Medicinrådet

Bilag til direkte indplacering af iptacopan i Medicinrådets evidensgennemgang vedr. lægemidler til paroksystisk natlig hæmoglobinuri

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. iptacopan
2. Forhandlingsnotat fra Amgros vedr. iptacopan
3. Ansøgers endelige ansøgning vedr. iptacopan

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13. november 2025

Kære Medicinråd,

Tak for et vel uarbejdet udkast til Tillæg til behandlingsvejledning vedr. lægemidler til PNH med direkte indplacering af iptacopan.

Vi har nu gennmlæst udkastet, og har ikke fundet faktuelle fejl.

Vi noterer os, at Medicinrådet i udkastet vurderer, at iptacopan har mindst lige så god effekt som C3- og C5-hæmmere, og at iptacopan desuden har en sikkerhedsprofil, der er håndterbar og sammenlignelig med de øvrige komplementhæmmere. Valget af behandling beror på en individuel vurdering og foretages af patient og kliniker i fællesskab. Den perorale administrationsvej fremhæves som en fordel for nogle patienter, som kan tage medicinen i eget hjem.

Det anføres yderligere i udkastet, at efterlevelsesprocenten i den kliniske rækkefølge af lægemidlerne (lægemiddelrekommandationen) giver mulighed for, at der kan tages individuelle patienthensyn. Dette er naturligvis positivt.

Det er dog en skuffelse, at der ikke er mulighed for at blive inkluderet i en lægemiddelrekommandation, før nyt udbud starter om knapt 1 år, den 1. november 2026. Det eksisterende udbud med kontraktstart den 1. november 2025 indeholder desværre ikke mulighed for prisregulering, hvilket i praksis betyder, at iptacopan kun i meget begrænset omfang kan blive ibrugtaget før slutningen af næste år.

Med venlig hilsen,
Novartis A/S

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21.11.2025

LSC/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	17.12.2025
Leverandør	Novartis
Lægemiddel	Fabhalta (iptacopan)
Ansøgt indikation	Behandling af voksne patienter med paroksystisk natlig hæmoglobinuri (PNH), som har hæmolytisk anæmi.
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har følgende pris på Fabhalta (iptacopan):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Nuværende SAIP, (DKK)	Forhandlet rabat ift. AIP
Fabhalta	200 mg (56 stk.)	203.448,00	[redacted]	[redacted]

Aftaleforhold

[redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

Fabhalta er vurderet via en direkte indplacering i behandlingsvejledningen vedrørende lægemidler til behandling af paroksystisk natlig hæmoglobinuri (PNH). Medicinrådet har tidligere vurderet, at lægemidlerne PiaSky (crovalimab), Epysqli (eculizumab), Aspaveli (pegcetacoplan) og Ultomiris (ravulizumab) er klinisk ligeværdige til behandling af PNH.

Der er ingen nye lægemidler til PNH på vej, men en indikationsudvidelse på Ultomiris til neuromyelitis optica spektrumforstyrrelse (NMOSD) er i proces i Medicinrådet, og en indikationsudvidelse på Aspaveli til C3G er i proces i EMA. Der er også en igangværende proces i Medicinrådet på Fabhalta til C3G.

[redacted]

Tabel 2 viser lægemiddeludgiften i relation til de øvrige lægemidler i behandlingsvejledningen for PNH. Sammenligningsperioden er 78 uger, og gennemsnitvægten for en patient er sat til 75 kg. jf. opsummering af Medicinrådets evidensgennemgang vedrørende lægemidler til paroksystisk natlig hæmoglobinuri (PNH).

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient, 78 uger

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandling (SAIP, DKK)
Fabhalta	200 mg, 56 stk. kapsler	200 mg p.o. to gange dagligt	[redacted]	[redacted]
PiaSky	340 mg, 1 stk. hætteglas	*Opstartsdosis:* Dag 1: 1.000 mg i.v. Dag 2, 8, 15, 22: 340 mg s.c. *Vedligeholdelsesdosis:* Dag 29 og derefter hver 4. uge: 680 mg s.c.	[redacted]	[redacted]
Epysqli	300 mg, 1 stk. hætteglas	*Opstartsdosis*: 600 mg i.v. 1 gang ugentligt i 4 uger	[redacted]	[redacted]

