen CE 2021, SOBI 2021)

An overview of the health-state utility values and the mapping method of these are presented in the table below.

Table 26 Overview of HSUV based on mapping

	Results [SE, 95% CI]	From Instrument	To instrument	Comments
Transfusion dependence	0.734 [0.020, 0.695- 0.774]	EORTC QLQ-C30	EQ-5D-5L	*Two approaches for mapping the utility values are available:* • *Direct – In this single-stage approach health-related utilities are directly mapped based on the response collected from the quality of life questionnaire (here EORTC). This approach is country specific, therefore the algorithm can not be used for various countries.* • *Indirect – This double-stage process requires mapping the response between two QoL questionnaires referred as response mapping (e.g. between EORTC and EQ5D-5L) followed by estimation of utilities using dedicated tariff, so the same model can be used for different countries* *Further details are described in appendix I*
Transfusion avoidance with hemoglobin level < 10.5	0.749 [0.019, 0.711- 0.787]	EORTC QLQ-C30	EQ-5D-5L	
Transfusion avoidance with hemoglobin level >=10.5	0.829 [0.019, 0.792- 0.867]	EORTC QLQ-C30	EQ-5D-5L	
Transfusion dependence	0.751 [0.016, 0.720 – 0.782]	EORTC QLQ-C30	EQ-5D-3L	For reference, the mapping to EQ-5D-3L is presented here. (Longworth 2014)
Transfusion avoidance with hemoglobin level < 10.5	0.788 [0.015, 0.757 - 0.818]	EORTC QLQ-C30	EQ-5D-3L	

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	Results [SE, 95% CI]	From Instrument	To instrument	Comments
Transfusion avoidance with hemoglobin level >=10.5	0.845 [0.015, 0.815 - 0.875]	EORTC QLQ-C30	EQ-5D-3L	

Patients filled the EORTC questionnaire at each visit of the PEGASUS trial. Therefore, we first estimated EQ-5D-5L utilities for each patient at each visit using previously mentioned mapping algorithm. In the next step all values (all patients, all visits) were pooled using tobit regression in order to estimate the utilities for the 3 predefined health states.

Table 27 displays the number of patients responding to the questionnaire at each visit with SD and CI.

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Table 27 Utility calculated with linear regression model

Visit	Utility calculated with a linear regression model with interactions			
	N	Mean [min : max]	SD	Median [q1; q3]
Screening	2	0.77 [0.73; 0.81]	0.06	0.77 [0.75; 0.79]
Week -4	76	0.73 [0.10; 1.05]	0.18	0.74 [0.67; 0.83]
Week -2	75	0.81 [0.24; 1.04]	0.16	0.83 [0.73; 0.93]
Day 1	77	0.86 [0.41; 1.04]	0.14	0.88 [0.79; 0.98]
Week 2	77	0.78 [-0.07; 1.04]	0.22	0.83 [0.72; 0.92]
Week 4	76	0.77 [-0.18; 1.09]	0.23	0.80 [0.69; 0.91]
Week 6	76	0.77 [0.00; 1.01]	0.19	0.80 [0.70; 0.89]
Week 8	75	0.78 [-0.03; 1.04]	0.19	0.82 [0.71; 0.91]
Week 12	75	0.77 [-0.27; 1.21]	0.22	0.81 [0.72; 0.88]
Week 16	74	0.76 [0.05; 1.01]	0.18	0.78 [0.66; 0.89]
Week 17	74	0.77 [-0.70; 1.04]	0.24	0.80 [0.68; 0.92]
Week 18	74	0.79 [-0.20; 1.04]	0.20	0.82 [0.70; 0.94]
Week 20	75	0.80 [0.32; 1.04]	0.17	0.83 [0.72; 0.94]
Week 22	74	0.85 [0.44; 1.13]	0.15	0.87 [0.77; 0.96]
Week 24	72	0.82 [0.22; 1.04]	0.18	0.86 [0.71; 0.96]
Week 28	73	0.80 [0.19; 1.05]	0.19	0.84 [0.71; 0.96]
Week 32	72	0.80 [0.11; 1.11]	0.21	0.82 [0.71; 0.96]
Week 36	69	0.81 [-0.08; 1.07]	0.22	0.82 [0.74; 0.98]
Week 40	62	0.82 [0.33; 1.05]	0.18	0.86 [0.68; 0.95]
Week 44	62	0.78 [-0.03; 1.08]	0.20	0.81 [0.68; 0.91]
Week 48	59	0.83 [0.41; 1.07]	0.16	0.83 [0.70; 0.99]
Week 54	7	0.89 [0.70; 1.02]	0.12	0.93 [0.81; 0.97]
Week 60	2	0.50 [0.10; 0.89]	0.56	0.50 [0.30; 0.69]

Source: Sobi data on file. Clinical study report PEGASUS trial

The base-case of the model assumes no difference in utility between treatments. Disutility associated with AEs is assumed to be accounted for within EQ-5D utility weights from mapped EORTC QLQ-C30 QOL data collected during the PEGASUS trial. Therefore, no additional disutility is included to avoid double counting.

8.4.2.1 Duration of complications

As there are no data on duration of thrombosis, this is an assumption. Nevertheless, the frequency of thrombosis is close to zero and has negligible impact on the analysis.

Table 28 Duration of complication

Complication	Duration (Days)	Source
Breakthrough hemolysis	2	(O'Connell T 2020)
Thrombosis	90	Assumption
Acute kidney damage	0	Assumption
Chronic kidney disease	0	Assumption
Pulmonary hypertension	0	Assumption
Iron overload	0	Assumption

8.4.2.2 Disutility associated with adverse events

In the base-case analysis, disutility associated with AEs is assumed to be accounted for within EQ-5D utility weights from mapped EORTC QLQ-C30 QOL data collected during the PEGASUS trial. Therefore, no additional disutility is included to avoid double counting.

Disutility due to AEs was explored as a scenario analysis. In this scenario analysis, the disutility based on probability of developing AEs per cycle and corresponding disutility per event was included. Lists of AEs included in the analysis were derived from the PEGASUS trial: serious treatment-emergent AEs for which the incidence differed by 2% or more between the pegcetacoplan arm and eculizumab arm. The probability of developing AEs per cycle are presented in Table 29. Data inputs for pegcetacoplan and eculizumab is estimated based on the PEGASUS trial. The probability of developing AE for patients receiving ravulizumab is estimated based on the ravulizumab 302 study (Kulasekararaj 2019a).

Table 29 Probability of developing adverse events per cycle

Adverse Event	Pegcetacoplan	Ravulizumab	Eculizumab
Anemia	0.000	0.000	0.013
Hemolytic anemia	0.000	0.000	0.006
Bacterial infection	0.006	0.003	0.000
Gastroenteritis	0.006	0.000	0.000
Atrial fibrillation	0.006	0.000	0.000
Hyperthermia	0.000	0.000	0.006
Facial paralysis	0.006	0.000	0.000
Dyspnea	0.006	0.000	0.000
Abdominal pain	0.000	0.000	0.006
Biliary colic	0.000	0.000	0.006
Hepatocellular injury	0.000	0.000	0.006
Hyperbilirubinemia	0.000	0.000	0.006
Jaundice	0.000	0.000	0.006

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8.4.2.3 Disutility associated with intravenous infusion

Stoner and colleagues conducted a systematic literature review and results suggest that patients prefer subcutaneous over IV delivery (Stoner KL 2015). The base-case analysis assumes there is no disutility associated with pegcetacoplan because it is administered subcutaneously, and patients are expected to self-administer subsequent doses at home after being given training during the first administration in a clinic.

Lloyd et al. (2019) conducted a stated preference discrete choice experiment survey in the UK general population aged ≥ 18 years old (Lloyd AJ 2019). The study suggested that participants preferred an infusion frequency of every 8 weeks (ravulizumab dosing frequency) compared with every 2 weeks (eculizumab dosing frequency). The disutility of 0.057 was reported for IV infusion every 2 weeks compared with every 8 weeks. Hence, the base-case analysis conservatively assumed that patients receiving ravulizumab had no disutility associated with IV infusion.

8.5 Resource use and costs

8.5.1 Drug acquisition costs

8.5.1.1 Complement inhibitors

Drug costs of complement inhibitors were estimated based on treatment dosing regimens and corresponding drug price (Table 30). The drug price for ravulizumab and eculizumab were derived from laegemiddelstyrelsen website

[redacted]

Table 30 Dosing regimens for complement inhibitors

Treatment	Drug Price, PPP (DKK)	Dosing regimen
Pegcetacoplan	[redacted]	Labelled dosing • Loading dose (first month): 1,080 mg SC administration twice weekly + current dose of eculizumab • Maintenance period: 1,080 mg SC administration twice weekly Dosing escalation Change to 1,080 mg every 3 days if a patient does not respond sufficiently to the planned dose of 1,080 mg twice weekly
Ravulizumab	37,388.73 DKK per 300 mg	Labelled dosing Loading dose: administer ravulizumab • 2 weeks after last dose of eculizumab • 2,400 mg for patient weights ≥ 40 to < 60 • 2,700 mg for patient weights ≥ 60 to < 100 • 3,000 mg for patient weights ≥ 100 Maintenance period: 8 weeks starting 2 weeks after the loading dose • 3,000 mg for patient weights ≥ 40 to < 60 • 3,300 mg for patient weights ≥ 60 to < 100 3,600 mg for patient weights ≥ 100
Eculizumab	34,273.00 DKK per 300 mg	Labelled dosing • 900 mg IV infusion every 14 ± 2 days Dosing escalation, if a patient does not respond sufficiently to the planned dose of 900 mg twice every 14 ± 2 days • IV 900 mg every 11 days

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- IV 1,200 mg every 11 days

IV 1,500 mg every 11 days

PPP = Pharmacy Purchasing Price, IV = intravenous; SC = subcutaneous.

In the base-case, pegcetacoplan patients' dosing levels are assumed to be according to the labelled dosing outlined in Table 30. However, some patients may receive a higher dose if they do not respond sufficiently to the labelled dosing, therefore, a scenario analysis explored the dose levels derived from the PEGASUS trial (Table 31), the results of this scenario is presented in Table 45.

Table 31 Pegcetacoplan dosing level

Treatment	Cycle in the model	Time observed in PEGASUS	Dosing Level	Usage	Source
Pegcetacoplan	0-1	Weeks 4 to 7 in the trial[a]	1,080 mg twice weekly	100.0%	SOBI data on file (2020b) (CSR); observed dosing level during the RCT period
			1,080 mg every 3 days	0.0%	
	2-3	Weeks 8 to 14 in the trial[b]	1,080 mg twice weekly	97.6%	
			1,080 mg every 3 days	2.4%	
	4	Weeks 15 to 16 in the trial[c]	1,080 mg twice weekly	95.1%	
			1,080 mg every 3 days	4.9%	
	5 - end of model time horizon	N/A	1,080 mg twice weekly	95.1%	Assumption
			1,080 mg every 3 days	4.9%	

CSR = clinical study report; RCT = randomized controlled trial. [a] Week's 1-11 in the model. [b] Weeks 12-18 in the model. [c] Weeks 19-20 in the model.

There is no reason to believe that the number of patients requiring an increased dose should continue to increase with time. If the percentages 2.4 and 4.9 are translated into actual number of patients, it is 1 and 2 patients, respectively. The reason to increase the dose was that laboratory tests indicated that intravascular haemolysis was not fully controlled. This should be seen as a random event and not something that would be expected to continuously increase with time in patients treated with pegcetacoplan.

8.5.1.2 Supportive treatments

Supportive treatments are used to manage PNH-related disease symptoms as concomitant medications for patients receiving pegcetacoplan or comparator treatments. The drug cost of supportive treatments is expected to differ by health states, which is estimated through a basket of non-active treatments and drug utilization per health states. The followings are the supportive treatments that were included in the model:

- Iron supplements
- Iron chelation
- Phlebotomy/venesection iron overload
- QT-prolonging medications

Supportive treatment costs are presented in Table 32 and drug utilization applied in the model is presented in Table 33.

Table 32 Supportive treatment costs

Treatment	Drug Name	Pack Price PPP (DKK)	Dosing Regimen	Cost Per Cycle (DKK)	Source
Corticosteroids/immunosuppressants	Prednisolon	68.50	5 mg once daily	19.18	(Laegemiddelstyrelsen 2021d)
Erythropoietin	Retacrit	3,049.90	Starting dose: 50 IU/kg 3 times weekly Maintenance dose: 75 to 300 IU/kg weekly	1,016.63	(Laegemiddelstyrelsen 2021c)
Iron-chelating medications	Desferal	611.45	Average daily dose 20 to 60 mg/kg	552.14	(Laegemiddelstyrelsen 2021a)
QT-prolonging medications	Flecainid	279.10	100 mg twice daily	156.30	(Laegemiddelstyrelsen 2021b)

In Table 33 the supportive treatment utilization from PEGASUS is presented.

Table 33 Supportive treatment utilization

Treatment	Drug Utilization by Health States (%)			Source
	Complement Inhibitors			
	Transfusion Avoidance Hb<10.5	Transfusion Avoidance Hb≥10.5	Transfusion Required	
Corticosteroids/immunosuppressants	0.0%	12.5%	12.8%	PEGASUS CSR (SOBI data on file, 2020b)
Erythropoietin	0.0%	0.0%	2.6%	
Iron-chelating medications	4.0%	0.0%	10.3%	
Prophylactic antibiotics	56.0%	68.8%	53.8%	
QT-prolonging medications	0.0%	0.0%	2.6%	
Rescue antibiotics	12.0%	25.0%	30.8%	

8.5.1.3 Administration costs

The base-case analysis assumes patients on pegcetacoplan will have their first administration in a clinic and receive training on self-administration. Patients self-administer subsequent doses at home. The unit cost for subcutaneous administration training was estimated to be 3,203 DKK (assuming one subcutaneous administration visit using the interaktiv DRG service provided by Sundhedsdatastyrelsen) (Sundhedsdatastyrelsen 2021a). A one-off pump cost for pegcetacoplan in-home infusion is included in the base-case at an assumed cost of approximately 4,500 DKK. The cost of DKK 4500 comes from a feasibility estimate directly from the pump distributor. The pump is already in use in clinical practice, and the low number of PNH patients requiring a pump will have a low budget impact upon introduction of pegcetacoplan in Denmark.

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Ravulizumab IV infusion cost was estimated to be 3,203 DKK per infusion (Sundhedsdatastyrelsen 2021b).

8.5.2 Health state costs

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

8.5.2.1 Costs of complications

Cost of complications were estimated based on the probability of developing complications per cycle (Table 21) and corresponding unit cost per complication (Table 34).

Table 34 Unit costs of managing complications

	Unit Cost (DKK)	Source
Breakthrough hemolysis	50,095.00	17MA02 Patienter med hæmatologiske komplikationer (Sundhedsdatastyrelsen 2021k)
Thrombosis	22,545.00	16MA10 Øvrige sygdomme i blod og bloddannende organer (Sundhedsdatastyrelsen 2021o)
Acute kidney damage	41,799.00	11MA01. Akutte medicinske nyresygdomme uden dialyse og uden plasmaferese. (sundhedsdatastyrelsen 2021l)
Chronic kidney disease	34,245.00	11MA02 Andre primære eller sekundære medicinske nyresygdomme uden dialyse. (Sundhedsdatastyrelsen 2021m)
Pulmonary hypertension	14,155.00	05MA11. Hypertension (Sundhedsdatastyrelsen 2021e)
Iron overload	22,545.00	16MA10 Øvrige sygdomme i blod og bloddannende organer (Sundhedsdatastyrelsen 2021o)

8.5.2.2 Costs of blood transfusion

Costs of blood transfusion is incurred by patients in Transfusion Required health states, consisting of blood transfusion cost and costs of treating severe acute reactions of blood transfusion.

Blood transfusion costs are estimated based on unit cost per transfusion and transfusion frequency per cycle. The unit cost per transfusion is estimated to be 4,628 DKK derived from the DRG takster 2021 (Sundhedsdatastyrelsen 2021p) specified in Table 36. In terms of the transfusion frequency, the model assumes patients in Transfusion Required health state to undergo a number of transfusions corresponding with treatment, estimated based on patients' level data from PEGASUS clinical trial (Table 35).

Table 35 Number of transfusions per treatment in the transfusion required health state

Treatment	Number of transfusions per cycle	Source
Pegcetacoplan	1	

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Eculizumab	1.36	Patients level data from PEGASUS clinical trial
Ravulizumab	1.36	Assumed the same as eculizumab

Table 36 Unit cost per blood transfusion

Source	Reported Unit Cost (DKK)	Cost Year
16PR02. Transfusion af blod, øvrig. (Sundhedsdatastyrelsen 2021p)	4,628.00	2021

Costs of managing severe acute reactions per blood transfusion were excluded from the base case scenario as the impact on the results is negligible. The exclusion of this cost can also be considered a conservative scenario since transfusions are more common in patients treated with ravulizumab.

The probability of developing severe acute reactions per transfusion can be estimated using UK data. Every year in the UK, the Serious Hazards of Transfusion (SHOT) Steering Group collect hemovigilance reports across the country (SHOT 2019). The SHOT report is one of the largest databases regarding transfusion hazards and is assumed representative of the Norwegian setting. The 2019 SHOT report revealed that a total of 2,334,515 blood components were issued from the UK Blood Service in the 2018 calendar year. The report also included the total number of major morbidities in people who had a blood transfusion that occurred during 2018, which was used to calculate the probability of developing a severe acute reaction per blood transfusion (Table 37).

Table 37 Probability of developing severe acute reaction from a blood transfusion

Severe Acute Reaction	Total Issues of Blood Components	Total Number of Major Morbidities in People Who Had a Blood Transfusion[a]	Probability Per Transfusion
Over transfusion	2,334,515	0	0.000000
Febrile, allergic, and hypotensive	2,334,515	60	0.000026
Incorrect blood component transfused	2,334,515	4	0.000002
Circulatory overload	2,334,515	36	0.000015
Dyspnea	2,334,515	1	0.000000
Acute lung injury	2,334,515	1	0.000000
Hemolytic transfusion reactions	2,334,515	4	0.000002
Transfusion-transmitted infection	2,334,515	1	0.000000

Hb = hemoglobin; SHOT = Serious Hazards of Transfusion.

[a] Major morbidity in the SHOT report is defined as: 1) intensive care or high dependency admission and/or ventilation, renal dialysis, and/or renal impairment; 2) major hemorrhage from transfusion-induced coagulopathy; 3) evidence of acute intravascular hemolysis (e.g., hemoglobinemia or severe hemoglobinuria); 4) life threatening acute reaction requiring immediate medical intervention; 5) persistent viral infection; 6) acute symptomatic confirmed infection; 7) sensitization to D or K in a woman of childbearing potential; 8) reaction resulting in a low or high Hb level of a degree sufficient to cause risk to life unless there is immediate medical intervention.

8.5.3 Other resource use costs

Apart from the costs mentioned earlier, other health care resource use such as general practitioner (GP) visit, hematologist visit, oncologist visit, and blood tests are expected to differ by health states. The total health care resource use cost for each health state was estimated based on number of visits/tests per cycle (Table 38) multiplied by the respective unit costs for each resource (Table 39).

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Table 38 Number of physician visits/tests per cycle (4 weeks)

Resource	TA Hb <10.5g/dL	TA Hb ≥10.5g/dL	Transfusion Required	Spontaneous Remission	Source
Hematologist	0.33	0.33	0.33	0.00	Clinical experts opinion (Danish PNH experts 2021)
Blood test	2	2	2	0.00	Clinical experts opinion (Danish PNH experts 2021)

GP = general practitioner; Hb = hemoglobin; TA = transfusion avoidance.

In order to capture the limited societal perspective in the health economic model, the unit costs in Table 39 includes transportation cost of 100 DKK and time spent at hospital (assumed time is 1 hour) at a cost of 179 DKK.

Table 39 Unit costs of physician visits/tests

Resource	Unit Costs (DKK)	Patient costs (DKK)	Total costs (DKK)	Source
GP visit	146.79	279	425.79	(DMC 2021c)
Hematologist	662.20	279	941.20	(DMC 2021b)
Oncologist	662.20	279	941.20	(DMC 2021b)
Blood test	197.09	279	476.09	(DMC 2021a)

GP = general practitioner;.

8.5.4 Adverse event costs

Adverse event (AE) costs are estimated based on the probability of developing AE per cycle (Table 29) and corresponding unit cost per AE (Table 40).

Table 40 Unit costs of managing adverse events

Adverse Event	Unit Cost (DKK)	Source
Anemia	22,545.00	16MA10 Øvrige sygdomme i blod og bloddannende organer (Sundhedsdatastyrelsen 2021o)
Hemolytic anemia	40,604.00	16MA05 Hæmolystiske anæmier og anæmier forårsaget af enzymatiske forstyrrelser m.m. (Sundhedsdatastyrelsen 2021n)
Bacterial infection	26,478.00	09MA04 Infektioner i hud og underhud, pat. mindst 18 år (Sundhedsdatastyrelsen 2021j)
Gastroenteritis	22,789.00	06MA14 Andre sygdomme i fordøjelsesorganerne, pat. mindst 18 år (Sundhedsdatastyrelsen 2021g)
Atrial fibrillation	4,684.00	05MA15 Observation for sygdom i kredsløbsorganerne (Sundhedsdatastyrelsen 2021f)
Hyperthermia	2,692.00	Værdisætning af enhedsomkostninger. Praktiserende Lægers Organisation. Honorartabel dagtid, Overenskomst om almen praksis. Konsultation. (DMC 2021c)
Facial paralysis	26,027.00	01MA15 10MA07 Observation for endokrine sygdomme (Sundhedsdatastyrelsen 2021c)
Dyspnea	23,580.00	04MA24 Andre sygdomme i luftveje (Sundhedsdatastyrelsen 2021d)

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Adverse Event	Unit Cost (DKK)	Source
Abdominal pain	22,789.00	Andre sygdomme i fordøjelsesorganerne, pat. mindst 18 år (Sundhedsdatastyrelsen 2021h)
Biliary colic	22,789.00	Andre sygdomme i fordøjelsesorganerne, pat. mindst 18 år (Sundhedsdatastyrelsen 2021h)
Hepatocellular injury	25,512.00	07MA14 Observation for sygdom i lever, galdeveje eller bugspytkirtel u. Endoskopi (Sundhedsdatastyrelsen 2021i)
Hyperbilirubinemia	25,512.00	07MA14 Observation for sygdom i lever, galdeveje eller bugspytkirtel u. Endoskopi (Sundhedsdatastyrelsen 2021i)
Jaundice	25,512.00	07MA14 Observation for sygdom i lever, galdeveje eller bugspytkirtel u. Endoskopi (Sundhedsdatastyrelsen 2021i)

AE = adverse event.

8.6 Results

8.6.1 Base case overview

The base-case analysis includes the following assumptions:

- Patients receive the first dose of pegcetacoplan in the clinic and self-administer the subsequent doses at home
- Mortality of patients receiving complement inhibitors is assumed to be the same as age- and sex-adjusted general mortality
- Patients on complement inhibitors do not discontinue active treatment due to AEs or loss of treatment efficacy
- Disutility of complications and AEs that were observed in the trial were not included based on the assumption that such disutility was already accounted for within mapped utility data from the trial
- One patient in the pegcetacoplan arm died at Week 44 in the PEGASUS clinical trial due to COVID-19, this was excluded from the analysis

An overview of the base case inputs is presented in Table 17.

8.6.2 Base case results

[redacted]

Table 41 Summary base case results

Results Summary	Pegcetacoplan	Ravulizumab
Total discounted costs (DKK)	[redacted]	
Total discounted LYs		
Total discounted QALYs		
Incremental Results Summary		
Incremental costs (DKK)		
Incremental LYs		

Results Summary	Pegcetacoplan	Ravulizumab
Incremental QALYs		
Incremental cost per LY gained (DKK/LY gained)		
Incremental cost per QALY gained (DKK/QALY gained)		

A breakdown of disaggregated clinical outcomes and costs (discounted), by product, is shown in Table 42.

Table 42 Disaggregated base case results

Disaggregated Costs (Discounted)	Costs		Incremental Costs
	Pegcetacoplan	Ravulizumab	Pegcetacoplan vs. Ravulizumab

A breakdown of disaggregated clinical outcomes (discounted), by product, is shown in Table 43.

Table 43 Disaggregated base case outcomes results

Disaggregated Costs (Discounted)	Outcomes		Incremental Outcomes
	Pegcetacoplan	Ravulizumab	Pegcetacoplan vs. Ravulizumab
Total life years			
Total QALYs			
Transfusion avoidance AND Hb<10.5			
Transfusion avoidance AND Hb≥10.5			
Transfusion required			
Spontaneous remission			

Disaggregated Costs (Discounted)	Outcomes		Incremental Outcomes
	Pegcetacoplan	Ravulizumab	Pegcetacoplan vs. Ravulizumab
Disutility associated with complications	[redacted]		
Disutility associated with AEs			
Disutility associated with IV infusion			

8.7 Sensitivity analyses

8.7.1 Deterministic sensitivity analyses

As the outcome of the cost effectiveness analysis resulted in a dominant scenario, one-way sensitivity analysis displaying changes in ICER in a tornado diagram is not feasible.

In a dominant cost-effectiveness analysis scenario, i.e. when the comparator treatment being associated with higher cost and lower efficacy, there is no ICER value generated in the model. The model may still generate an OWSA even in such dominant scenario, but as the OWSA describes each model parameters' individual impact on the ICER, the OWSA results are not relevant to consider in this case as there is not an ICER value generated by the model.

8.7.2 Probabilistic sensitivity analyses

Joint parameter uncertainty was tested through probabilistic sensitivity analysis (PSA), in which all parameters were assigned distributions and varied jointly. 1,000 Monte Carlo simulations were recorded. The results of the PSA

[redacted]

Table 44 Figure 9) were highly congruent with the base-case results. Results were plotted on a cost-effectiveness plane (CEP; Figure 9) and a multiple cost-effectiveness acceptability curve was generated (CEAC; Figure 10).

[redacted]

Table 44 Probabilistic sensitivity analysis results

Costs and outcomes	Pegcetacoplan		Ravulizumab	
	Mean	SD	Mean	SD
Total expected cost (DKK, discounted)	[redacted]			
Total expected outcomes (QALYs, discounted)				

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Figure 9 Cost effectiveness plane

Figure 10 Cost-effectiveness acceptability curve (CEAC)

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8.7.3 Scenario analyses

Scenario analyses were undertaken to investigate the effect of certain model inputs on costs and outcomes. Table 45 provides a descriptions of the scenarios and the results.

Table 45 List of scenario analyses

Variable	Scenario value	+/- Costs (DKK)	+/- QALYS	ICER (DKK/QALY)
Base case	Base case	[redacted]		
N. of Transfusion Per Cycle for Patients in the Transfusion Required Health State is 1 for both treatments	Pegcetacoplan: 1, ravulizumab: 1			
Dosing pegcetacoplan	Observed dose in PEGASUS			
Death due to severe acute reactions of blood transfusion	Included			
Relative risk (RR) for death: PNH vs. general population	RR=1.1			
Disutility's due to AE	Included			
Comparator	Eculizumab			
Time horizon	40 years			
	20 years			
	10 years			
Discount rate	Costs & Outcomes: 0%			

9. Budget impact analysis

A budget impact analysis was performed over a five-year period. Two scenarios are presented, one scenario without the introduction of pegcetacoplan presented in Table 48 and one scenario where pegcetacoplan is introduced to the market presented in Table 49. The expected patient population is presented in Table 46.

[redacted]

Table 46 Population without pegcetacoplan

Population	Year 1	Year 2	Year 3	Year 4	Year 5
Pegcetacoplan	[redacted]				
Ravulizumab					
Total number of patients					

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Table 47 Population with pegcetacoplan

Population	Year 1	Year 2	Year 3	Year 4	Year 5
Pegcetacoplan					
Ravulizumab					
Total number of patients					

Table 48 Scenario without pegcetacoplan (current treatment pathway)

	Year 1	Year 2	Year 3	Year 4	Year 5
Pegcetacoplan (DKK)					
Ravulizumab (DKK)					
Total cost (DKK)					

Note: This scenario details the costs for patients who remain anemic despite C5 treatment (all patients treated with ravulizumab)

Table 49 Scenario with pegcetacoplan (future treatment pathway)

	Year 1	Year 2	Year 3	Year 4	Year 5
Pegcetacoplan (DKK)					
Ravulizumab (DKK)					
Total cost (DKK)					

Note: This scenario details the costs for when pegcetacoplan is introduced to patients who remain anemic despite C5 treatment and thus a share of patients are treated with pegcetacoplan and a share of patients are treated with ravulizumab.

Table 50 Total budget impact

	Year 1	Year 2	Year 3	Year 4	Year 5
Total budget impact (DKK)					
Total aggregated budget impact (DKK)					

10. Discussion on the submitted documentation

Pegcetacoplan is the first and only targeted C3 therapy that provides broader control of hemolysis in PNH patients by targeting the central hub of the complement cascade, upstream of C5. The aim of this analysis was to assess the cost-effectiveness of pegcetacoplan in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who are anaemic after treatment with a C5 inhibitor for at least 3 months.

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11. List of experts

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Appendix A – Literature search for efficacy and safety of intervention and comparator(s)

A summary of the literature search is included in section 6.

For full details on the literature search, please refer to the separate document [SLR NICE submission].

Time horizon

The original electronic database searches were not limited by date. Original searches of conference proceedings were limited to abstracts published in the last 2 years because it is expected that high-quality studies presented earlier will have already been published. Searching conference proceedings for this period ensured that recent conference abstracts that may not yet have been indexed in Embase or any of the other databases were captured. The updated electronic database searches were subject to a date restriction of between July 30, 2020 to March 11, 2021.

Language limits

Electronic database searches had no language limitations. However, we did not identify any relevant non–English-language sources.

Study selection process

Citations were downloaded using EndNote X9.2 and then exported into Microsoft Excel. Duplicates were identified and removed by EndNote by comparing the author, journal, year, title, and page number. Once all abstracts of potentially relevant published articles had been identified, the screening of titles and abstracts was performed to determine study eligibility based on the inclusion and exclusion criteria. The study selection process was performed in two phases. At level 1 screening, titles and abstracts of identified studies were double-screened by two researchers independently to determine eligibility according to the predefined inclusion and exclusion criteria. If there was disagreement about study relevance, consensus was reached with a third researcher. At level 2 screening, full texts of studies selected at level 1 were obtained and double-screened by two researchers independently using the same inclusion and exclusion criteria used in the level 1 screening. Any disagreements about study relevance were resolved by consensus.

Data extraction

Draft data extraction table shells were developed in Microsoft Word prior to data extraction. These tables were designed to accommodate study characteristics and the reported outcomes of interest. Data were extracted by one researcher and quality checked by a second researcher, which included verification of the data with the original source.

Study characteristics which were extracted included study design, interventions, inclusion/exclusion criteria, primary and secondary endpoints, baseline characteristics and primary and secondary endpoint results. Results reported in the data extraction included:

- Lactate dehydrogenase levels / lactate dehydrogenase normalisation
- Haemoglobin levels/ haemoglobin stabilisation and normalisation
- Breakthrough haemolysis and other haemolysis outcomes

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- Reticulocyte, RBC, erythrocyte, and granulocytes outcomes
- Transfusion avoidance / transfusion independence
- FACIT-fatigue results
- EORTC results
- Adverse events and drug discontinuations

Data were extracted from full text publications, where available (i.e., abstracts or posters were not used unless an abstract or poster was the terminal source document). When a full-text journal publication was not available, the source used (e.g., abstract or poster) were noted.

Quality assessment strategy

Quality assessment of RCTs was conducted in line with the NICE single technology appraisal submission requirements (1) and consisted of the following seven questions:

- Was randomisation carried out appropriately?
- Was the concealment of treatment allocation adequate?
- Were the groups similar at the outset of the study in terms of prognostic factors?
- Were the care providers, participants, and outcome assessors blinded to treatment allocation?
- Were there any unexpected imbalances in dropouts between groups?
- Is there any evidence to suggest that the authors measured more outcomes than they reported?
- Did the study include an intention-to-treat analysis? If so, was the analysis appropriate and were appropriate methods used to account for missing data?

Nonrandomised, single-arm, and extension trials were quality assessed using the Critical Appraisal Skills Programme (CASP) checklist for cohort studies (2).

The quality assessments were performed by one researcher, and quality checked by a second researcher in order to verify the completed assessments against the source documents.

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Eligibility criteria

	Inclusion	Exclusion
Population	Patients with PNH	Patients without PNH
Intervention/comparator	• **Pegcetacoplan** • **Eculizumab** • **Ravulizumab** • **Best supportive care (corticosteroids, erythropoietin, immunosuppressants (e.g., cyclophosphamide))** • **Androgens**	No intervention / comparators of interest
Outcomes	• **Efficacy measurements** • **Health-related quality of life** • **Safety outcomes reported at study endpoint** • **Patient characteristics of interest** • **Treatment usage and patterns (UK or US only)** • **Long-term clinical and safety outcomes, specifically in patients receiving eculizumab, ravulizumab, or BSC (pre-eculizumab)** • **Spontaneous remission**	No reported outcomes of interest
Study type	• **Randomised, controlled, prospective clinical trials (including crossover trials)** • **Long-term follow-up studies (e.g., open-label follow-up studies)** • **Observational studies (e.g., cohort studies, cross-sectional studies, longitudinal studies, nonrandomized studies, retrospective studies, prospective studies, registry studies, phase 4 studies)** • **Systematic reviews (including meta-analyses)**	• Preclinical studies • Phase 1 studies • Pilot studies • Case reports • Case series with fewer than 10 patients • Commentaries and letters (publication type • Consensus reports • Non-systematic reviews • Genetics studies

Abbreviations: BSC, best supportive care; SLR, systematic literature review; PNH, paroxysmal nocturnal haemoglobinuria; QALY, quality adjusted life year

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Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Embase.com	Last 2 years	Conducted July 30, 2020, updated on March 11, 2021
MEDLINE	MEDLINE		
	MEDLINE In-Process		
Cochrane	Cochrane Central Register of Controlled Trials		
	Cochrane Database of Systematic Reviews		
	Database of Abstracts of Reviews of Effectiveness		
BioSciences Information Services	BIOSIS		Conducted July 30, 2020 BIOSIS was not searched in the SLR update, as searches in this database were captured via the MEDLINE and Embase searches

Embase literature search strategy (conducted July 30, 2020, updated on March 11, 2021)

Search no.	Search terms	No. of acticles (July 30th 2020)	No. of articles (March 11th, 2021)
#1 Disease	'paroxysmal nocturnal hemoglobinuria'/exp OR (('paroxysmal hemoglobinuria':ti,ab,de OR 'paroxysmal haemoglobinuria':ti,ab,de OR 'paroxysmal cold hemoglobinuria':ti,ab,de OR 'paroxysmal cold haemoglobinuria':ti,ab,de OR 'marchiafava-micheli syndrome':ti,ab,de OR 'chronic hemolytic disease':ti,ab,de OR 'chronic hemolytic diseases':ti,ab,de) AND nocturnal:ti,ab,de) OR 'paroxysmal nocturnal hemoglobinuria':ti,ab,de OR 'paroxysmal nocturnal haemoglobinuria':ti,ab,de	6,316	6,583
#2 Intervention	'pegcetacoplan'/exp OR 'pegcetacoplan':ti,ab,de OR 'apl 2':ti,ab,de OR apl2:ti,ab,de OR '2019171-69-6':ti,ab,de,rn	132	162
#3 Comparators	'eculizumab'/exp OR eculizumab:ti,ab,de OR 'monoclonal antibody 5g1.1':ti,ab,de OR soliris:ti,ab,de OR '219685-50-4':ti,ab,de,rn	5,273	6,050
#4 Comparators	'ravulizumab'/exp OR ravulizumab:ti,ab,de OR "ravulizumab-cwvz":ti,ab,de OR 'alxn 1210':ti,ab,de OR 'alxn 1810':ti,ab,de OR alxn1210:ti,ab,de OR alxn1810:ti,ab,de OR ultomiris:ti,ab,de OR '1803171-55-2':ti,ab,de,rn	93	197

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Search no.	Search terms	No. of acticles (July 30th 2020)	No. of articles (March 11th, 2021)
#5 **Comparators**	'best supportive care'/exp OR bsc:ti,ab OR 'supportive care':ti,ab,de OR 'supportive therapy'/exp OR 'supportive therap*':ti,ab,de OR 'symptom management'/exp OR ((symptom* NEAR/1 management):ti,ab,de) OR 'symptomatic treatment':ti,ab,de OR 'palliative therapy'/exp OR palliative:ti,ab,de OR palliation:ti,ab,de OR 'comfort care':ti,ab,de	203,472	214,265
#6 **Comparators**	'corticosteroid'/exp OR corticosteroid*:ti,ab,de OR 'cortical steroid':ti,ab,de OR 'cortico steroid*':ti,ab,de OR (((adrenal OR adreno*) NEXT/2 (hormone* OR steroid*)):ti,ab,de)	1,019,197	1,057,096
#7 **Comparators**	'recombinant erythropoietin'/exp OR erythropoietin*:ti,ab,de OR abseamed:ti,ab,de OR aranesp:ti,ab,de OR aranest:ti,ab,de OR 'bi 71.052':ti,ab,de OR 'bi71.052':ti,ab,de OR binocrit:ti,ab,de OR biopoin:ti,ab,de OR darbepoetin:ti,ab,de OR darbepoietin:ti,ab,de OR darbopoetin:ti,ab,de OR darbopoietin:ti,ab,de OR dynepo:ti,ab,de OR epoade:ti,ab,de OR epoconn:ti,ab,de OR epoetin:ti,ab,de OR epogen:ti,ab,de OR epogin:ti,ab,de OR epoietin:ti,ab,de OR epokine:ti,ab,de OR epomax:ti,ab,de OR eporatio:ti,ab,de OR epostim:ti,ab,de OR epoxitin:ti,ab,de OR eprex:ti,ab,de OR erantin:ti,ab,de OR erypo:ti,ab,de OR espo:ti,ab,de OR exprex:ti,ab,de OR globuren:ti,ab,de OR heberitro:ti,ab,de OR hemapo:ti,ab,de OR hemax:ti,ab,de OR 'hx 575':ti,ab,de OR hx575:ti,ab,de OR 'krn 321':ti,ab,de OR 'krn 5702':ti,ab,de OR krn321:ti,ab,de OR krn5702:ti,ab,de OR marogen:ti,ab,de OR neorecormon:ti,ab,de OR nesp:ti,ab,de OR nespo:ti,ab,de OR procrit:ti,ab,de OR recormon:ti,ab,de OR recormone:ti,ab,de OR retacrit:ti,ab,de OR silapo:ti,ab,de OR 'snb 5001':ti,ab,de OR snb5001:ti,ab,de OR 'tyb 5220':ti,ab,de OR tyb5220:ti,ab,de OR '113427-24-0':ti,ab,de,rn OR '122312-54-3':ti,ab,de,rn OR '130455-76-4':ti,ab,de,rn OR '148363-16-0':ti,ab,de,rn OR '154725-65-2':ti,ab,de,rn OR '879555-13-2':ti,ab,de,rn	60,348	61,823
#8 **Comparators**	'immunosuppressive agent'/exp OR immunosuppressive*:ti,ab,de OR 'immune suppressant':ti,ab,de OR 'immuno suppressive':ti,ab,de OR immunodepressant*:ti,ab,de OR immunosuppressant*:ti,ab,de OR immunosuppressor*:ti,ab,de	1,167,066	1,251,813
#9 **Comparators**	'androgen'/exp OR androgen*:ti,ab,de	257,361	264,886
#10	#1 AND (#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)	2,560	2,755
#11 **Randomised controlled trials**	'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti	2,591,346	2,716,717
#12	#10 AND #11	232	269

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Search no.	Search terms	No. of acticles (July 30th 2020)	No. of articles (March 11th, 2021)
#13 **Observational studies**	'observational study'/exp OR 'cohort analysis'/exp OR 'longitudinal study'/exp OR 'follow up'/exp OR 'evaluation study'/exp OR 'cross-sectional study'/exp OR 'retrospective study'/exp OR 'controlled clinical trial (topic)'/exp OR 'register'/exp OR 'case control study'/exp OR cohort*:ti,ab,de OR longitudinal*:ti,ab,de OR 'follow up':ti,ab,de OR evaluation:ti,ab,de OR 'cross sectional*':ti,ab,de OR 'non random*':ti,ab,de OR 'nonrandom*':ti,ab,de OR 'observation*':ti,ab,de OR retrospective:ti,ab,de OR 'phase iv':ti,ab,de OR 'phase four':ti,ab,de OR 'phase 4':ti,ab,de	6,951,232	7,386,168
#14	#10 AND #13	887	981
#15 **Exclusions**	'animal'/exp NOT 'human'/exp	5,470,608	5,581,888
#16 **Exclusions**	comment*:ti OR 'letter':it OR 'editorial':it OR 'case report'/exp OR 'case stud*':ti OR 'case report*':ti OR 'case series':ti OR 'case histor*':ti	4,326,991	4,484,165
#17 **Total**	((#12 OR #14) NOT (#15 OR #16))	863	950
#18 **Total with limits**	#17 AND ([article]/lim OR [article in press]/lim OR [erratum]/lim OR [review]/lim)	412	440
#19	#17 AND ([conference abstract]/lim OR [conference paper]/lim OR 'conference abstract':it OR 'conference paper':it) (ORIGINAL: AND [30-7-2018]/sd AND [2018-2020]/py)	62	487
#20	#18 OR #19 (UPDATE: AND [30-7-2020]/sd NOT [11-3-2021]/sd)	474	91

PubMed (MEDLINE, MEDLINE In-Process) literature search strategies (conducted July 30th 2020, updated on March 11th, 2021)

Search no.	Search terms	No. of articles (July 30th 2020)	No. of articles (March 11th 2021)
#1 **Disease**	"Hemoglobinuria, Paroxysmal"[Mesh] OR (("paroxysmal hemoglobinuria"[Text Word] OR "paroxysmal haemoglobinuria"[Text Word] OR "paroxysmal cold hemoglobinuria"[Text Word] OR "paroxysmal cold haemoglobinuria"[Text Word] OR "marchiafava-micheli syndrome"[Text Word] OR "chronic hemolytic disease"[Text Word] OR "chronic hemolytic diseases"[Text Word]) AND nocturnal[Text Word]) OR "paroxysmal nocturnal hemoglobinuria"[Text Word] OR "paroxysmal nocturnal haemoglobinuria"[Text Word]	4,181	4,280