		Vedligeholdelsesdosis: 900 mg i.v. hver 14. dag +/- 2 dage, startende fra uge 5		
Aspaveli	1080 mg, 8 stk. hætteglas	*Opstartsdosis:* 1.080 mg s.c. to gange/uge på 1. og 4. dag (+ nuværende dosis af enten eculizumab eller ravulizumab i 4 uger) *Vedligeholdelsesdosis:* 1.080 mg s.c. to gange/uge på 1. og 4. dag (pegcetacoplan alene)	[redacted]	[redacted]
Ultomiris	100 mg/ml, 11 ml. hætteglas	*Opstartsdosis*: 2.700 mg i.v. *Vedligeholdelsesdosis*: 3.300 mg i.v. hver 8. uge, startende 2 uger efter opstartsdosis	[redacted]	[redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Ikke ansøgt	
England	Anbefalet	Link til vurdering
Sverige	Ikke ansøgt	

Opsummering

[redacted]

Application for the assessment of iptacopan (Fabhalta®) by updating the Medicines Council's treatment guideline for paroxysmal nocturnal haemoglobinuria (PNH)

Contact information

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List of Tables and Figures

The application does not include any figures.

Abbreviations

Abbreviation	Full term
AE	Adverse event
ARC	Absolute reticulocyte count
BMI	Body mass index
BTH	Breakthrough haemolysis
C3i	Complement 3-inhibitor
C5i	Complement 5-inhibitor
CFB	Change from baseline
Ci	Complement inhibitor
CI	Confidence interval
DMC	Danish Medicines Council
EMA	European Medicines Agency
EORTC QLQ-C30	European Organization of Research and Treatment of Cancer 30-item Core Quality of Life Questionnaire
EOS	End of study
EPAR	European Public Assessment Report
EQ-5D-5L	EuroQol – 5 Dimensions– 5 Level
ESS	Effective sample size
FACIT	Functional Assessment of Chronic Illness Therapy
IPD	Individual patient data
ITC	Indirect treatment comparison
ITT	Intention-to-treat
i.v.	Intravenous
LASA	Linear analog scale assessment
LDH	Lactate dehydrogenase
LDH-N	Normalization of LDH levels
LLN	Lower limit of normal
LS	Least squares
MAIC	Matching-adjusted indirect comparison
MAVE	Major adverse vascular event
MMRM	Mixed Model for Repeated Measures
n	Number of patients
NA	Not applicable
NICE	National Institute for Health and Care Excellence
NYHA	New York Heart Association
OR	Odds ratio

Abbreviation	Full term
P_{inf}	Post hoc noninferiority p-value
pRBC	Packed red blood cells
PNH	Paroxysmal nocturnal haemoglobinuria
p.o.	Per os
RAS	Renin-angiotensin system
RBC	Red blood cells
RCP	Randomised controlled period
RCT	Randomised controlled trial
SAE	Serious adverse event
SE	Standard error
SD	Standard deviation
SMD	Standardized mean difference
s.c.	Subcutaneous
SLR	Systematic literature search
STC	Simulated treatment comparison
ULN	Upper limit of normal
WHO	World Health Organization

1. Regulatory information on the pharmaceutical

Overview of the pharmaceutical	
Proprietary name	Fabhalta
Generic name	iptacopan
Therapeutic indication as defined by EMA	Fabhalta is indicated as monotherapy in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia.
Marketing authorization holder in Denmark	Novartis Europharm Limited Vista Building Elm Park, Merrion Road Dublin 4 Ireland
ATC code	L04AJ08
Combination therapy and/or co-medication	None
(Expected) Date of EC approval	May 17, 2024
Has the pharmaceutical received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	Yes
Other therapeutic indications approved by EMA	Fabhalta is also indicated for the treatment of adult patients with complement 3 glomerulopathy in combination with a renin-angiotensin system (RAS) inhibitor, or in patients who are RAS-inhibitor intolerant, or for whom a RAS inhibitor is contraindicated.
Other indications that have been evaluated by the DMC (yes/no)	No
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Fabhalta 200 mg hard capsules Blister packages with 56 hard capsules

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	Fabhalta is indicated as monotherapy in the treatment of adult patients with PNH who have haemolytic anaemia.
Dosage regiment and administration:	The recommended dose is 200 mg taken orally twice daily.
Choice of comparator [if any]	This application focuses on the treatment of complement inhibitor (Ci)-naïve patients, (the population in the clinical question in the PNH treatment guideline from the Danish Medicines Council (DMC)) but also includes data on patients with residual anemia despite treatment with complement 5-inhibitors (C5i's), addressed in *4.3 Considerations regarding switch between medicinal products* in the PNH guideline. **Comparators for Ci-naïve patients:** Eculizumab, ravulizumab and pegcetacoplan. **Comparator for patients with residual anemia despite C5i treatment:** Pegcetacoplan
Most important efficacy endpoints (Difference/gain compared to comparator)	All comparisons are narratively, as in the PNH treatment guideline from the DMC. **Ci-naïve patients** [1–3] <u>Transfusion avoidance</u> The proportion of patients achieving transfusion independence on iptacopan was 98% (95% confidence interval (CI), 92 to 100), and as such higher than for ravulizumab and eculizumab (respectively 73.6% and 66.1%), and in the same range as for pegcetacoplan (91.4%). <u>Fatigue</u> The average change in the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score was higher for iptacopan 10.8 (95%CI 8.7 to 12.8) than for pegcetacoplan 7.8 (standard error (SE): 1.2), ravulizumab 7.1 (95%CI 5.6 to 8.6) and eculizumab 6.4 (95%CI 4.9 to 8.0). The matching-adjusted indirect comparison (MAIC) showed similar results for iptacopan vs. ravulizumab and eculizumab, however the differences were not statistically significant, respectively 3.78 points (95%CI -1.38 to 8.94), P=0.1514 for ravulizumab and 4.45 points (95%CI -0.72 to 9.62), P=0.0918 for eculizumab. <u>Stabilisation of haemoglobin</u> Due to the difference in definition of the outcome it is difficult to compare across studies. Haemoglobin stabilisation was achieved by 92% (95% CI, 82 to 100) of patients treated with iptacopan. For pegcetacoplan haemoglobin stabilisation was achieved by 85.7%, and for ravulizumab and eculizumab the numbers were 68.0% (95% CI, 59.8 to 76.2), and 64.5% (95% CI, 55.9 to 73.0), respectively. <u>Normalisation of lactate dehydrogenase (LDH)</u> Due to the difference in definition of the outcome it is difficult to compare across studies. In the APPOINT-PNH study 95% of the iptacopan-treated patients achieved the outcome, which is more than for pegcetaclopanpegcetacoplan (65.7%), ravulizumab (53.6%, 95%CI 45.9 to 61.2) and eculizumab (49.4%, 95%CI 41.7 to 57.0). <u>Health related quality of life</u> The average change in European Organization of Research and Treatment of Cancer 30-item Core Quality of Life Questionnaire (EORTC QLQ-C30) global health score was 25.1 (standard deviation (SD) 18.72) for iptacopan, 18.9 (SE 2.9) for pegcetacoplan,

Summary	
	13.2 (SD 21.4) ravulizumab and 12.9 (SD 21.8) for eculizumab. Thus, both iptacopan and pegcetacoplan may lead to an increased quality of life compared to ravulizumab and eculizumab. **Patients with residual anemia despite C5i treatment** [1, 4] <u>Transfusion avoidance</u> The proportion of patients achieving transfusion independence on iptacopan in APPLY-PNH was 95% (95%CI, 88 to 100) at week 24. For pegcetacoplan, 85% of patients in PEGASUS achieved transfusion independence at weel 16. <u>Fatigue</u> The mean change from baseline in FACIT-Fatigue score at 24 weeks was 8.6 points for patients on iptacopan APPLY-PNH. The mean change from baseline in FACIT-Fatigue score at 16 weeks for patients treated with pegcetacoplan in PEGASUS was 9.2 points (SE±1.6). The results seem similar, which is confirmed in an indirect treatment comparison (ITC). <u>Stabilisation of haemoglobin</u> The definitions of the outcome differed significantly between studies. The proportion of patients achieving stabilisation of haemoglobin on iptacopan in APPLY-PNH was 82% (95%CI, 75 to 90) at week 24. For pegcetacoplan, 34.1% of patients in PEGASUS achieved stabilisation of haemoglobin at week 16. **Conclusion** Based on the results described above iptacopan seems to have similar efficacy as the comparators in Ci-naive PNH patient as well as in PNH patients with residual anemia despite C5i-treatment.
Most important serious adverse events (SAEs) for the intervention and comparator	As assessed by the DMC, treatment with Ci's is generally well tolerated, as demonstrated by the low frequency of SAEs. This is also the case for iptacopan. For Ci-naïve patients, the frequencies of SAEs were 7.4% for eculizumab, 8.8% for ravulizumab [2], 8.7% for pegcetacoplan [3] and 10% for iptacopan [1]. There were two deaths in PRINCE, one in the pegcetacoplan arm and one in the supportive care arm, both considered unrelated to treatment [3]. None of the studies reported meningococcal infections [1–3]. Other serious infections were reported by 3.3% in the eculizumab arm and 1.6 in the ravulizumab arm [2]. No serious infections were reported for pegcetacoplan [3], and one patient, 3%, had a serious infection with iptacopan. APPOINT-PNH was conducted during the covid pandemic and 15% experienced a covid-19 infection [1]. Major adverse vascular events (MAVEs) were experienced by very few patients: 0.8% with eculizumab and 1.6% with ravulizumab in the 301 study [2]. For patients with residual anemia despite treatment with C5i, the safety profiles were generally similar. One patient, 1.6%, had transient ischaemic attack while on iptacopan in APPLY-PNH [1] and in PEGASUS, 3 patients in the pegcetacoplan arm stopped treatment due to an adverse event (AE) (all due to breakthrough haemolysis (BTH)) [4]. Except for administration related AEs (e.g. injection-related for pegcetacoplan [3, 4], and infusion-related for ravulizumab and eculizumab) [2, 4], the safety profile of iptacopan seems to be in the same range as the comparators.