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Search no.	Search terms	No. of articles (July 30th 2020)	No. of articles (March 11th 2021)
#2 Intervention	"pegcetacoplan"[Text Word] OR "apl 2"[Text Word] OR apl2[Text Word] OR "2019171-69-6"[Text Word]	45	50
#3 Comparators	"eculizumab"[Supplementary Concept] OR eculizumab[Text Word] OR "monoclonal antibody 5g1.1"[Text Word] OR soliris[Text Word] OR "219685-50-4"[Text Word]	1,758	1,962
#4 Comparators	"ravulizumab"[Supplementary Concept] OR ravulizumab[Text Word] OR "ravulizumab-cwvz"[Text Word] OR "alxn 1210"[Text Word] OR "alxn 1810"[Text Word] OR alxn1210[Text Word] OR alxn1810[Text Word] OR ultomiris[Text Word] OR "1803171-55-2"[Text Word]	29	59
#5 Comparators	Bsc[Title/Abstract] OR "supportive care"[Text Word] OR "supportive therap*"[Text Word] OR "symptom management"[Text Word] OR "symptoms management"[Text Word] OR "symptomatic management"[Text Word] OR "symptomatic treatment"[Text Word] OR "Palliative Care"[Mesh] OR palliative[Text Word] OR palliation[Text Word] OR "comfort care"[Text Word]	126,434	132,276
#6 Comparators	"Adrenal Cortex Hormones"[Mesh] OR "Adrenal Cortex Hormones"[Text Word] OR corticosteroid*[Text Word] OR "cortical steroid"[Text Word] OR "cortico steroid*"[Text Word] OR "adrenal cortex hormone"[Text Word] OR "adrenal cortical hormone"[Text Word] OR "adrenal cortical hormones"[Text Word] OR "adrenal cortical steroid"[Text Word] OR "adrenal steroid"[Text Word] OR "adrenal steroid hormone"[Text Word] OR "adreno cortical steroid"[Text Word] OR "adreno corticosteroid"[Text Word] OR "adrenocortical hormone"[Text Word] OR "adrenocortical steroid"[Text Word]	345,426	352,513
#7 Comparators	"epoetin beta"[Supplementary Concept] OR "Epoetin Alfa"[Mesh] OR erythropoietin*[Text Word] OR abseamed[Text Word] OR aranesp[Text Word] OR aranest[Text Word] OR "bi 71.052"[Text Word] OR "bi71.052"[Text Word] OR binocrit[Text Word] OR biopoin[Text Word] OR darbepoetin[Text Word] OR darbepoietin[Text Word] OR darbopoetin[Text Word] OR darbopoietin[Text Word] OR dynepo[Text Word] OR epoade[Text Word] OR epoconn[Text Word] OR epoetin[Text Word] OR epogen[Text Word] OR epogin[Text Word] OR epoietin[Text Word] OR epokine[Text Word] OR epomax[Text Word] OR eporatio[Text Word] OR epostim[Text Word] OR epoxitin[Text Word] OR eprex[Text Word] OR erantin[Text Word] OR erypo[Text Word] OR espo[Text Word] OR exprex[Text Word] OR globuren[Text Word] OR heberitro[Text Word] OR hemapo[Text Word] OR hemax[Text Word] OR "hx 575"[Text Word] OR hx575[Text Word] OR "krn 321"[Text Word] OR "krn 5702"[Text Word] OR krn321[Text Word] OR krn5702[Text Word] OR marogen[Text Word] OR neorecormon[Text Word] OR nesp[Text Word] OR nespo[Text Word] OR procrit[Text Word] OR recormon[Text Word] OR recormone[Text Word] OR retacrit[Text Word] OR silapo[Text Word] OR "snb 5001"[Text Word] OR snb5001[Text Word] OR "tyb	32,193	32,684

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Search no.	Search terms	No. of articles (July 30th 2020)	No. of articles (March 11th 2021)
	5220"[Text Word] OR tyb5220[Text Word] OR "113427-24-0"[Text Word] OR "122312-54-3"[Text Word] OR "130455-76-4"[Text Word] OR "148363-16-0"[Text Word] OR "154725-65-2"[Text Word] OR "879555-13-2"[Text Word]		
#8 **Comparators**	"Immunosuppressive Agents"[Mesh] OR immunosuppressive*[Text Word] OR "immune suppressant"[Text Word] OR "immuno suppressive"[Text Word] OR immunodepressant*[Text Word] OR immunosuppressant*[Text Word] OR immunosuppressor*[Text Word]	160,226	165,812
#9 **Comparators**	"Androgens"[Mesh] OR androgen*[Text Word]	96,491	99,095
#10	#1 AND (#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)	801	860
#11 **Randomised controlled trials**	randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[title/abstract] OR placebo[title/abstract] OR clinical trials as topic[mesh:noexp] OR randomly[title/abstract] OR trial[title]	1,311,730	1,362,274
#12	#10 AND #11	53	60
#13 **Observational studies**	"Observational Study"[Publication Type] OR "Cohort Studies"[Mesh] OR "Longitudinal Studies"[Mesh] OR "Follow-Up Studies"[Mesh] OR "Evaluation Study" [Publication Type] OR "Cross-Sectional Studies"[Mesh] OR "Retrospective Studies"[Mesh] OR "Controlled Clinical Trials as Topic"[Mesh] OR "Registries"[Mesh] OR "Case-Control Studies"[Mesh] OR cohort*[Text Word] OR longitudinal*[Text Word] OR "follow up"[Text Word] OR evaluation[Text Word] OR "cross sectional*"[Text Word] OR "non random*"[Text Word] OR nonrandom*[Text Word] OR observation*[Text Word] OR retrospective[Text Word] OR "phase iv"[Text Word] OR "phase four"[Text Word] OR "phase 4"[Text Word]	5,556,756	5,811,333
#14	#10 AND #13	229	250
#15 **Exclusions**	Animals[Mesh] NOT Humans[Mesh]	4,722,745	4,797,787
#16 **Exclusions**	"Comment"[Publication Type] OR "Letter"[Publication Type] OR "Editorial"[Publication Type] OR "Case Reports"[Publication Type] OR "case stud*"[Title] OR "case report*"[Title] OR "case series"[Title] OR "case histor*"[Title]	3,855,123	3,975,492
#17 **Total**	((#12 OR #14) NOT (#15 OR #16))	218	240
#18	#17 AND 2020/07/30:2021/03/10[edat]		18

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Cochrane (the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews and the Database of Abstracts of Reviews of Effectiveness) literature search strategies (conducted July 30 2020, updated on March 10, 2021)

Sarch no.	Search terms	No. of articles (July 30th 2020)	No. of articles (March 11th, 2021)
#1 Disease	[mh "Hemoglobinuria, Paroxysmal"] OR (("paroxysmal hemoglobinuria" OR "paroxysmal haemoglobinuria" OR "paroxysmal cold hemoglobinuria" OR "paroxysmal cold haemoglobinuria" OR "marchiafava-micheli syndrome" OR "chronic hemolytic disease" OR "chronic hemolytic diseases") AND nocturnal) OR "paroxysmal nocturnal hemoglobinuria" OR "paroxysmal nocturnal haemoglobinuria"	137	159
#2 Intervention	pegcetacoplan OR "apl 2" OR apl2 OR "2019171-69-6"	30	39
#3 Comparators	eculizumab OR "monoclonal antibody 5g1.1" OR soliris OR "219685 50 4"	228	282
#4 Comparators	ravulizumab OR "ravulizumab-cwvz" OR "alxn 1210" OR "alxn 1810" OR alxn1210 OR alxn1810 OR ultomiris OR "1803171 55 2"	30	52
#5 Comparators	bsc:ti,ab OR "supportive care" OR (supportive NEXT therap*) OR (symptom* NEAR/1 management) OR "symptomatic treatment" OR [mh "Palliative Care"] OR palliative OR palliation OR "comfort care"	17,812	18,931
#6 Comparators	[mh "Adrenal Cortex Hormones"] OR "Adrenal Cortex Hormones" OR corticosteroid* OR "cortical steroid" OR (cortico NEXT steroid*) OR ((adrenal OR adreno*) NEXT/2 (hormone* OR steroid*))	33,833	35,163
#7 Comparators	[mh "Epoetin Alfa"] OR erythropoietin* OR abseamed OR aranesp OR aranest OR "bi 71.052" OR "bi71.052" OR binocrit OR biopoin OR darbepoetin OR darbepoietin OR darbopoetin OR darbopoietin OR dynepo OR epoade OR epoconn OR epoetin OR epogen OR epogin OR epoietin OR epokine OR epomax OR eporatio OR epostim OR epoxitin OR eprex OR erantin OR erypo OR espo OR exprex OR globuren OR heberitro OR hemapo OR hemax OR "hx 575" OR hx575 OR "krn 321" OR "krn 5702" OR krn321 OR krn5702 OR marogen OR neorecormon OR nesp OR nespo OR procrit OR recormon OR recormone OR retacrit OR silapo OR "snb 5001" OR snb5001 OR "tyb 5220" OR tyb5220 OR "113427-24-0" OR "122312 54 3" OR "130455 76 4" OR "148363 16 0" OR "154725 65 2" OR "879555 13 2"	5,305	5,470
#8 Comparators	[mh "Immunosuppressive Agents"] OR immunosuppressive* OR "immune suppressant" OR "immuno suppressive" OR immunodepressant* OR immunosuppressant* OR immunosuppressor*	12,306	12,926
#9	[mh "Androgens"] OR androgen*	7,487	7,881

Sarch no.	Search terms	No. of articles (July 30th 2020)	No. of articles (March 11th, 2021)
Comparators			
#10	#1 AND (#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)	103	125
#11 **Randomised controlled trials**	("randomized controlled trial" OR "controlled clinical trial"):pt OR (randomized OR placebo OR randomly OR trial OR groups):ti,ab,kw	1,300,006	1,373,874
#12	#10 AND #11	76	98
#13 **Observational studies**	"Observational Study":pt OR [mh "Cohort Studies"] OR [mh "Longitudinal Studies"] OR [mh "Follow-Up Studies"] OR "Evaluation Study":pt OR [mh "Cross-Sectional Studies"] OR [mh "Retrospective Studies"] OR [mh "Controlled Clinical Trials as Topic"] OR [mh "Registries"] OR [mh "Case-Control Studies"] OR cohort* OR longitudinal* OR "follow up" OR evaluation OR (cross NEXT sectional*) OR Nonrandomized OR "non-randomized" OR nonrandomised OR "non-randomised" OR observation* OR retrospective OR "phase iv" OR "phase four" OR "phase 4"	556,039	587,703
#14	#10 AND #13	49	58
#15 **Exclusions**	[mh animals] NOT [mh humans]	86	60
#16	(comment OR letter OR editorial OR "case reports"):pt OR ((Case NEXT report*) OR (Case NEXT stud*) OR "case series"):ti	17,474	18,219
#17	((#12 OR #14) NOT (#15 OR #16)) (AND [30-7-2020]/sd NOT [10-3-2021/sd	82	22

BIOSIS search strategy (conducted July 30 2020)

Search no.	Search terms	No. of articles (July 30th 2020)
#1 **Disease**	su(Hemoglobinuria N/0 Paroxysmal) OR (ti,ab,su("paroxysmal hemoglobinuria" OR "paroxysmal haemoglobinuria" OR "paroxysmal cold hemoglobinuria" OR "paroxysmal cold haemoglobinuria" OR "marchiafava-micheli syndrome" OR "chronic hemolytic disease" OR "chronic hemolytic diseases") AND ti,ab,su(nocturnal)) OR ti,ab,su("paroxysmal nocturnal hemoglobinuria" OR "paroxysmal nocturnal haemoglobinuria")	3,112
#2 **Intervention**	ti,ab,su,subst(pegcetacoplan OR "apl 2" OR "apl2" OR "2019171-69-6")	93
#3	ti,ab,su,subst(eculizumab OR "monoclonal antibody 5g1 1" OR soliris OR "219685-50-4")	1,416

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Search no.	Search terms	No. of articles (July 30th 2020)
Comparators		
#4 **Comparators**	ti,ab,su,subst(ravulizumab OR "ravulizumab-cwvz" OR "alxn 1210" OR "alxn 1810" OR alxn1210 OR alxn1810 OR ultomiris OR "1803171-55-2")	18
#5 **Comparators**	ti,ab("Bsc") OR ti,ab,su("supportive care" OR supportive P/0 therap* OR "symptom management" OR "symptoms management" OR "symptomatic management" OR "symptomatic treatment" OR palliative OR palliation OR "comfort care") OR su("Palliative Care")	40,685
#6 **Comparators**	su("Adrenal Cortex Hormones") OR ti,ab,su("Adrenal Cortex Hormones" OR corticosteroid* OR "cortical steroid" OR cortico P/0 steroid* OR "adrenal cortex hormone" OR "adrenal cortical hormone" OR "adrenal cortical hormones" OR "adrenal cortical steroid" OR "adrenal steroid" OR "adrenal steroid hormone" OR "adreno cortical steroid" OR "adreno corticosteroid" OR "adrenocortical hormone" OR "adrenocortical steroid")	71,349
#7 **Comparators**	subst("epoetin beta") OR su("Epoetin Alfa") OR ti,ab,su,subst(erythropoietin* OR abseamed OR aranesp OR aranest OR "bi 71 052" OR "bi71 052" OR binocrit OR biopoin OR darbepoetin OR darbepoietin OR darbopoetin OR darbopoietin OR dynepo OR epoade OR epoconn OR epoetin OR epogen OR epogin OR epoietin OR epokine OR epomax OR eporatio OR epostim OR epoxitin OR eprex OR erantin OR erypo OR espo OR exprex OR globuren OR heberitro OR hemapo OR hemax OR "hx 575" OR "hx575" OR "krn 321" OR "krn 5702" OR krn321 OR krn5702 OR marogen OR neorecormon OR nesp OR nespo OR procrit OR recormon OR recormone OR retacrit OR silapo OR "snb 5001" OR snb5001 OR "tyb 5220" OR tyb5220 OR "113427-24-0" OR "122312-54-3" OR "130455-76-4" OR "148363-16-0" OR "154725-65-2" OR "879555-13-2")	33,702
#8 **Comparators**	su("Immunosuppressive Agents") OR ti,ab,su(immunosuppressive* OR "immune suppressant" OR "immuno suppressive" OR immunodepressant* OR immunosuppressant* OR immunosuppressor*)	100,539
#9 **Comparators**	su("Androgens") OR ti,ab,su(androgen*)	85,549
#10	#1 AND (#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)	813
#11 **Randomised controlled trials**	su("randomized controlled trial" OR "controlled clinical trial" OR "clinical trials as topic") OR ti,ab(randomized OR placebo OR randomly) OR ti(trial)	699,260
#12	#10 AND #11	43
#13 **Observational studies**	su("Observational Study" OR "Cohort Studies" OR "Longitudinal Studies" OR "Follow-Up Studies" OR "Evaluation Study" OR "Cross-Sectional Studies" OR "Retrospective Studies" OR "Controlled Clinical Trials as Topic" OR "Registries" OR "Case-Control Studies") OR ti,ab,su(cohort* OR longitudinal* OR "follow up" OR evaluation OR cross P/0 sectional* OR non P/0 random* OR nonrandom* OR observation* OR retrospective OR "phase iv" OR "phase four" OR "phase 4")	2,865,327

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Search no.	Search terms	No. of articles (July 30th 2020)
#14	#10 AND #13	49
#15	su(animal) NOT su(human)	9,165,181
#16	dtype(Comment* OR Letter OR Editorial) OR su("Case Report" OR "Case Reports") OR ti(case P/0 stud* OR case P/0 report* OR "case series" OR case P/0 histor*)	377,966
#17	((#12 OR #14) NOT (#15 OR #16))	268
#18	#17 AND dtype(conference) Date: Before July 30 2018	138
#19	#17 NOT #18	130

Grey literature searches (conducted September 03, 2020, updated March 11, 2021)

Website/Database/Register Searched (Name, Address)	Search terms used	Date of search
EHA 2020 https://library.ehaweb.org/eha/#!*search=paroxysmal*browseby=8*listing=0*sortby=1	Paroxysmal	September 03, 2020
EHA 2019 https://library.ehaweb.org/eha/#!*ce_id=1550*search=paroxysmal*browseby=8*listing=0*sortby=1	Paroxysmal	September 03, 2020
ISPOR Annual International Meeting 2018	Paroxysmal	September 03, 2020
ClinicalTrials.gov www.clinicaltrials.gov	Pegcetacoplan	September 03, 2020
WHO ICTRP Search Portal http://apps.who.int/trialsearch	Pegcetacoplan	September 03, 2020

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Results

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram for the original SLR is reported in Figur 1 and Figur 2. In the original SLR carried out on July 30th, 2020, a total of 723 titles and abstracts (excluding duplicates) were screened at first pass. 533 publications were excluded at this stage. Full texts of the remaining 190 publications were retrieved and reviewed at second pass stage based on each of the selection criteria.

Of the 190 publications that met the selection criteria across all review questions during the title and abstract screening, 60 met selection criteria and were extracted. Therefore, 130 were excluded: 11 did not meet the population criteria, 18 did not meet the intervention criteria, 52 did not meet the outcomes criteria, 33 were the incorrect study type and 16 were excluded for other reasons. Trial registry sites searches (Clinicaltrials.gov, ICTRP Search Portal, and EU-CTR registry) identified six ongoing studies. These studies had not reported any results; as such, they were not included for data extraction.

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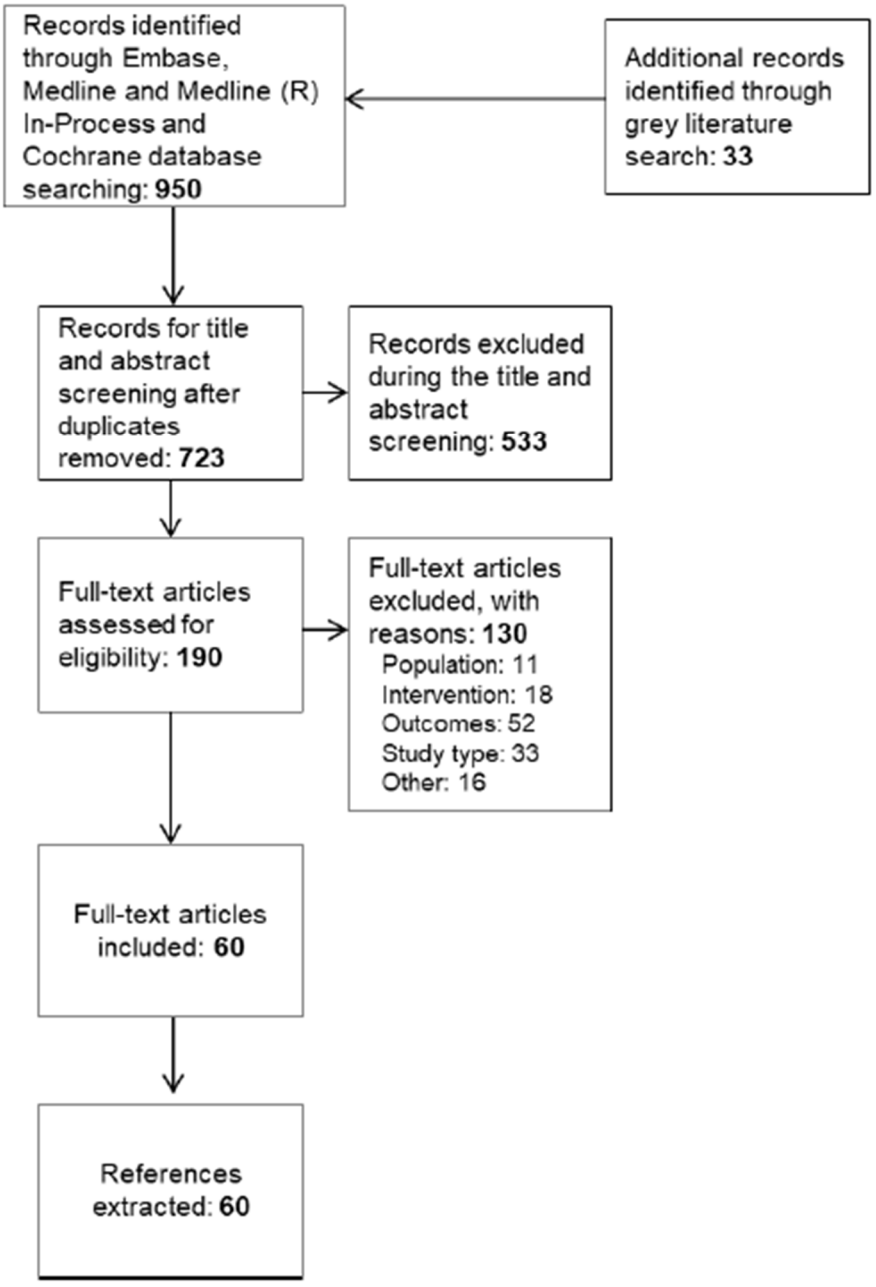
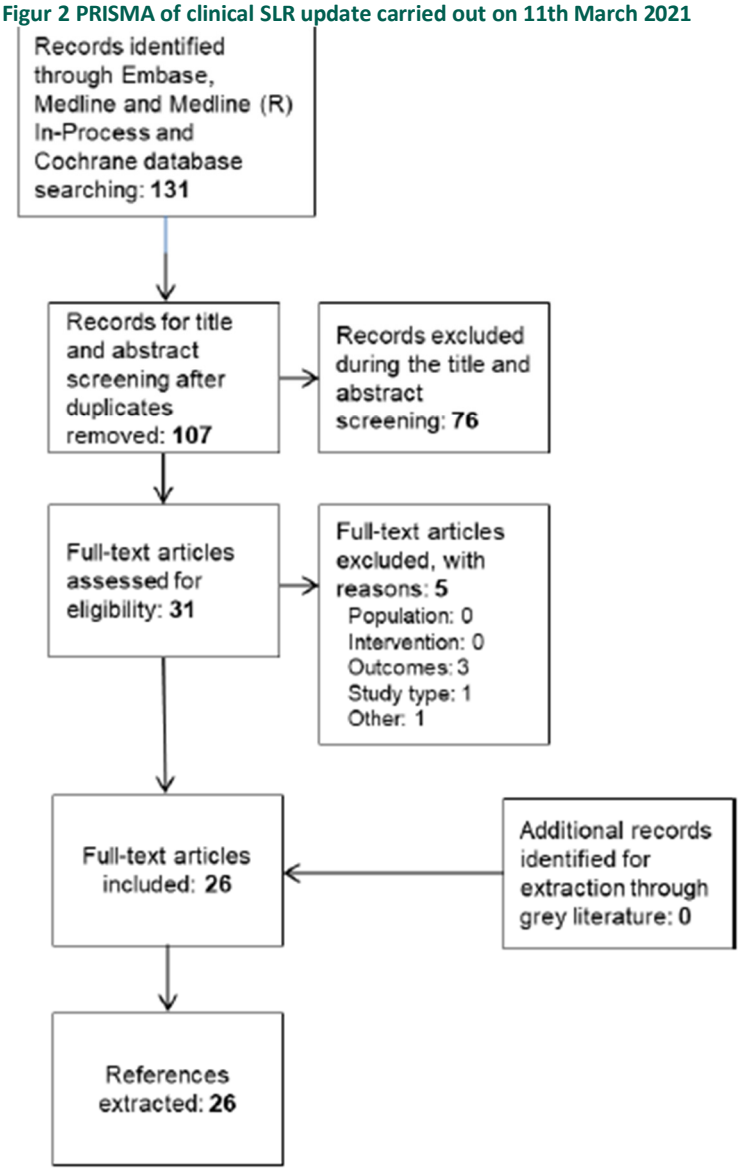
Figur 1 PRISMA of clinical SLR carried out on 30th July 2020



Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Of the 31 full text publications that met the selection criteria across all review questions during the title and abstract screening, 26 met the selection criteria and were extracted. Therefore, 5 were excluded: 3 did not meet the outcomes criteria, 1 was the incorrect study type and 1 was excluded for other reasons. Trial registry site searches identified one ongoing study, this study had not reported any results and was not included for data extraction.

Figur 2 PRISMA of clinical SLR update carried out on 11th March 2021



Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Original SLR

Of the 60 studies included in the original SLR, 28 were clinical trials and 32 were real-world studies. Six of the clinical trials were ongoing pegcetacoplan studies; these had not reported any results and were not included for data extraction. Of the remaining 22 clinical trials, eight were primary studies and 14 were classified as secondary reports (including study extensions, additional and interim analyses, and conference abstracts of trial publications).
A summary of the clinical trials and observational studies included within the original SLR is provided in Tabel 1.

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SLR update

Of the 26 studies identified during the SLR update, 19 were clinical trials and seven were real-world studies. Of the 19 clinical trials, all were classified as secondary reports to those identified in the original SLR (including study extensions and long-term follow ups, additional and interim analyses, conference abstracts of trial publications and one matched-indirect comparison).

A summary of the clinical trials and observational studies included within the SLR update is provided in Tabel 2.

Identified studies used to inform the submission

Only one trial (PEGASUS) (Hillmen 2021a) provided data for pegcetacoplan in patients with PNH and is described in detail in Section 0 of the submission. The other trials concerned other treatments and hence are not relevant to the assessment of the efficacy and safety of pegcetacoplan, the subject of this submission.

With regards to ravulizumab, two clinical trials were identified, Study 301 (NCT02946463) (Lee 2019b) and Study 302 (NCT03056040) (Kulasekararaj 2019b), also described in section 0.

For details, please refer to Table 51 in section 6.3 List of relevant studies.

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Tabel 1 Summary of identified RCTs and observational studies - original SLR

Study ID	Study name	Publication	Interventions(s)	Study design	N	Endpoints
NCT00122330	TRIUMPH	Hillmen et al. (2006) (3), Schubert et al. (2008) (4) Hill et al. (2010) (5)	Eculizumab Placebo	A double-blind, randomised, placebo-controlled, multicentre, phase 3 trial	N = 87 Eculizumab (n = 43) Placebo (n = 44)	• LDH AUC (change) • LDH (% change from baseline) • Stabilised Hb • Hb level (change from baseline) • Change in PNH type II RBCs (%) • Transfusion outcomes • Change in reticulocytes
NCT00130000	SHEPHERD	Brodsky et al. (2008) (6) Schubert et al. (2008) (4)	Eculizumab	An open-label, phase 3 trial	N = 97 Eculizumab (n = 97)	• Return of terminal complement activity and haemolysis • Sustained blockade of complement • Reduction in haemolysis • LDH AUC (change) • LDH (% change from baseline) • Hb level (change from baseline)

						• Inhibition of serum haemolytic activity • Change in PNH type II RBCs (%) • Change in PNH granulocytes • Transfusion outcomes • Change in reticulocytes
NCT00122330 and NCT00130000	TRIUMPH and SHEPHERD	Hillmen et al. (2010) (7)	Eculizumab	Extension of TRIUMPH and SHEPHERD studies evaluating effects on kidney function	N = 187 Eculizumab (n = 187)	See TRIUMPH and SHEPHERD.
NCT00122330 and NCT00130000	TRIUMPH and SHEPHERD	Hillmen et al. (2013) (8)	Eculizumab	Extension of TRIUMPH and SHEPHERD studies evaluating long-term safety and efficacy of sustained treatment	N = 195 Eculizumab (n = 195)	See TRIUMPH and SHEPHERD.

NCT00122317	TRIUMPH and SHEPHERD	Hillmen et al. (2007) (9)	Eculizumab Placebo	Multinational open-label extension of TRIUMPH and SHEPHERD studies evaluating effects on thromboembolism	N = 195 Eculizumab (n = 151) Placebo (n = 44)	See TRIUMPH and SHEPHERD.
NA	NA	Kulagin et al. (2019) (10)	Elizaria Soliris	Phase 3, randomised controlled trial evaluating efficacy and safety of the eculizumab biosimilar	N = 32 Elizaria (n = 16) Solirisb (n = 16)	• Breakthrough haemolysis • LDH AUC (change) • Hb level (change from baseline) • Transfusion outcomes
NA	AEGIS	Kanakura et al. (2011) (11) Kanakura et al. (2013) (12)	Eculizumab	Open-label, single-arm, multicentre study in Japanese patients	N = 29 Eculizumab (n = 29)	• Breakthrough haemolysis • Haemolysis control • LDH AUC (change) • LDH (% change from baseline) • Change in PNH type II RBCs (%) • Transfusion outcomes • Hb level (change from baseline)

NCT02946463	Study 301	Lee et al. (2019) (13) Schrezenmeier et al. (2018) (14) Schrezenmeier et al. (2019) (15)	Ravulizumab Eculizumab	Phase 3, multicentre, randomised, active-controlled, open-label study assessing noninferiority of ravulizumab to eculizumab in complement inhibitor naive patients	Primary evaluation period: N = 246 Ravulizumab (n = 125) Eculizumab (n = 121) Open-label extension: N = 243 Ravulizumab-ravulizumab (n = 124) Eculizumab-ravulizumab (n = 119)	• Normalisation of LDH levels • Transfusion outcomes • Breakthrough haemolysis • LDH (% change from baseline) • QoL (FACIT-Fatigue and EORTC QLQ-C30) • Stabilised Hb • Safety

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NCT03056040	Study 302	Kulasekararaj et al. (2019b) (16) Kulasekararaj et al. (2018) (17) Kulasekararaj et al. (2019a) (18)	Ravulizumab Eculizumab	Phase 3, multicentre, randomised, open-label, active-controlled study assessing noninferiority of ravulizumab to eculizumab in clinically stable patients during previous eculizumab therapy	Primary evaluation period: N = 195 Ravulizumab (n = 97) Eculizumab (n = 98) Open-label extension: N = 191 Ravulizumab-ravulizumab (n = 96) Eculizumab-ravulizumab (n = 95)	• LDH (% change from baseline) • LDH normalisation • Breakthrough hemolysis • QoL (FACIT-Fatigue and EORTC QLQ-C30) • Transfusion outcomes • Stabilised Hb • Safety
NCT02946463 and NCT03056040	Study 301 and Study 302	Hill et al. (2019b) (19)	Ravulizumab	A 52-week extension from Studies 301 and 302	N = 434 Ravulizumab (n = 434)	See 301 study and 302 study.

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NCT02605993	Study 201	Röth et al. (2018a) (20) Röth et al. (2018b) (21) Röth et al. (2020) (22)	Ravulizumab	Phase 1b/2, multicentre open-label study evaluating efficacy and safety of multiple doses and regimens of ravulizumab in complement inhibitor-naïve adult patients	N = 26 Ravulizumab (n = 26)	• Normalisation of LDH levels • LDH (% change from baseline) • Change in reticulocytes • Transfusion outcomes • Major adverse vascular events
NCT02598583	Study 103	Röth et al. (2018a) (20) Röth et al. (2018b) (21) Lee et al. (2016) (22)	Ravulizumab	Phase 1b/2, multicentre open-label study evaluating efficacy and safety of multiple doses and regimens of ravulizumab in complement inhibitor-naïve adult patients	N = 13 Ravulizumab (n = 13)	• Normalisation of LDH levels • LDH (% change from baseline) • Change in reticulocytes • Transfusion outcomes • Major adverse vascular events

NCT03500549	PEGASUS	Hillmen et al. (2020) (23)	Pegcetacoplan Eculizumab	Phase 3, randomised open-label, controlled study demonstrating superiority of pegcetacoplan compared with eculizumab	N = 80 Pegcetacoplan (n = 41) Eculizumab (n = 39)	• Hb level (change from baseline) • Transfusion outcomes • Change in reticulocytes • LDH (% change from baseline) • QoL (FACIT-Fatigue and EORTC QLQ-C30) • Safety • Hemoglobin stabilisation
-	-	Almeida et al. (2017) (24) Almeida et al. (2015) (25)	Eculizumab	Analysis of International PNH Registry data	N = 294	• Change in LDH • FACIT-Fatigue and EORTC-Fatigue • AEs
-	-	Choi et al. (2017) (26)	Eculizumab	Analysis of International PNH Registry data	N = 46	• Change in LDH • Transfusion independence • Symptoms and signs • PNH-related complications

-	-	Höchsmann et al. (2018) (27)	Eculizumab	Analysis of International PNH Registry data	N = 2,670	• Change in LDH • Transfusion independence • FACIT-Fatigue
-	-	Kulagin et al. (2018) (28)	Eculizumab	Observational cohort study	N = 354	• Survival • Transfusion independence • Breakthrough hemolysis

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-	-	Lee et al. (2020) (29)	Eculizumab	Analysis of PNH registry data	N = 1,807	• Change in LDH • Transfusion independence • Thrombotic events • Incidence of infection
-	-	Ninomiya et al. (2016) (30)	Eculizumab	Post marketing surveillance study	N = 319	• Change in LDH • AEs • Transfusion independence • Survival
-	-	Röth et al. (2020) (22)	Eculizumab	Analysis of International PNH Registry data	N = 895	• Change in LDH • Transfusion rates • Thrombotic events

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-	-	Urbano-Ispizua et al. (2019) (31)	Eculizumab	Analysis of International PNH Registry data	N = 1,678	• Change in LDH • Transfusion independence • Thrombotic events
-	-	Hill et al. (2019a) (32)	Immunosuppressive therapy with concomitant eculizumab (n = 1)	Analysis of International PNH Registry data	N = 283	• Change in LDH • Transfusions rates
-	-	Ghosh et al. (2013) (33)	Combinations of danazol, prednisolone, and cyclosporine	Case series	N = 32	• Response

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-	-	Socie et al. (2016) (34)	No treatment	Analysis of International PNH Registry data	N = 2,356	• Survival • Thrombotic events
-	-	Schrezenmeier et al. (2014) (35)	All treatments	Analysis of International PNH Registry data	N = 1,610	• EORTC QLQ-C30 QoL and FACIT-Fatigue • Symptoms and signs • Treatment patterns
-	-	Debureaux et al. (2019) (36)	Eculizumab	Observational cohort study	N = 93	• Response

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-	-	DeZern et al. (2013) (37)	Eculizumab	Observational cohort study	N = 30	• Survival • Response • Breakthrough hemolysis • Thrombotic events
-	-	Hanes et al. (2019) (38)	Eculizumab	Chart review study	N = 47	• Change in LDH • Symptoms and signs
-	-	Hochsmann et al. (2012) (39)	Eculizumab	Case series	N = 41	• Change in LDH • Transfusion independence

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-	-	Jalbert et al. (2019) (40)	Eculizumab	Database analysis	N = NR	• Treatment patterns • Transfusion patterns
-	-	Kang et al. (2020) (41)	Eculizumab	Database analysis	N = 1,340	• Survival • Transfusion independence • PNH-related complications • Incidence of infection
-	-	Karadağ et al. (2019) (42)	Eculizumab	Chart review study	N = 138	• Time to normalisation of Hb and LDH • Symptoms and signs

-	-	Kelly et al. (2011) (43)	Eculizumab	Observational cohort study	N = 79	• Survival • Change in LDH • Transfusion independence • PNH-related complications
-	-	Loschi et al. (2016) (44)	Eculizumab	Analysis of International PNH Registry data	N = 314	• Survival • Thrombotic events
-	-	Munoz-Linares et al. (2014) (45)	Eculizumab	Case series	N = 16	• Survival • Pregnancy • Thrombotic events

-	-	Plessier et al. (2019) (46)	Eculizumab	Observational cohort study	N = 54	• Survival • PNH-related complications
-	-	Röth et al. (2011) (47)	Eculizumab	Observational cohort study	N = 19	• Change in LDH • Units of packed red blood cells
-	-	Schaap et al. (2020) (48)	Eculizumab	Chart review study	N = 84	• Incidence of infection • Breakthrough hemolysis

-	-	Subias Hidalgo et al. (2017) (49)	Eculizumab	Case series	N = 12	• Change in LDH • Blood transfusions
-	-	Yamakawa et al. (2019) (50)	Eculizumab	Case series	N = 109	• Survival • LDH normalisation • Transfusion independence • Thrombotic events • Symptoms and signs
-	-	Yenerel et al. (2018) (51)	Eculizumab	Case series	N = 38	• Transfusion independence • AEs

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-	-	Fu et al. (2020) (52)	Glucocorticoid	Observational cohort study	N = 92	• Response • Transfusion independence • Survival • AEs • PNH-related complications
-	-	Zhao et al. (2002) (53)	Glucocorticoid	Observational cohort study	N = 78	• Response • AEs
-	-	De Latour et al. (2008) (54)	No treatment	Observational cohort study	N = 460	• Survival • PNH-related complications

Abbreviations: AE, adverse event; AUC, area under the curve; EORTC QLQ-C30, the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core Module; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue Scale; ID, identifier; Hb, haemoglobin; LDH, lactate dehydrogenase; NCT, National Clinical Trial number; PNH, paroxysmal nocturnal haemoglobinuria; QoL, quality of life

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Tabel 2 Summary of RCTs and observational studies – SLR update

Study ID	Study name	Publication	Interventions	Study design	N	Endpoints
NCT03056040	Study 302	Kulasekararaj et al. (2020a) (55) Kulasekararaj et al. (2020b) (18) Hill et al. (2020) (56) Rovo et al. (2020) (57) Brodsky et al. (2021) (58) De Latour et al. (2020) (59)	Ravulizumab Eculizumab	A phase 3, randomised, active-controlled trial of ravulizumab versus eculizumab in adult participants with PNH previously treated with eculizumab	Primary evaluation period: N = 195 Ravulizumab (n = 97) Eculizumab (n = 98) Open-label extension: N = 191 Ravulizumab-ravulizumab (n = 96) Eculizumab-ravulizumab (n = 95)	• LDH (% change from baseline) • LDH normalisation • Breakthrough haemolysis • QoL (FACIT-Fatigue and EORTC QLQ-C30) • Transfusion outcomes • Stabilised Hb • Safety
NCT02946463	Study 301	Schrezenmeier et al. (2020a) (60) Hill et al. (2020) (56) Schrezenmeier et al. (2020b) (60) Rovo et al. (2020) (57) Brodsky et al. (2021) (58) Risitano et al. (2020a) (22) Schrezenmeier et al. (2020c) (61)	Ravulizumab Eculizumab	A phase III, randomised, active-controlled trial of ravulizumab versus eculizumab in complement inhibitor treatment-naïve adult participants	Primary evaluation period: N = 246 Ravulizumab (n = 125) Eculizumab (n = 121) Open-label extension: N = 243 Ravulizumab-ravulizumab (n = 124) Eculizumab-ravulizumab (n = 119)	• Normalisation of LDH levels • Transfusion outcomes • Breakthrough haemolysis • LDH (% change from baseline) • QoL (FACIT-Fatigue and EORTC QLQ-C30) • Stabilised Hb • Safety

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		De Latour et al. (2020) (59)				
NCT03056040 and NCT02946463	Study 301 and Study 302	Ishiyama et al. (2020) (62)	Ravulizumab Eculizumab	Subgroup analysis of Japanese patients in studies 301 and 302	Study 301: N = 33 Ravulizumab (n = 18) Eculizumab (n = 15) Study 302: N = 12 Ravulizumab (n = 5) Eculizumab (n = 7)	See studies 301 and 302.
NCT03500549	PEGASUS	Hillmen et al. (2021) (23) Castro et al. (2020) (63) Weitz et al. (2020) (64) Röth et al. (2020b) (65) Risitano et al. (2020b) (66) Cella et al. (2020) (67)	Pegcetacoplan Eculizumab	A Phase III, Randomised, Multi-Centre, Open-Label, Active-Comparator Controlled Study to Evaluate the Efficacy and Safety of APL-2 in Patients With PNH	N = 80 Pegcetacoplan (n = 41) Eculizumab (n = 39)	• Hb level (change from baseline) • Transfusion outcomes • Change in reticulocytes • LDH (% change from baseline) • QoL (FACIT-Fatigue and EORTC QLQ-C30) • Safety • Hb stabilisation
-	-	Bhak et al. (2020) (68)	Pegcetacoplan Ravulizumab	A matched-indirect comparison of pegcetacoplan versus ravulizumab using	Pegcetacoplan = 36 Ravulizumab = 97 Eculizumab = 130	• Transfusion avoidance • Transfusion requirements

				data from PEGASUS and study 302		• Hb stabilisation • Change from baseline in FACIT-Fatigue
NCT01374360	-	Röth et al. (2020a) (22)	Eculizumab	Analysis of International PNH Registry data	N = 895	•Transfusion outcomes • Change in LDH ratio • Safety outcomes
NCT02605993	-	Röth et al. (2020c) (69)	Ravulizumab	Interim analysis of a phase 2, open-label, multiple ascending dose study extension period to compare ravulizumab IV 100 mg/Ml were comparable to the IV 10 mg/Ml formulation	N = 25	• LDL levels • Safety outcomes
-	-	Lee et al. (2020) (70)	Eculizumab	A large prospective, observational, real-world study of patients with PNH	N = 1,537	• Change in LDH ratio, • Transfusion outcomes • Safety outcomes
-	-	Cheng et al. (2020) (71)	Eculizumab	A retrospective longitudinal cohort study using provider-based claims	N = 707	• Dosing frequency and treatment patterns

-		Dingli et al. (2020) (72)	eculizumab ravulizumab	Cross-sectional survey of PNH patients in the United States	N = 58	• Impact of PNH on hematologic and clinical measures • Dosing frequency and treatment patterns
-	-	Füreder et al. (2020) (73)	Eculizumab	Retrospective analysis of a cohort of Austrian PNH patients	N = 59	• Clinical features and classification of PNH patients • Renal function • Overall survival • Safety
-	-	Schaap et al. (2020) (74)	Eculizumab	Electronical medical records of PNH patients treated with eculizumab at the Dutch PNH Expertise Centre Radboudumc were retrospectively reviewed	N = 84	• The incidence, type and severity of meningococcal infections • The occurrence of BTH
-	-	Shah et al. (2019) (75)	NA	A retrospective observational study to compare between aplastic and hemolytic variant of PNH	N = 20	• Flowcytometric findings • Clinical parameters

Abbreviations: AE, adverse event; AUC, area under the curve; BTH, breakthrough haemolysis; EORTC QLQ-C30, the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core Module; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue Scale; Hb, haemoglobin; ID, identifier; LDH, lactate dehydrogenase; NCT, National Clinical Trial number; PNH, paroxysmal nocturnal haemoglobinuria; QoL, quality of life

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Complete reference lists for excluded studies

A full list of all studies excluded from the original SLR and the SLR update at second pass alongside reasons for exclusion are given in the tables below.