3. The patient population, intervention and relevant outcomes

3.1 The medical condition, patient population, current treatment options and choice of comparator(s)

3.1.1 Medical condition

PNH is described in detail in the treatment guideline for PNH [5].

3.1.2 Patient population

The PNH patient population is described in detail in the treatment guideline for PNH [5].

3.1.3 Current treatment options

With the current treatment guideline for PNH, treatment options for patients with severe disease i.e., with daily significant discomfort, severe complications, and/or organ manifestations, include the C5i treatments eculizumab, ravulizumab and crovalimab and the complement 3-inhibitor (C3i) pegcetacoplan. Table 1 gives an overview of dose and administration for the current treatments.

Table 1 Administration and dosing of current treatments

Generic name (Proprietary name)	Administration and dosing	Mode of action
Eculizumab [6]	Start dose: 600 mg i.v. once weekly for 4 weeks. Maintenance dose: 900 mg i.v. every 14 days ± 2 days.	C5i
Ravulizumab [7]	Start dose: - 2400 mg i.v. for ≥ 40 to < 60 kg - 2700 mg i.v. for ≥ 60 kg to < 100 kg - 3000 mg i.v. for ≥ 100 kg Maintenance dose: Every 8 week, starting 2 weeks after start dose - 3000 mg i.v. for ≥ 40 to < 60 kg - 3300 mg i.v. for ≥ 60 kg to < 100 kg - 3600 mg i.v. for ≥ 100 kg	C5i

Generic name (Proprietary name)	Administration and dosing	Mode of action
Crovalimab [8]	Patients with body weight ≥ 40 kg to < 100 kg Start dose: Day 1: 1000 mg i.v., Day 2, 8, 15, 22: 340 mg s.c. Maintenance dose: Day 29 and hereafter every 4 weeks: 680 mg s.c. Patients with body weight ≥ 100 kg Start dose: Day 1: 1500 mg i.v., Day 2, 8, 15, 22: 340 mg s.c, Maintenance dose: Day 29 and hereafter every 4 weeks: 1020 mg s.c.	C5i
Pegcetacoplan [9]	Start dose: 1.080 mg s.c. twice weekly on day 1 and 4 (+ current dose of either eculizumab or ravulizumab for 4 weeks). Maintenance dose: 1.080 mg s.c. twice weekly on day 1 and 4 (pegcetacoplan alone). In case of inadequate response the dose can be escalated to 1.080 mg thrice weekly.	C3i

Abbreviations: C3i, complement 3 inhibitor; C5i: complement 5 inhibitor; i.v., intravenously; s.c., subcutaneously.

Both eculizumab and ravulizumab are given i.v., every 2 and 8 weeks, respectively. Pegcetacoplan is given twice weekly as two s.c. infusions, due to the relatively large volume (20 ml) to be administered. There is thus a major unmet need for more convenient oral treatment options, given the route of administration of current therapies.

3.1.4 Choice of comparator

In the DMC treatment guideline for PNH [5] the four medicinal products eculizumab, ravulizumab, crovalimab and pegcetacoplan are considered to be equal with regard to efficacy and tolerability.

The clinical question in the treatment guideline concerns efficacy in C5i-naïve patients ("Clinical question 1"). However, the efficacy of pegcetacoplan in patients with residual anaemia despite C5i-treatment (the PEGASUS population [4] is described in section *4.3 Considerations regarding switch between drugs*.

For this assessment, eculizumab, ravulizumab (C5i's, both presented in a MAIC-analysis evaluated by National Institute for Health and Care Excellence (NICE) [10] and pegcetacoplan (C3i) are included as comparators for the Ci-naïve patients. Crovalimab is not included, as it has the same mode of action as eculizumab and ravulizumab and these can be considered as proxy for crovalimab.

For patients with residual anemia despite C5i treatment pegcetacoplan is the comparator, as it is a C3i.

3.2 The intervention

Iptacopan is a proximal Ci that targets Factor B to selectively inhibit the alternative pathway. Inhibition of Factor B in the alternative pathway of the complement cascade prevents the activation of C3 convertase and the subsequent formation of C5 convertase to control both C3-mediated extravascular haemolysis and terminal complement-mediated intravascular haemolysis [11].

Notably, iptacopan is administered orally with 200 mg hard capsules taken twice daily.

An overview of Iptacopan is provided in Table 2 below.

Table 2 Overview of iptacopan

Overview of intervention	
Therapeutic indication relevant for the assessment	Fabhalta is indicated as monotherapy in the treatment of adult patients with PNH who have haemolytic anaemia.
Method of administration	Oral administration.
Dosing	200 mg taken twice daily.
Should the pharmaceutical be administered with other medicines?	No.
Treatment duration / criteria for end of treatment	Like for other Ci's for PNH, the treatment with iptacopan is expected to be lifelong. In case of loss of efficacy or in case of toxicity the treatment should be stopped.
Necessary monitoring, both during administration and during the treatment period	No monitoring is required during orally administration of iptacopan. Monitoring during the treatment period is expected to be similar to that of the other Ci's for PNH: Regular monitoring for

Overview of intervention	
	signs and symptoms of haemolysis, including measuring LDH levels. If treatment with iptacopan must be discontinued, patients with PNH should be closely monitored for signs and symptoms of haemolysis for at least 2 weeks after the last dose.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	As for other Ci's for PNH, controlled access is required. For iptacopan, the physician must ensure that the patient is vaccinated against neisseria meningitidis and streptococcus pneumoniae infections and/or receipt of prophylactic antibiotic, prior to start of treatment and during the entire treatment period.
Package size(s)	Fabhalta 200 mg hard capsules. Blister packages with 56 hard capsules.

3.2.1 The intervention in relation to Danish clinical practice

It is expected that iptacopan will be considered to have equal efficacy and safety for C5i-naïve patients with PNH, compared to the medicinal products included in the treatment guideline for PNH.

In addition, it is expected that iptacopan will be considered as an appropriate choice for patients with residual anaemia despite C5i-treatment.

4. Overview of literature

A systematic literature search (SLR) for the comparators has been omitted, since the SLR for the treatment guideline was conducted between 13 September and 8 November 2024.

At a dialogue meeting with the DMC secretariat, it was discussed that an SLR for iptacopan would not be necessary due to the limited number of studies and publications with iptacopan for PNH.

The secretariat suggested including a MAIC from the NICE assessment of iptacopan for PHN. This includes Ci-naïve patients [10].

The studies included in this application are listed in Table 3, and the studies are described in detail in Appendix A.

Table 3 Relevant literature included in the assessment of efficacy and safety

Trial name, NCT identifier and reference	Study design	Study duration	Dates of study	Patient population	Intervention	Comparator	Relevant for PICO in treatment guideline	Outcomes and follow-up period
APPOINT-PNH NCT04820530 Peffault de Latour R, et al (2024) Oral Iptacopan Monotherapy in Paroxysmal Nocturnal Hemoglobinuria. New England Journal of Medicine 390:994–1008 [1]	A single group phase 3 study	8-week screening period followed by a 24-week (168 days) treatment period and a 24-week extension period	Start: 19/07/21 Completion: 18/04/23 Data cut-off 02/11/22	Ci-naïve PNH patients with mean haemoglobin levels of less than 10 g/dL and with no evidence of bone marrow failure	Iptacopan p.o. 200 mg twice daily	N/A	Transfusion avoidance Fatigue (FACIT-Fatigue score) Stabilisation of haemoglobin Normalisation of LDH Safety Quality of life (EORTC QLQ- C30, global health score)	All of the following outcomes were assessed at 24 weeks (168 days) **Primary efficacy endpoint** Marginal proportion of participants with sustained increase in haemoglobin levels from baseline of ≥ 2 g/dL in the absence of RBC transfusions *Sustained increase in haemoglobin levels (responder) is defined as an increase from baseline in haemoglobin levels of ≥ 2 g/dL on three out of four measurements between Day 126 and 168 of the core treatment period, without requiring RBC transfusions between Day 14 and Day 168* **Secondary efficacy endpoints** Marginal proportion (expressed as percentage) with sustained