Summary of second pass exclusions in original SLR

Author	Year	Title and Reference	Reason for Exclusion
Alashkar F, Schemuth HP, Nensa F, Göbel J, Vance C, Forsting M, et al.	2018	The role of whole-body magnetic resonance imaging (WB-MRI) in patients with paroxysmal nocturnal hemoglobinuria (PNH). Scientific Reports. 2018;8(1):13458.	Study type
Alashkar F, Vance C, Herich-Terhürne D, Preising N, Dührsen U, Röth A	2017	Serologic response to meningococcal vaccination in patients with paroxysmal nocturnal hemoglobinuria (PNH) chronically treated with the terminal complement inhibitor eculizumab. Annals of Hematology. 2017;96(4):589-596.	Intervention
Araten DJ, Notaro R, Thaler HT, Kernan N, Boulad F, Castro-Malaspina H, et al.	2012	Thrombolytic therapy is effective in paroxysmal nocturnal hemoglobinuria: a series of nine patients and a review of the literature. Haematologica. 2012;97(3):344-352.	Study type
Araten DJ, Pachter HL, Dring RJ, Newman E, Cohen SM	2019	Symptomatic bilirubin gallstones in patients with PNH treated with eculizumab. Blood. 2019;134.	Outcome
Arcavi M, Ceballo F, Caracciolo MB, Lazarowski A	2020	Paroxysmal nocturnal hemoglobinuria: test to monitor the action of eculizumab treatment. International Journal of Laboratory Hematology. 2020;42(3):335-340.	Outcome
Boschetti C, Fermo E, Bianchi P, Vercellati C, Barraco F, Zanella A	2004	Clinical and molecular aspects of 23 patients affected by paroxysmal nocturnal hemoglobinuria. American Journal of Hematology. 2004;77(1):36-44.	Outcome
Brodsky RA, De Latour RP, Rottinghaus ST, Röth A, Risitano AM, Weitz IC, et al.	2019	Prospective analysis of breakthrough hemolysis in phase 3 studies of ravulizumab versus eculizumab in adults with PNH. Swiss Medical Weekly. 2019;149:32S.	Study type

Brodsky RA, De Latour RP, Rottinghaus ST, Röth A, Risitano AM, Weitz IC, et al.	2018	A prospective analysis of breakthrough hemolysis in 2 phase 3 randomized studies of ravulizumab (ALXN1210) versus eculizumab in adults with paroxysmal nocturnal hemoglobinuria. Blood. 2018;132.	Study type

Year		Title and Reference	Reason for Exclusion
Brodsky RA, Hill A, Peffault De Latour R, Rottinghaus ST, Röth A, Risitano AM, et al.	2019	A prospective analysis of breakthrough haemolysis in two Phase 3 randomised studies of ravulizumab (ALXN1210) versus eculizumab in adults with paroxysmal nocturnal haemoglobinuria. British Journal of Haematology. 2019;185:111-112.	Study type
Brodsky RA, Peffault de Latour R, Rottinghaus ST, Röth A, Risitano AM, Weitz IC, et al.	2020	Characterization of breakthrough hemolysis events observed in the phase 3 randomized studies of ravulizumab versus eculizumab in adults with paroxysmal nocturnal hemoglobinuria. Haematologica. 2020.	Study type
Burroughs LM, Shimamura A, Talano JA, Domm JA, Baker KK, Delaney C, et al.	2017	Allogeneic hematopoietic cell transplantation using treosulfan-based conditioning for treatment of marrow failure disorders. Biology of Blood and Marrow Transplantation. 2017;23(10):1669-1677.	Study type
Cangul SU, Karapinar DY, Erdem AY, Yarali HN, Ozdemir HH, Gumruk F, et al.	2018	Influence of paroxysmal nocturnal hemoglobinuria clone positivity on outcome of childhood acquired aplastic anemia: a multicenter center study. Blood. 2018;132.	Outcome
Chen F, Wu D, Tang X, Miao M, Fu C, Qiu H, et al.	2015	Outcomes of allogeneic hematopoietic stem cell transplantation for 18 patients with paroxysmal nocturnal haemoglobinuria. Zhonghua xue ye xue za zhi = Zhonghua xueyexue zazhi. 2015;36(12):1005-1010.	Intervention
Chou WC, Huang WH, Wang MC, Chang CS, Yeh SP, Chiou TJ, et al.	2016	Characteristics of Taiwanese patients of PNH in the International PNH Registry. Thrombosis Journal. 2016;14.	Outcome
Cooper JP, Farah RJ, Stevenson PA, Gooley TA, Storb R, Scott BL	2019	Hematopoietic cell transplantation for paroxysmal nocturnal hemoglobinuria in the age of eculizumab. Biology of Blood and Marrow Transplantation. 2019;25(7):1331-1339.	Intervention
Curran KJ, Kernan NA, Prockop SE, Scaradavou A, Small TN, Kobos R, et al.	2012	Paroxysmal nocturnal hemoglobinuria in pediatric patients. Pediatric Blood and Cancer. 2012;59(3):525-529.	Study type

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De Latour RP, Fremeaux-Bacchi V, Porcher R, Xhaard A, Rosain J, Castaneda DC, et al.	2015	Assessing complement blockade in patients with paroxysmal nocturnal hemoglobinuria receiving eculizumab. Blood. 2015;125(5):775-783.	Outcome
Devalet B, Wannez A, Bailly N, Alpan L, Gheldof D, Douxfils J, et al.	2019	Prospective and comparative study of paroxysmal nocturnal hemoglobinuria patients treated or not by eculizumab: Focus on platelet extracellular vesicles. Medicine. 2019;98(27):e16164.	Outcome
Author	Year	Title and Reference	Reason for Exclusion
DeZern AE, Jones RJ, Brodsky RA	2018	Eculizumab bridging before bone marrow transplant for marrow failure disorders is safe and does not limit engraftment. Biology of Blood and Marrow Transplantation. 2018;24(12):e26-e30.	Study type
Dias CZ, Zuppo IDF, Barbosa MM, Azevedo PS, Garcia MM, Araujo VE, et al.	2019	Effectiveness and safety of eculizumab in the treatment of paroxysmal nocturnal hemoglobinuria: systematic review and meta-analysis. Pharmacoepidemiology and Drug Safety. 2019;28:477.	Other
Evers P, Jansen A	2018	Quality of life in health technology assessment: the Dutch experience. Orphanet Journal of Rare Diseases. 2018;13.	Outcome
Fattizzo B, Giannotta J, Zaninoni A, Kulasekararaj A, Cro L, Barcellini W	2020	Small paroxysmal nocturnal hemoglobinuria clones in autoimmune hemolytic anemia: clinical implications and different cytokine patterns in positive and negative patients. Frontiers in Immunology. 2020;11.	Outcome
Fonseca AR, Zanao VA, Parisio K, De Oliveira JSR	2019	Reduced intensity conditioning for haploidentical transplantation using double source of hematopoietic stem cells and post-transplant cyclophosphamide for severe aplastic anemia. Blood. 2019;134.	Population
Füreder W, Cerny-Reiterer S, Sperr WR, Müllauer L, Jäger E, Schwarzinger I, et al.	2017	Evaluation of efficacy of alemtuzumab in 5 patients with aplastic anemia and/or myelodysplastic neoplasm. Wiener Klinische Wochenschrift. 2017;129(11-12):404-410.	Population
Halder R, Mishra P, Aggarwal M, Mannivanan P, Dhawan R, Seth T, et al.	2020	Outcomes of paroxysmal nocturnal hemoglobinuria in the pediatric age group in a resource-constrained setting. Pediatric Blood and Cancer. 2020;67(4).	Other

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Harder M, Höchsmann B, Anliker M, Weinstock C, Simmet T, Skerra A, et al.	2019	Incomplete C5 inhibition by eculizumab accounts for impaired clinical responses in patients with paroxysmal nocturnal hemoglobinuria (PNH). European Journal of Immunology. 2019;49:252.	Outcome
Hill A, Schrezenmeier H, Hillmen P, Szer J, Pullon H, Spearing R, et al.	2018	Ra101495, a subcutaneously administered peptide inhibitor of complement component C5, for the treatment of paroxysmal nocturnal hemoglobinuria: phase 2 results. HemaSphere. 2018;2:105.	Intervention
Kawahara K, Witherspoon RP, Storb R	1992	Marrow transplantation for paroxysmal nocturnal hemoglobinuria. American Journal of Hematology. 1992;39(4):283-288.	Study type
SI, Gavriilaki E, Miari A, Travlou A, Kyriakou E, Anagnostopoulos A, et al.	2018	Renal involvement in paroxysmal nocturnal hemoglobinuria: an update on clinical features, pathophysiology and treatment. Hematology. 2018;23(8):558-566.	Study type
Krishnan S, El Mehdi D, Kunzweiler C, Wu M, Sundaresan S, Huynh L, et al.	2020	PRO88 Literature review of fatigue-scales and association with clinically meaningful improvements in outcomes among patients with and without paroxysmal nocturnal hemoglobinuria. Value in Health. 2020;23:S344-S345.	Study type
Kulagin A, Lisukov I, Ivanova M, Golubovskaya I, Kruchkova I, Bondarenko S, et al.	2014	Prognostic value of paroxysmal nocturnal haemoglobinuria clone presence in aplastic anaemia patients treated with combined immunosuppression: results of two-centre prospective study. British Journal of Haematology. 2014;164(4):546-554.	Outcome
Kulagin AD, Lisukov IA, Kryuchkova IV, Sizikova SA, Gilevich AV, Denisova VV, et al.	2006	Diagnosis and treatment of acquired aplastic anemia. Terapevticheskii Arkhiv. 2006;78(11):48-54.	Outcome
Lazana I, Apap Mangion S, Babiker S, Fattizzo B, Bell K, Large J, et al.	2018	Complement activation and exacerbation of haemolysis secondary to respiratory viral infections in paroxysmal nocturnal haemoglobinuria (PNH) patients treated with eculizumab. Hemasphere. 2018;2:109.	Outcome
Lee JW, Kulasekararaj AG	2020	Ravulizumab for the treatment of paroxysmal nocturnal hemoglobinuria. Expert Opinion on Biological Therapy. 2020;20(3):227-237.	Study type
León Rodríguez E, Rivera Franco MM	2016	Decreased mortality in haematological malignancies with a new conditioning method for stem cell transplantation. Gaceta Mexicana de Oncologia. 2016;15(1):16-21.	Intervention

Lian Y, Shi J, Nie N, Huang Z, Shao Y, Zhang J, et al.	2019	Evolution patterns of paroxysmal nocturnal hemoglobinuria clone and clinical implications in acquired bone marrow failure. Experimental Hematology. 2019;77:41-50.	Outcome
Lin Y, Zhang RD, Chen RL	2019	Efficacy of low-dose combined chemotherapy for patients with relapsed and refractory aplastic anemia-paroxysmal nocturnal hemoglobinuria syndrome. Zhongguo shi yan xue ye xue za zhi. 2019;27(4):1215-1219.	Intervention
Lukina K, Tsvetaeva N, Nikulina O, Sysoeva E, Mershina E, Lukina E	2018	Tissue iron overload assessment in patients with paroxysmal nocturnal hemoglobinuria. HemaSphere. 2018;2:190-191.	Population
JP, Follmann D, Nakamura R, Saunthararajah Y, Rivera CE, Simonis T, et al.	2001	Increased frequency of HLA-DR2 in patients with paroxysmal nocturnal hemoglobinuria and the PNH/aplastic anemia syndrome. Blood. 2001;98(13):3513-3519.	Outcome
Malato A, Saccullo G, Lo Coco L, Mancuso S, Santoro M, Martino S, et al.	2012	Thrombotic complications in paroxysmal nocturnal haemoglobinuria: a literature review. Blood Transfusion. 2012;10(4):428-435.	Study type
Markiewicz M, Drozd-Sokolowska J, Biecek P, Dzierzak-Mietla M, Boguradzki P, Staniak M, et al.	2020	Allogeneic hematopoietic stem cell transplantation for paroxysmal nocturnal hemoglobinuria: multicenter analysis by the Polish Adult Leukemia Group: Allo-HSCT for Paroxysmal Nocturnal Hemoglobinuria. Biology of Blood and Marrow Transplantation. 2020.	Intervention
Martí-Carvajal AJ, Anand V, Cardona AF, Solà I	2014	Eculizumab for treating patients with paroxysmal nocturnal hemoglobinuria. Cochrane Database of Systematic Reviews. 2014;2014(10).	Other
Meppiel E, Crassard I, De Latour RP, De Guibert S, Terriou L, Chabriat H, et al.	2015	Cerebral venous thrombosis in paroxysmal nocturnal hemoglobinuria: a series of 15 cases and review of the literature. Medicine (United States). 2015;94(1):e362.	Study type
Moncharmont P, Barraco F, Bernaud J, Raffin A, Michallet M, Rigal D	2009	Follow-up of patients with paroxystic nocturnal haemoglobinuria treated by eculizumab. Immuno-Analyse et Biologie Specialisee. 2009;24(2):86-91.	Other
Mun YC, Kim JS, Jang JH, Jo DY, Lee JW	2018	Prognostic significance of renal dysfunction during the clinical course in patients with paroxysmal nocturnal hemoglobinuria: a Korean multicenter study. HemaSphere. 2018;2:108.	Intervention

Narita A, Muramatsu H, Sekiya Y, Okuno Y, Sakaguchi H, Nishio N, et al.	2015	Paroxysmal nocturnal hemoglobinuria and telomere length predicts response to immunosuppressive therapy in pediatric aplastic anemia. Haematologica. 2015;100(12):1546-1552.	Outcome
Niederwieser D, Maris M, Shizuru JA, Petersdorf E, Hegenbart U, Sandmaier BM, et al.	2003	Low-dose total body irradiation (TBI) and fludarabine followed by hematopoietic cell transplantation (HCT) from HLA-matched or mismatched unrelated donors and postgrafting immunosuppression with cyclosporine and mycophenolate mofetil (MMF) can induce durable complete chimerism and sustained remissions in patients with hematological diseases. Blood. 2003;101(4):1620-1629.	Population
Nissen -Meyer LS, Tjønnfjord GE, Golebiowska E, Kjeldsen-Kragh J, Akkök Ç A.	2015	Paroxysmal nocturnal haemoglobinuria at Oslo University Hospital 2000-2010. Tidsskr Nor Laegeforen. 2015;135(11):1039-43.	Study type
Pantin J, Tian X, Geller N, Ramos C, Cook L, Cho E, et al.	2014	Long-term outcome of fludarabine-based reduced intensity allogeneic hematopoietic cell transplantation for debilitating paroxysmal nocturnal hemoglobinuria. Biology of Blood and Marrow Transplantation. 2014;20(9):1435-1439.	Intervention
Park SS, Min GJ, Jeon YW, Yoon JH, Lee SE, Cho BS, et al.	2018	Distinct dynamics of PNH clone and hemolytic manifestations according to baseline clone size in patients with aplastic anemia/PNH after immunosuppressive treatment: prospective observational study. HemaSphere. 2018;2:832.	Outcome
Patriquin CJ, Kulasekararaj A, De Latour RP, Jang JH, Langemeijer S, Maschan AA, et al.	2019	Prophylactic antibiotic use and risk of meningococcal infections in patients with paroxysmal nocturnal hemoglobinuria (PNH) treated with eculizumab who received meningococcal vaccination: results from the International PNH Registry. Blood. 2019;134.	Intervention
Peffault De Latour R, Mitchell L, Brodsky RA, Ortiz S, Risitano AM, Jang JH, et al.	2019	Ravulizumab (ALXN1210) versus eculizumab in adults with paroxysmal nocturnal hemoglobinuria: pharmacokinetics and pharmacodynamics observed in two Phase 3 randomized, multicenter studies. British Journal of Haematology. 2019;185:110.	Outcome
Peipert J, Kulasekararaj A, Gonzalez-Fernandez F, Yount S, Martens C, Sparling A, et al.	2019	Patient preferences for the treatment of paroxysmal nocturnal hemoglobinuria: interim results of a patient survey of ravulizumab	Outcome

(ALXN1210) and eculizumab. Journal of Managed Care and Specialty Pharmacy. 2019;25:S37.

Rahman K, Mittal N, Gupta R, Kumar S, Gupta T, Gupta A, et al.	2018	Clinicopathological profile of paroxysmal nocturnal haemoglobinuria clone–positive aplastic anaemia paediatric patients—a single centre study from North India. International Journal of Laboratory Hematology. 2018;40(5):604-610.	Outcome
Raiola AM, Van Lint MT, Lamparelli T, Gualandi F, Benvenuto F, Figari O, et al.	2000	Bone marrow transplantation for paroxysmal nocturnal hemoglobinuria. Haematologica. 2000;85(1):59-62.	Intervention
Rizk S, Youssry Ibrahim I, Mansour IM, Kandil D	2002	Screening for paroxysmal nocturnal hemoglobinuria (PNH) clone in Egyptian children with aplastic anemia. Journal of Tropical Pediatrics. 2002;48(3):132-137.	Outcome
Rondelli T, Risitano AM, de Latour RP, Sica M, Peruzzi B, Ricci P, et al.	2014	Polymorphism of the complement receptor 1 gene correlates with the hematologic response to eculizumab in patients with paroxysmal nocturnal hemoglobinuria. Haematologica. 2014;99(2):262-6.	Study type
Röth A, Araten D, Larratt L, Kulasekararaj A, Maciejewski J, Wilson A, et al.	2018	Effect of eculizumab on transfusion needs in PNH patients with and without transfusion history. HemaSphere. 2018;2:107-108.	Other
Röth A, Dührsen U, Schrezenmeier H, Schubert J	2009	Paroxysmal nocturnal hemoglobinuria (PNH). Pathogenesis, diagnosis and treatment. Deutsche Medizinische Wochenschrift. 2009;134(9):404-409.	Study type
Röth A, Nishimura JI, Nagy Z, Gaàl-Weisinger J, Panse J, Yoon SS, et al.	2020	The complement C5 inhibitor crovalimab in paroxysmal nocturnal hemoglobinuria. Blood. 2020;135(12):912-920.	Intervention
Şahin F, Keklik Karadağ F, Saydam G	2019	The evaluation of paroxismal nocturnal hemoglobinuria patients who underwent eculizumab therapy. Research and Practice in Thrombosis and Haemostasis. 2019;3:414-415.	Outcome
Saito C, Ishiyama K, Yamazaki H, Zaimoku Y, Nakao S	2016	Hypomegakaryocytic thrombocytopenia (HMT): an immune-mediated bone marrow failure characterized by an increased number of PNH-phenotype cells and high plasma thrombopoietin levels. British Journal of Haematology. 2016;175(2):246-251.	Outcome

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Sanchez-Valle E, Morales-Polanco MR, Gomez-Morales E, Gutierrez-Alamillo LI, Gutierrez-Espindola G, Pizzuto-Chavez J	1993	Antilymphocyte globulin therapy for paroxysmal nocturnal hemoglobinuria. Revista de Investigacion Clinica. 1993;45(5):457-461.	Intervention
Santarone S, Bacigalupo A, Risitano AM, Tagliaferri E, Di Bartolomeo E, Iori AP, et al.	2010	Hematopoietic stem cell transplantation for paroxysmal nocturnal hemoglobinuria: long-term results of a retrospective study on behalf of the gruppo italiano trapianto midollo osseo (GITMO). Haematologica. 2010;95(6):983-988.	Intervention
Scheinberg P, Marte M, Nunez O, Young NS	2010	Paroxysmal nocturnal hemoglobinuria clones in severe aplastic anemia patients treated with horse antithymocyte globulin plus cyclosporine. Haematologica. 2010;95(7):1075-1080.	Outcome
Shimoni A, Hardan I, Shem-Tov N, Rand A, Herscovici C, Yerushalmi R, et al.	2007	Comparison between two fludarabine-based reduced intensity conditioning regimens before allogeneic hematopoietic stem cell transplantation: fludarabine/melphalan is associated with higher incidence of acute graft-versus-host disease and non-relapse mortality and lower incidence of relapse than fludarabine/busulfan. Leukemia. 2007;21(10):2109-2116.	Population
Sinan Dal M, Karakuş A, Ekmen MÖ, Ayyildiz O	2016	Presentation and management of paroxysmal nocturnal hemoglobinuria: a single-center experience. Hematol Rep. 2016;8(1):10-3.	Study type
Stahl M, DeVeaux M, De Witte T, Neukirchen J, Sekeres MA, Brunner AM, et al.	2018	The use of immunosuppressive therapy in MDS: clinical outcomes and their predictors in a large international patient cohort. Blood Advances. 2018;2(14):1765-1772.	Outcome
Timeus F, Crescenzio N, Foglia L, Doria A, Saracco P	2016	Paroxysmal nocturnal haemoglobinuria from the perspective of paediatric haematologists. Current Drug Targets. 2016;17(9).	Study type
Timeus F, Crescenzio N, Longoni D, Doria A, Foglia L, Pagliano S, et al.	2014	Paroxysmal nocturnal hemoglobinuria clones in children with acquired aplastic anemia: a multicentre study. PLoS ONE. 2014;9(7).	Population
Tutelman PR, Aubert G, Milner RA, Dalal BI, Schultz KR, Deyell RJ	2014	Paroxysmal nocturnal haemoglobinuria phenotype cells and leucocyte subset telomere length in childhood acquired aplastic anaemia. British Journal of Haematology. 2014;164(5):717-721.	Outcome

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Urbano-Ispizua Á, Kulasekararaj AG, Bartels M, Patriquin CJ, Hoechsmann B, Maschan AA, et al.	2018	Efficacy of eculizumab in pediatric patients with paroxysmal nocturnal hemoglobinuria in the International PNH Registry. Blood. 2018;132.	Other
Vernon MJ, Kuo KHM, Leroux R, Patriquin CJ	2018	Excellence in PNH in Canada (EPIC): a single centre pilot project evaluating disease trajectory for PNH patients receiving eculizumab. Blood. 2018;132.	Outcome
Villegas A, Núñez R, Gaya A, Cuevas-Ruiz MV, Bosch JM, Carral A, et al.	2017	Presence of acute and chronic renal failure in patients with paroxysmal nocturnal hemoglobinuria: results of a retrospective analysis from the Spanish PNH Registry. Annals of Hematology. 2017;96(10):1727-1733.	Outcome
Wang J, Shen P, Wu X, Jin W	2020	Risk factors associated with poor response to immunosuppressive therapy in acquired aplastic anemia: a meta-analysis of retrospective studies. Experimental and Therapeutic Medicine. 2020;19(4):3104-3112.	Other
Wang W, Meyers G, Li H, Wang Y, Shen L, Fan G	2019	Retrospect reviews of PNH tests with long-term follow-up in a single institution. Blood. 2019;134.	Population
Wong R, Pullon H, Deschatelets P, Francois C, Hamdani M, Issargrisil S, et al.	2019	Inhibition of C3 with APL-2 results in normalisation of markers of intravascular and extravascular haemolysis in patients with paroxysmal nocturnal haemoglobinuria. British Journal of Haematology. 2019;185:7.	Study type
Yang HS, Park SH, Choi JR, Kim JG	2013	Isolated central retinal artery occlusion as an initial presentation of paroxysmal nocturnal hemoglobinuria and successful long-term prevention of systemic thrombosis with eculizumab. Japanese Journal of Ophthalmology. 2013;57(5):424-428.	Population
Yood MU, Jick S, Vasilakis-Scaramozza C, Donato BMK, Tomazos I, L'Italien G, et al.	2018	Baseline characteristics of patients with paroxysmal nocturnal hemoglobinuria identified in the department of defense database. Blood. 2018;132.	Outcome
Zhang J, Li X, Shi J, Ge M, Shao Y, Huang J, et al.	2016	Clinical characteristics and evolution of paroxysmal nocturnal hemoglobinuria clones in patients with acquired aplastic anemia. Zhonghua xue ye xue za zhi = Zhonghua xueyexue zazhi. 2016;37(2):124-129.	Outcome
Zhang J, Shao YQ, Li XX, Shi J, Ge ML, Huang JB, et al.	2013	[The clinical study of myelodysplastic syndromes with PNH clones]. Zhonghua xue ye xue za zhi = Zhonghua xueyexue zazhi. 2013;34(3):242-246.	Outcome

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Zhang JL, Liu TF, Chang LX, Chen X, Ren YY, Sun CC, et al.	2017	Clinical characteristics of clonal evolution after immunosuppressive therapy in children with severe/very severe aplastic anemia. Chinese Journal of Contemporary Pediatrics. 2017;19(1):27-33.	Outcome
2009		Eculizumab: new drug. Nocturnal paroxystic haemoglobinuria: fewer transfusions. Prescrire International. 2009 Feb;18(99):13.	Study type
Hallstensen RF, Bergseth G, Foss S, Jæger S, Gedde-Dahl T, Holt J, et al.	2015	Eculizumab treatment during pregnancy does not affect the complement system activity of the newborn. Immunobiology. 2015 Apr;220(4):452-9.	Population
Hata T, Tsushima H, Baba M, Imaizumi Y, Taguchi J, Imanishi D, et al.	2013	Long-term outcome of immunosuppressive therapy for Japanese patients with lower-risk myelodysplastic syndromes. International Journal of Hematology. 2013 Dec;98(6):687-693.	Outcome
Kelly RJ, Höchsmann B, Szer J, Kulasekararaj A, de Guibert S, Röth A, et al.	2015	Eculizumab in pregnant patients with paroxysmal nocturnal hemoglobinuria. New England Journal of Medicine. 2015 Sep;373(11):1032-1039.	Outcome
Naithani R, Mahapatra M, Dutta P, Kumar R, Pati HP, Choudhry VP	2008	Paroxysmal nocturnal hemoglobinuria in childhood and adolescence--a retrospective analysis of 18 cases. Indian Journal of Pediatrics. 2008 Jun;75(6):575-578.	Other
Nakakuma H	2011	[Progress in the management of paroxysmal nocturnal hemoglobinuria by eculizumab]. Rinsho Ketsueki. 2011 Aug;52(8):633-644.	Study type
Nishimura J	2012	[Paroxysmal nocturnal hemoglobinuria]. Rinsho Ketsueki. 2012 Jan;53(1):15-24.	Study type
Reiss UM, Schwartz J, Sakamoto KM, Puthenveetil G, Ogawa M, Bedrosian CL, et al.	2014	Efficacy and safety of eculizumab in children and adolescents with paroxysmal nocturnal hemoglobinuria. Pediatric Blood and Cancer. 2014 Sep;61(9):1544-1550.	Outcome

Sakurai M, Okamoto S	2017	[Clinical features and quality of life assessment in Japanese PNH patients enrolled in the International PNH Registry]. Rinsho Ketsueki. 2017;58(11):2261-2267.	Outcome
Sánchez-Valle E, Morales-Polanco MR, Gómez-Morales E, Gutiérrez-Alamillo LI, Gutiérrez-Espíndola G, Pizzuto-Chávez J	1993	[Treatment of paroxysmal nocturnal hemoglobinuria with antilymphocyte globulin]. Rev Invest Clin. 1993 Sep-Oct;45(5):457-461.	Other
Schubert J, Scholz C, Geissler RG, Ganser A, Schmidt RE	1997	G-CSF and cyclosporin induce an increase of normal cells in hypoplastic paroxysmal nocturnal hemoglobinuria. Annals of Hematology. 1997 May;74(5):225-230.	Outcome
Shichishima T, Saitoh Y, Noji H, Terasawa T, Maruyama Y	1996	In vivo effects of various therapies on complement-sensitive erythrocytes in paroxysmal nocturnal hemoglobinuria. International Journal of Hematology. 1996 Jun;63(4):291-302.	Population
Srinivasan R, Takahashi Y, McCoy JP, Espinoza-Delgado I, Dorrance C, Igarashi T, et al.	2006	Overcoming graft rejection in heavily transfused and allo-immunised patients with bone marrow failure syndromes using fludarabine-based haematopoietic cell transplantation. British Journal of Haematology. 2006 May;133(3):305-314.	Intervention
Stoppa AM, Vey N, Sainty D, Arnoulet C, Camerlo J, Cappiello MA, et al.	1996	Correction of aplastic anaemia complicating paroxysmal nocturnal haemoglobinuria: absence of eradication of the PNH clone and dependence of response on cyclosporin A administration. British Journal of Haematology. 1996 Apr;93(1):42-44.	Population
Sugimori C, Mochizuki K, Qi Z, Sugimori N, Ishiyama K, Kondo Y, et al.	2009	Origin and fate of blood cells deficient in glycosylphosphatidylinositol-anchored protein among patients with bone marrow failure. British Journal of Haematology. 2009 Oct;147(1):102-112.	Outcome
Sun YX, Zhu MQ, He GS, Wang XL, Fang BZ, Lu C, et al.	2013	[The variation and clinical significance of paroxysmal nocturnal hemoglobinuria clone in patients with aplastic	Outcome

		anemia before and after immunosuppressive therapy]. Zhonghua Nei Ke Za Zhi. 2013 Jul;52(7):585-589.	
Tamura S, Furuya Y, Hori Y, Hiroi T, Yamashita Y, Oiwa T, et al.	2020	[Paroxysmal nocturnal hemoglobinuria treated with eculizumab in Wakayama, Japan: a retrospective analysis]. Rinsho Ketsueki. 2020;61(6):605-611.	Other
Tichelli A, Gratwohl A, Nissen C, Würsch A, Signer E, Speck B	1988	[Late complications in patients with aplastic anemia]. Schweiz Med Wochenschr. 1988 Oct 22;118(42):1528-1532.	Outcome
Weitz IC, Razavi P, Rochanda L, Zwicker J, Furie B, Manly D, et al.	2012	Eculizumab therapy results in rapid and sustained decreases in markers of thrombin generation and inflammation in patients with PNH independent of its effects on hemolysis and microparticle formation. Thrombosis Research. 2012 Sep;130(3):361-368.	Outcome
Zhao X, Zhang L, Jing L, Zhou K, Li Y, Peng G, et al.	2015	The role of paroxysmal nocturnal hemoglobinuria clones in response to immunosuppressive therapy of patients with severe aplastic anemia. Annals of Hematology. 2015 Jul;94(7):1105-1110.	Outcome
Haspel RL, Hillmen P	2008	Which patients with paroxysmal nocturnal hemoglobinuria (PNH) should be treated with eculizumab? ASH evidence-based review 2008. Hematology / the Education Program of the American Society of Hematology. 2008;35.	Other
Hill A, Gava A, Taubel J, Bush J, Borodovsky A, Kawahata N, et al.	2016	A subcutaneously administered investigational RNAi therapeutic (ALN-CC5) targeting complement C5 for treatment of PNH and complement-mediated diseases: interim phase 1 study results. Haematologica. 2016;101:172.	Outcome
A, Valls AG, Griffin M, Munir T, Borodovsky A, Kawahata N, et al.	2016	A subcutaneously administered investigational RNAi therapeutic (ALN-CC5) targeting complement C5 for treatment of PNH and complement-mediated diseases: preliminary phase 1/2 study results in patients with PNH. Blood. Conference: 58th Annual Meeting of the	Study type

		American Society of Hematology, ASH 2016. United states. Conference start: 20161203. Conference end: 20161206. 2016;128(22).	
Hillmen P, Young NS, Schubert J, Brodsky RA, SociÐ¹ G, Muus P, et al.	2006	Safety and efficacy of the terminal complement inhibitor eculizumab in a phase III trial in patients with paroxysmal nocturnal hemoglobinuria. Haematologica, the hematology journal: abstract book. 2006;91(Suppl 1):198.	Other
Hillmen P, Young NS, Schubert J, Brodsky RA, Socie G, Muus P	2006	Safety and efficacy of the terminal complement inhibitor eculizumab in a phase III trial in patients with paroxysmal nocturnal hemoglobinuria. Haematologica. 2006;91:0535.	Other
Clinivaltrials.gov	2016	NCT. ALXN1210 (Ravulizumab) Versus Eculizumab in Complement Inhibitor Treatment-Naïve Adult Participants With Paroxysmal Nocturnal Hemoglobinuria (PNH). https://clinicaltrials.gov/show/NCT02946463.	Outcome
Omine M, Kinoshita T, Nakakuma H, Maciejewski JP, Parker CJ, Socie G	2005	Paroxysmal nocturnal hemoglobinuria. International Journal of Hematology. 2005;82(5):417-421.	Study type
Per	2019	Per. A phase 3, randomized, multicenter, open-label, controlled study to evaluate the efficacy and safety of APL-2 in patients with paroxysmal nocturnal hemoglobinuria (PNH). http://www.who.int/trialsearch/Trial2.aspx?TrialID=PER-014-19.	Outcome
Stenger M, Battiwalla M	2008	Eculizumab for paroxysmal nocturnal hemoglobinuria. Community Oncology. 2008;5(2):67-69.	Study type
Lindorfer MA, Pawluczkowycz AW, Peek EM, Hickman K, Taylor RP, Parker CJ	2010	A novel approach to preventing the hemolysis of paroxysmal nocturnal hemoglobinuria: both complement-mediated cytolysis and C3 deposition are blocked by a monoclonal antibody specific for the	Outcome

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		alternative pathway of complement. Blood. 2010 Mar 18;115(11):2283-2291.	
NA	2015	Small molecule factor D inhibitors block complement activation in paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome. 2015 Dec 3;126(23):275.	Outcome
NA	2015	An interim 4-year analysis of prospective multicenter observational study of PNH-type cells in Japanese patients with bone marrow failure syndrome (OPTIMA study). 2015 Dec 3.	Outcome
NA	2017	Allogeneic hematopoietic stem cell transplantation for paroxysmal nocturnal hemoglobinuria: a retrospective single-center study. 2017 Dec.	Intervention
NA	2017	Treatment of paroxysmal nocturnal hemoglobinuria patients by an inhibitor of complement. 2017 Aug 8.	Study type
NA	2018	A phase 3 study of ravulizumab (ALXN1210) versus eculizumab in adults with paroxysmal nocturnal hemoglobinuria naive to complement inhibitors: results of a subgroup analysis with patients stratified by baseline hemolysis level, transfusion history, and demographics. 2018 Nov 29.	Outcome
NA	2018	Iron overload in patients with paroxysmal nocturnal hemoglobinuria. 2018 Nov 29.	Outcome
NA	2018	Combined intensive immunosuppression and eculizumab for aplastic anemia in the context of hemolytic paroxysmal nocturnal hemoglobinuria: a retrospective analysis. 2018 Jan.	Intervention
NA	2018	Ravulizumab (ALXN1210) versus eculizumab in adults with paroxysmal nocturnal hemoglobinuria: pharmacokinetics and pharmacodynamics observed in	Outcome

		two phase 3 randomized, multicenter studies. 2018 Nov 29.	
NA	2018	The SMART anti-hC5 antibody (SKY59/RO7112689) shows good safety and efficacy in patients with paroxysmal nocturnal hemoglobinuria (PNH). 2018 Nov 29.	Intervention
NA	2019	Clone of paroxysmal nocturnal haemoglobinuria and other predictors of the response to immunosuppressive therapy in patients with idiopathic aplastic anaemia. 2019.	Outcome
NA	2020	Treatment of paroxysmal nocturnal hemoglobinuria patients by an inhibitor of complement. 2020 Jul 7.	Study type
Kanakura Y, Ohyashiki K, Shichishima T, Okamoto S, Ando K, Ninomiya H, et al.	2011	Safety and efficacy of the terminal complement inhibitor eculizumab in Japanese patients with paroxysmal nocturnal hemoglobinuria: the AEGIS clinical trial. International Journal of Hematology. 2011;93(1):36-46.	Other
JS, Lee JW, Kim BK, Lee JH, Chung J	2010	The use of the complement inhibitor eculizumab (Soliris®) for treating Korean patients with paroxysmal nocturnal hemoglobinuria. Korean Journal of Hematology. 2010;45(4):269-274.	Study type
Hill A, Hillmen P, Richards SJ, Elebute D, Marsh JC, Chan J, et al.	2005	Sustained response and long-term safety of eculizumab in paroxysmal nocturnal hemoglobinuria. Blood. 2005;106(7):2559-2565.	Study type
Hillmen P, Hall C, Marsh JC, Elebute M, Bombara MP, Petro BE, et al.	2004	Effect of eculizumab on hemolysis and transfusion requirements in patients with paroxysmal nocturnal hemoglobinuria. New England Journal of Medicine. 2004;350(6):552-559.	Study type
Paquette RL, Yoshimura R, Veiseh C, Kunkel L, Gajewski J, Rosen PJ	1997	Clinical characteristics predict response to antithymocyte globulin in paroxysmal nocturnal	Study type

haemoglobinuria. British Journal of Haematology. 1997;96(1):92-97.

Hillmen P, Muus P, Dührsen U, et al.	2007	Effect of the complement inhibitor eculizumab on thromboembolism in patients with paroxysmal nocturnal hemoglobinuria. Blood. 2007;110(12):4123-4128.	Other
Hillmen P, Muus P, Röth A, et al.	2013	Long-term safety and efficacy of sustained eculizumab treatment in patients with paroxysmal nocturnal haemoglobinuria. British Journal of Haematology. 2013;162(1):62-73.	Other

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Summary of second pass exclusions in SLR update

Author	Year	Title and Reference	Reason for Exclusion
-	2019	A Research Study to Gather Scientific Information About the Efficacy and Safety of the Investigational Drug APL-2 In Treating Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH), a Disease Associated with Anemia, In a Randomly Assigned Comparison with the Current Standard of Care Treatment Approved for PNH. www.who.in. 2019	Other
-	2020	Efficacy and Safety of Elizaria® vs. Soliris® in Patients With PNH. Clinicaltrials.gov. 2020	Outcomes
Dingli, D.; Matos, J.E.; Lehrhaupt, K.; Krishnan, S.; Baver, S.B.; Sarda, S.P.	2020	Work productivity loss and quality of life in paroxysmal nocturnalhemoglobinuria among patients receiving c5 inhibitors in the United States. Blood. 2020.	Outcomes
T.; Dhawan, R.; Aggarwal, M.; Tyagi, S.; Seth, T.; Mahapatra, M.	2020	Clinical profile of paroxysmal nocturnal hemoglobinuria (PNH) from a tertiary care centre in North India. HemaSphere. 2020.	Outcomes
Bernuy-Guevara, Coralina; Chehade, Hassib; Muller, Yannick D.; Vionnet, Julien; Cachat, François; Guzzo, Gabriella; Ochoa-Sangrador, Carlos; Álvarez, F. Javier; Teta, Daniel; Martín-García, Débora; Adler, Marcel; de Paz, Félix J.; Lizaraso-Soto, Frank; Pascual, Manuel; Herrera-Gómez, Francisco	2020	The Inhibition of Complement System in Formal and Emerging Indications: Results from Parallel One-Stage Pairwise and Network Meta-Analyses of Clinical Trials and Real-Life Data Studies. Biomedicines. 2020.	Study type

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Appendix B Main characteristics of included studies

Table 52: Overview of Study PEGASUS

Trial name: PEGASUS	NCT number: NCT03500549
Objective	The primary objective was to establish the efficacy and safety of pegcetacoplan compared with eculizumab in patients with PNH who continue to have hemoglobin levels < 10.5 g/dL despite treatment with eculizumab.
Publications	Hillmen P, Szer J, Weitz I, Röth A, Höchsmann B, Panse J, Usuki K, Griffin M, Kiladjian JJ, de Castro C, Nishimori H, Tan L, Hamdani M, Deschatelets P, Francois C, Grossi F, Ajayi T, Risitano A, de la Tour RP. Pegcetacoplan versus Eculizumab in Paroxysmal Nocturnal Hemoglobinuria. N Engl J Med. 2021 Mar 18;384(11):1028-1037. doi: 10.1056/NEJMoa2029073.
Study type and design	Phase 3, prospective, randomized, multicenter, open-label, active-comparator controlled study in patients with PNH who are receiving eculizumab but continue to have hemoglobin levels < 10.5 g/dL. Patients were randomized to receive either pegcetacoplan or eculizumab. The treatment period of the study consisted of three parts: (1) a 4-week run-in period, (2) a 16-week randomized control period, and (3) a 32-week open-label pegcetacoplan-only period
Sample size (n)	80 (41 in the pegcetacoplan group and 39 in the eculizumab group)

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Main inclusion and exclusion criteria	**Inclusion criteria** Key inclusion criteria were as follows (Apellis Pharmaceuticals data on file 2019): • Age at least 18 years old • Primary diagnosis of PNH confirmed by high-sensitivity flow cytometry • Patient is currently receiving treatment with eculizumab; the dose of eculizumab must have been stable for at least 3 months prior to the screening visit • Hemoglobin was < 10.5 g/dL at the screening visit • Absolute reticulocyte count was > 1.0 times ULN at the screening visit • Platelet count was > 50 000/mm^3 at the screening visit • Absolute neutrophil count > 500/mm^3 at the screening visit • Vaccination against *N. meningitidis* types A, C, W, Y, and B, *Streptococcus pneumoniae* and *Haemophilus influenzae* Type B (Hib) either within 2 years prior to Day 1 dosing, or within 14 days after starting treatment with pegcetacoplan • Women of childbearing potential must have a negative pregnancy test at screening and Day 28, and agree to use protocol-defined contraception for the duration of the study • Males must agree to use protocol-defined methods of contraception and refrain from donating sperm for the duration of the study and 90 days after the last dose of study drug • Willing and able to self-administer pegcetacoplan (administration by a caregiver was allowed) • Had a body mass index < 35.0 kg/m^2 **Exclusion criteria** Key exclusion criteria were as follows (Hillmen 2021b): • Patients had an active bacterial infection that was not resolved within 1 week of Day 28 (first dose of pegcetacoplan) • Patients were receiving iron, folic acid, vitamin B12 and erythropoietin, unless the dose was stable, in the 4 weeks prior to screening • Patients had hereditary complement deficiency • History or presence of hypersensitivity or idiosyncratic reaction to compounds related to the investigational product of SC administration • Participation in any other investigational drug trial or exposure to other investigational agent within 30 days or five half-lives (whichever is longer) • If female, currently breastfeeding Cardiovascular specific exclusion criteria (to avoid confounding the cardiac safety outcomes): • History or family history of Long QT Syndrome or torsade de pointes, unexplained syncope, syncope from an uncorrected cardiac etiology, or family history of sudden death • Myocardial infarction, coronary artery bypass surgery, coronary or cerebral artery stenting and/or angioplasty, stroke, cardiac surgery, or hospitalization for congestive heart failure within 3 months or >Class 2 angina pectoris or New York Heart Association Heart Failure Class > 2 • Fridericia's corrected QT (QTcF) > 470 ms, PR > 280 ms

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Trial name: PEGASUS	NCT number: NCT03500549
	• Mobitz II 2nd degree atrioventricular (AV) Block, 2:1 AV block, high grade AV block, or complete heart block unless the patient has an implanted pacemaker or implantable cardiac defibrillator • Receiving Class 1 or Class 3 antiarrhythmic agents, or arsenic, methadone, ondansetron, or pentamidine at screening • Receiving any other QTc-prolonging drugs, at a stable dose for less than 3 weeks prior to dosing • Receiving prophylactic ciprofloxacin, erythromycin, or azithromycin for less than 1 week prior to the first dose of study medication (must have a repeat screening ECG after 1 week of prophylactic antibiotics with QTcF < 470 ms)
Intervention	Pegcetacoplan
Comparator	Eculizumab
Follow-up time	After completion of the randomized controlled period (end of Week 16), patients continued into a 32-week open-label period
Is the study used in the health economic model?	Yes

Primary, secondary and exploratory endpoints	**Primary endpoint:** • Change from baseline to Week 16 hemoglobin level, excluding data before the randomized controlled period **Key secondary endpoints:** • Transfusion avoidance (yes/no), defined as the proportion of patients who do not require a transfusion during the 16-week randomized controlled period • Change from baseline to Week 16 reticulocyte count, excluding data before the randomized controlled period • Change from baseline to Week 16 LDH level, excluding data before the randomized controlled period • Change from baseline to Week 16 in the FACIT-Fatigue scale total score version 4, excluding data before the randomized controlled period **Other secondary efficacy endpoints during the randomized controlled period:** • Hemoglobin response in the absence of transfusions (yes/no); hemoglobin response was defined as an increase of at least ≥ 1 g/dL in hemoglobin from baseline at Week 16, excluding data before the randomized controlled period • Reticulocyte normalization in the absence of transfusions (yes/no); reticulocyte normalization was defined as the reticulocyte count being below the upper limit of the normal range at Week 16 • Hemoglobin normalization in the absence of transfusions (yes/no); hemoglobin normalization is defined as the hemoglobin level being above the lower limit of the normal range at Week 16 • Change from baseline to Week 16 in indirect bilirubin level, excluding data before the randomized controlled period • Change from baseline to Week 16 in haptoglobin level, excluding data before the randomized controlled period • Change from baseline to Week 16 in Linear Analog Assessment Scale (LASA) scores, excluding data before the randomized controlled period • Change from baseline to Week 16 in EORTC QLQ-C30 scores, excluding data before the randomized controlled period • Number of PRBC units transfused during the randomized controlled period **Secondary efficacy endpoints to Week 17 and Week 48:** • Change from baseline to Week 17 and Week 48 in hemoglobin level • Change from baseline to Week 17 and Week 48 in reticulocyte count • Change from baseline to Week 17 and Week 48 in LDH level • Change from baseline to Week 17 and Week 48 in FACIT-Fatigue scale score • Change from baseline to Week 17 and Week 48 in LASA scores • Change from baseline to Week 17 and Week 48 in EORTC QLQ-C30 scores **Secondary efficacy endpoints during the open-label pegcetacoplan period:** • Number of PRBC units transfused during the open-label pegcetacoplan period **Safety endpoints (entire study):** • Incidence and severity of treatment-emergent adverse events (TEAEs)

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Trial name: PEGASUS	NCT number: NCT03500549
	• Incidence of thromboembolic events • Changes in baseline in laboratory parameters • Changes in baseline in ECG parameter
Method of analysis	The primary endpoint was conducted on the ITT data set, which included all patients who were randomized, censored for transfusion (Hillmen 2021b) . Key secondary endpoints were tested in a hierarchical manner, after statistical significance was reached for the primary endpoint. The testing was conducted on the ITT data set. If one hypothesis tested was not significant, all subsequent tests would not be assessed for statistical significance. The key secondary endpoint hierarchy was as follows: 1. Proportion of patients with transfusion avoidance (TA) in both treatment groups 2. Change from baseline to Week 16 in absolute reticulocyte count 3. Change from baseline to Week 16 in LDH 4. Change from baseline to Week 16 in FACIT-Fatigue total scores

Table 53: Overview of Study 301

Trial name: ALXN1210-PNH-301	NCT number: NCT02946463
Objective	Study assessed the noninferiority of ravulizumab to eculizumab in complement inhibitor–naive adults with paroxysmal nocturnal hemoglobinuria (PNH).
Publications	Lee, J. W., Sicre de Fontbrune, F., Wong Lee, L., Pessoa, V., Gualandro, S., et al. (2019b). Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study. Blood 133(6): 530-539.
Study type and design	Phase 3,multicenter, randomized, active-controlled, open-label study. 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). Enrollment of patients without a history of transfusion in the past year was capped at 20%.
Sample size (n)	246 patients were randomized to ravulizumab (n = 125) or eculizumab (n = 121)

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Trial name: ALXN1210-PNH-301	NCT number: NCT02946463
Main inclusion and exclusion criteria	The study enrolled patients ≥ 18 years of age with documented diagnosis of PNH, confirmed by high-sensitivity flow cytometry of red and white blood cells with granulocyte or monocyte clone size of at least 5%, and LDH level ≥ 1.53 ULN at screening. Within 3 months of screening, ≥ 1 of the following PNH-related signs or symptoms must have been present: fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), anemia (ie, hemoglobin level , 10 g/dL), or history of MAVEs (including thrombosis), dysphagia, erectile dysfunction, or history of packed red blood cell transfusion because of PNH. Key exclusion criteria included current or previous exposure to a complement inhibitor; weight , 40 kg; history of bone marrow transplantation; history of meningococcal or unexplained, recurrent infection; platelet count ,30 3 109/L; or absolute neutrophil count ,0.5 3 109/L at screening.
Intervention	Ravulizumab
Comparator(s)	Eculizumab
Follow-up time	The study consisted of a 4-week screening period and a 26-week randomized treatment period
Is the study used in the health economic model?	No. Ravulizumab is included as comparator but with eculizumab data as proxy. See explanation for rationale in section 7.1.4
Primary, secondary and exploratory endpoints	The two primary endpoints were: (1) transfusion avoidance (TA), defined as the proportion of patients who remain transfusion free and do not require a transfusion per protocol-specified guidelines through Day 183; and (2) hemolysis as measured by LDH normalization (ULN, 246 U/L) from days 29 through 183. Key secondary endpoints included percentage change from baseline to Day 183 in LDH and change from baseline to Day 183 in QOL.
Method of analysis	Efficacy analyses were performed on the full analysis set, which included all patients who received ≥ 1 dose of ravulizumab or eculizumab and had ≥ 1 efficacy assessment after the first infusion. Safety analyses were performed on the safety set, defined as all patients who received ≥ 1 dose of study drug. Pharmacodynamic analyses were performed on all patients who received ≥ 1 dose of study drug and had evaluable pharmacodynamic data.

Table 54: Overview of Study 302

Trial name: ALXN1210-PNH-302	NCT number: NCT03056040
Objective	This study assessed noninferiority of ravulizumab to eculizumab in clinically stable PNH patients during previous eculizumab therapy
Publications	Kulasekararaj, A. G., Hill, A., Rottinghaus, S. T., Langemeijer, S., Wells, R., et al. (2019b). Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor-experienced adult patients with PNH: the 302 study. Blood 133(6): 540-549.
Study type and design	Phase 3, open-label, multicenter study. Patients who were clinically stable on eculizumab treatment were stratified according to transfusion history and were randomly assigned (1:1) to 26 weeks of open-label treatment with intravenous (IV) ravulizumab or eculizumab.

Trial name: ALXN1210-PNH-302	NCT number: NCT03056040
Sample size (n)	A total of 197 patients were randomly assigned (1:1) to ravulizumab or eculizumab. Two patients withdrew before receiving study drug, and 195 received treatment (ravulizumab, n = 97; eculizumab, n = 98)
Main inclusion and exclusion criteria	The study enrolled adult patients (≥ 18 years of age) who had documented diagnoses of PNH, confirmed by high-sensitivity flow cytometry evaluation of red blood cells and white blood cells with granulocyte or monocyte clone size of ≥ 5% and who were clinically stable on eculizumab treatment. Eligible patients must have received eculizumab treatment of ≥ 6 months at labeled dose before study entry, had an LDH level #1.53 the upper limit of normal (ULN; 246 U/L) at screening, and been vaccinated against Neisseria meningitidis, 3 years before dosing or at the time of study drug initiation to reduce the risk of meningococcal infections. Key exclusion criteria included LDH value .23 the ULN in the 6 months before day 1, major adverse vascular event within 6 months before day 1, platelet count 30 3 109/L, absolute neutrophil count ,0.5 3 109/L, body weight ,40 kg at screening, history of bone marrow transplantation, and history of N meningitidis infection.
Intervention	Ravulizumab
Comparator(s)	Eculizumab
Follow-up time	The study consisted of a 4-week screening period followed by a 26-week randomized treatment period and an extension period during which all patients received ravulizumab for up to 2 years
Is the study used in the health economic model?	No. Ravulizumab is included as comparator but with eculizumab data as proxy. See explanation for rationale in section 7.1.4
Primary, secondary and exploratory endpoints	The primary efficacy endpoint was hemolysis, as directly measured by percentage change in LDH levels from baseline to Day 183. Key secondary efficacy endpoints were proportion of patients with BTH, defined as at least one new or worsening symptom or sign of intravascular hemolysis. Additional secondary efficacy endpoints included total number of units of packed RBC transfused, proportion of patients with LDH in the normal range, change in EORTC QLQ-C30 scale, change in clinical manifestations of PNH.
Method of analysis	The primary efficacy end point of percentage change in LDH from baseline to day 183 was analyzed by mixed model for repeated measures with the fixed, categorical effects of treatment, study visit, and study visit by treatment group interaction as well as the fixed covariate of baseline LDH and the stratification randomization indicator of packed red blood cell transfusion history. The key secondary end points were tested for noninferiority in a hierarchical manner provided that noninferiority was declared for the primary end point. If noninferiority was established for all key secondary end points, then superiority was assessed via a closed-testing procedure, using a 2-sided 0.05 test for each parameter, in the following order: percentage change in LDH, FACIT-Fatigue, breakthrough hemolysis, stabilized hemoglobin, and transfusion avoidance
Subgroup analyses	Subgroup analyses were performed for the randomization stratification variable of transfusion history and for sex, race, region, and age for the primary end point and key secondary end points. No sensitive subgroups were identified.

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Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Table 55: Demographics and baseline clinical characteristics

	PEGASUS Study		301 Study		302 Study	
Characteristic	Pegcetacoplan (N = 41)	Eculizumab (N = 39)	Ravulizumab (N = 125)	Eculizumab (N = 121)	Ravulizumab (N = 97)	Eculizumab (N = 98)
Age						
Mean (range) — yr	50.2 (19–81)	47.3 (23–78)				
>65 yr — no. (%)	10 (24)	7 (18)	Male 65 (52.0)	Male 69 (57.0)	50 (51.5)	48 (49.0)
Female sex — no. (%)	27 (66)	22 (56)	Female 60 (48.0)	Female 52 (43.0)	47 (48.5)	50 (51.0)
Age at PNH diagnosis, mean (SD), y			37.9 (14.9)	39.6 (16.7)		
Race, n (%) 2						
Asian	5 (12)	7 (18)	72 (57.6)	57 (47.1)	23 (23.7)	19 (19.4)
Black	2 (5)	0	2 (1.6)	4 (3.3)	5 (5.2) (African American)	3 (3.1) (African American)
White	24 (59)	25 (64)	43 (34.4)	51 (42.1)	50 (51.5)	61 (62.2)
Other	0	1 (3)	4 (3.2)	4 (3.3)	3 (3.1)	1 (1.0)
Not reported	10 (24)	6 (15)	3 (2.4)	4 (3.3)	16 (16.5)	14 (14.3)
Weight, mean (SD), kg			68.2 (15.6)	69.2 (14.9)	72.4 (16.8)	73.4 (14.6)
Height, mean (SD), cm			166.3 (9.0)	166.2 (10.7)	168.3 (10.1)	168.8 (9.9)
Years on eculizumab before first study infusion					6.0 (3.5)	5.6 (3.5)
LDH, mean (SD), U/L			1,633.5 (778.8)	1,578.3 (727.1)	228.0 (48.7)	235.2 (49.7)
LDH ratio, n (%)			18 (14.4)	16 (13.2)		
1.5 to < 33 ULN a			107 (85.6)	105 (86.8)		
≥ 33 ULN						

	PEGASUS Study		301 Study		302 Study	
Characteristic	Pegcetacoplan (N = 41)	Eculizumab (N = 39)	Ravulizumab (N = 125)	Eculizumab (N = 121)	Ravulizumab (N = 97)	Eculizumab (N = 98)
Packed RBC units received within 1 y before study entry, randomization strata, n (%)					13 (13.4)	12 (12.2)
0 U			23 (18.4)	21 (17.4)		
1-14 U			79 (63.2)	78 (64.5)		
> 14 U			23 (18.4)	22 (18.2)		
Number of years from PNH diagnosis to consent, median (minimum, maximum), y			3.8 (0-41)	3.9 (0-34)		
LDH, mean (SD), U/L			1,633.5 (778.8)	1,578.3 (727.1)		
PNH clone size, mean (SD), %						
Type 2 RBCs			12.4 (20.5)	13.7 (17.7)	14.9 (19.6)	16.3 (23.6)
Type 3 RBCs			26.3 (17.2)	25.2 (16.9)	44.6 (30.5)	43.5 (29.7)
Total RBCs			38.4 (23.7)	38.7 (23.2)	60.6 (32.5)	59.5 (31.4)
Granulocytes			84.2 (21.0)	85.3 (19.0)	82.6 (23.6)	84.0 (21.4)
Monocytes			86.9 (18.1)	89.2 (15.2)	85.6 (20.5)	86.1 (19.7)
History of MAVEs, n (%)			17 (13.6)	25 (20.7)	28 (28.9)	22 (22.4)
Body-mass index 3	26.7±4.3	25.9±4.3				
No transfusions within previous 12 mo — no. (%)	10 (24)	10 (26)				
History of aplastic anemia — no. (%)	11 (27)	9 (23)			34 (35.1)	39 (39.8)
Median time since PNH diagnosis (range) — yr	6.0 (1–31)	9.7 (1–38)				
Median duration of prior treatment with eculizumab (range) — yr	4.4 (0.4–17.1)	3.4 (0.3–13.8)				
Eculizumab dose at screening — no. (%)						

	PEGASUS Study		301 Study		302 Study	
Characteristic	Pegcetacoplan (N = 41)	Eculizumab (N = 39)	Ravulizumab (N = 125)	Eculizumab (N = 121)	Ravulizumab (N = 97)	Eculizumab (N = 98)
900 mg every 2 wk	26 (63)	30 (77)				
1200 mg every 2 wk	13 (32)	9 (23)				
1500 mg every 2 wk	2 (5)	0				
Platelets — ×10−9/liter	166.6±98.3	146.9±68.8				
≥4 transfusions in previous 12 mo — no. (%)	21 (51)	23 (59)				
Hemoglobin — g/dl 4	8.69±1.08	8.68±0.89				
Reticulocyte count — ×10−9/liter (normal reference range)	217.5±75.0 (30–120)	216.2±69.1 (30–120)				
Lactate dehydrogenase — U/liter (normal reference range)	257.5±97.6 (113–226)	308.6±284.8 (113–226)				
Total bilirubin — µmol/liter (normal reference range)	42.5±31.5 (1.7–18.8)	40.5±26.6 (1.7–18.8)				
Indirect bilirubin — µmol/liter	34.7±28.5	32.9±23.0				
FACIT–F score 5	32.2±11.4	31.6±12.5				

1 Plus–minus values are means ±SD. PNH denotes paroxysmal nocturnal hemoglobinuria. 2 Race and ethnic group were reported by the patient. 3 The body-mass index is the weight in kilograms divided by the square of the height in meters. 4 One patient in the pegcetacoplan group received 900 mg of eculizumab every 11 days. 5 The normal reference range for women is 12 to 16 and for men is 13.6 to 18. 6 Scores on the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT–F) scale range from 0 to 52, with higher scores indicating less fatigue

Table 56: Demographics and Baseline Clinical Characteristics of 301 Study

Characteristic	Ravulizumab (N = 125)	Eculizumab (N = 121)	Total (N = 246)
Age			
Male	65 (52.0)	69 (57.0)	134 (54.5)
Female	60 (48.0)	52 (43.0)	112 (45.5)
Age at first infusion of study drug, mean (SD), y	44.8 (15.2)	46.2 (16.2)	45.5 (15.7)
Race, n (%)			
Asian	72 (57.6)	57 (47.1)	129 (52.4)
Japanese	19 (15.2)	15 (12.4)	34 (13.8)
White	43 (34.4)	51 (42.1)	94 (38.2)
Black or African American	2 (1.6)	4 (3.3)	6 (2.4)
American Indian or Alaska Native	1 (0.8)	1 (0.8)	2 (0.8)
Other	4 (3.2)	4 (3.3)	8 (3.3)
Not reported	3 (2.4)	4 (3.3)	7 (2.8)
Weight, mean (SD), kg	68.2 (15.6)	69.2 (14.9)	68.7 (15.2)
Height, mean (SD), cm	166.3 (9.0)	166.2 (10.7)	166.2 (9.8)
LDH ratio, n (%)			
1.5 to < 33 ULN a	18 (14.4)	16 (13.2)	34 (13.8)
≥ 33 ULN	107 (85.6)	105 (86.8)	212 (86.2)
Packed RBC units received within 1 y before study entry, randomization strata, n (%)			
0 U	23 (18.4)	21 (17.4)	44 (17.9)
1-14 U	79 (63.2)	78 (64.5)	157 (63.8)
> 14 U	23 (18.4)	22 (18.2)	45 (18.3)
Age at PNH diagnosis, mean (SD), y	37.9 (14.9) b	39.6 (16.7) c	38.7 (15.8) d
Number of years from PNH diagnosis to consent, median (minimum, maximum), y	3.8 (0-41) b	3.9 (0-34) c	3.9 (0-41) d
LDH, mean (SD), U/L	1,633.5 (778.8)	1,578.3 (727.1)	1,606.4 (752.7)
PNH clone size, mean (SD), %			
Type 2 RBCs	12.4 (20.5) e	13.7 (17.7) f	13.0 (19.2) g
Type 3 RBCs	26.3 (17.2) e	25.2 (16.9) f	25.8 (17.1) g
Total RBCs	38.4 (23.7)	38.7 (23.2)	38.6 (23.4)
Granulocytes	84.2 (21.0)	85.3 (19.0)	84.7 (20.0)
Monocytes	86.9 (18.1)	89.2 (15.2)	88.0 (16.7)
History of MAVEs, n (%)	17 (13.6)	25 (20.7)	42 (17.1)

LDH = lactate dehydrogenase; MAVE = major adverse vascular event; PNH = paroxysmal nocturnal hemoglobinuria; RBC = red blood cell; SD = standard deviation; ULN = upper limit of normal. [a] The ULN for LDH is 246 U/L., [b] n = 123., [c] n = 118., [d] n = 241., [e] n = 124., [f] n = 120., [g] n = 244. Source: Lee (2019).

Table 57: Demographics and Baseline Clinical Characteristics of 302 Study

Characteristic	Ravulizumab (N = 97)	Eculizumab (N = 98)	Total (N = 195)
Sex			
Male	50 (51.5)	48 (49.0)	98 (50.3)
Female	47 (48.5)	50 (51.0)	97 (49.7)
Age at first infusion of study drug, mean (SD), y	46.6 (14.4)	48.8 (14.0)	47.7 (14.2)
Race, n (%)			
White	50 (51.5)	61 (62.2)	111 (56.9)
Asian	23 (23.7)	19 (19.4)	42 (21.5)
Japanese	5 (5.2)	7 (7.1)	12 (6.2)
African American	5 (5.2)	3 (3.1)	8 (4.1)
Other/multiple	3 (3.1)	1 (1.0)	4 (2.1)
Not reported/unknown	16 (16.5)	14 (14.3)	30 (15.4)
Weight, mean (SD), kg	72.4 (16.8)	73.4 (14.6)	72.9 (15.7)
Height, mean (SD), cm	168.3 (10.1)	168.8 (9.9)	168.5 (10.0)
Years on eculizumab before first study infusion	6.0 (3.5)	5.6 (3.5)	5.8 (3.5)
Patients with packed red blood cells/whole blood transfusions received within 1 y before first dose, no. (%)	13 (13.4)	12 (12.2)	25 (12.8)
Age at PNH diagnosis, mean (SD), y	34.1 (14.4)	36.8 (14.1)	35.5 (14.3)
Time from PNH diagnosis to consent, mean (SD), y	12.4 (8.4)	11.9 (9.4)	12.2 (8.9)
LDH, mean (SD) a U/L	228.0 (48.7)	235.2 (49.7)	231.6 (49.2)
PNH clone size, mean (SD), %			
Type 2 red blood cells	14.9 (19.6)	16.3 (23.6)	15.6 (21.6)
Type 3 red blood cells b	44.6 (30.5)	43.5 (29.7)	44.0 (30.0)
Total red blood cells	60.6 (32.5)	59.5 (31.4)	60.1 (31.9)
Granulocytes	82.6 (23.6)	84.0 (21.4)	83.3 (22.5)
Monocytes	85.6 (20.5)	86.1 (19.7)	85.9 (20.0)
Hemoglobin, g/L, mean (SD) c	110.8 (18.4)	109.1 (18.4)	Not available
Haptoglobin, g/L, mean (SD) d	0.283 (0.235)	0.255 (0.174)	Not available
History of MAVEs, no. (%)	28 (28.9)	22 (22.4)	50 (25.6)
History of aplastic anemia, no. (%)	34 (35.1)	39 (39.8)	73 (37.4)

LDH = lactate dehydrogenase; MAVE = major adverse vascular event; PNH = paroxysmal nocturnal hemoglobinuria; SD = standard deviation. [a] Normal range, 120 to 246 U/L. [b] Erythrocytes with complete deficiency in glycosylphosphatidylinositol-anchored proteins, including complement regulatory proteins CD59 and CD55. [c] Normal range, 11.5-16.0 g/dL (women) and 13.0-17.5 g/dL (men). [d] Normal range, 0.4-2.4 g/dL. Source: (Kulasekararaj 2019b)

Comparability of patients across studies

Please refer to section 7.1.4 above for the discussion on comparative analyses of efficacy across studies.

Comparability of the study populations with Danish patients eligible for treatment

Non applicable

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Appendix D Efficacy and safety results per study

Definition, validity and clinical relevance of included outcome measures

Clinical Relevance of Changes in Hemoglobin Level

Cancer-related anemia leads to significant reduction of QoL with symptoms, including fatigue, weakness, headache, dyspnea, chest pain, palpitations, and decrease in cognitive functions (Cartenì 2007). In anemic patients receiving chemotherapy for solid tumors, hemoglobin increase has been correlated with improved QoL. Clinically significant improvements in QoL measures as assessed with Functional Assessment of Cancer Therapy–Anemia (FACT-An) and Cancer Linear Analogue Scale (CLAS) scores were evident in patients who had a ≥ 2 g/dL (1.24 mmol/L) when compared with those who did not have this increase. The greatest QoL increase was seen when patients approached 12 g/dL (7.44 mmol/L) irrespective of the baseline hemoglobin level (Cartenì 2007).

An analysis of a random sample of data (> 500,000 individuals) obtained on adult South Koreans from the National Health Insurance Service showed that low hemoglobin level and anemia are also risk factors for end-stage renal disease in the general population with or without chronic kidney disease (Yi 2019). Even mild anemia, defined as 11-11.9 g/dL (6.82 – 7.34 mmol/L) in women and 11-12.9 g/dL (6.82 – 8 mmol/L) in men has been associated with more than two- to four-fold increase in end-stage renal disease when compared with their respective counterparts (Yi 2019).

Outcome measures in the PEGASUS study

Definitions of primary and secondary endpoints in the PEGASUS study are presented in Table 52.

The primary endpoint was conducted on the ITT data set, which included all patients who were randomized, censored for transfusion (Hillmen 2021b).

Key secondary endpoints were tested in a hierarchical manner, after statistical significance was reached for the primary endpoint. The testing was conducted on the ITT data set. If one hypothesis tested was not significant, all subsequent tests would not be assessed for statistical significance.

The key secondary endpoint hierarchy was as follows:

1. Proportion of patients with transfusion avoidance (TA) in both treatment groups
2. Change from baseline to Week 16 in absolute reticulocyte count
3. Change from baseline to Week 16 in LDH
4. Change from baseline to Week 16 in FACIT-Fatigue total score

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Table 58 provides a description of the patient-reported outcomes measures used in PEGASUS.

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Table 58: Patient-reported outcomes measures used in PEGASUS

Measure	Description	Validity	Clinical relevance
FACIT-Fatigue	• 13-item Likert scale • Total score range 0-52 • A higher score corresponds to higher QOL (lower fatigue) • An increase in score of 3 or more is considered to be clinically meaningful	**Internal consistency (Cronbach's alpha)** • Cronbach's alpha = 0.93 • No single item significantly impacted the overall scale internal consistency • All items correlated well with the overall score (Acaster 2015) **Test-retest reliability** • Good with an ICC of 0.87 reported across Weeks 3 and 4 among hemoglobin stable patients (Acaster 2015) **Construct validity** • Most highly correlated with the SF-36 vitality domain (r = 0.74), LASA Energy (r = 0.71) and ADL (r = 0.71) domains. The LASA QOL and SF-36 physical functioning and social functioning domains all showed similar correlations with the FACIT-Fatigue (r = 0.68,0.67,0.66, respectively) • For known groups validity, patients with higher hemoglobin levels and who were receiving active treatment reported significantly lower levels of fatigue (Acaster 2015) **Scoring** Items are scored on a 0-4 response scale with anchors ranging from "not at all" to "very much so." To score the FACIT-Fatigue, all items are summed to create a fatigue score with a range from 0-52. Items	**Scales/items** • Fatigue • Weak all over • Listless (washed out) • Tired • Trouble starting things because of being tired • Trouble finishing things because of being tired • Energy • Able to do usual activities • Need to sleep during the day • Too tired to eat • Need help with usual activities • Frustrated about being tired • Limit social activity due to being tired **Minimally important difference** Clinically meaningful improvements in FACIT-Fatigue total score is an increase by ≥ 3 points (Cella 2005) **Responsive to change** Changes in the FACIT-Fatigue directly reflect changes in the SF-36 vitality domain. Significant improvements in FACIT-Fatigue scale scores corresponded with significant differences between minimal, moderate, and much improved vitality cohorts (P < 0.05) (Acaster 2015)

Measure	Description	Validity	Clinical relevance
		are reverse scored when appropriate to provide a scale in which higher scores represent better functioning or less fatigue (Acaster 2015)	
LASA for Quality of Life	• 3 item scale asking respondents to rate their perceived level of functioning • Domains include activity level, ability to carry out daily activities, and overall QOL • Scores are analyzed for the individual components and the combined scale	To allow comparison across measures, all scores were converted to a scale of 0–100 with higher scores indicating better QOL. LASA mean scores ranged from 60–78; SDS, POMS, and FACT-Br ranged from 62–81. FACT-Br physical (P<0.001) and POMS fatigue subscale (P=0.005) decreased over time, as did LASA physical (P=0.08). LASA scales were strongly associated with corresponding scales on SDS, POMS, and FACT-Br (0.44<rho<0.65; P<0.001). LASA was negatively associated with PS and positively with MMSE, with associations similar in magnitude to the other QOL and psychosocial measures. The data suggest that the singleitem LASA scales are valid for assessing QOL of cancer patients and are an appropriate alternative when a shorter instrument is warranted (Locke 2007)	Many of the QoL scales used in PNH are formally used in oncology patients. The foremost finding by Dona *et al.* (Locke 2007) was that the summary statistics suggest that the LASA items have adequate variability within them to be clinically meaningful. That is, patients score along the entire spectrum of possible scores on the scales, avoiding restriction of range, ceiling or floor effects, and providing information that is meaningful and can be different across individual patients and across time. These results are consistent with findings from other studies (Locke 2007)
EORTC QLQ-C30 Questionnaire (version 3.0)	• 30 item questionnaire composed of both multi-item scales and single-item measures to assess overall QOL • Domains are functional scales, symptom scales and global QOL/perceived health status • Scoring followed guidelines provided by the EORTC	**Internal consistency (Cronbach's alpha)** • Range: 0.54-0.86 before treatment • Range: 0.52-0.89 during treatment • Scale reliabilities were similar for young vs. older patients, low vs. high education, good vs. poor performance status, and those receiving assistance completing the questionnaire vs. not • Reliability of the nausea and vomiting scale was lower for Southern European patients than Northern Europe or English-speaking countries (Aaronson 1993)	**Scales/items** **Functioning scales:** • Physical • Role • Emotional • Cognitive • Social • Global QOL **Symptom scales:** • Fatigue • Nausea/vomiting • Pain **Single items:**

Measure	Description	Validity	Clinical relevance
		Test-retest reliability • 4-day interval (N = 190) • Pearson r high for functional scales (range, 0.82-0.91) • r = 0.85 for global QOL • Symptom scales: r = 0.63 nausea/vomiting; r = 0.83 fatigue; r = 0.86 pain **Construct validity** • Able to discriminate patients by clinical status (ECOG performance status), weight loss, and treatment toxicity • All inter-scale correlations were statistically significant (P < 0.01) • Strongest correlations before and during treatment were between physical functioning, role functioning and fatigue scales (range, 0.54-0.63) • Substantial correlations (> 0.040) were between the fatigue, emotional, and social functioning scales (Aaronson 1993) **Scoring** No overall score; all scale and single-item scores are linearly transformed to a 0-100 scale, with higher scores indicating a better level of functioning (for functioning and global QOL scales) or more symptoms (for symptom scales and single items) (Aaronson 1993)	• Dyspnea • Sleep disturbance • Appetite loss • Constipation • Diarrhea • Financial impact **Minimally important difference** 246 patients with breast cancer and 80 patients with small cell lung cancer completed the EORTC QLQ-C30 and the Subjective Significance Questionnaire (SSQ) at baseline and a follow up time point in separate clinical trials; based on patient SSQ ratings on a 7-point scale ranging from much worse through no change to much better, corresponding differences in QLQ-C30 scores were calculated and effect sizes below were determined based on physical, emotional, social, and global QOL functional scales: Small change, mean change in score of 5 10 points Moderate change, 10-20 points Large change, greater than 20 points (Osoba 1998)

EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire–Core Module; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy–Fatigue Subscale; LASA = Linear Analog Assessment Scale; QOL = quality of life.

Clinical relevance of the FACIT-fatigue improvement in pegcetacoplan treated patients

Fatigue experienced by PNH patient's is debilitating and may result in loss of independence, loss of productivity (e.g., inability to work); it does not simply equate to being "tired". The MID for the FACIT-fatigue score is a ≥3-point change from baseline (Cella 2004); patients treated with pegcetacoplan improved their FACIT-fatigue score by 10-points from baseline, over 3 times the MID threshold (Hillmen 2021b) . In addition, FACIT-fatigue also achieved statistical significance at the 0.05 alpha level in post-hoc analyses, with a LS mean numerical difference of 11.87 at Week 16 in the pegcetacoplan vs. eculizumab groups (95% CI 5.49, 18.25; nominal P value .0005) (Röth 2021) .

Post-hoc analyses of PEGASUS found that an increase in FACIT-fatigue scores (i.e., lesser fatigue) was correlated with an increase in hemoglobin, reticulocytes, and indirect bilirubin, regardless of absolute hemoglobin levels in patients, supporting credibility of FACIT-fatigue outcomes (Data on file, [Evidera post-hoc analysis of PEGASUS]). In addition, pegcetacoplan provided significant improvements in other PNH-appropriate PRO outcome instruments (e.g., LASA, EQ-5D, EORTC) that support its benefits to patient quality of life beyond fatigue alone (Röth 2021) .

Pegcetacoplan patients reached nearly double the minimal clinically important point difference on the EORTC QLQ-C30 scale (10-points), with a difference of 19 points between the pegcetacoplan vs. eculizumab treatment arms at 16 weeks (71 vs. 52 points, respectively) (Hillmen, 2021).

Results per study

Table 59 Results of PEGASUS

Table A3a Results of PEGASUS

				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 Hb Level	Pegcetacoplan	41	2.4±0.4 (2.27, 2.53)	3.84	2.3, 5.3	0.001	-	-	-	The between-group comparison for the primary end point was performed with the use of a mixed-effect model for repeated measures (MMRM), with baseline hemoglobin as a continuous variable, time point as a categorical variable, and treatment group, stratification variables, and time-by-treatment interaction as fixed effects.	(Hillmen 2021b)
	Eculizumab	39	−1.5±0.7 (-1.73,-1.27)								
	Pegcetacoplan	41	85.4% (74.5, 96.2)	63	48,77		RR 5.55	2.63-11.71	<0.001	Risk difference was mentioned in the publication.	

Table A3a Results of PEGASUS									
Freedom from Transfusion	Eculizumab	39	15.4% (4.1%, 26.7%)						Absolute difference was calculated based on the equation in the DMC guidelines ($RD = ACR * RR - ACR$)
Change from Baseline in Reticulocyte Count	Pegcetacoplan	41	−136±6.5×10^{9} (-138.05, -133.95)	-164	−189.9, −137.3	-	-	-	
	Eculizumab	39	28±11.9×10^{9} (24.14, 31.86)						
Change from Baseline in LDH	Pegcetacoplan	41	−15±42.7 U (-28.48, -1.52)	-5.0	−181.3, 172.0	-	-	-	
	Eculizumab	39	−10±71 U (-33.02, 13.02)						
Change from Baseline in FACIT-F Score	Pegcetacoplan	41	9.2±1.6 (8.69, 9.71)	11.9	5.5, 18.3	-	-	-	
	Eculizumab	39	−2.7±2.8 (-3.61, -1.79)						

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Table 60 Results of Study 301

Table A3b Results of Study 301

				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**		(Lee 2019)
Transfusion avoidance rate, %	Ravulizumab	125	73.6 (65.87, 81.33)	6.8	-4.66, 18.14	0.0001	-	-	-		
	Eculizumab	121	66.1 (57.68, 74.55)								
LDH normalization, %	Ravulizumab	125	53.6 (45.9, 61.2)	0.09			OR: 1.19	0.80, 1.77	-	OR was reported in the publication. Absolute difference was calculated based on the equation in the DMC guidelines ($RD = ACR * RR - ACR$)	
	Eculizumab	121	49.4 (41.7, 57)								
LDH, least squares mean % change	Ravulizumab	125	-76.84 (-79.96, -73.73)	-0.83	-5.21, 3.56		-	-	-		
	Eculizumab	121	-76.02 (-79.2, -72.83)								

Table A3b Results of Study 301									
FACIT-Fatigue score, least squares mean change	Ravulizumab	125	7.07 (5.55, 8.6)	0.67	-1.21, 2.55	-	-	-	
	Eculizumab	121	6.40 (4.85, 7.96)						
Breakthrough hemolysis rate, %	Ravulizumab	125	4 (0.56, 7.44)	-6.7	- 14.21, 0.18	-	-	-	
	Eculizumab	121	10.7 (5.23, 16.26)						
Hemoglobin stabilization rate, %	Ravulizumab	125	68 (59.82, 76.18)	2.9	-8.80, 14.64				
	Eculizumab	121	64.5 (55.93, 72.99)						

Table 61 Results of study 302

Table A3c Results of Study 302											
				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**		

Table A3c Results of Study 302											
LDH, least squares mean % change	Ravulizumab	97	-0.82 (-7.8, 6.1)	9.2	-0.42, 18.84	0.0006	-	-	-	The primary efficacy end point was analyzed by mixed model for repeated measures with the fixed, categorical effects of treatment, study visit, and study visit by treatment group interaction as well as the fixed covariate of baseline LDH and the stratification randomization indicator of packed red blood cell transfusion history.	(Kulasekararaj 2019a)
	Eculizumab	98	8.4 (1.5, 15.3)								
Breakthrough hemolysis rate	Ravulizumab	97	0 (0, 3.7)	5.1	-8.9, 19	0.0004	-	-	-		
	Eculizumab	98	5.1 (1.7, 11.5)								
FACIT-Fatigue score, least squares mean	Ravulizumab	97	2.0 (0.6, 3.4)	1.5	-0.2, 3.2	0.0001	-	-	-		
	Eculizumab	98	0.54 (-0.8, 1.9)								
Transfusion avoidance rate, %	Ravulizumab	97	87.6 (81.1, 94.2)	5.5	-4.3, 15.7	0.0001	-	-	-		
	Eculizumab	98	82.7 (75.2, 90.2)				-	-	-		

Table A3c Results of Study 302										
Stabilized hemoglobin rate, %	Ravulizumab	97	76.3 (67.8, 84.8)	1.4	-10.4, 13.3	0.0005	-	-	-
	Eculizumab	98	75.5 (67.0, 84.0)						

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Appendix E Safety data for intervention and comparator(s)

For PEGASUS study safety data, please refer to section 7.1.3 above.

Safety results ravulizumab Study 301

Adverse events are summarized in Table 62. The most frequently reported AE was headache (36.0% and 33.1% in the ravulizumab and eculizumab groups, respectively). Twenty patients experienced SAEs (11 ravulizumab and 9 eculizumab patients); pyrexia was the only SAE reported in > 1 patient (1 ravulizumab patient and 2 eculizumab patients). Two patients (1.6%) in the ravulizumab group and 4 (3.3%) in the eculizumab group experienced serious infections (leptospirosis and systemic infection [causative agents not identified]) and serious infections observed in patients treated with eculizumab included limb abscess, cellulitis, infection, pneumonia, and viral upper respiratory tract infection (causative agents not identified). There were no discontinuations of ravulizumab, and there were two discontinuations of eculizumab during the randomized treatment period: one due to a physician's decision and 1 patient withdrew consent. Immunogenicity was low with one treatment-emergent antidrug antibody–positive sample in each treatment arm.

Table 62: Adverse Events—301 Study

Variable	Ravulizumab (N = 125)	Eculizumab (N = 121)
Patients with AEs, n (%)	110 (88.0)	105 (86.8)
Most common AEs (‡5% of patients in either treatment group), n (%)		
Headache	45 (36.0)	40 (33.1)
Nasopharyngitis	11 (8.8)	18 (14.9)
Nausea	11 (8.8)	10 (8.3)
Upper respiratory tract infection	13 (10.4)	7 (5.8)
Pyrexia	6 (4.8)	13 (10.7)
Viral upper respiratory tract infection	9 (7.2)	10 (8.3)
Arthralgia	8 (6.4)	8 (6.6)
Dizziness	9 (7.2)	7 (5.8)
Pain in extremity	9 (7.2)	7 (5.8)
Diarrhea	10 (8.0)	5 (4.1)
Myalgia	7 (5.6)	9 (7.4)
Abdominal pain	7 (5.6)	7 (5.8)
Oropharyngeal pain	8 (6.4)	6 (5.0)

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Back pain	7 (5.6)	6 (5.0)
Cough	4 (3.2)	8 (6.6)
Hypokalemia	6 (4.8)[a]	6 (5.0)
Dyspepsia	4 (3.2)	6 (5.0)
Insomnia	2 (1.6)	6 (5.0)
Patients with serious AEs, n (%)[a]	11 (8.5)	9 (7.4)
Meningococcal infections, n (%)	0	0
Death, n (%)	0	1 (0.8)[b]
Patients with AEs leading to withdrawal of study drug, n (%)	0	1 (0.8)[b]
Patients with serious AEs leading to withdrawal of study drug, n (%)	0	1 (0.8)

MAVE = major adverse vascular event; PNH = paroxysmal nocturnal hemoglobinuria; RBC = red blood cell; SD = standard deviation.

[a] Serious AEs in the ravulizumab group included anemia, aplastic anemia, neutropenia, thrombocytopenia, left ventricular failure, myocardial ischemia, pyrexia, leptospirosis, systemic infection, laceration, uterine leiomyoma, renal colic, and deep vein thrombosis (n = 1 patient each). Serious AEs in the eculizumab group included pyrexia (n = 2 patients), ileus, neutropenic colitis, limb abscess, cellulitis, infection, pneumonia, viral upper respiratory tract infection, adenocarcinoma of colon, lung adenocarcinoma, and PNH (n = 1 patient each).

[b] One patient in the eculizumab arm died of lung cancer (unrelated to treatment) during the extension phase of the study.

Source: (Lee 2019)

Safety results ravulizumab Study 302

An overview of AEs is shown in Table 63 . The most frequently reported AE occurring in 3% or more of patients in either treatment group was headache, which occurred in 26.8% of patients treated with ravulizumab and in 17.3% of patients treated with eculizumab.
Twelve patients experienced SAEs (4 ravulizumab patients and 8 eculizumab patients). Pyrexia and hemolysis were the only SAEs reported by > 1 patient (3 and 2 patients, respectively, all in the eculizumab group).
Serious infections occurred in 2 patients (2.1%) in the ravulizumab group (influenza and lower respiratory tract infection [without positive culture]) and in 1 eculizumab-treated patient (1.0%) (acute pyelonephritis [causative agent unknown]). None of these SAEs led to discontinuation from the study.

Table 63: Adverse Events—302 Study

Variable	Ravulizumab (N = 97)	Eculizumab Group (N = 98)
Patients with AEs	85 (87.6)	86 (87.8)
Most common AEs (≥ 5% of patients in either treatment group)		
Headache	26 (26.8)	17 (17.3)

Variable	Ravulizumab (N = 97)	Eculizumab Group (N = 98)
Nasopharyngitis	21 (21.6)	20 (20.4)
Upper respiratory tract infection	18 (18.6)	10 (10.2)
Diarrhea	9 (9.3)	7 (7.1)
Pyrexia	9 (9.3)	5 (5.1)
Nausea	8 (8.2)	9 (9.2)
Constipation	7 (7.2)	5 (5.1)
Influenza-like illness	7 (7.2)	8 (8.2)
Abdominal pain	6 (6.2)	9 (9.2)
Anemia	6 (6.2)	3 (3.1)
Fatigue	6 (6.2)	6 (6.1)
Vomiting	6 (6.2)	4 (4.1)
Cough	5 (5.2)	10 (10.2)
Pain in extremity	5 (5.2)	4 (4.1)
Rhinitis	5 (5.2)	4 (4.1)
Oropharyngeal pain	4 (4.1)	9 (9.2)
Chest pain	3 (3.1)	9 (9.2)
Dizziness	3 (3.1)	7 (7.1)
Musculoskeletal pain	2 (2.1)	5 (5.1)
Dyspnea	0 (0.0)	6 (6.1)
Patients with serious AEs, n (%)[a]	4 (4.1)	8 (8.2)
Meningococcal infections, n (%)	0	0
Death	0	0
Patients with AEs leading to withdrawal of study drug	0	0
Patients with serious AEs leading to withdrawal of study drug	0	0

AE = adverse event.

[a] Values are reported as n (%) of patients.

Source: (Kulasekararaj 2019b)

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Appendix F Comparative analysis of efficacy and safety

Head-to-head comparison for pegcetacoplan vs. eculizumab is available from the PEGASUS trial (see section 7.1.2). Hence, indirect comparisons were not required for this submission.

For results from PEGASUS, see Table 59 in Appendix G, and Table A4 below.

Table 64 Study comparing pegcetacoplan to eculizumab for patients with PNH

Table A4 Study comparing pegcetacoplan to eculizumab for patients with PNH									
Outcome	**Studies included in the analysis**	**Absolute difference in effect**			**Relative difference in effect**			**Method used for quantitative synthesis**	**Result used in the health economic analysis?**
		Difference	**CI**	***P* value**	**Difference**	**CI**	***P* value**		
Change from Baseline in Hb Level	PEGASUS Pegcetacoplan arm	3.84	2.3, 5.3	0.001	-	-	-	The between-group comparison for the primary end point was performed with the use of a mixed-effect model for repeated measures (MMRM), with baseline hemoglobin as a continuous variable, time point as a categorical variable, and treatment group, stratification variables, and time-by-treatment interaction as fixed effects.	Yes
	PEGASUS Eculizumab arm	-							
Freedom from Transfusion	PEGASUS Pegcetacoplan arm	63	48,77		0.6253	0.483, 0.7677		Risk difference was mentioned in the publication (Hillmen 2021a)	Yes
	PEGASUS Eculizumab arm								

Table A4 Study comparing pegcetacoplan to eculizumab for patients with PNH								
Change from Baseline in Reticulocyte Count	PEGASUS Pegcetacoplan arm	-164	-189.9 - -137.3	-	-	-	Absolute difference was calculated based on the equation in the DMC guidelines ($RD = ACR * RR - ACR$)	No
	PEGASUS Eculizumab arm							
Change from Baseline in LDH	PEGASUS Pegcetacoplan arm	-5.0	−181.3, 172.0	-	-	-		No
	PEGASUS Eculizumab arm							
Change from Baseline in FACIT-F Score	PEGASUS Pegcetacoplan arm	11.9	5.5, 18.3	-	-	-		Yes (indirectly)
	PEGASUS Eculizumab arm							

Appendix G – Extrapolation

No extrapolation is applied in the model, the relative efficacy is assumed to be constant over the modelled time horizon.

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Appendix H – Literature search for HRQoL data

An economic SLR was conducted in order to capture health economic evidence in related to treatments and health economic analyses of PNH. The full report is available as a separate attachment to this application (SOBI 2020b).

The objective of the systematic literature review (SLR) was to systematically assemble, in a transparent and reproducible manner, the health economics evidence relevant for a NICE submission for a new PNH treatment. Specific objectives of the economic SLR were as follows:

- Identify utility, resource-use, and cost data for PNH that are relevant to the economic analysis
- Systematically identify published articles of economic models in PNH
- Critically appraise the relevant economic evaluations using validated appraisal tools
- Prepare summaries of the included studies in accordance with the guidelines set forth in Specification for Manufacturer/Sponsor Submission of Evidence
- Extract utility, resource-use, and cost data from the selected studies in a format suitable for inclusion in the economic analysis.

Search strategy

The guidelines set forth in Specification for Manufacturer/Sponsor Submission of Evidence for a single technology appraisal by NICE (2015) are widely considered to be the gold standard for methodological approaches and are acceptable to any international health technology assessment (HTA) organization. Our SLR was consistent not only with the requirements of NICE's single technology appraisal specifications document (NICE, 2015) but also with the Centre for Reviews and Dissemination's Guidance for Undertaking Reviews in Health Care (CRD, 2009) and the Cochrane Collaboration Handbook (Higgins et al., 2019). The review also was conducted to comply with the German "Act on the Reform of the Market for Medical Products" requirements by the Institute for Quality and Efficiency in Health Care (IQWiG) as outlined in their General Methods Version 5.0, April 2015 document (IQWiG, 2017).

The review was performed in accordance with the approved literature review protocol from July 28, 2020.

Identification of Studies
Electronic Databases

The following electronic medical literature databases were searched on July 30, 2020:

- MEDLINE and MEDLINE In-Process (using PubMed platform)
- Embase (using Elsevier platform)
- BioSciences Information Service of Biological Abstracts (using Dialog platform)
- EconLit
- Cochrane Library, including the following:
  - Database of Abstracts of Reviews of Effectiveness
  - National Health Service's Economic Evaluation Database
  - HTA database

Details of the search strategy developed for use in Embase are provided in Appendix A,
Table A-1 in the external document Economic Systematic Literature Review: Final Report (SOBI 2020b).
The Embase search strategy was adapted to search other electronic databases.

Additional Sources
Internet Searches

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In addition to searching the published literature, RTI Health Solutions (RTI-HS) conducted targeted desktop research to identify relevant information from the following online sources:

- European Hematology Association3: https://ehaweb.org
- International Network of Agencies for Health Technology Assessment (INAHTA): www.inahta.org
- NICE: www.nice.org.uk
- Scottish Medicines Consortium (SMC): www.scottishmedicines.org.uk/Home
- Canadian Agency for Drugs and Technologies in Health (CADTH): www.cadth.ca/about-cadth/what-we-do/products-services/hta
- Pharmaceutical Benefits Advisory Committee (PBAC): www.pbs.gov.au/pbs/search?term=&search-type=medicines
- Cost-Effectiveness Analysis Registry (to identify utility estimates) https://cevr.tuftsmedicalcenter.org/databases/cea-registry

Bibliographic lists of relevant systematic reviews, as well as included economic analyses and HTA reports, were searched for potentially relevant articles that were not identified in the electronic searches.

The electronic database searches were not limited by date. Internet searches of conference proceedings were limited to abstracts published in the last 2 years because it is expected that high-quality studies presented earlier will have already been published. Searching conference proceedings for this period ensured that we captured recent conference abstracts that may not yet have been indexed in Embase or any of the other databases.

Search terms included combinations of free text and Medical Subject Headings or Emtree subject headings. The following concepts were included in the search strategy:

- Search terms relating to the population of interest (PNH)
- Search terms relating to study type (economic evaluations, cost, and utility studies)
- Exclusionary terms: unwanted publication types (e.g., comments, editorials, letters, and case reports) and studies in animals but not in humans

A complete listing of search terms used in the Embase search is provided in Appendix A, Table A-1 in the external SLR report (SOBI 2020b). This Embase search strategy was adapted to search other electronic databases. Search terms for the searches performed in the online resources were drawn from the listings in Appendix A, as appropriate for the search features of individual sites. A log of these searches is presented in Appendix B, Table B-1 in the SLR report (SOBI 2020b).

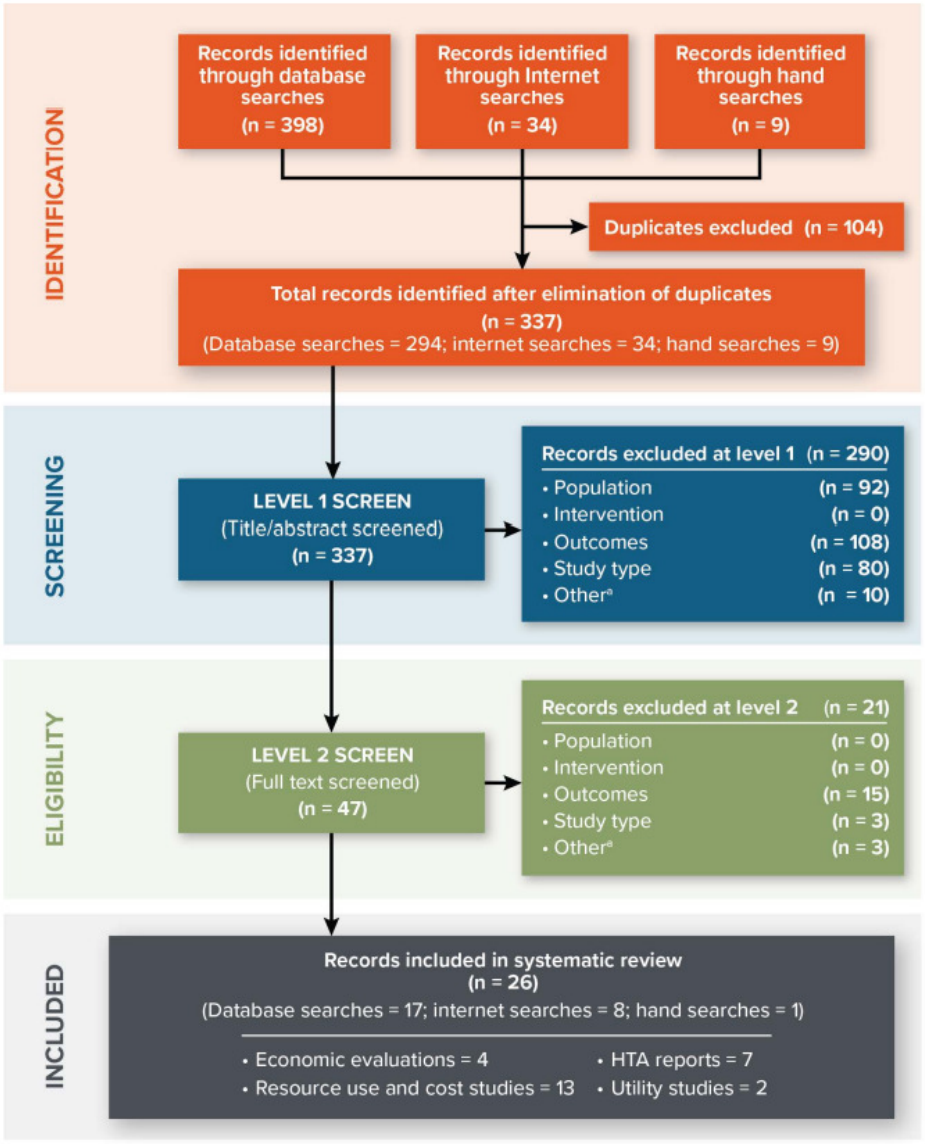
The 337 records selected (databases = 294; Internet searches = 34; hand searches = 9) were manually screened to identify studies that met the predefined inclusion/exclusion criteria presented in the protocol. Titles and abstracts of studies were reviewed independently (level 1 screening) by two researchers for eligibility according to the predefined inclusion and exclusion criteria. Any discrepancies were resolved through additional discussion.

After the initial screening of titles/abstracts (level 1 screening), 47 publications (databases = 38; Internet searches = 8; Hand searches = 1) were selected for further screening (level 2) using the full-text record. Among the 38 studies identified via the database searches, 17 were included in the review following full-text review. Therefore, after the level 2 screening, 26 references (database searches = 17; Internet searches = 8; hand searches = 1) were selected for inclusion in the review.

The inclusion and exclusion processes were documented. Figur 3 presents the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart detailing the number of articles

identified in the literature search, as well as the number of articles included and excluded at each stage and the reason for exclusion. A list of studies excluded at level 2, and the reason for each exclusion, is presented in Appendix C, Table C-1 in the SLR report (SOBI 2020b).

Figur 3 PRISMA Diagram



HTA = health technology assessment; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

[a] Studies conducted in animals, duplicates, or where the report/data were unavailable.

Quality assessment and generalizability of estimates

A quality assessment was performed for each published economic analysis using the Drummond checklist (Drummond and Jefferson, 1996).4 One researcher performed the quality assessment, and a second researcher performed a quality-control check of the final completed assessment to verify the completed assessments against the source documents.

Unpublished data

No unpublished data was included in the SLR.

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Appendix I Mapping of HRQoL data

Two approaches for mapping the utility values were considered:

- Direct – In this single-stage approach health-related utilities are directly mapped based on the response collected from the quality-of-life questionnaire (here EORTC). This approach is country specific, therefore the algorithm cannot be used for various countries.

- Indirect – This double-stage process requires mapping the response between two QoL questionnaires referred as response mapping (e.g., between EORTC and EQ5D-5L) followed by estimation of utilities using dedicated tariff, so the same model can be used for different countries

The direct mapping approach was adopted because of small sample size and not enough responses at all levels for each dimensions. Three regression models were tested with utility values as dependent variables:

- Ordinal linear regression model (OLM)

- Adjusted limited dependent variable mixture model (ALDVMM)

- Beta inflated distribution for fitting the generalized additive model for location scale and shape (GAMLSS)

All linear regression models performed well in prediction of the mean utility, however the model with interactions allows for the most accurate prediction of both mean utility together with associated standard deviation. The ALDVMM model and beta inflated models slightly under- and over-estimated mean utility values, respectively. The Beta inflated model performed best in predicting median utility, although the range of predicted values was noticeable narrowed compared with data. The other models slightly overestimated median utility but the ranges were more consistent with the dataset. Linear regression model was best regarding prediction of lower-value utilities but can produce values >1. The performance of the models is presented in Table 65.

Table 65 Performance of models

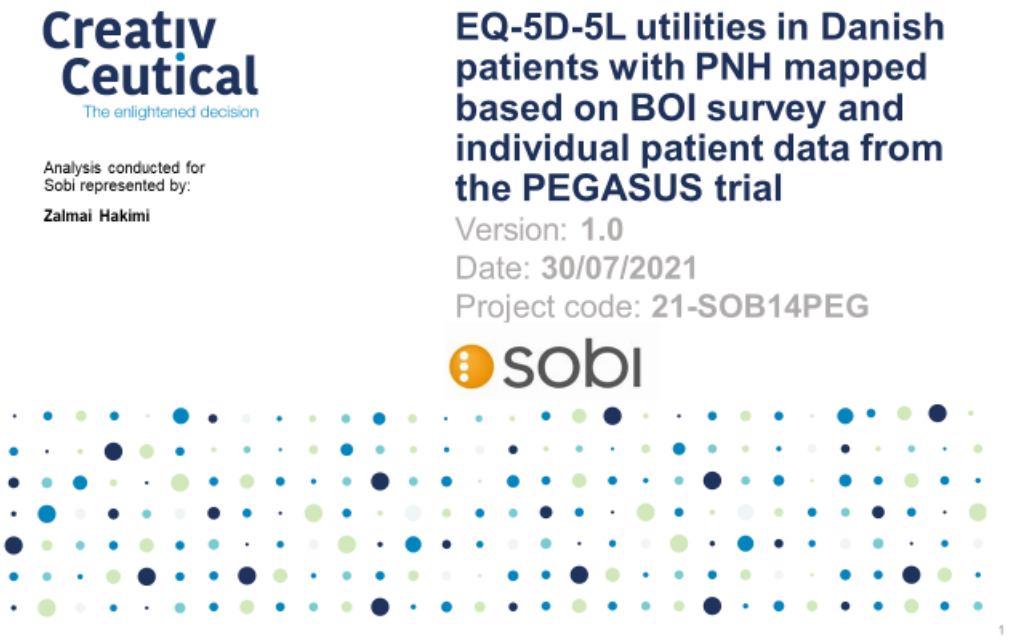
Summary statistics	Observed values	Linear			ALDVMM	Beta inflated
		Full model	Model without interactions	Model with interactions	Best from GA	Best from GA
Mean (SD)	0.78 (0.17)	0.78 (0.16)	0.78 (0.16)	0.78 (0.17)	0.75 (0.12)	0.79 (0.15)
Median	0.78	0.81	0.83	0.80	0.82	0.78
Range	[0.26; 1.0]	[0.33; 0.98]	[0.30; 0.96]	[0.25; 1.04]	[0.35; 0.97]	[0.35; 0.86]

The restricted linear regression model with interactions was associated with the best performance as indicated by information criterion and lowest RMSE (Table 66). This model was therefore used for the mapping of EQ5D-5L utilities in Danish patients based on the PEGASUS trial data

Table 66 Model selection based on performance

Summary statistics	Parameter	Full model	Model without interaction ~PF+EF+PA+DY	Model with interactions ~PF*DY+DY*CF+AP+ NV*PA+FA*DY+PA*SL+ EF*FA+CF*DY+SF+QL*PF
BIC	Linear	-108.8792	-148.5517	-**162.0092**
	ALDVMM	355.7375	19.2582	370.3165
	Beta	Model could not be calculated	-60.0778	Model could not be calculated
RMSE	Linear	0.06354	0.07099	**0.04242**
	ALDVMM	0.2549	0.1746	0.2271
	Beta	Model could not be calculated	0.09231	Model could not be calculated

BIC = Bayesian information criterion; RMSE = Root-mean-square



Abbreviations

Abbreviation	Definition
EORTC-QLQ-C30	European Organization for Research and Treatment of Cancer 30 Item Core Quality of Life Questionnaire
EQ-5D-5L	EuroQol-5 Dimensions 5level
AIC	Akaike Information Criterion
ALDVMM	Adjusted limited dependent variable mixture model
AP	Appetite loss
BIC	Bayesian Information Criterion
CF	Cognitive functioning
CO	Constipation
DI	Diarrhoea
DY	Dyspnoea
EF	Emotional functioning
FA	Fatigue
FI	Financial difficulties
GA	Genetic algorithm
GAMLSS	Generalized additive model for location scale and shape
Hb	Hemoglobin
NV	Nausea and vomiting
PA	Pain
PF	Physical functioning
PNH	Paroxysmal nocturnal hemoglobinuria
QL	Global health
RCT	Randomised controlled trial
RF	Role functioning
RMSE	Root mean square error
SF	Social functioning
SL	Insomnia
VAS	Visual analogue scale

Main objectives

- **Background:**
  - The PEGASUS trial was a randomised controlled trial (RCT) comparing pegcetacoplan with eculizumab in patients with paroxysmal nocturnal haemoglobinuria (PNH). During the PEGASUS trial, several patient reported outcomes scales were collected, including EORTC-QLQ-C30 along with clinical data, however EQ-5D data were not collected.
  - Several algorithms were published allowing to map between EORTC-QLQ-C30 scale and EQ-5D-3L response, including the algorithm proposed by Longworth.
  - No algorithms were identified allowing to map between EORTC-QLQ-C30 and EQ5D-5L responses or utilities
  - SOBI conducted a survey among PNH patients in which both EORTC and EQ5D- 5L data were collected
- **Aims:**
  - This post-hoc analysis was conducted to obtain EQ5D-5L utility values patients and transition probabilities for a cost-effectiveness model for pegcetacoplanin Danish patients with PNH. In particular following activities were conducted:
    1. Development of an algorithm to map EQ5D -5L utilities (Denmark specific) from EORTC data
    2. Mapping utilities of the participants of the PEGASUS trial using the developed algorithm
    3. Estimation of the utilities for three independent health states in Denmark:
       - Transfusion dependence,
       - Transfusion avoidance withhemoglobin level < 10.5
       - Transfusion avoidance withhemoglobin level >=10.5

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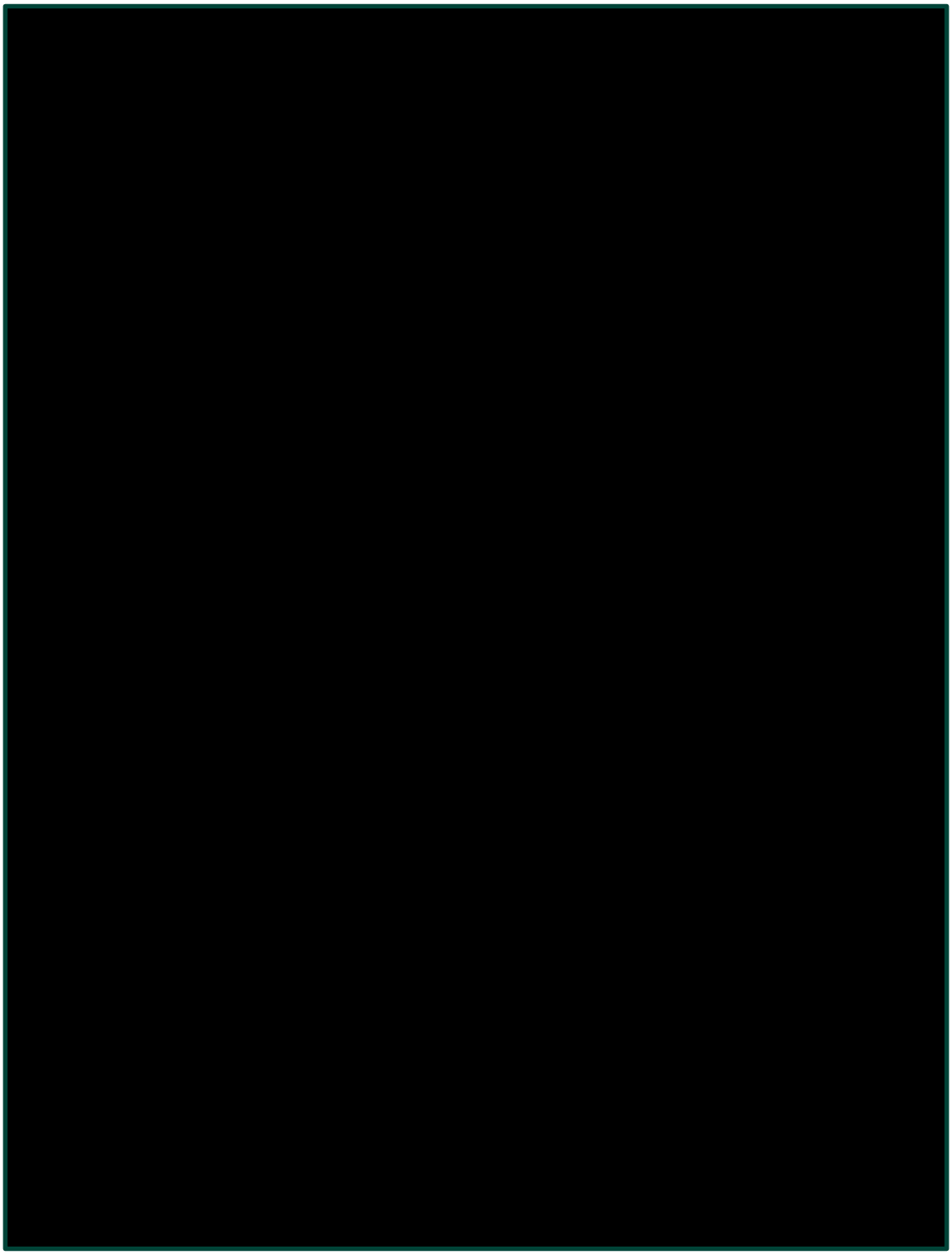

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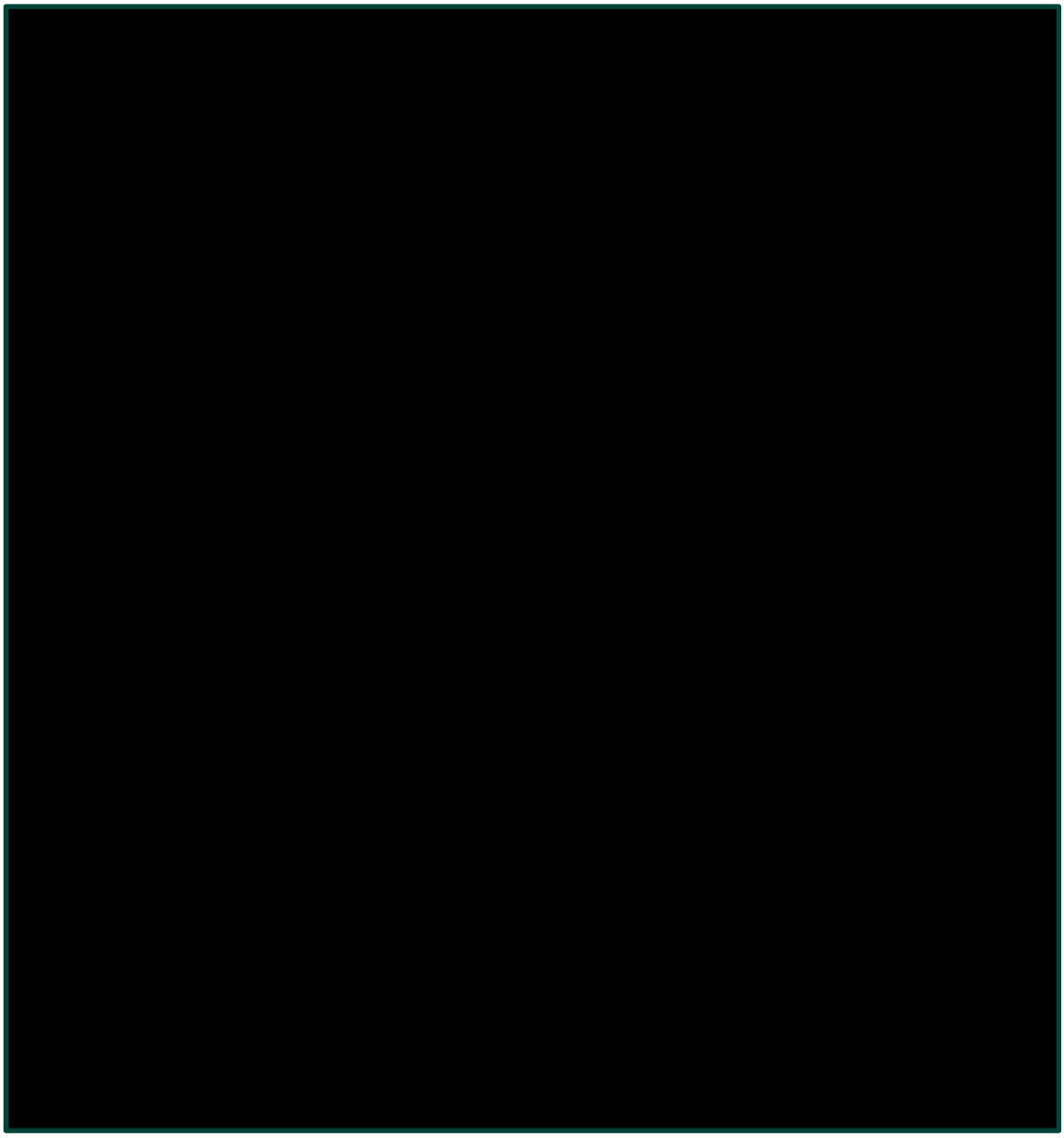

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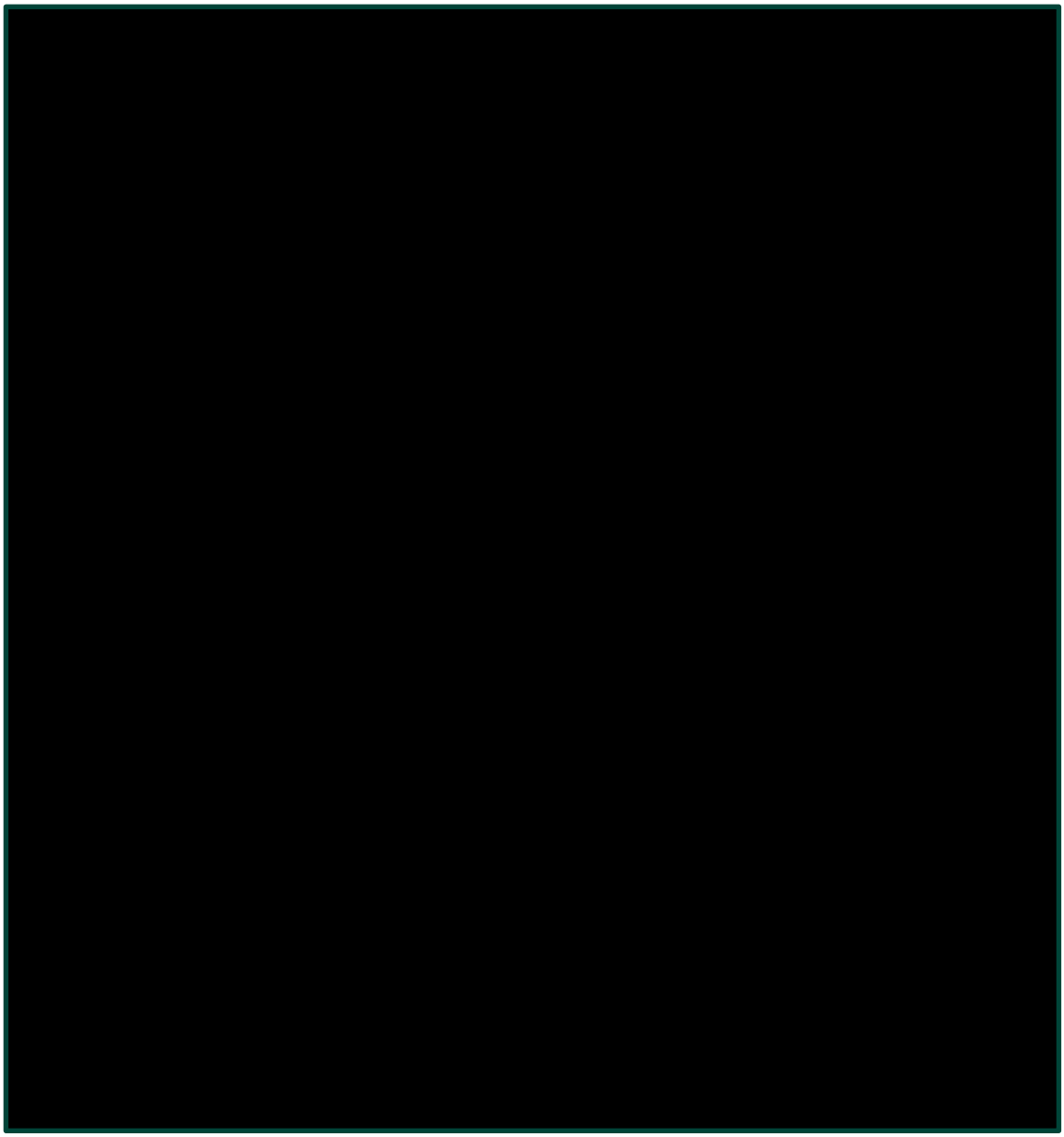

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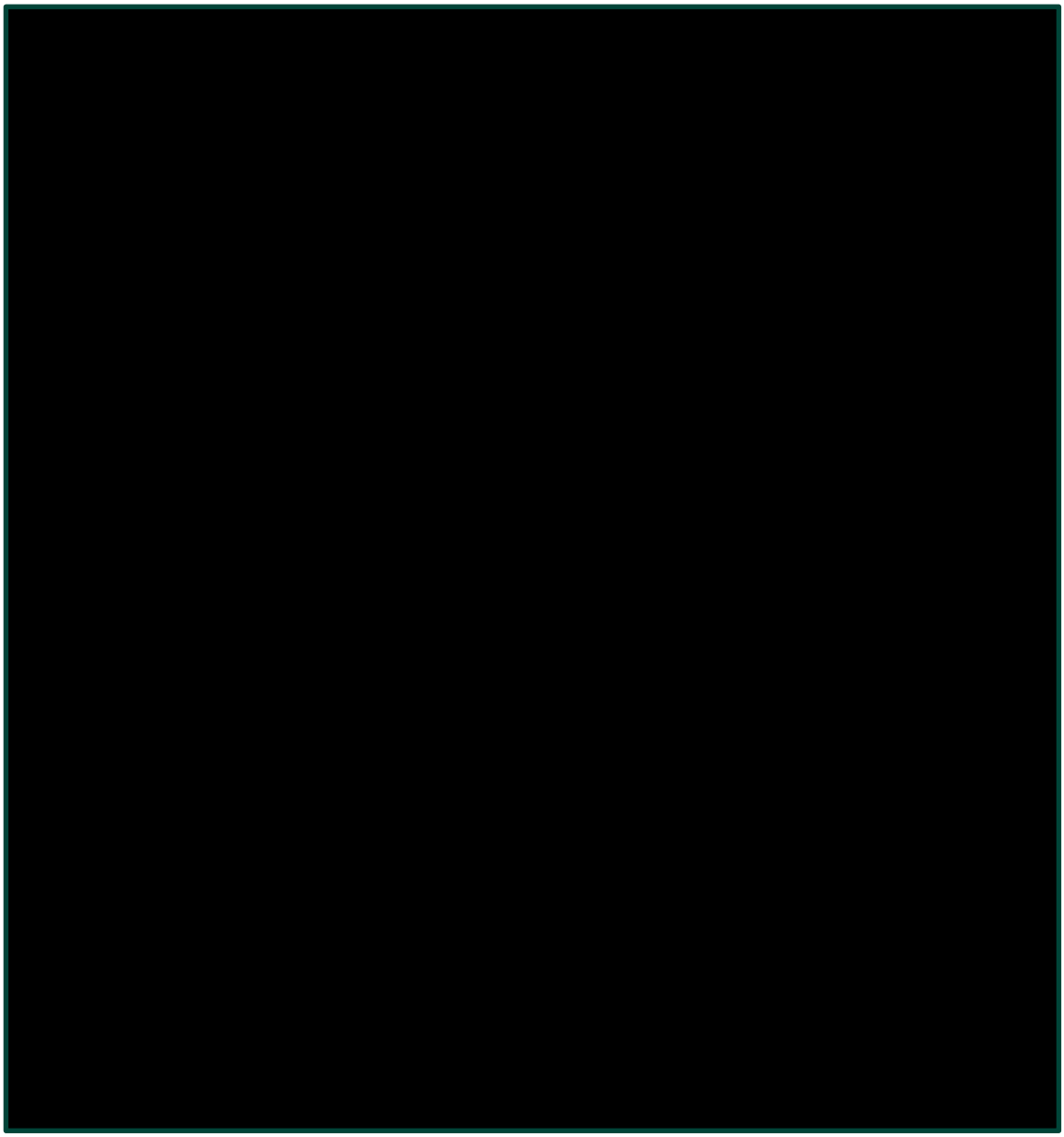

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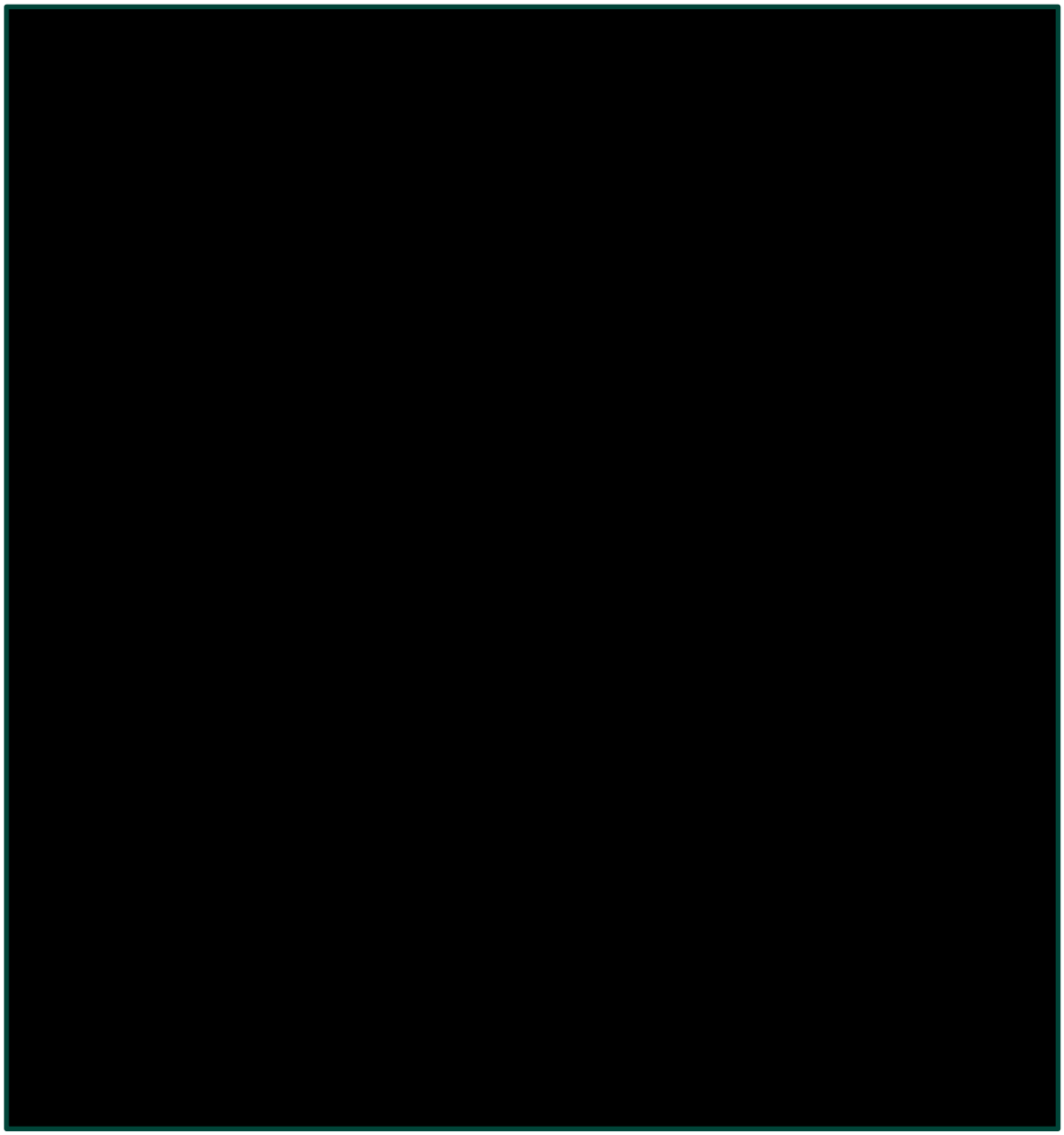

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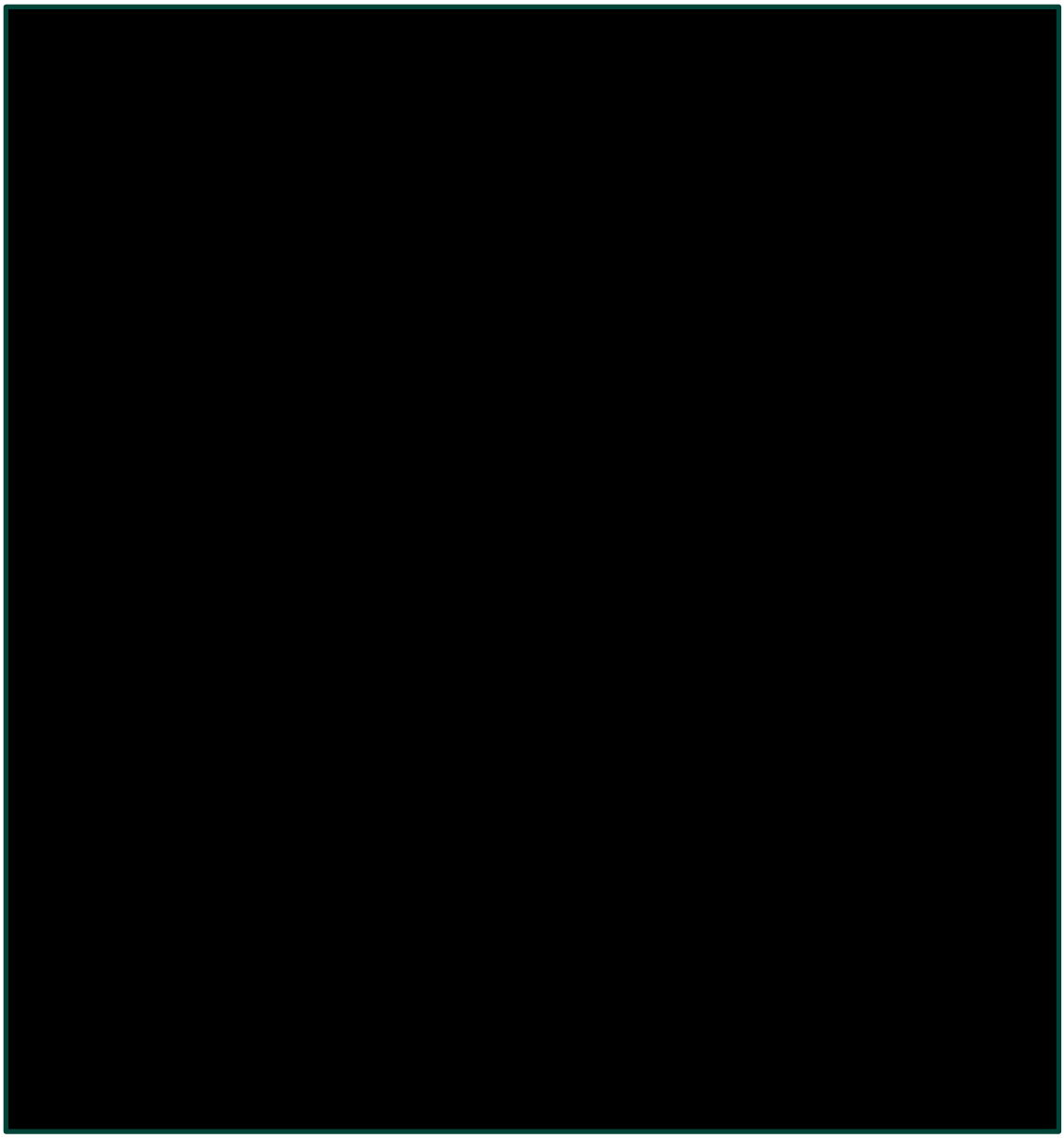

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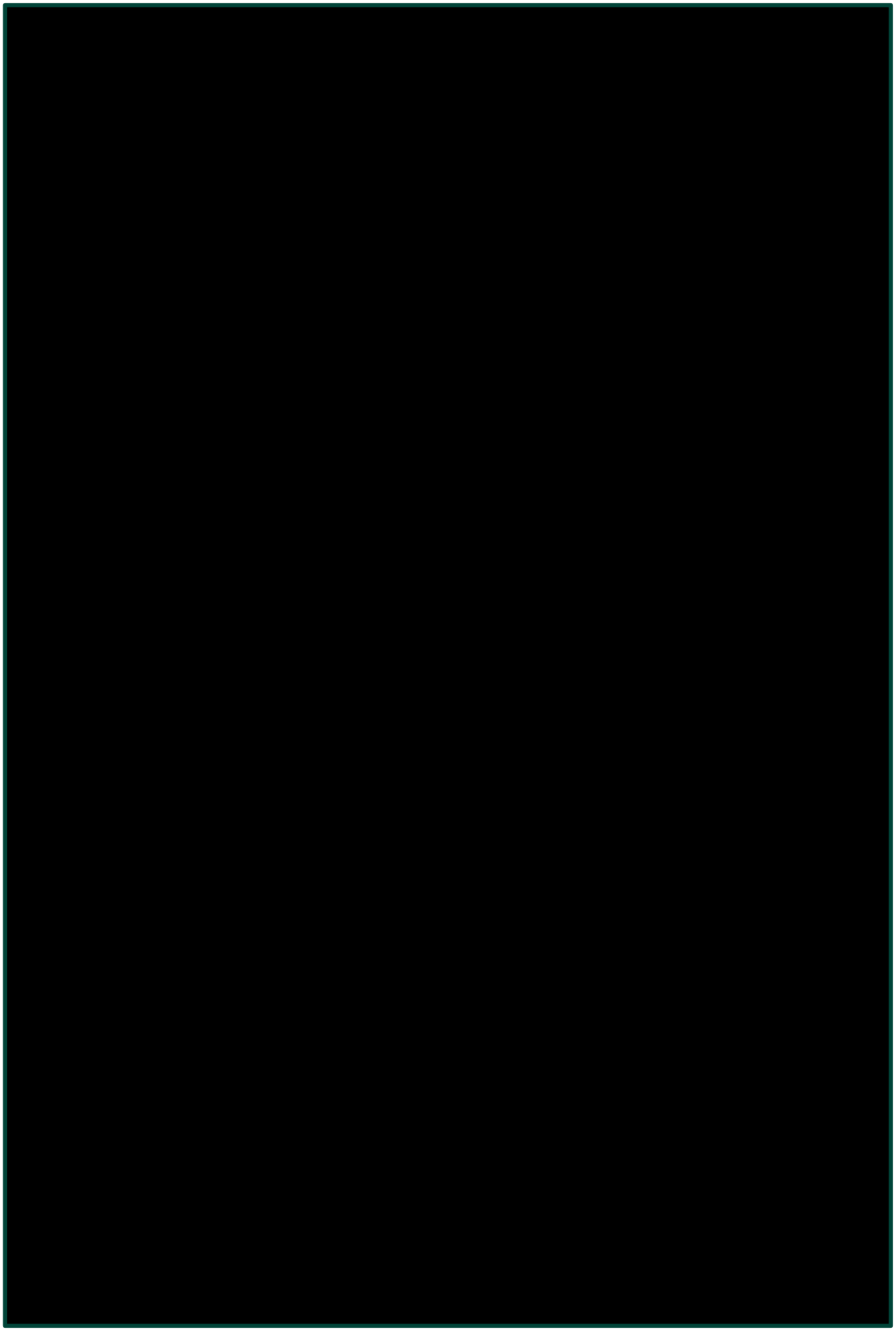

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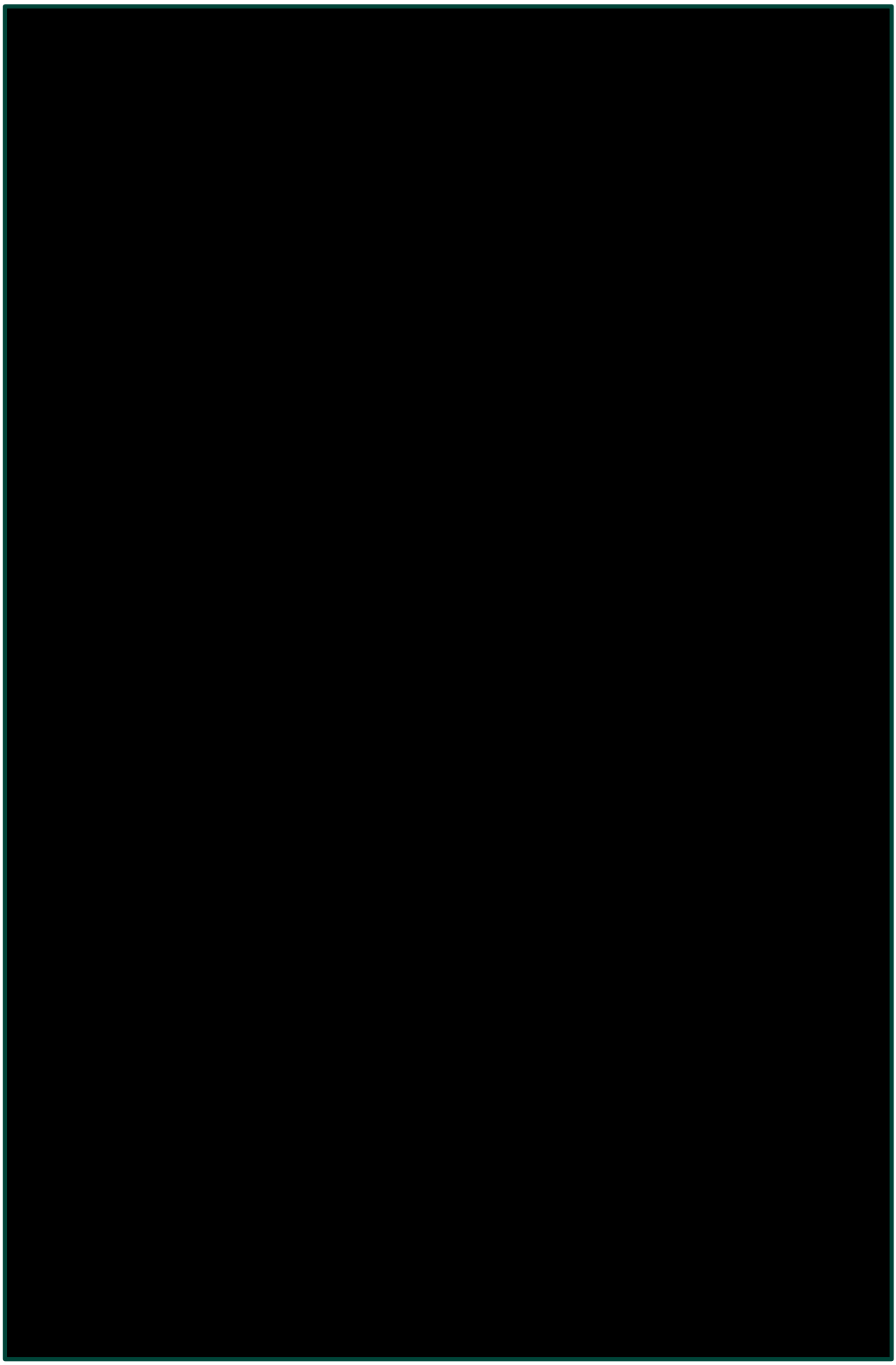

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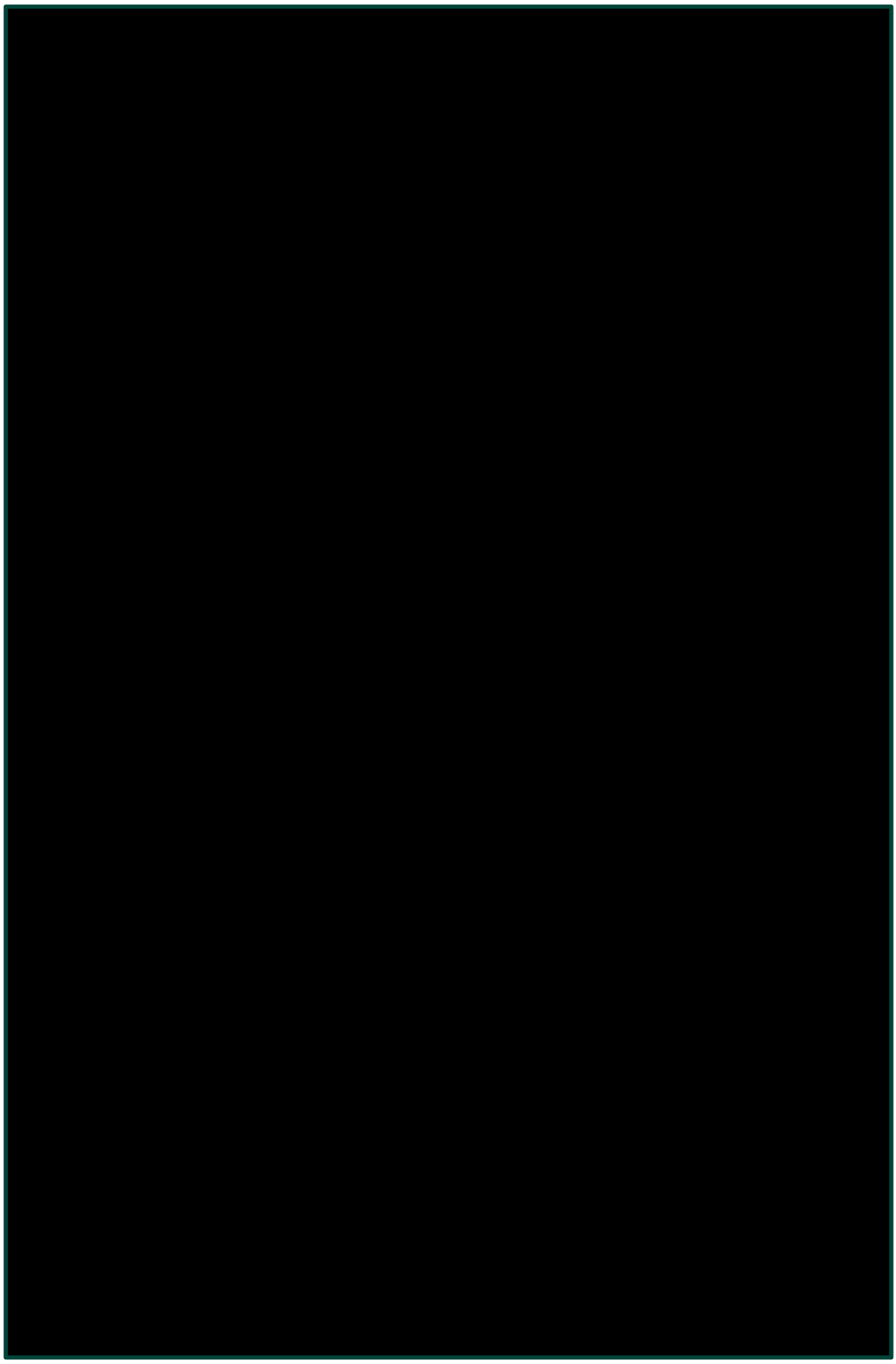

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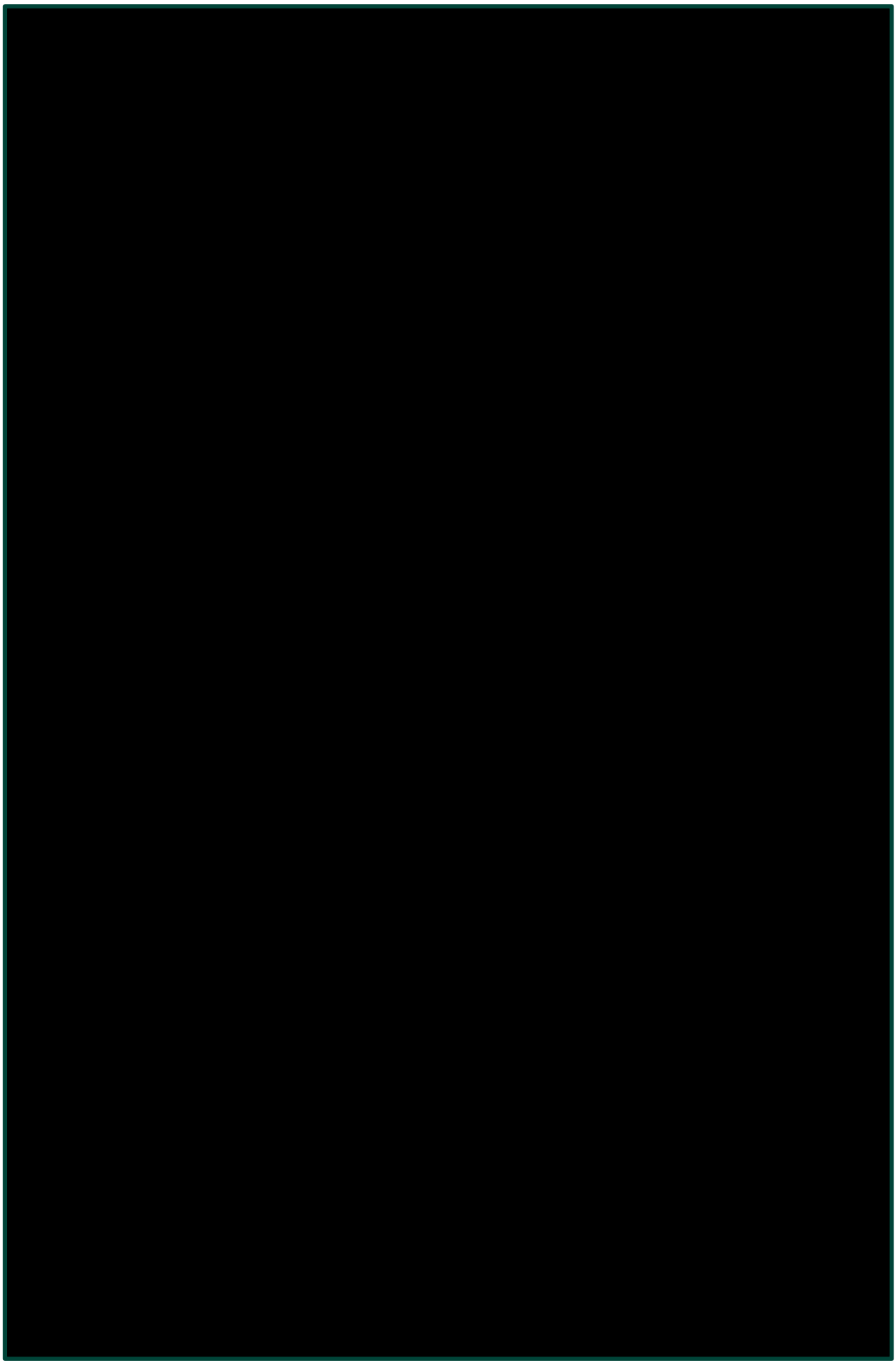

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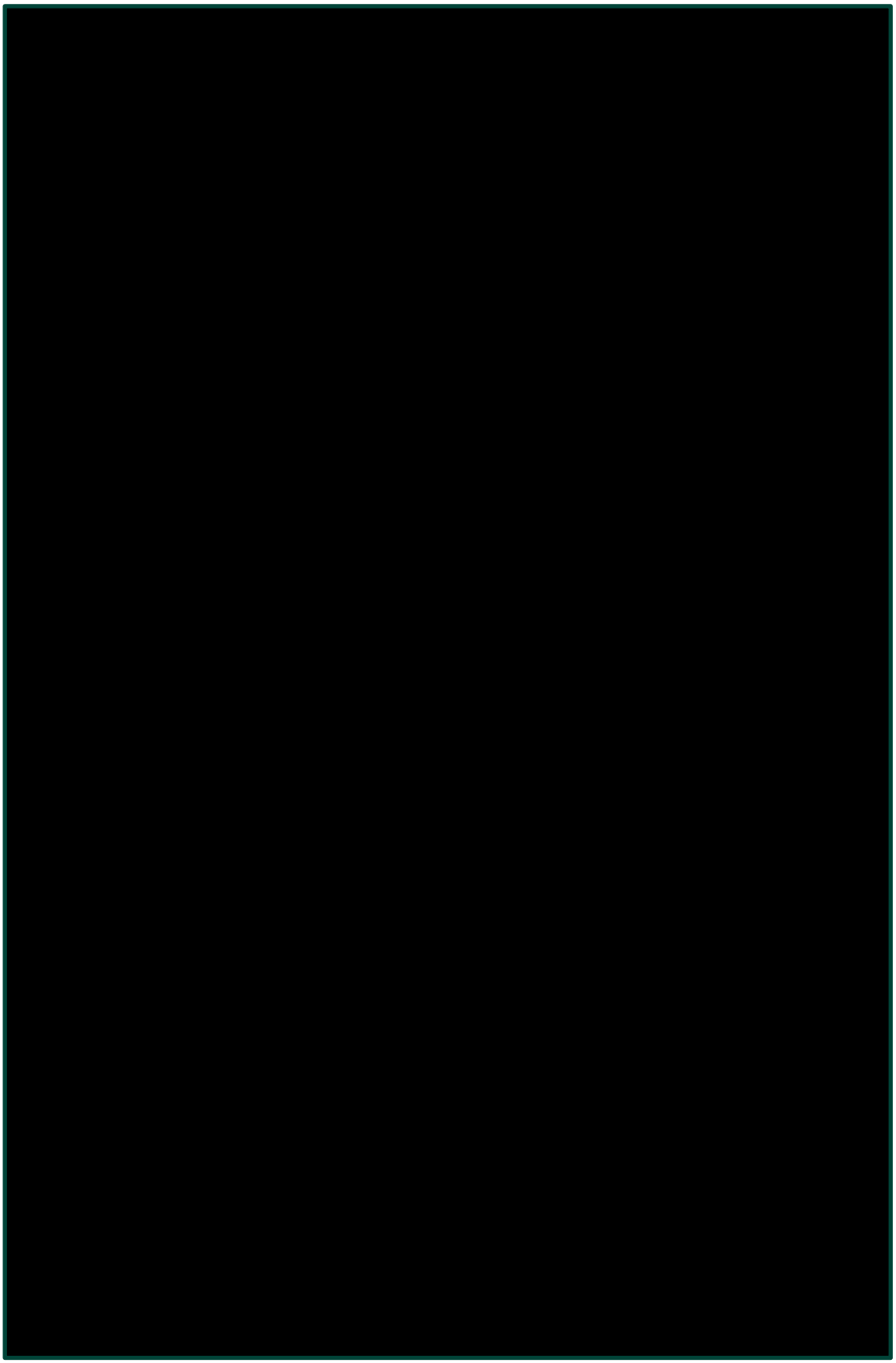

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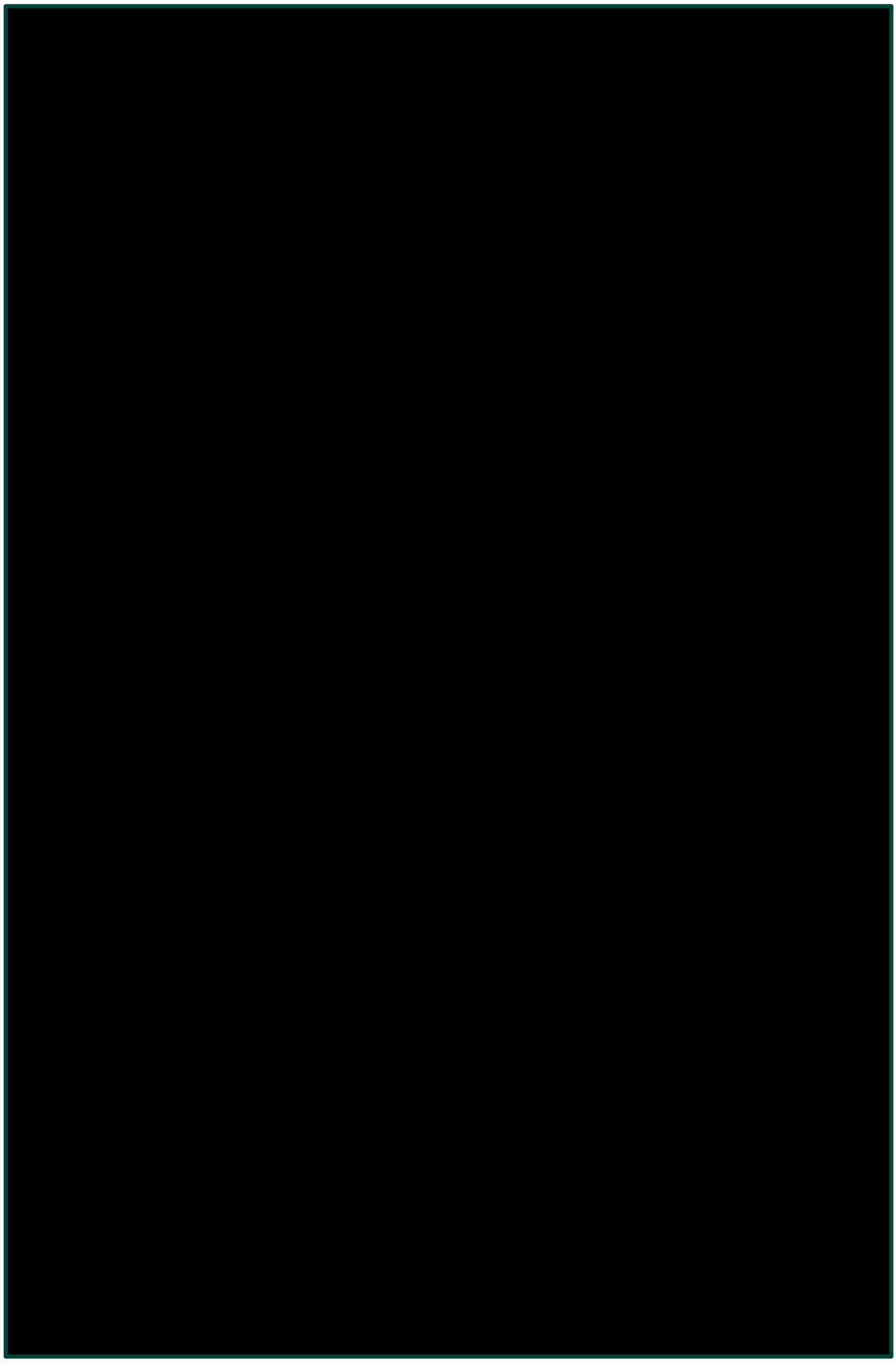

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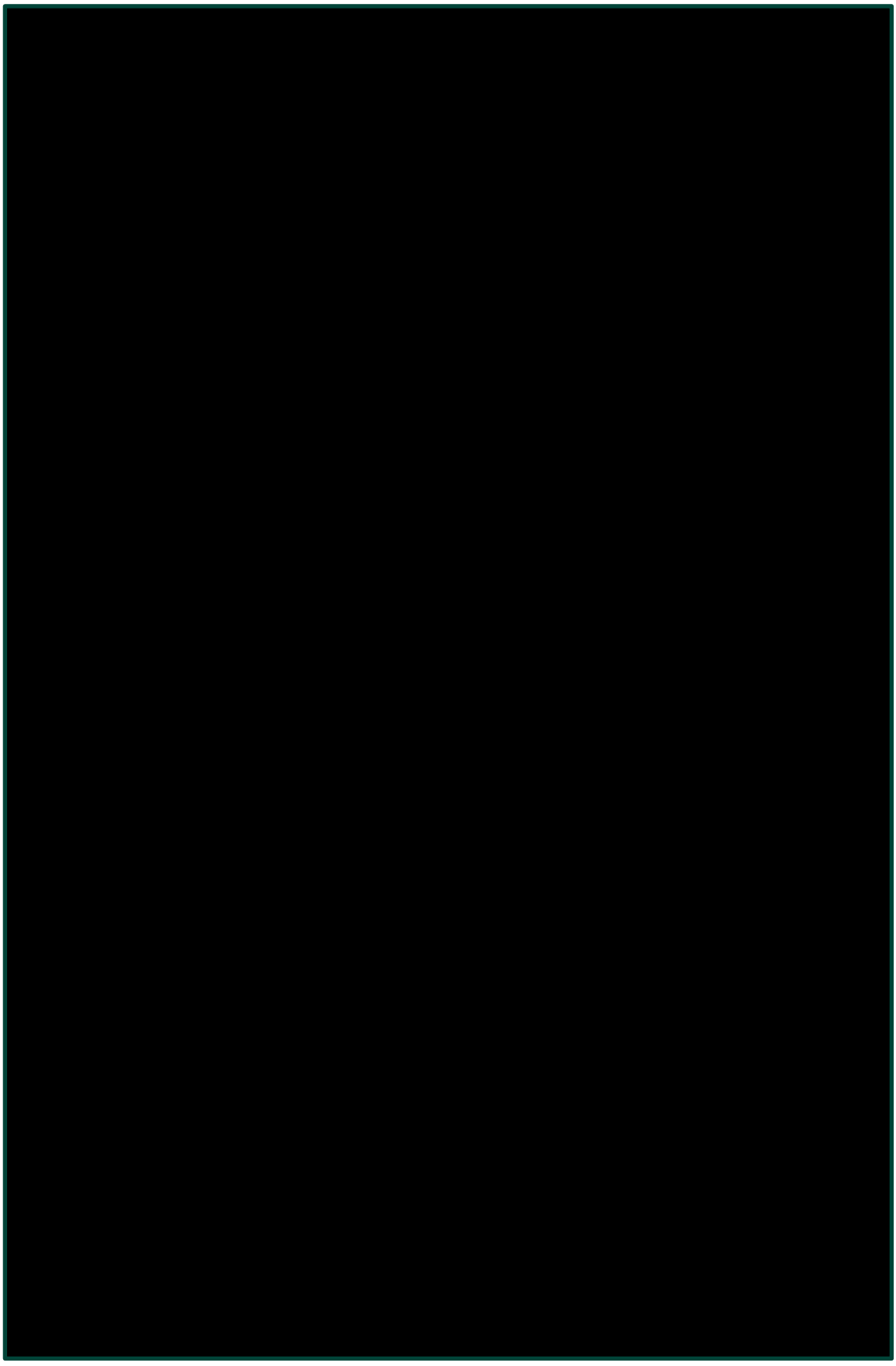

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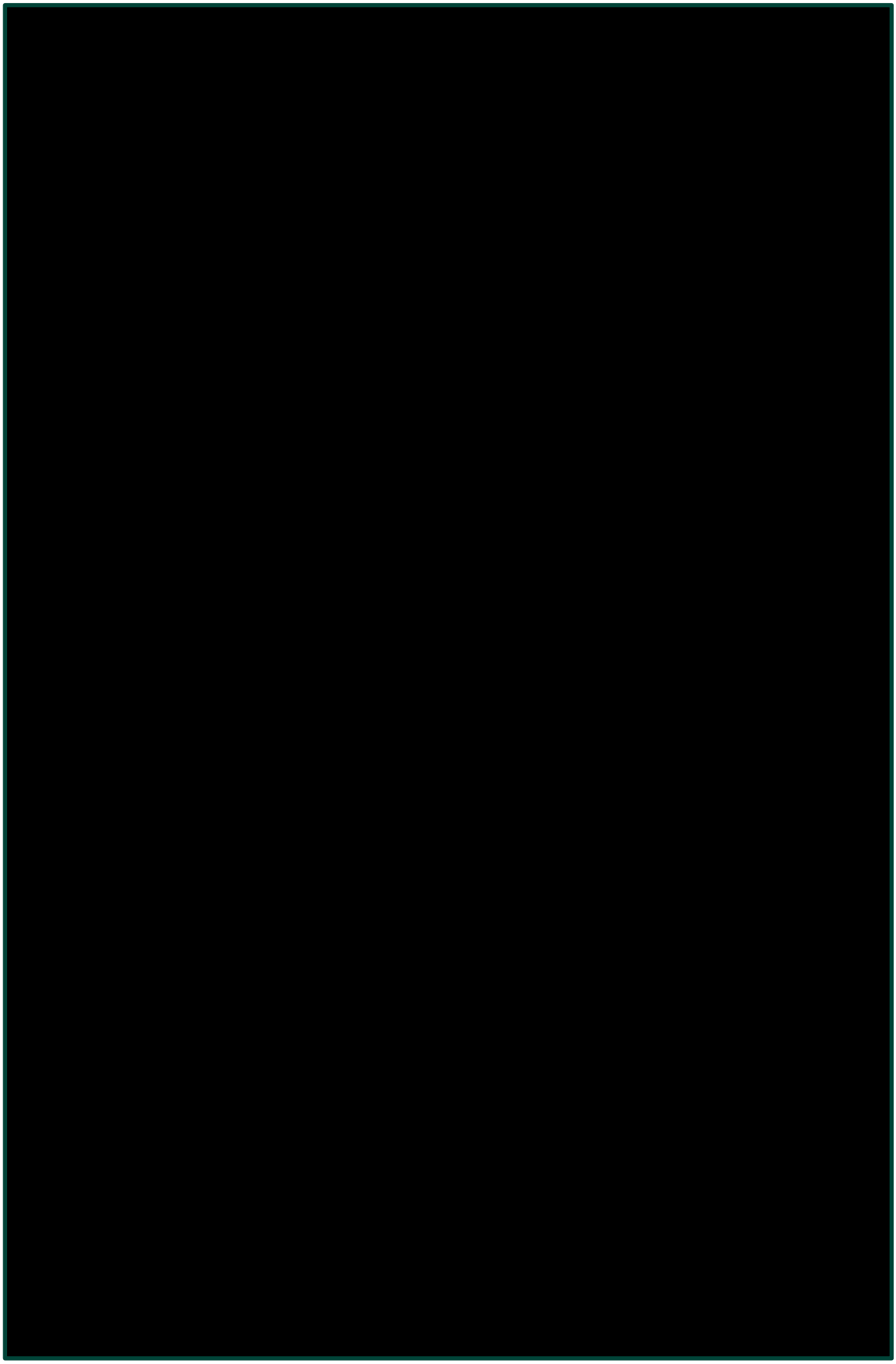

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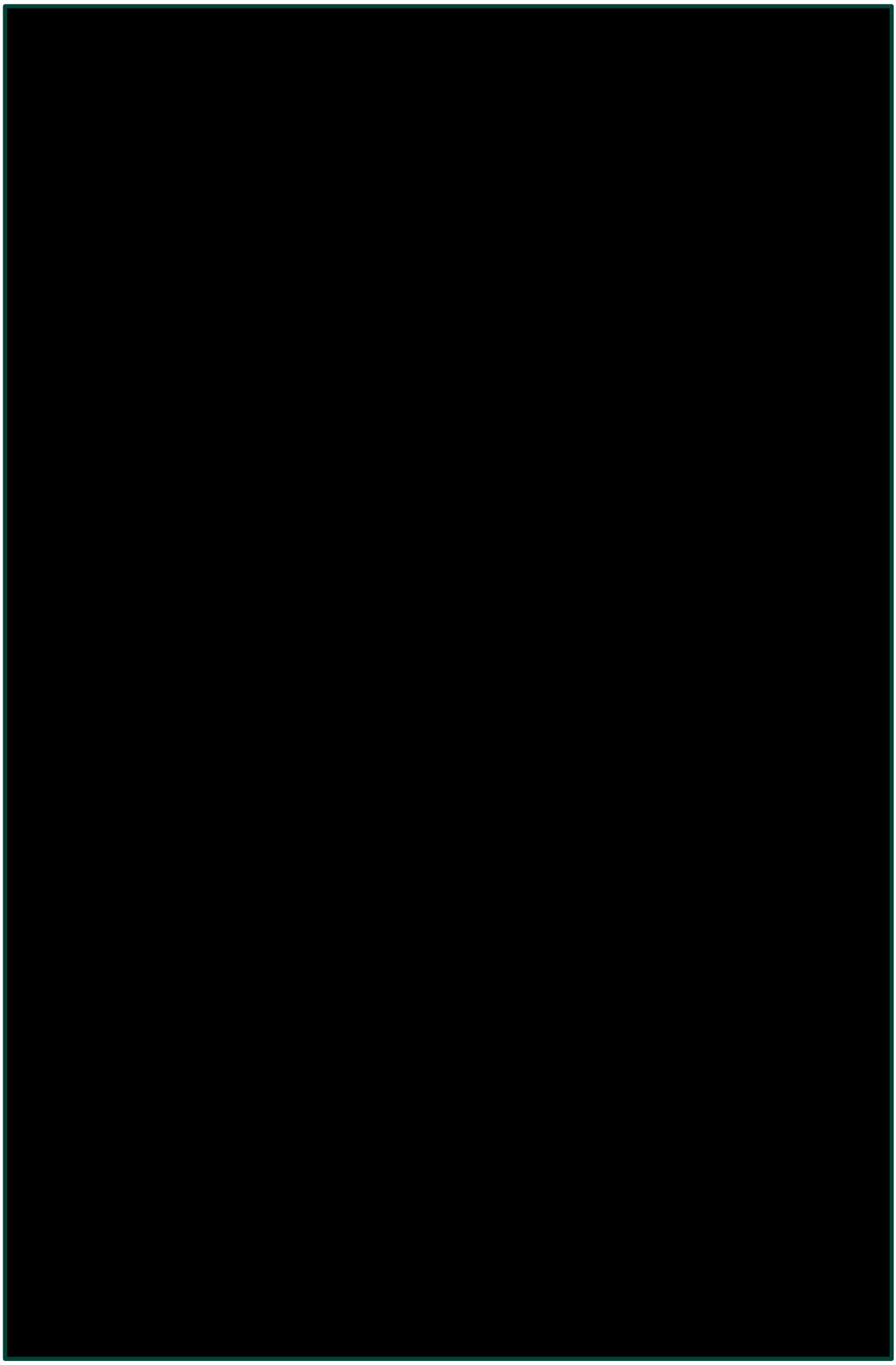

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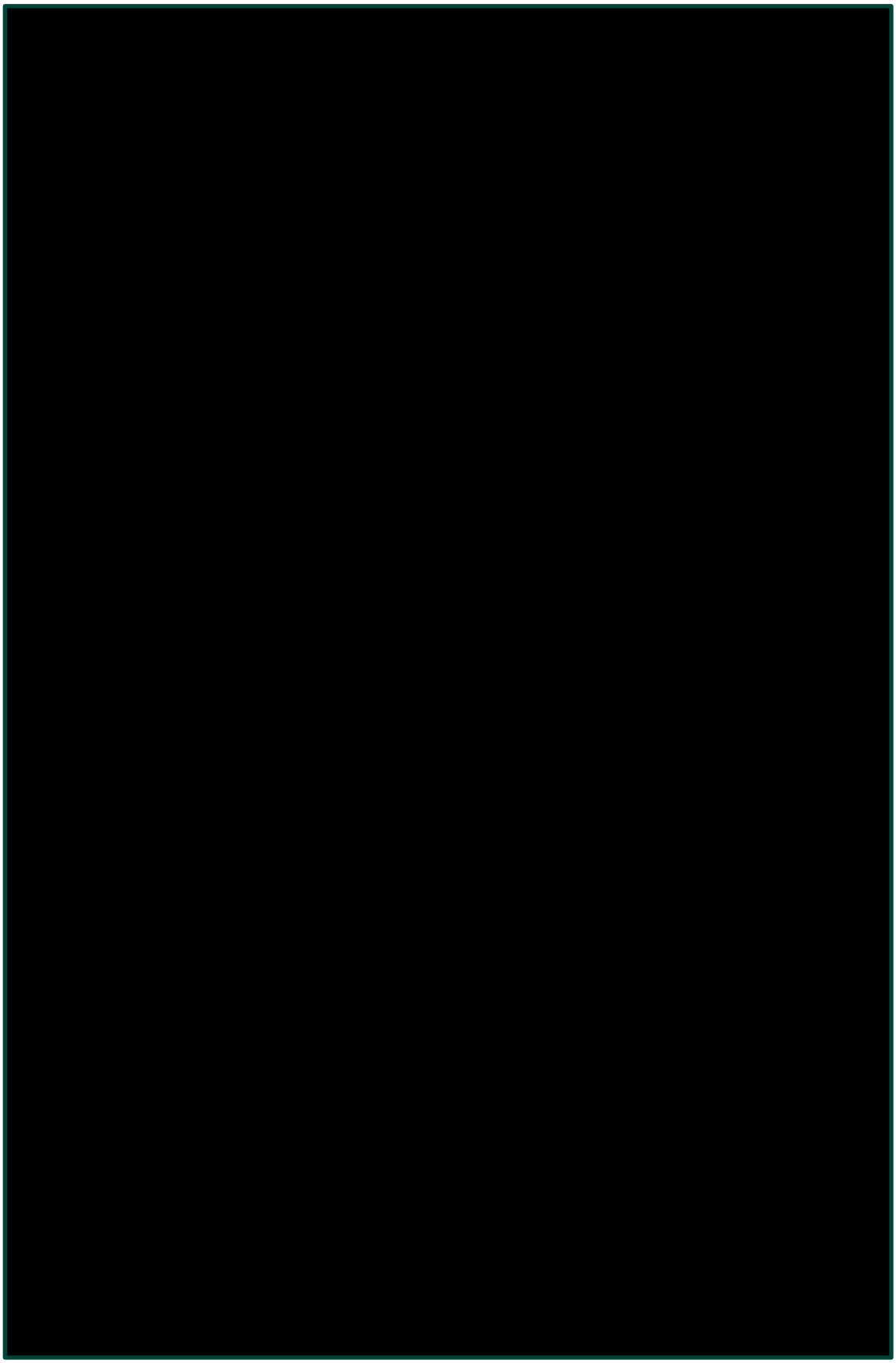

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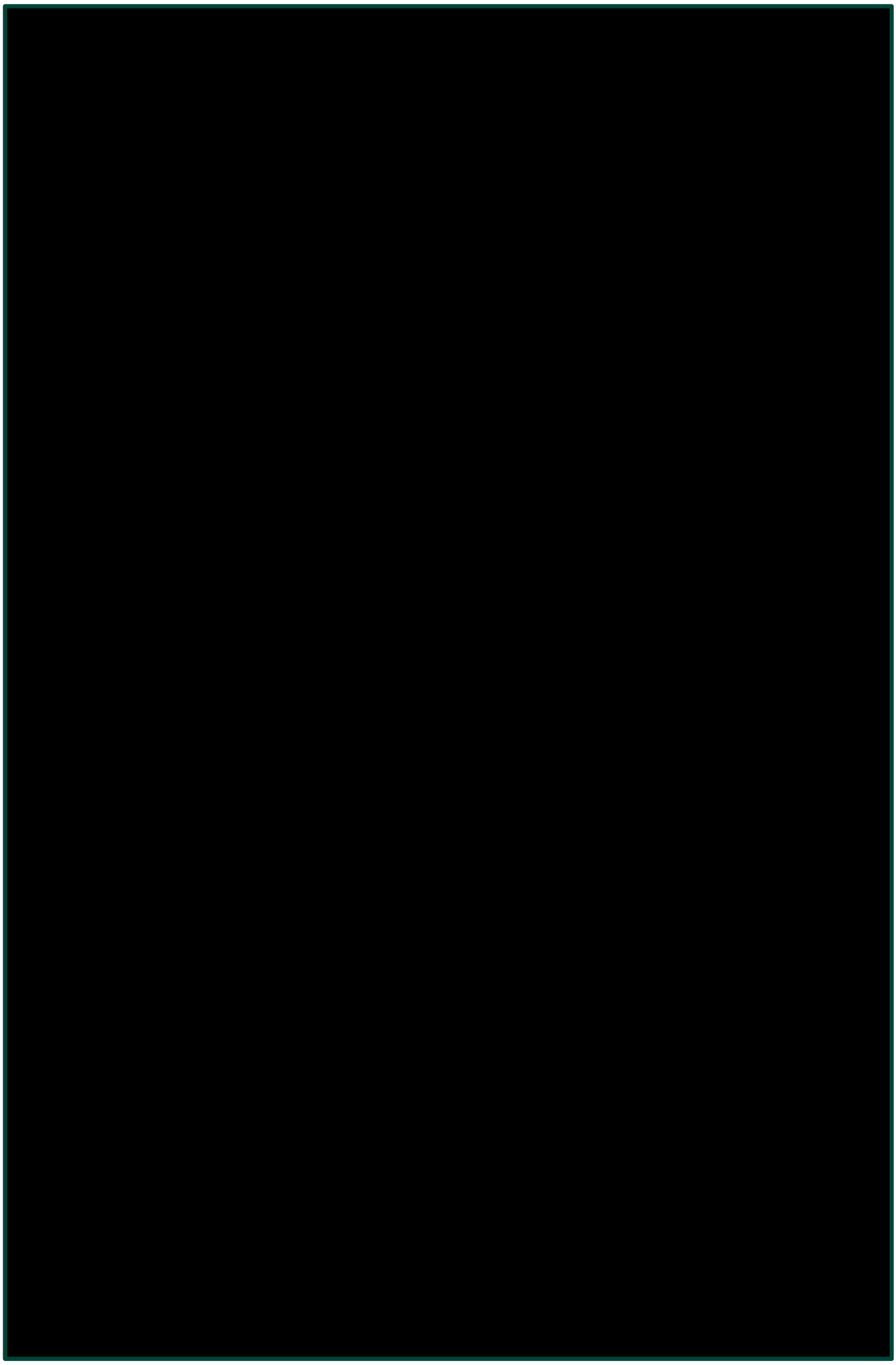

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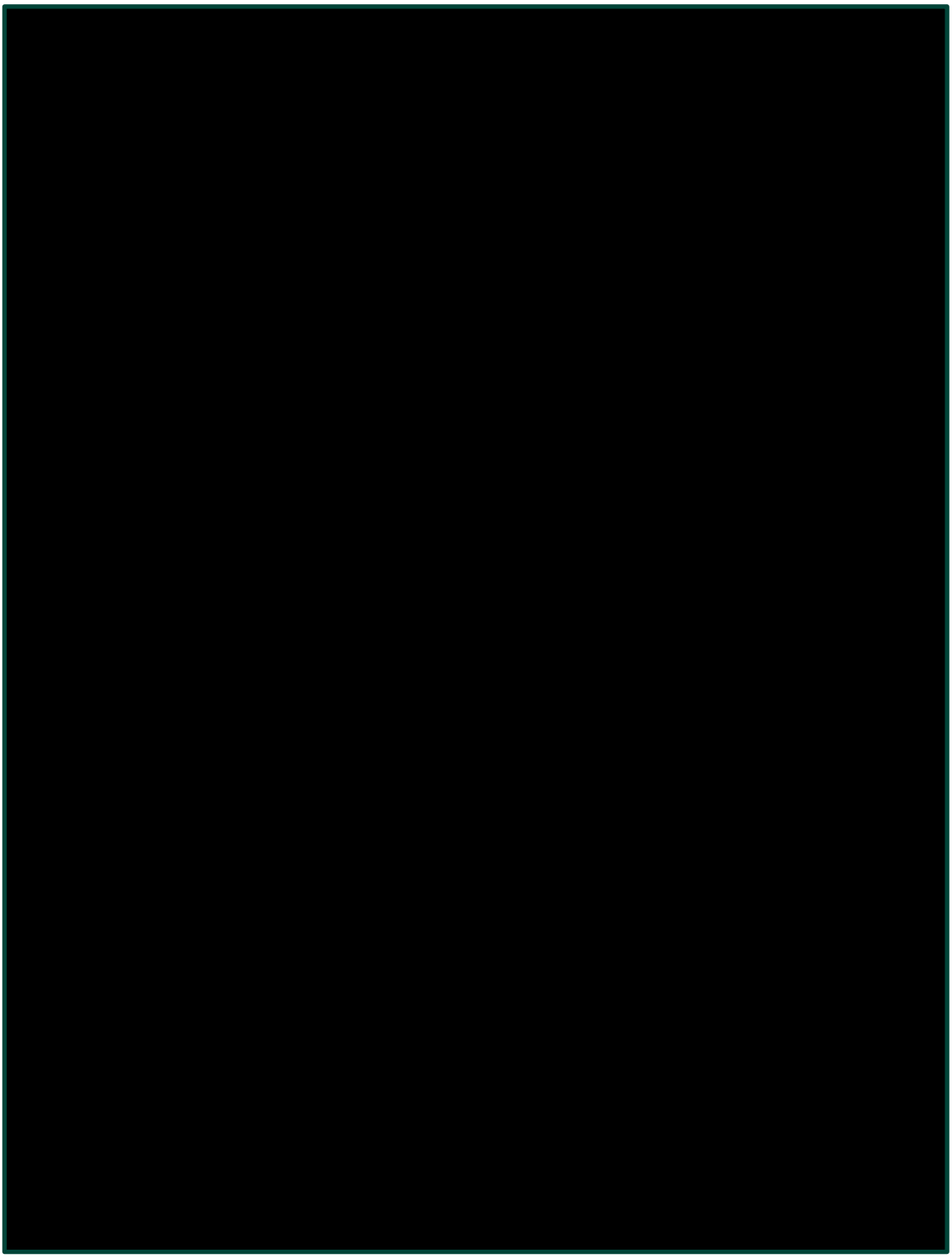

Appendix J Probabilistic sensitivity analyses

The probabilistic sensitivity analysis (PSA) includes all model parameters. Estimates of uncertainty are based on the uncertainty in the source data (where data availability permitted).

Parameters presented in Table 67 were sampled from appropriate statistical distributions (Briggs AH 2005). The complete PSA can be found in sheet the CEM Excel file “Pegcetacoplan CEM DK v1.0” and sheet “2.7 SA Inputs_Switch”.

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Table 67 : Summary of probabilistic distributions applied in the PSA

Parameter cluster	Parameters	Distribution
Hazard ratios	Mortality rate vs general population	Sampled from a log-normal distribution of the parameter
Cost data	Disease management costs Acquisition cost Administration cost AE cost Other costs	Gamma distribution*
Utility data	Health state utilities Disutility of AE's	Beta distribution* Gamma distribution*

AE: Adverse event; DoT: Duration of treatment; OS: Overall survival; PD: Progressed disease; PF: Progression-free; PFS: Progression free survival; PSA: Probabilistic sensitivity analysis;
*For each variable the deterministic value and the standard error (SE) were used to generate the alpha and beta values to construct the gamma and beta distributions in Microsoft Excel (Office 365).

Transition probabilities were sampled from Dirichlet Distribution based on the approach from Briggs et al. (Briggs AH 2003)

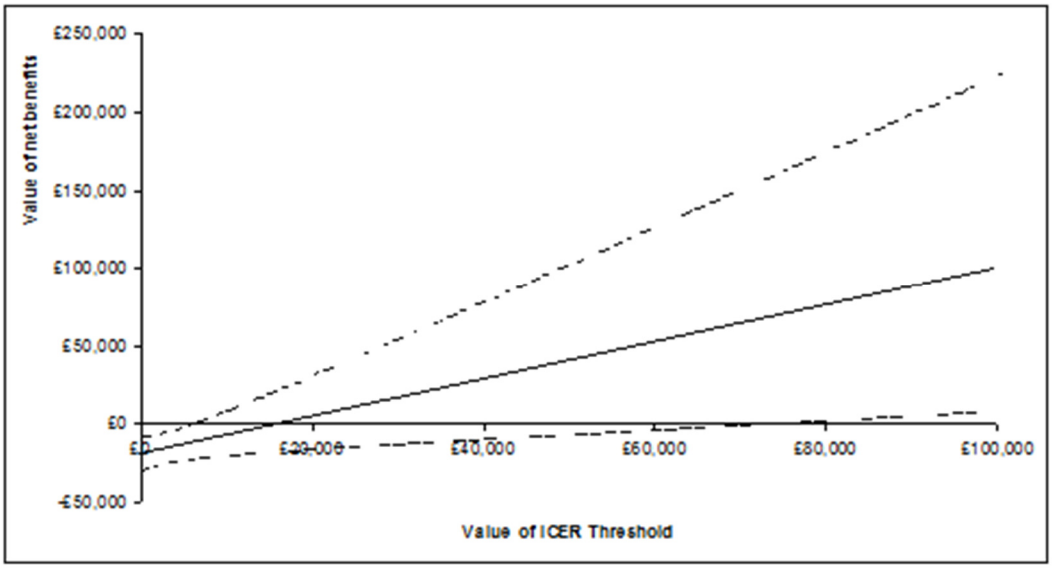
The PSA was performed on the secondary analysis evaluating the cost-effectiveness of pegcetacoplan by estimating the net monetary benefit (NMB) for each of 1,000 simulations of the probabilistic model at a series of incremental cost-effectiveness ratio (ICER) thresholds according to the following formula:

$$NMB = \Delta b \times ICER_t - \Delta c,$$

where NMB is the net monetary benefit, Δb is the incremental benefit, ICERt is the ICER threshold, and Δc is the incremental cost.

The probability of cost-effectiveness at each ICER threshold was estimated as the percentage of the 1,000 simulations with a NMB greater than zero. The probabilistic estimate of the mean ICER was calculated as the difference in the probabilistic mean cost divided by the difference in the probabilistic mean outcome (LY or QALY). The 95% confidence intervals (CIs) were estimated by solving for the ICER threshold at which the 95% CI is zero ().

Figure 11 Net benefit as a function of the incremental cost-effectiveness ratio threshold



CI = confidence interval; ICER = incremental cost-effectiveness ratio.

Note: Data are for demonstration purposes only and do not reflect model output. The mean net benefit is zero when the ICER equals the ICER threshold. Similarly, the lower and upper 95% CIs for the mean net benefit equal zero when the CI for the ICER equals the ICER threshold. Therefore, the 95% CIs for the mean ICER can be estimated by solving for the ICER threshold at which the 95% CI is zero (the points at which the CI functions intersect the x-axis).

The results of the PSA are as follows:

- Probabilistic mean and 95% CIs for the discounted total cost, LYs, and QALYs for each cohort
- Probabilistic mean and 95% CIs for the discounted incremental cost, LYs, and QALYs
- Probabilistic mean and 95% CIs for the incremental cost per LY saved and the incremental cost per QALY
- The probability of cost-effectiveness at a user-defined willingness-to-pay threshold (e.g., 1,000,000 DKK per QALY)
- Individual simulation results, presented on the cost-effectiveness plane
- Cost-effectiveness acceptability curves

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Appendix K Company-specific appendix

I. Key Secondary Endpoint #1: Transfusion Avoidance

Transfusion Avoidance

As shown in Table 68, a larger number and percentage of patients in the pegcetacoplan group than in the eculizumab group avoided transfusions during the 16-week RCP. In the pegcetacoplan group, 35/41 (85.4%) did not require a transfusion whereas in the eculizumab group, only 6/35 (15.4%) did not require transfusion. Noninferiority was met as the lower bound of the 95% CI of the 62.5% adjusted treatment difference (48.3%-76.8%) was greater than the prespecified noninferiority margin of −20%.

Table 68: Summary of the Number of Patients with Transfusion Avoidance During the Randomized Controlled Period (Intent-to-Treat Set)—PEGASUS

Transfusions avoidance	Statistics	Pegcetacoplan (N = 41)	Eculizumab (N = 39)
Yes (no transfusion)	n (%)	35 (85.4)	6 (15.4)
No	n (%)	6 (14.6)	33 (84.6)
Received at least one transfusion[a]	n (%)	5 (83.3)	33 (100)
Withdrew from the study without having had a transfusion[a]	n (%)	1 (16.7)	0
Difference in percentage (pegcetacoplan - eculizumab)	Risk difference 95% CI Nominal *P* value	0.6253 0.4830, 0.7677 < 0.0001	

CI = confidence interval; RCP = randomized controlled period.

Notes: Transfusion avoidance is the proportion of subjects who did not require a transfusion during the RCP.

Subjects who experienced more than one transfusion during RCP are only counted once.

Subjects who did not have a transfusion but withdrew before Week 16 were considered as having a transfusion in the analysis of transfusion avoidance.

The 95% CI for difference in percentage between treatments is constructed using the stratified (Miettinen-Nurminen) method.

a Percentages are based on the number of subjects in No category for each column.

Source: Hillmen (2021b).

Table 69 summarizes the results of the analysis of TA during the RCP by PRBC transfusion strata (< 4 transfusions and ≥ 4 transfusions within the 12 months prior to Day 28). The proportion of subjects who were transfusion avoidant was similar in the pegcetacoplan group, regardless of PRBC transfusion strata (85% vs. 85.7% for < 4 transfusions vs. ≥ 4 transfusions, respectively). This is not the case for the eculizumab group, in which more subjects achieved TA in the < 4 transfusion stratum (31.3%) than in the ≥ 4 transfusion stratum (4.3%).

Table 69: Summary for Number of Subjects With Transfusion Avoidance During Randomized Controlled Period by Number of Packed Red Blood Cell Transfusion Prior to Baseline (Intent-to-Treat Set)

Transfusions Avoidance	Statistics	Pegcetacoplan (N = 20)	Eculizumab (N = 16)
Number of PRBC transfusion prior to baseline: < 4			
Yes (no transfusion)	n (%)	17 (85.0)	5 (31.3)
No	n (%)	3 (15.0)	11 (68.8)
Received at least one transfusion[a]	n (%)	2 (66.7)	11 (100)
Withdrew from the study without having had a transfusion[a]	n (%)	1 (33.3)	0
Difference in percentage (pegcetacoplan - eculizumab)	Risk difference 95% CI	0.5375 0.2617, 0.8133	NA
Number of PRBC transfusion prior to baseline: ≥ 4			
		Pegcetacoplan Group (N = 21)	**Eculizumab Group (N = 23)**
Yes (no transfusion)	n (%)	18 (85.7)	1 (4.3)
No	n (%)	3 (14.3)	22 (95.7)
Received at least one transfusion[a]	n (%)	3 (100)	22 (100)
Withdrew from the study without having had a transfusion[a]	n (%)	0	0
Difference in Percentage (pegcetacoplan - eculizumab)	Risk difference 95% CI	0.8137 0.6424, 0.9850	NA

CI = confidence interval; NA = not applicable; PRBC = packed red blood cell; RCP = randomized controlled period.

Notes: Transfusion avoidance is the proportion of subjects who do not require a transfusion during the RCP

Subjects who experienced more than one transfusion during RCP is only counted as once.

Subjects who have not had a transfusion but withdraw before Week 16 will be considered as having a transfusion in the analysis of transfusion avoidance.

The 95% CI for difference in percentage between treatments is constructed using the asymptotic method.

[a] Percentages are based on the number of subjects in No category for each column.

Source: Hillmen, 2021.

Number of PRBC Units Transfused

As shown in Table 70, patients in the pegcetacoplan cohort needed fewer transfusions of PRBC than the patients in the eculizumab cohort. The mean number of PRBC units required during the RCP (>Day 1 to Week 16 and Week 4 to Week 16) in the pegcetacoplan group was 0.6 units and in the eculizumab group was 5.1 (95% CI, 2.0-4.0).

Table 70: Number of Packed Red Blood Cell Units Transfused During Randomized Controlled Period, Censored for Transfusion (Intent-to-Treat Set)—PEGASUS

Statistics	Pegcetacoplan (N = 41)	Eculizumab (N = 39)
Total units	26	198
Mean (SD)	0.6 (2.03)	5.1 (5.60)
Median	0.0	3.0
Min, Max	0, 11	0, 27
95% CI	2.0, 4.0	NA

CI = confidence interval; max = maximum; min = minimum; NA = not applicable; PRBC = packed red blood cell; SD = standard deviation.

Notes: Wilcoxon rank-sum test *P* value for the comparison between treatments is based on median using stratified nonparametric analysis. The 95% CI is constructed using Hodges-Lehmann Estimation of Location Shift.

Subjects who withdraw during the randomized controlled period before Week 16 will have their number of units of PRBC estimated from the duration they were in the study (i.e., number per week × duration of endpoint). Hence, the analysis of this endpoint will equate to an analysis of the frequency of transfusions. APL-302-01010003 discontinued before transfusion hence the units of transfusion are 0.

Source: Hillmen, 2021b.

Table 71 presents the number of PRBC units transfused during the RCP by number of transfusions in the previous 12 months (0 or > 0). Among subjects who had no PRBC transfusions in the past 12 months, subjects in the pegcetacoplan group had a mean of 0.4 PRBC transfusions, and subjects in the eculizumab group had a mean of 1.5 PRBC transfusions. For subjects who had > 0 PRBC transfusions in the previous 12 months, the pegcetacoplan group had a mean of 0.7 PRBC transfusions, and the eculizumab group had a mean of 6.3 PRBC transfusions during this time.

Table 71: Number of Packed Red Blood Cell Units Transfused During Randomized Controlled Period by the Number of Transfusion in the Past 12 Months, Censored for Transfusion (Intent-to-Treat Set)

Statistics	Pegcetacoplan (N = 31)	Eculizumab (N = 29)
# of Transfusions in the past 12 months = 0		
n	10	10
Mean (SD)	0.4 (1.26)	1.5 (1.08)
Median	0.0	2.0
Min, Max	0, 4	0, 3
# of Transfusions in the past 12 months > 0		
n	31	29
Mean (SD)	0.7 (2.24)	6.3 (6.00)
Median	0.0	6.0
Min, Max	0, 11	0, 27

max = maximum; min = minimum; PRBC = packed red blood cell; SD = standard deviation.

Notes: Wilcoxon rank-sum test *P* value for the comparison between treatments is based on median using stratified nonparametric analysis. The 95% CI is constructed using Hodges-Lehmann Estimation of Location Shift.

Subjects who withdraw during the randomized controlled period before Week 16 will have their number of units of PRBC estimated from the duration they were in the study (i.e., number per week × duration of endpoint). Hence, the analysis of this endpoint will equate to an analysis of the frequency of transfusions.

APL-302-01010003 discontinued before transfusion hence the units of transfusion are 0.

Source: Hillmen, 2021b

Total Number of PRBC Transfusions

Table 72 shows that the mean total number of PRBC transfusions during the RCP was higher in the eculizumab group (2.4 transfusions) than in the pegcetacoplan group (0.3 transfusions).

Table 72: Total Number of Packed Red Blood Cell Transfusions During Randomized Controlled Period (Intent-to-Treat Set)

Statistics	Pegcetacoplan (N = 41)	Eculizumab (N = 39)
Mean (SD)	0.3 (1.06)	2.4 (2.50)
Median	0.0	1.0
Min, Max	0, 6	0, 11
95% CI	1.0, 2.0	

CI = confidence interval; max = maximum; min = minimum; SD = standard deviation.

Notes: Wilcoxon rank-sum test *P* value for the comparison between treatments is based on median using stratified nonparametric analysis. The 95% CI is constructed using Hodges-Lehmann Estimation of Location Shift.

Subjects who withdraw during the randomized controlled period before Week 16 will have their number of units of PRBC estimated from the duration they were in the study (i.e., number per week × duration of endpoint). Hence, the analysis of this endpoint will equate to an analysis of the frequency of transfusions.

Source: Hillman, 2021b

II. Key Secondary Endpoint #2: Change From Baseline in Absolute Reticulocyte Count to Week 16

After noninferiority was established for TA, noninferiority was assessed for CFB to Week 16 in ARC. Table 73 shows the CFB in ARC during the RCP using the MMRM model for the ITT set, censored for transfusion. The mean ARC at baseline was similar in both treatment groups. The difference in LS mean at Week 16 was −163.61 × 109 cell/L, with a 95% CI of −189.91 to −137.30 × 109 cell/L (nominal P value < 0.0001). The upper bound of the 95% CI of the adjusted treatment difference was less than the prespecified noninferiority margin of 10, so noninferiority was met.

Table 73: MMRM Model: Changes From Baseline in Reticulocyte Count During Randomized Controlled Period, Censored for Transfusion (Intent-to-Treat Set)—PEGASUS

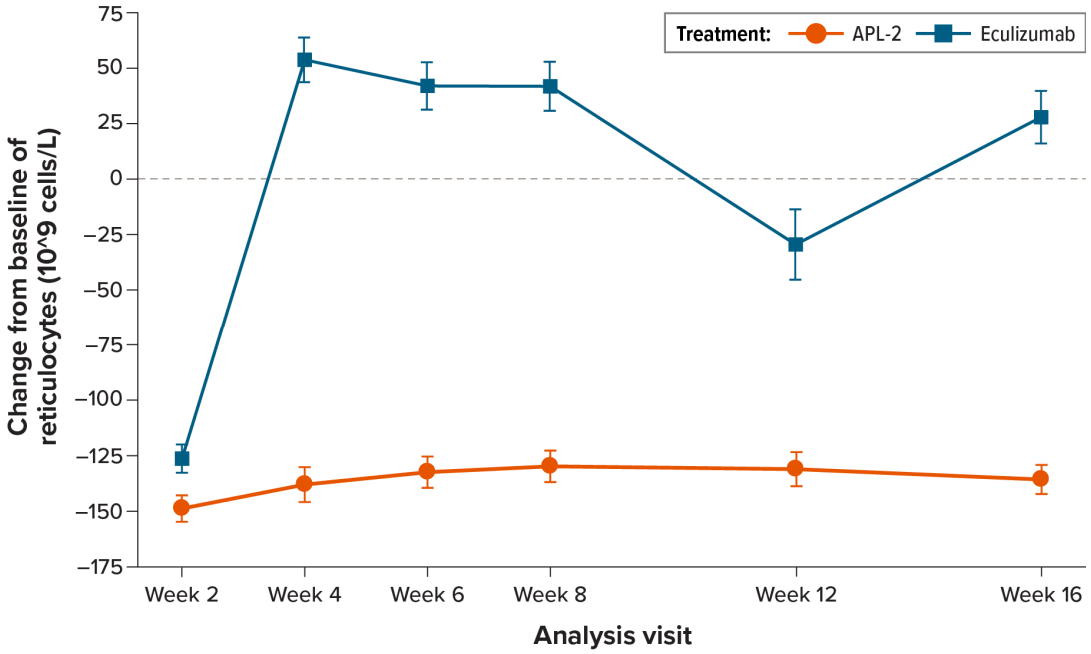
	Pegcetacoplan (N = 41) LS Mean (SE) (10^9 Cells/L)	Eculizumab (N = 39) LS Mean (SE) (10^9 Cells/L)	Difference (95% CI) in LS Mean (vs. Eculizumab) (10^9 Cells/L)	Nominal *P* Value
Week 2	−148.88 (5.945)	−126.42 (6.349)	−22.46 (−38.72 to −6.20)	0.0075
Week 4	−138.11 (7.838)	53.64 (10.068)	−191.76 (−216.51 to −167.0)	< 0.0001
Week 6	−132.54 (7.029)	41.86 (10.686)	−174.40 (−199.25 to −149.55)	< 0.0001
Week 8	−129.91 (7.083)	41.71 (11.059)	−171.62 (−197.20 to −146.03)	< 0.0001
Week 12	−131.17 (7.680)	−29.63 (15.851)	−101.54 (−136.51 to −66.57)	< 0.0001
Week 16	−135.82 (6.543)	27.79 (11.859)	−163.61 (−189.91 to −137.30)	< 0.0001

CI = confidence interval; LS = least square; n = number of subjects with available data; SE = standard error.

Note: Baseline is the average of available measurements recorded from central laboratory before taking the first dose of pegcetacoplan. Model includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of stratification factors number of transfusions and platelet count at screening.

Source: Hillmen (2021b).

Figure 12 is a plot of CFB in ARC censored for transfusion using the MMRM model. Absolute reticulocyte count in the pegcetacoplan group decreased from baseline and stayed below baseline through Week 16. In the eculizumab group, the initial decrease from baseline seen during the run-in period was reversed by Week 4 of the RCP, and the ARC generally remained above baseline.



APL-2 = pegcetacoplan, ICE = intercurrent event; MMRM = mixed model for repeated measures; PRBC = packed red blood cell; SE = standard error.

Note: Baseline is the average of available measurements records from central labs prior to taking the first dose of pegcetacoplan. For PRBC transfusion and withdrawal from the study: all measurements after the ICE events were set to missing.

Source: Hillmen (2021b).

Absolute reticulocyte count observed values and CFB censored for transfusion (unadjusted data) support the finding of an overall trend of decreasing ARC in the pegcetacoplan group (Table 74 and Table 75).

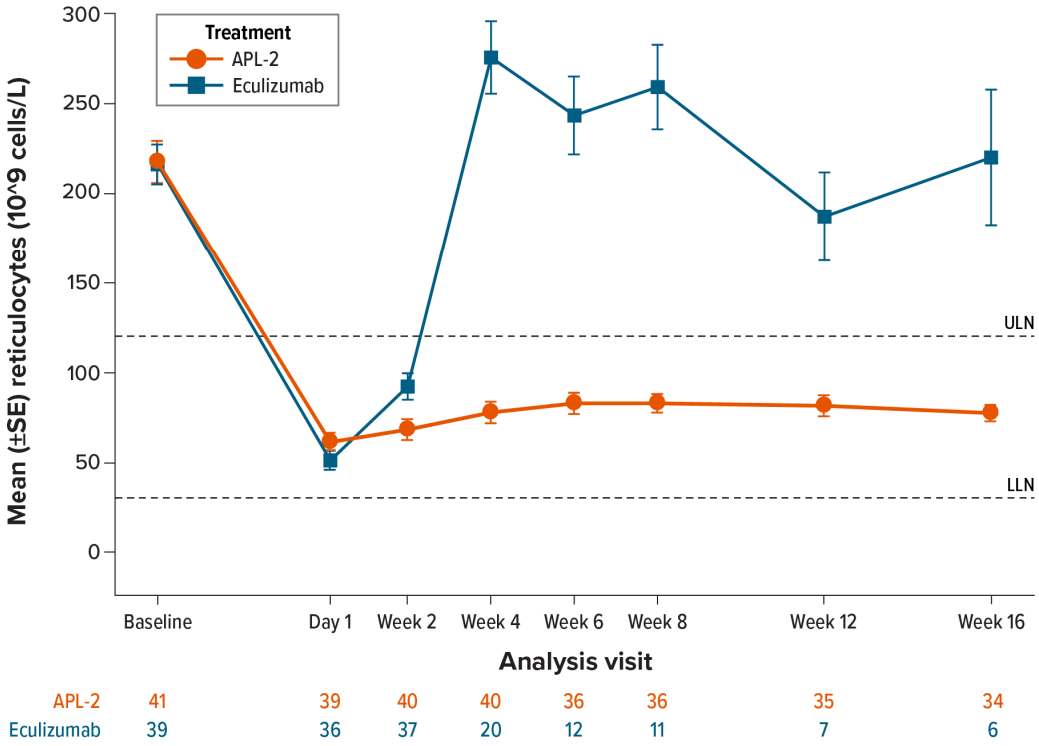
Table 74: Descriptive Summary: Observed Values and Changes From Baseline in Reticulocyte Count During Randomized Controlled Period, Censored for Transfusion (Intent-to-Treat Set)—PEGASUS

Visit	Pegcetacoplan N = 41			Eculizumab N = 39		
	n	Mean (SD) (10^9 cells/L)	CFB (10^9 cells/L)	n	Mean (SD) (10^9 cells/L)	CFB (10^9 cells/L)
Baseline	41	217.52 (74.964)	NA	39	216.15 (69.136)	NA
Week 2	40	68.50 (36.624)	−151.96 (73.120)	37	92.43 (44.622)	−124.73 (48.417)
Week 4	40	78.00 (37.771)	−140.21 (69.375)	20	275.50 (89.882)	36.08 (45.664)
Week 6	36	83.06 (35.361)	−127.87 (62.905)	12	243.33 (74.874)	29.03 (53.614)
Week 8	36	83.06 (30.782)	−132.18 (69.969)	11	259.09 (77.776)	27.88 (50.012)
Week 12	35	81.71 (34.512)	−137.52 (65.760)	7	187.14 (64.991)	−20.71 (104.260)
Week 16	34	77.65 (26.862)	−142.75 (64.382)	6	220.00 (92.304)	11.67 (43.321)

CFB = change from baseline; NA = not applicable; RCP = randomized controlled period; SD = standard deviation.

Note: Baseline is the average of available measurements recorded from central laboratory before taking the first dose of pegcetacoplan. All values after the intercurrent events during RCP were set to missing. This table summarizes data as observed with no imputation of missing data.

Source: Hillmen, 2021



APL-2 = pegcetacoplan, LLN = lower limit of normal; SE = standard error; ULN = upper limit of normal.

III. Key Secondary Endpoint #3: Change From Baseline in Lactate Dehydrogenase to Week 16

After noninferiority was established for ARC, noninferiority was assessed for CFB to Week 16 in LDH. As shown in Table 75, the LS mean CFB for LDH at Week 16 was −14.76 U/L in the pegcetacoplan group and −10.12 U/L in the eculizumab group, for a difference in LS mean of −4.63 U/L (95% CI, −181.30 to 172.04 U/L; nominal P value, 0.9557). The upper bound of the 95% CI of the adjusted treatment difference was not less than the prespecified noninferiority margin of 20, so LDH did not meet the predefined criterion for noninferiority.

Table 75: MMRM Model: Change From Baseline in Lactate Dehydrogenase Level During Randomized Controlled Period, Censored for Transfusion (Intent-to-Treat Set)—PEGASUS

Visit	Pegcetacoplan (N = 41) LS Mean (SE) U/L	Eculizumab (N = 39) LS Mean (SE) U/L	Difference (95% CI) in LS Mean (vs. Eculizumab) U/L	Nominal *P* Value
Week 2	−90.99 (27.734)	90.09 (29.524)	−181.08 (−257.68 to −104.47)	< 0.0001
Week 4	−57.57 (20.188)	27.28 (26.876)	−84.85 (−148.47 to −21.23)	0.0107
Week 6	−24.83 (41.925)	30.12 (66.338)	−54.94 (−210.01 to 100.12)	0.4807
Week 8	26.05 (75.861)	19.28 (121.259)	6.77 (−290.68 to 304.23)	0.9625
Week 12	−11.11 (51.257)	−24.68 (83.745)	13.57 (−190.18 to 217.32)	0.8905
Week 16	−14.76 (42.708)	−10.12 (71.025)	−4.63 (−181.30 to 172.04)	0.9557

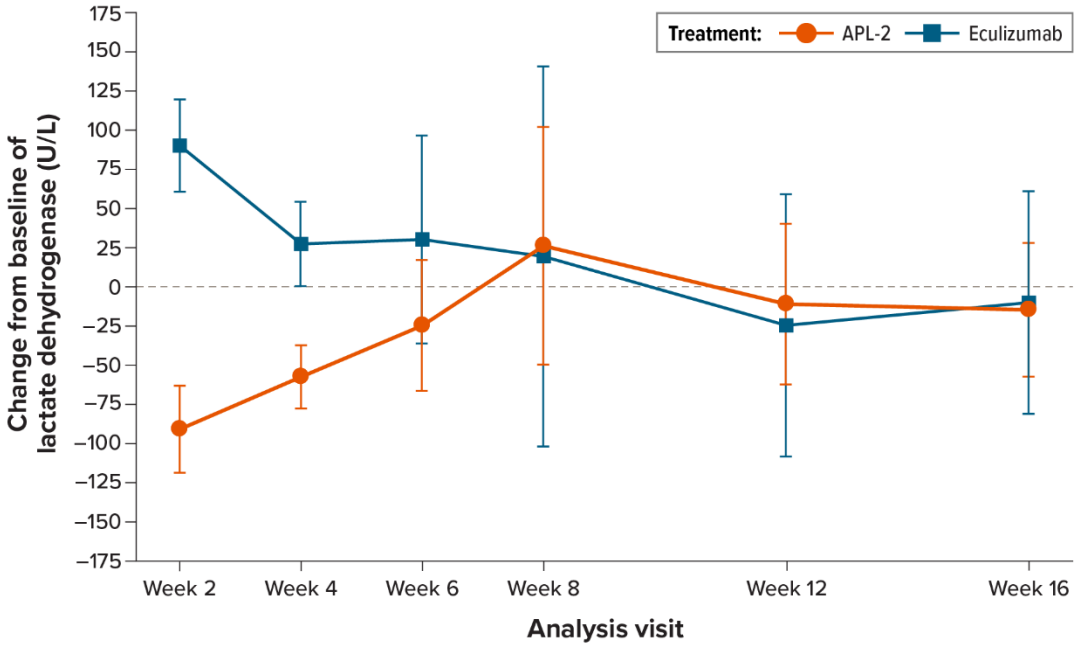
CI = confidence interval; LS = least square; SE = standard error.

Note: Baseline is the average of available measurements recorded from central laboratory prior to taking the first dose of investigational product pegcetacoplan. Model includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of stratification factors number of transfusions and platelet count at screening. Data excluded from the model: All values after intercurrent events were set to missing.

Source: Hillmen (2021b).

Figure 14 is a plot of the CFB in low-density lipoprotein (LDL) level using the MMRM model, censored for transfusion. Lactate dehydrogenase level was higher in the eculizumab group at baseline and through Week 6. By Week 16, LDH level was similar in the two treatment groups.

Figure 14: Mean (± SE) Change From Baseline in Lactate Dehydrogenase Level Using MMRM Over Time, Censored for Transfusion—Randomized Controlled Period (Intent-to-Treat Set)



APL-2 = pegcetacoplan, ICE = intercurrent event; ITT = intent-to-treat; LDH = lactate dehydrogenase; MMRM = mixed-effect model for repeated measures; PRBC = packed red blood cell; SE = standard error.

Note: Baseline is the average of available measurements records from central labs prior to taking the first dose of pegcetacoplan. For PRBC transfusion and withdrawal from the study: all measurements after the ICE events were set to missing.

Source: Hillmen (2021b).

Observed values and CFB in LDH levels during the RCP using data censored for transfusion (unadjusted data) are shown in Table 76. At baseline, the mean LDH level was higher in the eculizumab group. By Week 2, the mean value was decreased in the pegcetacoplan group and increased in the eculizumab group. By Week 16, the mean observed LDH level was similar in the two treatment groups.

Table 76: MMRM Model: Change From Baseline in Lactate Dehydrogenase Level During Randomized Controlled Period, Censored for Transfusion (Intent-to-Treat Set)—PEGASUS

Visit	Pegcetacoplan N = 41 Mean (SD) U/L			Eculizumab N = 39 Mean (SD) U/L		
	n	Observed	CFB	n	Observed	CFB
Baseline	41	257.48 (97.648)	NA	39	308.64 (284.842)	NA
Week 2	41	163.49 (62.742)	−93.99 (92.241)	39	377.28 (330.658)	68.65 (230.139)
Week 4	40	188.63 (86.694)	−69.05 (100.098)	21	287.29 (132.217)	−9.38 (175.545)
Week 6	38	226.66 (230.399)	−20.79 (238.227)	14	371.86 (459.723)	33.32 (281.977)
Week 8	36	216.25 (149.162)	−37.82 (171.894)	10	209.10 (43.124)	−34.10 (144.353)
Week 12	36	187.56 (76.074)	−68.53 (104.208)	7	175.00 (54.397)	−85.79 (143.122)
Week 16	35	188.77 (79.167)	−67.26 (105.020)	6	183.33 (28.794)	−88.67 (195.711)

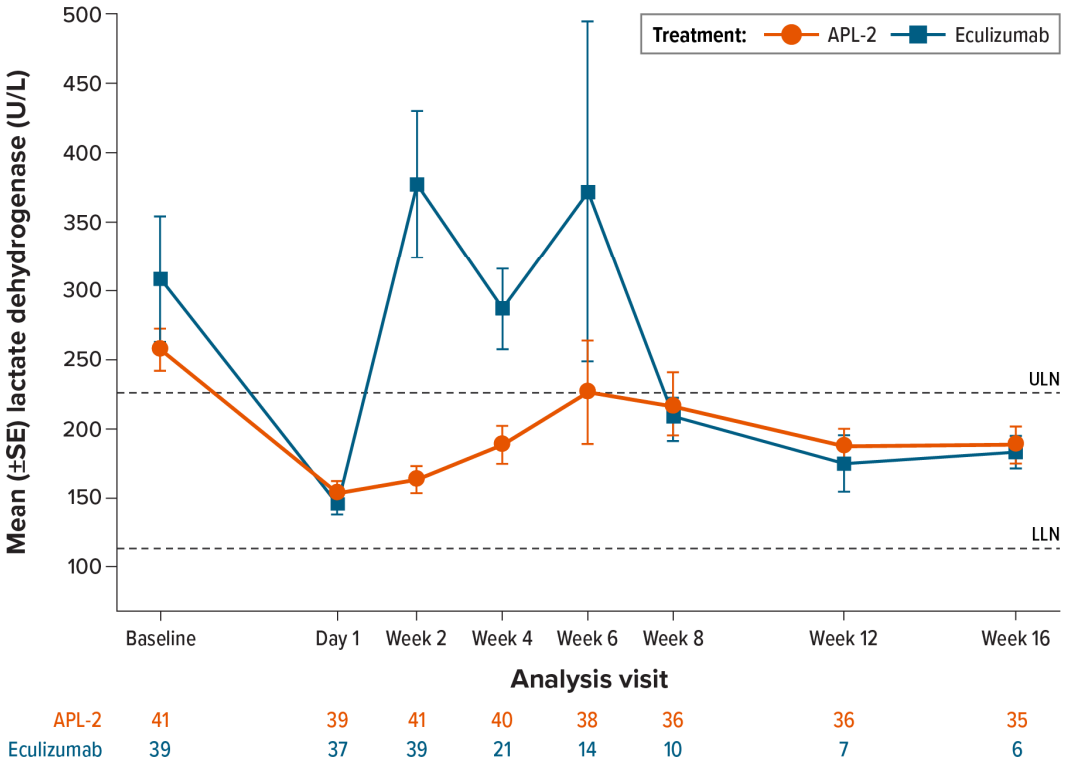
CFB = change from baseline; LDH = lactate dehydrogenase; MMRM = mixed-effect model for repeated measures; NA = not applicable; RCP = randomized controlled period; SD = standard deviation.

Note: Baseline is the average of available measurements recorded from central laboratory prior to taking the first dose of investigational product pegcetacoplan. All values after the intercurrent events during RCP were set to missing. This table summarizes data as observed with no imputation of missing data.

Source: Hillmen (2021b).

Figure 15 shows the LDH level censored for transfusion during the RCP for the observed values (unadjusted data). Lactate dehydrogenase levels were higher at most time points among patients in the eculizumab group by Week 16, and LDH levels at this time point were similar between the two groups.

Figure 15: Mean (± SE) Plot of Lactate Dehydrogenase Over Time, Censored for Transfusion—Randomized Controlled Period (Intent-to-Treat Set)



APL-2 = pegcetacoplan, ICE = intercurrent event; ITT = intent-to-treat; LDH = lactate dehydrogenase; PRBC = packed red blood cell; SE = standard error.

Note: Baseline is the average of available measurements records from central labs prior to taking the first dose of pegcetacoplan. For PRBC transfusion and withdrawal from the study, all measurements after the ICE events were set to missing. The normal range of central LDH (U/L) is [113, 226].

Source: Apellis Pharmaceuticals data on file (2020).

Normalization of LDH using data censored for transfusion was assessed for the ITT set using the category for normalization of ≤ ULN (Table 77). Lactate dehydrogenase normalization occurred for the majority of subjects in the pegcetacoplan group (70.7%) in both the ITT and the modified ITT sets. In contrast, only 6 subjects (15.4%) in the eculizumab group achieved LDH normalization. Results were the same for both analysis sets.

Table 77: Number and Percentage of Subjects With Lactate Dehydrogenase Normalization at Week 16, Censored for Transfusion (Intent-to-Treat Set)—PEGASUS

	Statistics	Pegcetacoplan (N = 41)	Eculizumab (N = 39)
LDH normalization censored for transfusion			
Yes	n (%)	29 (70.7)	6 (15.4)

	Statistics	Pegcetacoplan (N = 41)	Eculizumab (N = 39)
No	n (%)	12 (29.3)	33 (84.6)
Difference in percentage (pegcetacoplan vs. eculizumab)	Difference 95% CI	0.4879 0.3228, 0.6530	NA
OR (pegcetacoplan vs. eculizumab)	OR 95% CI	20.7137 5.3520, 80.1672	NA

CI = confidence interval; ITT = intent-to-treat; LDH = lactate dehydrogenase; NA = not applicable; OR = odds ratio.

Notes: LDH normalization is an LDH level at or below the upper limit of the gender-specific normal range at Week 16. Subjects who received a transfusion between Day 1 and Week 16 or withdraw without providing efficacy data at Week 16 will be classified as non-normalization.

95% CI for difference in percentage is constructed using the stratified Miettinen-Nurminen method.

Both *P* value and 95% CI for OR are obtained using the stratified Cochran-Mantel-Haenszel χ-square test.

Source: Hillmen, 2021

IV. Key Secondary Endpoint #4: Change From Baseline in FACIT-Fatigue to Week 16

Because noninferiority was not met for LDH, noninferiority was not tested for FACIT-Fatigue scores; however, analyses were still conducted. The CFB at Week 16 in FACIT-Fatigue score was analyzed using the same methods described for the primary analysis of the primary efficacy endpoint, except using its own baseline as a covariate.

FACIT-Fatigue scores increased nearly 10 points in the pegcetacoplan group at Week 16 (Table 78). A LS mean numerical difference of 11.87 was observed at Week 16 in the pegcetacoplan vs. eculizumab groups (95% CI, 5.49-18.25). This result was statistically significant at the 0.05 alpha level (95% CI, 5.49-18.25; nominal P value, 0.0005). Although the noninferiority was not assessed because of the prespecified hierarchical testing, the lower bound of the 95% CI of the adjusted treatment difference was greater than the prespecified noninferiority margin of −3. Additionally, a 3-point increase in FACIT-Fatigue score is generally accepted as clinically meaningful (Cella 2002). Patients in the eculizumab group had a decrease from baseline at all time points from Week 4 through Week 16.

Table 78: MMRM Model: Change From Baseline in FACIT-Fatigue Score During Randomized Controlled Period, Censored for Transfusion (Intent-to-Treat Set)—PEGASUS

Visit	Pegcetacoplan (N = 41) LS Mean (SE)	Eculizumab (N = 39) LS Mean (SE)	Difference (95% CI) in LS Mean (vs. Eculizumab)	Nominal *P* Value
Week 2	10.79 (1.257)	0.45 (1.363)	10.34 (6.90-13.78)	< 0.0001
Week 4	8.69 (1.526)	−4.41 (1.946)	13.10 (8.35-17.84)	< 0.0001
Week 6	7.59 (1.600)	−5.37 (2.258)	12.95 (7.60-18.31)	< 0.0001
Week 8	10.01 (1.438)	−3.49 (2.065)	13.50 (8.67-18.33)	< 0.0001
Week 12	10.02 (1.328)	−3.71 (2.256)	13.74 (8.67-18.80)	< 0.0001
Week 16	9.22 (1.607)	−2.65 (2.821)	11.87 (5.49-18.25)	0.0005

CI = confidence interval; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy–Fatigue Subscale; LS = least square; MMRM = mixed-effect model for repeated measures; SE = standard error.

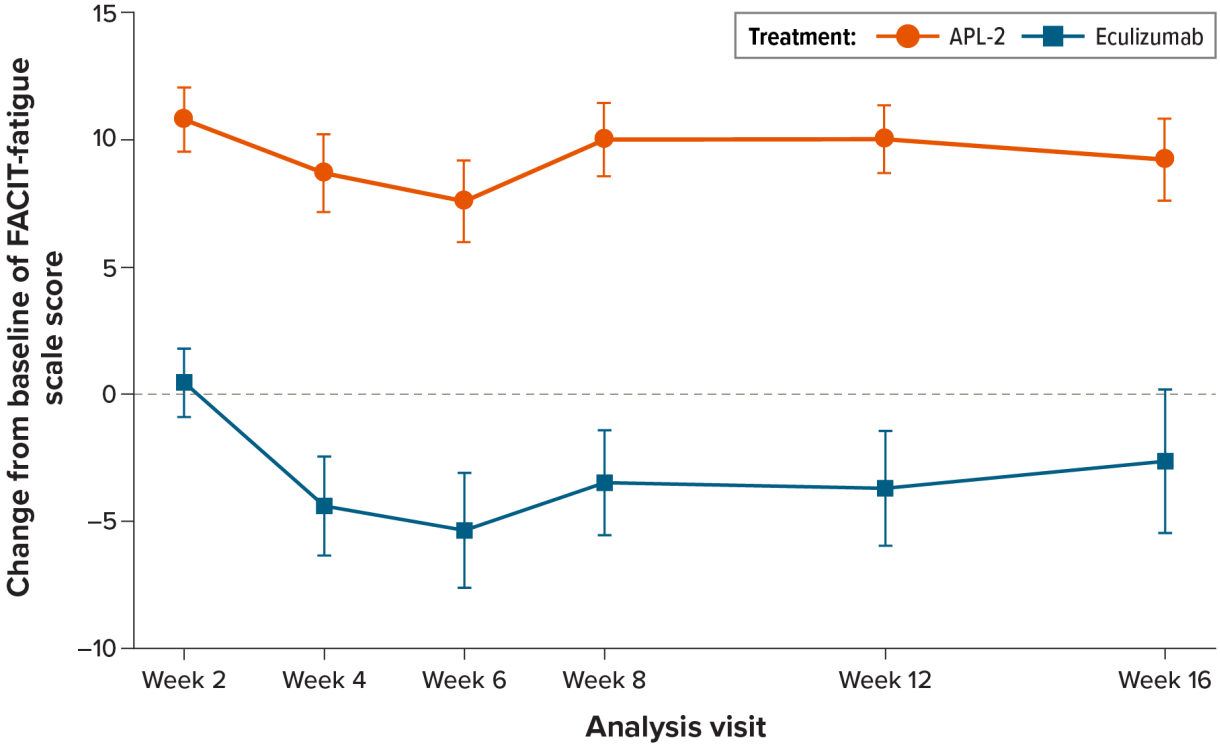
Note: Baseline is the last available, nonmissing observation before taking the first dose of pegcetacoplan.

Model includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of stratification factors number of transfusions and platelet count at screening. Data excluded from the model: All values after intercurrent events were set to missing.

Source: Hillmen, 2021

Figure 16 shows the CFB in FACIT-Fatigue score using the MMRM model, censored for transfusion. Scores were numerically higher for patients in the pegcetacoplan group at all time points from Week 2 through Week 16.

Figure 16: Mean (± SE) Change From Baseline in FACIT-Fatigue Scale Score Using MMRM Over Time, Censored for Transfusion—Randomized Controlled Period (Intent-to-Treat Set)



APL-2 = pegcetacoplan, FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy–Fatigue Subscale; ICE = intercurrent event; MMRM = mixed-effect model for repeated measures; PRBC = packed red blood cell; SE = standard error.

Notes: Baseline is the last available, nonmissing observation prior to first study drug administration. For PRBC transfusion and withdrawal from the study: all measurements after the ICE events were set to missing.

Source: Hillmen, 2021

Observed values and CFB in FACIT-Fatigue score during the RCP using data censored for transfusion (unadjusted data) are shown in Table 79. FACIT-Fatigue score increased by more than 10 points in the pegcetacoplan group by Week 8. From Day 1 to Week 16, the FACIT-Fatigue score in the pegcetacoplan group had increased 11.41 points, and scores in the eculizumab group had decreased 5.83 points. Of note, the FACIT-Fatigue score of 43.11 at Week 2 and 12 is similar to reference values for FACIT-Fatigue mean fatigue score of 43.6 in the general population (Cella 2002, Schrezenmeier 2020). In contrast, the highest FACIT-Fatigue score was 34.67 at Week 16 for the eculizumab group, showing fatigue levels much higher than the general population despite treatment.

Table 79: Descriptive Summary: Observed Values and Changes From Baseline in FACIT-Fatigue Score During Randomized Controlled Period, Censored for Transfusion (Intent-to-Treat Set)—PEGASUS

Visit	Pegcetacoplan (N = 41), Mean (SD)			Eculizumab (N = 39), Mean (SD)		
	n	Observed	CFB	n	Observed	CFB
Baseline	41	32.16 (11.380)	NA	38	31.55 (12.513)	NA
Week 2	40	43.38 (6.893)	10.86 (8.654)	37	32.76 (11.054)	1.51 (11.169)
Week 4	39	41.00 (10.503)	8.98 (10.713)	19	30.05 (12.536)	−2.53 (9.365)
Week 6	38	40.52 (10.048)	8.16 (11.080)	13	28.23 (16.068)	−5.15 (7.244)
Week 8	37	42.79 (8.527)	10.93 (10.713)	9	29.22 (16.612)	−6.00 (3.536)
Week 12	36	43.11 (6.973)	12.04 (8.614)	7	31.71 (15.976)	−5.86 (3.891)
Week 16	35	42.49 (8.830)	11.41 (9.111)	6	34.67 (16.354)	−5.83 (3.251)

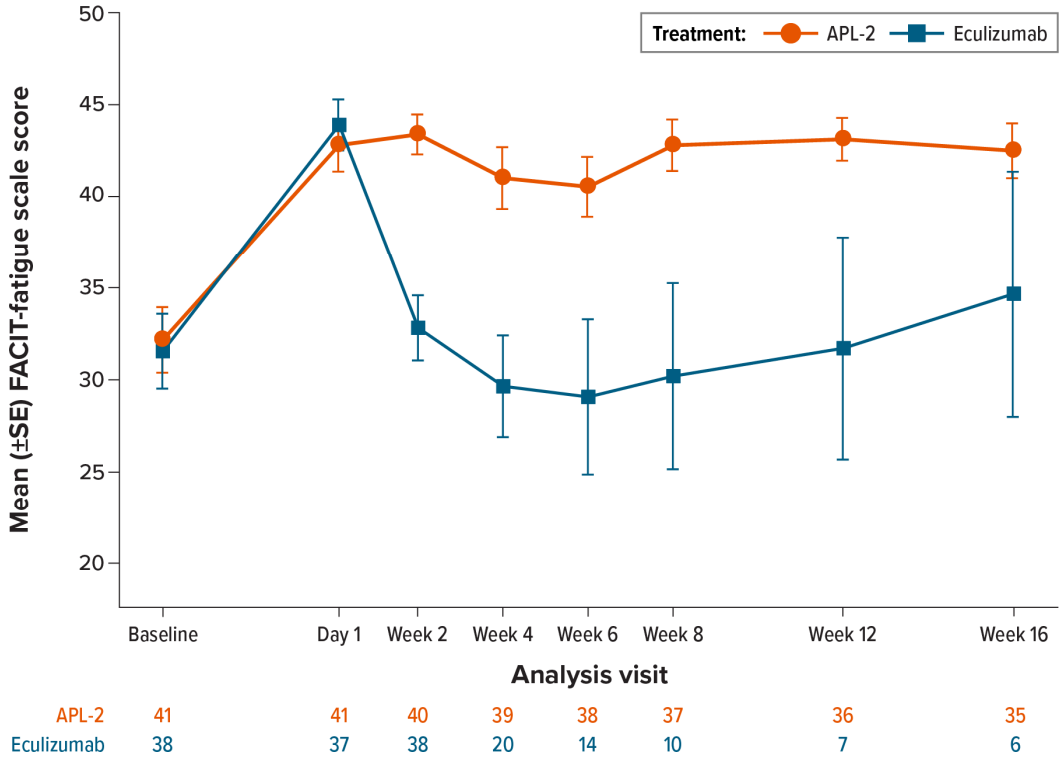
CFB = change from baseline; FACIT = Functional Assessment of Chronic Illness Therapy; NA = not applicable; SD = standard deviation.

Note: Baseline is the last available, nonmissing observation before taking the first dose of pegcetacoplan. Data collected after transfusion is excluded from analysis. This table summarizes data as observed with no imputation of missing data.

Source: Hillmen 2021

Figure 17 shows a plot of mean (± SE) FACIT-Fatigue score using data censored from transfusion over time during the RCP (ITT set). Scores were generally lower in the eculizumab group at all time points from Week 2 through Week 16.

Figure 17: Mean (± SE) Plot of FACIT-Fatigue Scale Score Over Time, Censored for Transfusion—Randomized Controlled Period (Intent-to-Treat Set)



APL-2	41	41	40	39	38	37	36	35
Eculizumab	38	37	38	20	14	10	7	6

APL-2 = pegcetacoplan, FACIT = Functional Assessment of Chronic Illness Therapy; ICE = intercurrent event; SE = standard error.

Notes: Baseline is the last available, nonmissing observation prior to first study drug administration. For PRBC transfusion and withdrawal from the study: all measurements after the ICE events were set to missing.

Source: Hillmen, 2021

Table 80 shows the CFB in FACIT-Fatigue score during the RCP using the MMRM model using all available data, uncensored for transfusion. FACIT-Fatigue scores increased nearly 10 points in the pegcetacoplan group at Week 16, with an 11.34 difference between the Week 16 scores in pegcetacoplan versus eculizumab group (nominal P value < 0.0001). A 3-point increase in FACIT-Fatigue score is generally accepted as clinically meaningful (Cella 2002). Subjects in the eculizumab group had a decrease from baseline at all time points from Week 4 through Week 16.

Table 80: MMRM Model: Changes From Baseline in FACIT-Fatigue Score During Randomized Controlled Period—Uncensored for Transfusion (Intent-to-Treat Set)

Estimates/ Comparisons	Pegcetacoplan (N = 41) LS Mean (SE)	CI	Eculizumab (N = 39) LS Mean (SE)	CI	Difference (95% CI) in LS Mean (vs. Eculizumab)	Nominal *P* Value
Week 2	11.14 (1.230)	8.654 - 13.626	0.69 (1.315)	-1.972 - 3.352	10.45 (7.05-13.84)	< 0.0001
Week 4	9.03 (1.452)	6.095 - 11.965	—3.76 (1.541)	-6.88 - -0.64	12.78 (8.73-16.83)	< 0.0001
Week 6	8.17 (1.411)	5.318 - 11.022	—1.29 (1.490)	-4.306 - 1.726	9.46 (5.54-13.38)	< 0.0001
Week 8	10.51 (1.305)	7.872 - 13.148	—0.32 (1.375)	-3.104 - 2.464	10.83 (7.25-14.42)	< 0.0001
Week 12	10.34 (1.316)	7.68 - 13	—0.71 (1.372)	-3.487 - 2.067	11.04 (7.45-14.64)	< 0.0001
Week 16	9.65 (1.409)	6.802 - 12.498	—1.69 (1.466)	-4.658 - 1.278	11.34 (7.47-15.22)	< 0.0001

CI = confidence interval; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy–Fatigue Subscale; LS = least square; MMRM = mixed model for repeated measures; SE = standard error.

Notes: Baseline is the last available, nonmissing observation before taking the first dose of pegcetacoplan. Model includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of stratification factors number of transfusions and platelet count at screening.

Source: Hillmen, 2021

Table 81 provides a descriptive summary of observed values and CFB in FACIT-Fatigue score during the RCP using data uncensored for transfusion. At Week 16, the mean CFB in both groups differed slightly from that seen when using data censored for transfusion (see Table 79). However, the increase in the pegcetacoplan group was > 10 points for both analyses, and the eculizumab group had a decrease from baseline with both analyses.

Table 81: Descriptive Summary: Observed Values and Changes From Baseline in FACIT-Fatigue Score During Randomized Controlled Period—Uncensored for Transfusion (Intent-to-Treat Set)—PEGASUS

Visit	Pegcetacoplan N = 41			Eculizumab N = 39		
	n	Mean (SD)	CFB	n	Mean (SD)	CFB
Baseline	41	32.16 (11.380)	NA	38	31.55 (12.513)	NA
Week 2	40	43.38 (6.893)	10.86 (8.654)	37	32.62 (11.106)	1.38 (10.968)
Week 4	39	41.00 (10.503)	8.98 (10.713)	36	28.26 (12.225)	-3.46 (8.955)
Week 6	39	40.28 (10.032)	8.24 (10.943)	37	30.59 (12.276)	-0.70 (8.708)
Week 8	38	42.45 (8.663)	10.91 (10.569)	37	32.09 (11.745)	0.23 (7.970)
Week 12	38	42.18 (7.874)	11.03 (9.967)	38	31.37 (11.605)	-0.18 (9.678)
Week 16	36	41.81 (9.612)	10.34 (11.028)	37	30.62 (11.765)	-1.35 (8.731)

CFB = change from baseline; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy–Fatigue Subscale; NA = not applicable.

Notes: Baseline is the last available, nonmissing observation before taking the first dose of pegcetacoplan. This table summarizes data as observed with no imputation of missing data.

Source: Hillmen, 2021

FACIT-Fatigue score improvement by at least three points using data censored for transfusion is shown in Table 82. At Week 16, 73.2% of pegcetacoplan subjects had an improved FACIT-Fatigue score ≥ 3 points CFB, while no patients in the eculizumab group had improvement at that level.

Table 82: Number and Percentage of Subjects With FACIT-Fatigue Score Improvement From Baseline During Randomized Controlled Period, Censored for Transfusion (Intent-to-Treat Set)

Analysis Visit	Score Improvement ≥ 3 Points CFB	Statistics	Pegcetacoplan (N = 41)	Eculizumab (N = 39)
Week 2	Yes	n (%)	33 (80.5)	18 (46.2)
	No	n (%)	7 (17.1)	19 (48.7)
Week 4	Yes	n (%)	31 (75.6)	5 (12.8)
	No	n (%)	8 (19.5)	14 (35.9)
Week 6	Yes	n (%)	29 (70.7)	1 (2.6)
	No	n (%)	9 (22.0)	12 (30.8)
Week 8	Yes	n (%)	30 (73.2)	0
	No	n (%)	7 (17.1)	9 (23.1)
Week 12	Yes	n (%)	31 (75.6)	0
	No	n (%)	5 (12.2)	7 (17.9)
Week 16	Yes	n (%)	30 (73.2)	0
	No	n (%)	5 (12.2)	6 (15.4)

CFB = change from baseline; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy–Fatigue Subscale.

Notes: Baseline is the last available, nonmissing observation before taking the first dose of pegcetacoplan.

Data collected after transfusion duration randomized controlled period is excluded from analysis. This table summarizes data as observed with no imputation of missing data.

Source: Hillmen, 2021

Change from baseline in FACIT-Fatigue score censored for transfusion by PRBC transfusion strata was generally consistent with the results of the primary analysis of FACIT-Fatigue score. There were numerical differences at Week 16 for pegcetacoplan versus eculizumab for both strata (< 4 and ≥ 4 PRBC transfusions prior to baseline; Table 83). The largest CFB at Week 16 was shown in the pegcetacoplan group with ≥ 4 PRBC transfusions, with an 11-point increase in score for this group and a 21.52-point difference between the pegcetacoplan group and eculizumab group for this stratum.

Table 83: MMRM Model: Changes From Baseline in FACIT-Fatigue Score During Randomized Controlled Period by Number of Packed Red Blood Cell Transfusions, Censored for Transfusion (Intent-to-Treat Set)

	Pegcetacoplan LS Mean (SE)	Eculizumab LS Mean (SE)	Difference (95% CI) in LS Mean vs. Eculizumab	Nominal *P* Value
Number of PRBC transfusions < 4				
n	20	16	NA	NA
Week 16	8.98 (1.593)	1.15 (3.035)	7.83 (0.65-15.00)	0.0341
Number of PRBC transfusions ≥ 4				
n	21	23	NA	NA
Week 16	10.94 (2.268)	−10.59 (5.778)	21.52 (8.89-34.16)	0.0015

CI = confidence interval; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy–Fatigue Subscale; LS = least square; MMRM = mixed model for repeated measures; NA = not applicable; PRBC = packed red blood cell; SE = standard error.

Notes: Baseline is the last available, nonmissing observation before taking the first dose of pegcetacoplan.

Model includes treatment + baseline value + analysis visit + analysis visit × treatment. Data excluded from the model: All values after intercurrent events were set to missing.

Source: Hillmen, 2021

Subjects in the pegcetacoplan group had a similar increase in FACIT-Fatigue score in both transfusion strata (< 4 PRBC transfusions and ≥ 4 PRBC transfusions; Table 84). The score at Week 16 was similar among subjects who had fewer than 4 PRBC transfusions prior to baseline in both treatment groups. Few subjects remained for evaluation at Week 8 and Week 12 in the eculizumab group among subjects who had ≥ 4 PRBC transfusions prior to baseline. FACIT-Fatigue score among these subjects exhibited a CFB of −4.50.

Table 84: Descriptive Summary: Observed Values and Changes From Baseline for FACIT-Fatigue Score During Randomized Controlled Period by Number of Packed Red Blood Cell Transfusions, Censored for Transfusion (Intent-to-Treat Set)

Visit	Pegcetacoplan (N = 20)			Eculizumab (N = 16)		
	n	Mean (SD)	CFB	n	Mean (SD)	CFB
Stratification: Number of PRBC transfusions < 4						
Baseline	20	32.90 (11.159)	NA	16	32.56 (15.015)	NA
Week 2	20	43.85 (5.081)	10.95 (9.428)	16	34.06 (10.266)	1.50 (9.906)
Week 4	19	41.11 (10.796)	9.21 (13.193)	13	30.46 (11.666)	−3.15 (9.668)
Week 6	19	39.42 (10.330)	6.47 (12.942)	8	27.88 (16.557)	−7.63 (5.706)
Week 8	19	42.47 (8.922)	10.58 (12.786)	7	31.29 (16.740)	−6.43 (3.867)
Week 12	17	43.47 (5.186)	13.18 (8.413)	6	36.50 (10.672)	−5.50 (4.135)
Week 16	17	41.65 (6.314)	11.35 (9.440)	5	41.00 (5.788)	−5.40 (3.435)
Stratification: Number of PRBC transfusions ≥ 4						
		Pegcetacoplan (N = 21)			**Eculizumab (N = 23)**	
Baseline	21	31.46 (11.817)	NA	22	30.82 (10.653)	NA
Week 2	20	42.90 (8.440)	10.77 (8.052)	21	31.76 (11.768)	1.52 (12.287)
Week 4	20	40.90 (10.498)	8.77 (8.033)	6	29.17 (15.420)	−1.17 (9.390)
Week 6	19	41.63 (9.914)	9.85 (8.879)	5	28.80 (17.152)	−1.20 (8.289)
Week 8	18	43.12 (8.336)	11.30 (8.348)	2	22.00 (19.799)	−4.50 (2.121)
Week 12	19	42.79 (8.390)	11.02 (8.890)	1	3.00 (-)	−8.00 (-)
Week 16	18	43.28 (10.818)	11.46 (9.063)	1	3.00 (-)	-8.00 (-)

CFB = change from baseline; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy–Fatigue Subscale; NA = not applicable; PRBC = packed red blood cell; SD = standard deviation.

Notes: Baseline is the last available, nonmissing observation before taking the first dose of pegcetacoplan.

Data collected after transfusion is excluded from analysis. This table summarizes data as observed with no imputation of missing data.

Source: Hillmen, 2021

V. Additional Secondary Efficacy Endpoints During the Randomized Controlled Period

Hemoglobin Response

Hemoglobin response was defined as at least a 1 g/dL increase in hemoglobin. As shown in Table 85, 31/41 (75.6%) of patients in the pegcetacoplan group met the definition for hemoglobin response at Week 16, censored for transfusion, for the ITT set versus 0 patients in the eculizumab group.

Table 85: Number and Percentage of Subjects With Hemoglobin Response at Week 16, Censored for Transfusion (Intent-to-Treat Set)—PEGASUS

	Statistics	Pegcetacoplan (N = 41)	Eculizumab (N = 39)
Hemoglobin response			
Yes	n (%)	31 (75.6)	0
No	n (%)	10 (24.4)	39 (100.0)
Difference in percentage (pegcetacoplan vs. eculizumab)	Difference	0.6745	
	95% CI	0.5452, 0.8039	

CI = confidence interval; RCP = randomized controlled period.

Note: Hemoglobin response is an increase of at least ≥ 1 g/dL in hemoglobin from baseline at Week 16, excluding data before the RCP. Subjects who received a transfusion between Day 1 and Week 16 or withdraw without providing efficacy data at Week 16 were classified as nonresponders; 95% CI for difference in percentage is constructed using the stratified Miettinen-Nurminen method.

Source: Hillmen, 2021

Hemoglobin Stabilization (Post hoc Analysis)

Table 86 shows that 35 subjects (85.4%) in the pegcetacoplan group and 6 subjects (15.4%) in the eculizumab group achieved hemoglobin stabilization at Week 16. The TA difference in percentage (pegcetacoplan vs. eculizumab) was 0.6253.

Table 86: Post hoc Analysis: Number and Percentage of Subjects With Hemoglobin Stabilization Censored for Transfusion at Week 16 (Intent-to-Treat Set)

	Statistics	Pegcetacoplan (N = 41)	Eculizumab (N = 39)
Hemoglobin stabilization (censored for transfusion)			
Yes	n (%)	35 (85.4)	6 (15.4)
No	n (%)	6 (14.6)	33 (84.6)
Difference in percentage (pegcetacoplan vs. eculizumab)	Difference	0.6253	NA
	95% CI	0.4830, 0.7677	NA

CI = confidence interval; NA = not applicable.

Notes: Hemoglobin stabilization defined as avoidance of a > 1 g/dL decrease in hemoglobin levels from baseline censored for transfusion through Week 16 (yes/no).

Subjects who received a transfusion between Day 1 and Week 16 or withdraw without providing efficacy data at Week 16 were classified as nonstabilized; 95% CI for difference in percentage is constructed using the stratified Miettinen-Nurminen method.

Source: Hillmen, 2021

Reticulocyte Normalization

Reticulocyte normalization was defined as the ARC being below the upper limit of gender-specific normal range at Week 16. As shown in Table 87, reticulocyte normalization occurred for the majority of patients in the pegcetacoplan group (78%), vs. only 2.6% (1 patient) in the eculizumab group.

Table 87: Number and Percentage of Subjects With Reticulocyte Normalization at Week 16, Censored for Transfusion (Intent-to-Treat Set)—PEGASUS

	Statistics	Pegcetacoplan (N = 41)	Eculizumab (N = 39)
Reticulocyte normalization censored for transfusion			
Yes	n (%)	32 (78.0)	1 (2.6)
No	n (%)	9 (22.0)	38 (97.4)
Difference in percentage (pegcetacoplan vs. eculizumab)	Difference 95% CI	0.6639 0.5309, 0.7968	
OR (pegcetacoplan vs. eculizumab)	OR 95% CI	135.5938 15.1916, 1210.2532	

CI = confidence interval; OR = odds ratio.

Notes: Reticulocyte normalization is a reticulocyte level below the upper limit of the gender-specific normal range at Week 16. Subjects who received a transfusion between Day 1 and Week 16 or withdraw without providing efficacy data at Week 16 will be classified as nonresponders.

95% CI for difference in percentage is constructed using the stratified Miettinen-Nurminen method.

Both *P* value and 95% CI for OR are obtained using the stratified Cochran-Mantel-Haenszel χ^2 test.

Source: Hillmen, 2021

Hemoglobin Normalization in the Absence of Transfusions

Hemoglobin normalization in the absence of transfusions was defined as hemoglobin level at or above the lower limit of the gender-specific normal range without a transfusion at that time point. As shown in Table 88, 34.1% of patients in the pegcetacoplan group achieved hemoglobin normalization versus 0 patients in the eculizumab group.

Table 88: Number and Percentage of Subjects With Hemoglobin Normalization at Week 16, Censored for Transfusion (Intent-to-Treat Set)—PEGASUS

	Statistics	Pegcetacoplan (N = 41)	Eculizumab (N = 39)
Hemoglobin normalization			
Yes	n (%)	14 (34.1)	0
No	n (%)	27 (65.9)	39 (100.0)
Difference in percentage (pegcetacoplan vs. eculizumab)	Difference	0.3043	
	95% CI	0.1493, 0.4593	

CI = confidence interval; OR = odds ratio.

Note: Hemoglobin normalization is a hemoglobin level at or above the lower limit of the gender-specific normal range at Week 16. Subjects who received a transfusion between Day 1 and Week 16 or withdrew without providing efficacy data at Week 16 are classified as non-normalization. 95% CI for difference in percentage is constructed using the stratified Miettinen-Nurminen method. Both *P* value and 95% CI for OR are obtained using the stratified Cochran-Mantel-Haenszel χ^2 test.

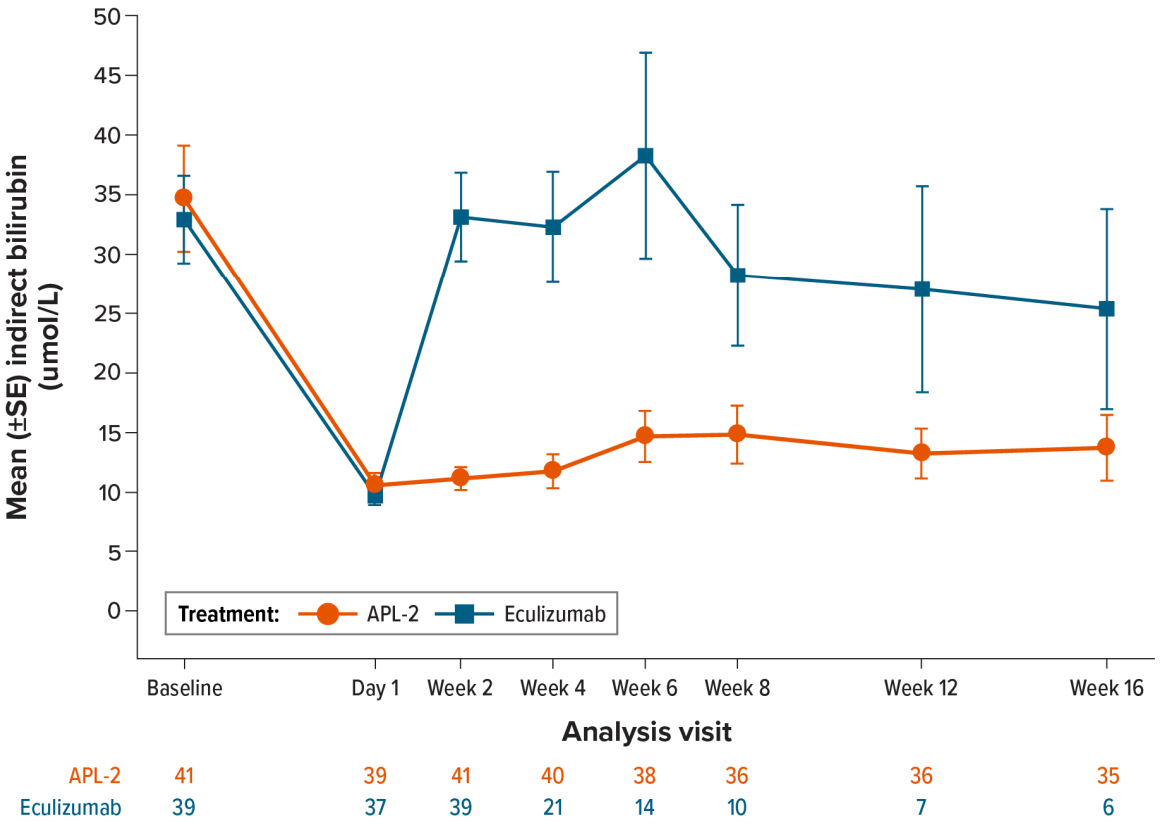
Source: Hillmen, 2021

Indirect Bilirubin

Figure 18 is a plot of mean (± SE) indirect bilirubin censored for transfusion over time during the RCP (ITT set). After patients were randomly assigned to pegcetacoplan or eculizumab, indirect bilirubin levels

increased in patients who received eculizumab. In the pegcetacoplan group, the decrease in indirect bilirubin levels was maintained from baseline through Week 16.

Figure 18: Mean (± SE) Plot of Indirect Bilirubin Over Time, Censored for Transfusion—Randomized Controlled Period (Intent-to-Treat Set)



APL-2	41	39	41	40	38	36	36	35
Eculizumab	39	37	39	21	14	10	7	6

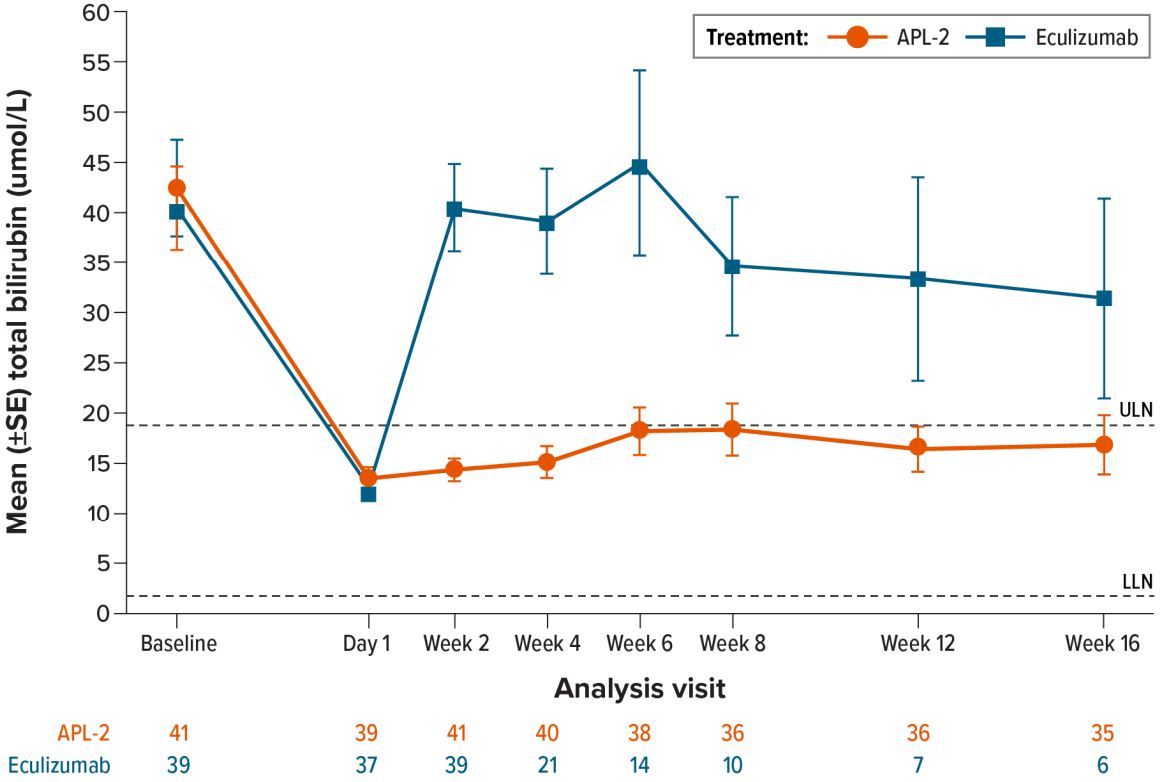
APL-2 = pegcetacoplan, ICE = intercurrent event; PRBC = packed red blood cell; SE = standard error

Notes: Baseline is the average of available measurements records from central labs prior to taking the first dose of pegcetacoplan. For PRBC transfusion and withdrawal from the study, all measurements after the ICE events were set to missing.

Source: Hillmen (2021b).

Figure 19 is a plot of mean (± SE) total bilirubin using data censored for transfusion over time during the RCP (ITT set). After subjects were randomly assigned to pegcetacoplan or eculizumab, total bilirubin levels began to increase in subjects who received eculizumab, while subjects in the pegcetacoplan maintained the decrease from baseline through Week 16.

Figure 19: Mean (± SE) Plot of Total Bilirubin Over Time, Censored for Transfusion—Randomized Controlled Period (Intent-to-Treat Set)



APL-2	41	39	41	40	38	36	36	35
Eculizumab	39	37	39	21	14	10	7	6

APL-2 = pegcetacoplan, ICE = intercurrent event; PRBC = packed red blood cell; SE = standard error.

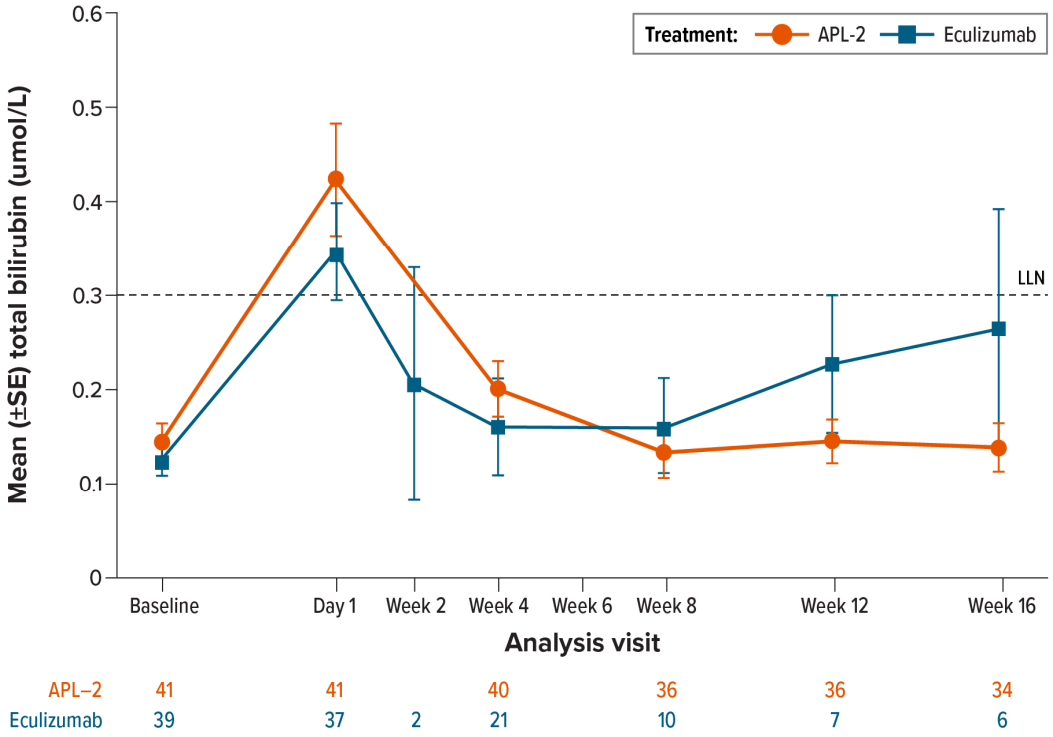
Note: Baseline is the average of available measurements records from central labs prior to taking the first dose of pegcetacoplan. For PRBC transfusion and withdrawal from the study, all measurements after the ICE events were set to missing. The normal range of total bilirubin (µmol/L) is [1.7, 18.8].

Source: Hillmen (2021b).

Haptoglobin

Figure 20 shows mean (± SE) haptoglobin censored for transfusion over time during the RCP (ITT set). After the initial increase in the run-in period, haptoglobin in both treatment groups decreased below the lower limit of normal by Week 4. By Week 8, haptoglobin in the eculizumab group was higher.

Figure 20: Mean (± SE) Plot of Haptoglobin Level Over Time, Censored for Transfusion—Randomized Controlled Period (Intent-to-Treat Set)



APL-2 = pegcetacoplan, SE = standard error.

Note: Baseline is the average of available measurements records from central labs prior to taking the first dose of pegcetacoplan.

Source: Hillmen (2021b).

Linear Analog Scale Assessments Scores

As shown in Table 89, the difference in LS mean for LASA scores using data censored for transfusion in the ITT set was 59.10 (95% CI, 16.88-101.32) at Week 16 for the comparison of the pegcetacoplan group with the eculizumab group.

Table 89: MMRM Model: Change From Baseline in LASA Scores During Randomized Controlled Period, Censored for Transfusion (Intent-to-Treat Set)—PEGASUS

Visit	Pegcetacoplan (N = 41) LS Mean (SE)	Eculizumab (N = 39) LS Mean (SE)	Difference (95% CI) in LS Mean (vs. Eculizumab)
Week 2	56.90 (8.653)	−0.94 (9.272)	57.84 (34.05-81.63)
Week 4	54.57 (9.664)	−42.69 (12.267)	97.26 (67.29-127.23)
Week 6	45.53 (9.997)	−49.53 (14.578)	95.06 (60.79-129.33)
Week 8	52.24 (9.344)	−49.22 (15.515)	101.46 (66.39-136.53)
Week 12	57.76 (10.394)	−26.29 (18.127)	84.05 (43.12-124.98)
Week 16	49.38 (10.189)	−9.72 (18.988)	59.10 (16.88-101.32)

CI = confidence interval; LASA = Linear Analog Scale Assessments; LS = least square; MMRM = mixed model for repeated measures; SE = standard error

Notes: Baseline is the last available, nonmissing observation before taking the first dose of pegcetacoplan.

Model includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of stratification factors number of transfusions and platelet count at screening. Data excluded from the model: All values after intercurrent events were set to missing.

Source: Hillmen, 2021

Observed values in LASA scores were similar at baseline for both treatment groups. The observed values and CFB (unadjusted data) through Week 16 align with the MMRM results, showing a numerically larger CFB in the pegcetacoplan group than in the eculizumab group (Table 90).

Table 90: Descriptive Summary: Observed Values and Changes From Baseline in LASA Score During Randomized Controlled Period, Censored for Transfusion (Intent-to-Treat Set)—PEGASUS

Visit	Pegcetacoplan N = 41 Mean (SD)			Eculizumab N = 39 Mean (SD)		
	n	Observed	CFB	n	Observed	CFB
Baseline	40	161.0 (67.99)	NA	38	156.7 (61.27)	NA
Week 2	39	221.4 (54.60)	56.3 (53.87)	37	159.9 (63.39)	4.8 (67.56)
Week 4	38	218.4 (71.25)	56.3 (62.27)	20	130.9 (68.28)	−24.6 (60.67)
Week 6	36	213.1 (74.93)	46.7 (62.72)	13	126.4 (68.77)	−29.4 (52.66)
Week 8	36	217.5 (63.67)	58.0 (62.03)	9	124.2 (68.41)	−45.3 (44.69)
Week 12	34	226.2 (60.28)	69.6 (69.16)	7	152.0 (84.33)	−30.4 (41.32)
Week 16	34	217.6 (65.69)	60.6 (61.74)	6	175.7 (88.92)	−13.3 (39.71)

CFB = change from baseline; LASA = Linear Analog Scale Assessment; NA = not applicable; SD = standard deviation.

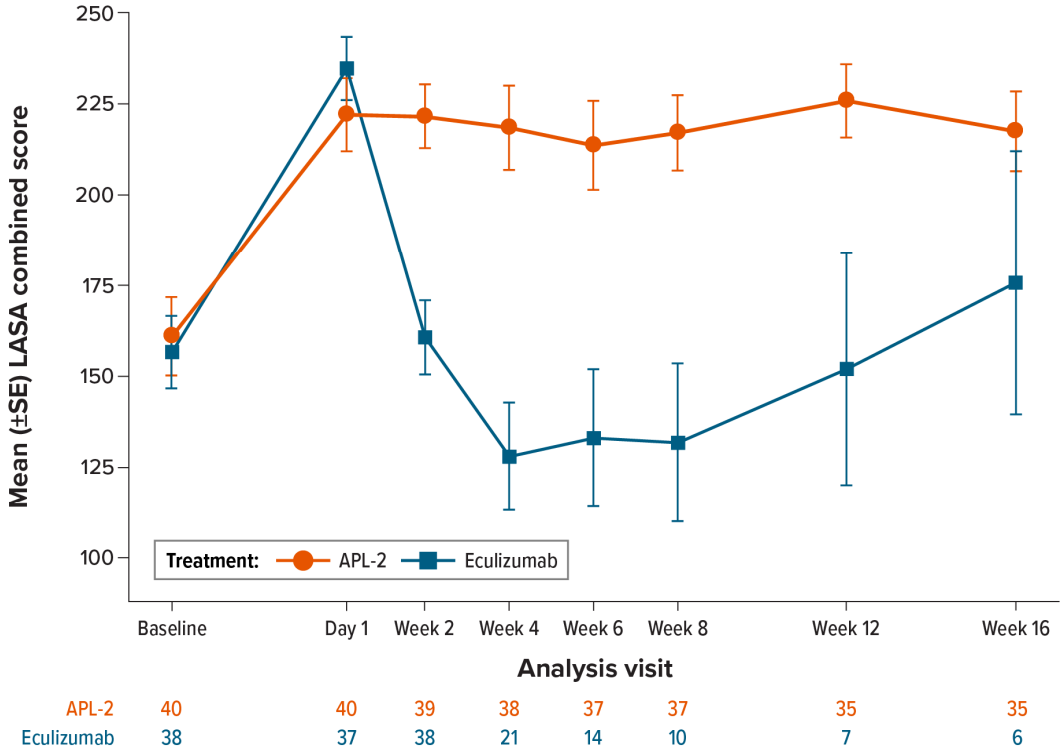
Notes: Baseline is the last available, nonmissing observation before taking the first dose of pegcetacoplan.

All values after the intercurrent events during randomized controlled period were set to missing. This table summarizes data as observed with no imputation of missing data.

Source: Hillmen (2021), Röth (2021)

A plot of LASA scores using data censored for transfusion over time during the RCP (ITT set) is shown in Figure 21. In the pegcetacoplan group, LASA scores for patients maintained the increase seen in the run-in period from baseline through Week 16. After the initial increase in LASA scores in the run-in period, the eculizumab group decreased below baseline from Week 4 to Week 12, then increased above baseline by Week 16.

Figure 21: Mean (SE) Plot of LASA Scores Over Time, Censored for Transfusion—Randomized Controlled Period (Intention to Treat)



APL-2 = pegcetacoplan, ICE = intercurrent event; LASA = Linear Analog Scale Assessments; PRBC = packed red blood cell; SE = standard error.

Notes: Baseline is the last available, nonmissing observation prior to first study drug administration.

For PRBC transfusion and withdrawal from the study: all measurements after the ICE events were set to missing.

Source: Hillmen (2021), Röth (2021).

EORTC QLQ-C30

As shown in Table 91, for the EORTC QLQ-C30 results at Week 16 using data censored for transfusion, the global health status/quality of life (GHS/QoL) and all functional scales showed an increase in score (improvement) in the pegcetacoplan group at Week 16.

Table 91: MMRM Model: Change From Baseline to Week 16 in EORTC QLQ-C30 Scores During Randomized Controlled Period (Intent-to-Treat Set) by Parameter, Censored for Transfusion—PEGASUS

	Pegcetacoplan N = 41 LS Mean (SE)	Eculizumab N = 39 LS Mean (SE)	Difference (95% CI)
Global Health Status/QOL	15.91 (3.635)	−2.71 (8.515)	18.62 (0.12-37.13)
Functional scales			
Physical functioning	16.92 (2.081)	4.06 (3.605)	12.86 (4.86-20.86)
Role functioning	15.39 (3.930)	−9.04 (6.954)	24.43 (8.84-40.01)
Emotional functioning	7.98 (3.366)	3.86 (7.237)	4.11 (−11.58, 19.80)
Cognitive functioning	5.76 (3.258)	−3.80 (6.420)	9.56 (−4.52, 23.64)
Social functioning	15.08 (2.946)	3.82 (6.349)	11.27 (−2.38, 24.92)

Symptom scales			
Fatigue	−22.93 (3.321)	−2.18 (6.644)	−20.74 (−35.29 to −6.19)
Nausea and vomiting	−0.34 (1.632)	−0.33 (3.876)	−0.01 (−8.38, 8.35)
Pain	−0.74 (4.323)	2.01 (7.841)	−2.76 (−20.36, 14.85)
Dyspnea	−20.12 (3.488)	−5.55 (7.019)	−14.57 (−29.90, 0.76)
Insomnia	−9.18 (3.955)	−9.50 (7.090)	0.32 (−15.67, 16.30)
Appetite loss	−3.76 (3.357)	4.19 (7.009)	−7.95 (−23.23, 7.33)
Constipation	2.98 (3.248)	1.19 (8.129)	1.79 (−15.70, 19.29)
Diarrhea	0.31 (3.711)	1.68 (8.204)	−1.38 (−19.28, 16.52)
Financial difficulties	−6.82 (3.853)	0.58 (6.297)	−7.40 (−21.76, 6.95)

CI = confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire—Core 30 Scale; LS = least square; MMRM = mixed model for repeated measures; QOL = quality of life; SE = standard error.

Notes: Baseline is the last available, nonmissing observation before taking the first dose of pegcetacoplan.

Model includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of stratification factors number of transfusions and platelet count at screening. Data excluded from the model: All values after intercurrent events were set to missing.

Source: Röth (2021).

Observed values and CFB in EORTC QLQ-C30 scores (unadjusted data) showed an overall mean increase from baseline in the pegcetacoplan group for GHS/QOL and all functional scales. The mean CFB for the emotional functioning scale score was similar at Week 16 in both treatment groups (9.76 in the pegcetacoplan group and 8.33 in the eculizumab group). The eculizumab group had a mean decrease from baseline in the GHS/QOL and role functioning scale score (Table 92).

Table 92: Descriptive Summary: Mean Changes From Baseline in EORTC QLQ-C30 at Week 16 During Randomized Controlled Period, Censored for Transfusion (Intent-to-Treat Set)

	Pegcetacoplan		Eculizumab	
	n	Mean (SD)	n	Mean (SD)
Global Health Status/QOL	35	16.43 (22.000)	5	−1.67 (31.950)
Functional scales				
Physical functioning	35	18.86 (15.882)	6	5.56 (8.861)
Role functioning	35	19.52 (28.147)	6	−5.56 (13.608)
Emotional functioning	35	9.76 (21.626)	5	8.33 (19.543)
Cognitive functioning	35	10.00 (19.470)	5	0.00 (11.785)
Social functioning	35	14.76 (20.119)	5	6.67 (9.129)
Symptom scales				
Fatigue	35	−25.71 (23.146)	6	−1.85 (23.744)
Nausea and vomiting	35	0.00 (9.039)	6	−2.78 (16.387)
Pain	35	−1.90 (32.280)	6	5.56 (8.607)
Dyspnea	35	−21.90 (21.302)	6	−5.56 (13.608)

Insomnia	35	−11.43 (26.744)	6	−16.67 (18.257)
Appetite loss	35	−5.71 (18.935)	6	−5.56 (13.608)
Constipation	35	2.86 (20.407)	5	−6.67 (14.907)
Diarrhea	35	0.00 (30.250)	5	6.67 (14.907)
Financial difficulties	35	−10.48 (26.533)	5	−13.33 (18.257)

ITT = intent-to-treat; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire–Core 30 Scale; QOL = quality of life; SD = standard deviation.

Notes: Baseline is the last available, nonmissing observation before taking the first dose of pegcetacoplan.

All values after the intercurrent events during randomized controlled period were set to missing. This table summarizes data as observed with no imputation of missing data.

Source: Röth (2021).

Table 93 shows the observed values and changes from baseline in the EORTC QLQ-C30 scores during the RCP (ITT set). For the GHS, the mean GHS score at Week 16 for the pegcetacoplan group of 71.67 is close to the mean European population norm of 75.0, whereas the GHS score for the eculizumab group decreased slightly to a score of 51.67, indicating continued poor QOL (Hinz 2014). For the functioning scales all showed improved functioning for the pegcetacoplan group versus eculizumab, approaching European normative values for physical and emotional functioning in the pegcetacoplan group. The largest mean decrease in symptoms for the pegcetacoplan group was seen for fatigue, dyspnea, and insomnia.

Table 93: Descriptive Summary: Observed Values and Changes from Baseline in EORTC QLQ-C30 Scores During Randomized Controlled Period (Intent-to-Treat Set)—PEGASUS

	Pegcetacoplan				Eculizumab				European Norm (Hinz 2014)
	n	Baseline Mean (SD), Median, Range	Week 16 Observed Mean (SD), Median, Range	CFB Mean (SD), Median, Range	n	Baseline Mean (SD), Median, Range	Week 16 Observed Mean (SD), Median, Range	CFB Mean (SD), Median, Range	
Global health status/quality-of-life scales	35	55.24 (20.017), 50.00, 8.3, 100.0	71.67 (23.501), 83.33, 8.3, 100.0	16.43 (22.000), 16.67, −25.0, 58.3	5	53.33 (34.661), 58.33, 0.0, 83.3	51.67 (23.863), 50.00, 25.0, 83.3	−1.67 (31.950), 8.33, −50.0, 25.0	75.0
Functional scales									
Physical functioning	35	70.67 (20.719), 73.33, 20.0, 100.0	89.52 (11.803), 93.33, 46.7, 100.0	18.86 (15.882), 13.33, 0.0, 60.0	6	82.22 (24.465), 90.00, 33.3, 100.0	87.78 (18.579), 96.67, 53.3, 100.0	5.56 (8.861), 6.67, −6.7, 20.0	92.2
Role functioning	35	60.95 (29.963), 66.67, 0.0, 100.0	80.48 (24.080), 100.00, 16.7, 100.0	19.52 (28.147), 33.33, −33.3, 83.3	6	72.22 (38.968), 83.33, 0.0, 100.0	66.67 (36.515), 66.67, 0.0, 100.0	−5.56 (13.608), 0.00, −33.3, 0.0	90.4
Emotional functioning	35	71.90 (26.590), 83.33, 8.3, 100.0	81.67 (22.849), 83.33, 0.0, 100.0	9.76 (21.626), 0.00, −16.7, 66.7	5	70.00 (31.513), 66.67, 25.0, 100.0	78.33 (36.132), 100.00, 16.7, 100.0	8.33 (19.543), 0.00, −8.3, 41.7	83.5
Cognitive functioning	35	75.24 (25.364), 83.33, 16.7, 100.0	85.24 (20.119), 100.00, 16.7, 100.0	10.00 (19.470), 0.00, −16.7, 66.7	5	76.67 (43.461), 100.00, 0.0, 100.0	76.67 (43.461), 100.00, 0.0, 100.0	0.00 (11.785), 0.00, −16.7, 16.7	93.5

Social functioning	35	68.57 (29.641), 66.67, 0.0, 100.0	83.33 (24.254), 100.00, 0.0, 100.0	14.76 (20.119), 16.67, −33.3, 66.7	5	73.33 (41.833), 83.33, 0.0, 100.0	80.00 (44.721), 100.00, 0.0, 100.0	6.67 (9.129), 0.00, 0.0, 16.7	93.4
Symptom scales									
Fatigue	35	52.38 (29.468), 55.56, 0.0, 100.0	26.67 (20.381), 22.22, 0.0, 77.8	−25.71 (23.146), −22.22, −77.8, 11.1	6	40.74 (39.545), 27.78, 0.0, 100.0	38.89 (34.960), 27.78, 0.0, 100.0	−1.85 (23.744), 0.00, −33.3, 33.3	15.5
Nausea and vomiting	35	3.33 (8.856), 0.00, 0.0, 33.3	3.33 (7.880), 0.00, 0.0, 33.3	0.00 (9.039), 0.00, −33.3, 33.3	6	13.89 (22.153), 0.00, 0.0, 50.0	11.11 (27.217), 0.00, 0.0, 66.7	−2.78 (16.387), 0.00, −33.3, 16.7	2.2
Pain	35	20.00 (27.947), 0.00, 0.0, 83.3	18.10 (24.711), 0.00, 0.0, 66.7	−1.90 (32.280), 0.00, −66.7, 66.7	6	11.11 (27.217), 0.00, 0.0, 66.7	16.67 (25.820), 8.33, 0.0, 66.7	5.56 (8.607), 0.00, 0.0, 16.7	16.7
Dyspnea	35	36.19 (28.436), 33.33, 0.0, 100.0	14.29 (23.271), 0.00, 0.0, 100.0	−21.90 (21.302), −33.33, −66.7, 0.0	6	27.78 (38.968), 16.67, 0.0, 100.0	22.22 (40.369), 0.00, 0.0, 100.0	−5.56 (13.608), 0.00, −33.3, 0.0	7.5
Insomnia	35	35.24 (35.187), 33.33, 0.0, 100.0	23.81 (35.766), 0.00, 0.0, 100.0	−11.43 (26.744), 0.00, −66.7, 66.7	6	33.33 (36.515), 33.33, 0.0, 100.0	16.67 (40.825), 0.00, 0.0, 100.0	−16.67 (18.257), −16.67, −33.3, 0.0	12.4
Appetite loss	35	11.43 (16.053), 0.00, 0.0, 33.3	5.71 (15.094), 0.00, 0.0, 66.7	−5.71 (18.935), 0.00, −33.3, 33.3	6	22.22 (40.369), 0.00, 0.0, 100.0	16.67 (40.825), 0.00, 0.0, 100.0	−5.56 (13.608), 0.00, −33.3, 30.0	3.8
Constipation	35	13.33 (21.693), 0.00, 0.0, 66.7	16.19 (24.749), 0.00, 0.0, 66.7	2.86 (20.407), 0.00, −66.7, 66.7	5	26.67 (43.461), 0.00, 0.0, 100.0	20.00 (44.721), 0.00, 0.0, 100.0	−6.67 (14.907), 0.00, −33.3, 0.0	2.2
Diarrhea	35	13.33 (24.522), 0.00, 0.0, 100.0	13.33 (21.693), 0.00, 0.0, 66.7	0.00 (30.250), 0.00, −66.7, 66.7	5	0.00 (0.000), 0.00, 0.0, 0.0	6.67 (14.907), 0.00, 0.0, 33.3	6.67 (14.907), 0.00, 0.0, 33.3	2.5

CFB = change from baseline; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire–Core 30 Scale; SD = standard deviation.

Notes: All values after intercurrent events were set to missing.

Higher scores for global health status and functional scales indicates improvement, lower scores for the symptom scales indicates improvement.

Source: Hillmen (2021), Röth (2021), Hinz (2014).

Table 94 describes the change from baseline in QOL-C30 scores during the randomized control period using all available data set (ITT).

Table 94 Change from Baseline in QOL-C30 Scores during RCP - using all available data set (ITT set)

	Pegcetacoplan			Eculizumab			Difference	
	n	Mean (SD)	CI	n	Mean (SD)	CI	Mean (SD)	CI
Global Health Status/QOL	36	16.20 (21.726)	8.849 - 23.551	36	-4.86 (18.514)	-11.124 - 1.404	21.06 (20.184)	11.572 - 30.548
Functional scales								
Physical functioning	36	17.78 (16.941)	12.048 - 23.512	37	0.72 (14.722)	-4.189 - 5.629	17.06 (15.855)	9.659 - 24.461
Role functioning	36	16.67 (32.611)	5.636 - 27.704	37	-5.41 (26.659)	-14.299 - 3.479	22.08 (29.742)	8.197 - 35.963
Emotional functioning	36	7.64 (24.831)	-0.762 - 16.042	36	0.23 (21.128)	-6.919 - 7.379	7.41 (23.054)	-3.428 - 18.248
Cognitive functioning	36	7.41 (24.703)	-0.948 - 15.768	36	-5.56 (17.817)	-11.588 - 0.468	12.97 (21.537)	2.846 - 23.094
Social functioning	36	12.96 (22.577)	5.321 - 20.599	36	0.93 (22.868)	-6.807 - 8.667	12.03 (22.723)	1.348 - 22.712
Symptom scales								
Fatigue	35	-23.46 (26.531)	-32.574 - -14.346	37	-0.90 (21.497)	-7.456 - 5.656	22.56 (23.254)	11.624 - 33.496
Nausea and vomiting	36	0.00 (8.909)	-3.014 - 3.014	37	5.41 (19.663)	-1.146 - 11.966	5.41 (15.335)	-1.748 - 12.568
Pain	36	-0.46 (32.971)	-11.616 - 10.696	37	10.36 (22.344)	2.91 - 17.81	10.82 (28.09)	-2.292 - 23.932
Dyspnea	36	-19.44 (25.666)	-28.124 - -10.756	37	-6.31 (28.151)	-15.696 - 3.076	13.13 (26.955)	0.548 - 25.712
Insomnia	36	-11.11 (26.427)	-20.052 - -2.168	37	-5.41 (24.233)	-13.49 - 2.67	5.7 (25.338)	-6.128 - 17.528
Appetite loss	36	-5.56 (18.687)	-11.883 - 0.763	37	0.00 (23.570)	-7.859 - 7.859	5.56 (21.303)	-4.384 - 15.504
Constipation	36	2.78 (20.119)	-4.027 - 9.587	36	-5.56 (16.903)	-11.279 - 0.159	8.34 (18.581)	-0.395 - 17.075
Diarrhea	36	0.00 (29.814)	-10.088 - 10.088	36	8.33 (21.639)	1.008 - 15.652	8.33 (26.049)	-3.916 - 20.576
Financial difficulties	36	-10.19 (26.210)	-19.058 - -1.322	36	-2.78 (28.031)	-12.264 - 6.704	7.41 (27.136)	-5.346 - 20.166

EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire–Core 30 Scale;

CI = confidence interval; ITT = intent-to-treat; SD = standard deviation

Source: CSR = clinical study report