Trial name, NCT identifier and reference	Study design	Study duration	Dates of study	Patient population	Intervention	Comparator	Relevant for PICO in treatment guideline	Outcomes and follow-up period
								haemoglobin levels of ≥ 12 g/dL in the absence of RBC transfusions Marginal proportion of participants who remain free from transfusions Change from baseline in haemoglobin levels in the core treatment period Percent change from baseline in LDH between day 126 and day 168 Adjusted annualized clinical BTH rate in the core treatment period Change from baseline in ARC Change from baseline in FACIT-Fatigue score Adjusted annualized MACEs rate in the core treatment period

Trial name, NCT identifier and reference	Study design	Study duration	Dates of study	Patient population	Intervention	Comparator	Relevant for PICO in treatment guideline	Outcomes and follow-up period
Study 301 NCT02946463 Wook Lee J, et al (2019) Ravulizumab (ALXN1210) vs. eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study. Blood 133:530–539. [2]	A randomised phase 3 open label, active comparator-controlled study	4-week screening period followed by a 26-week RCP and an extension period of up to two years, where all patients were treated with ravulizumab	Start: 12/12/16 Completion: 28/02/23	Ci-naïve PNH patients with ≥ 1 of the following: fatigue, haemoglobinuria, abdominal pain, dyspnea, anemia (ie, haemoglobin level ,10 g/dL), or history of MAVEs dysphagia, erectile dysfunction, or history of packed red blood cell (pRBC) transfusion because of PNH	Ravulizumab i.v. A loading dose (2400 mg for patients weighing ≥ 40 to < 60 kg, 2700 mg for patients ≥ 60 kg to < 100 kg, and 3000 mg for patients ≥ 100 kg) on day 1, followed by maintenance doses (3000 mg for patients ≥ 4 0 to < 60 kg, 3300 mg for patients ≥ 6 0 to < 100 kg, and 3600 mg for patients ≥ 100 kg) on day 15 and every 8 weeks thereafter	Eculizumab i.v. Induction doses of 600 mg on days 1, 8, 15, and 22, followed by maintenance dosing of 900 mg on day 29 and every 2 weeks thereafter	Transfusion avoidance Fatigue (FACIT-Fatigue score) Stabilisation of haemoglobin Normalisation of LDH Safety Quality of life (EORTC QLQ- C30, global health score)	All of the following outcomes were assessed at 183 days **Primary efficacy endpoint** Proportion of participants with normalization of LDH levels *LDH is an indicator of intravascular haemolysis that occurs in participants with PNH. A decrease in LDH from above the ULN to below the ULN indicates reduction (improvement) in haemolysis. Normalization of LDH levels (LDH-N) was LDH levels less than or equal to 1 x ULN, from Day 29 through Day 183. The ULN for LDH is 246 U/L* Percentage of participants who achieved transfusion avoidance *Transfusion avoidance was defined as the percentage of participants who remained transfusion free and did not require a transfusion per*

Trial name, NCT identifier and reference	Study design	Study duration	Dates of study	Patient population	Intervention	Comparator	Relevant for PICO in treatment guideline	Outcomes and follow-up period
								protocol-specified guidelines through Day 183 **Secondary efficacy endpoints** Percentage of participants with BTH Percent change from baseline in LDH levels Change from baseline in quality of life as assessed by the FACIT-Fatigue Percentage of participants with stabilized haemoglobin levels
PRINCE NCT04085601 Wong RSM, et al (2023) Pegcetacoplan controls hemolysis in complement inhibitor–naive patients with paroxysmal	A randomised phase 3 open label, active comparator-controlled study	≤ 4-week screening period followed by a 26-week treatment period	Start: 27/08/2019 Completion: 23/06/21	PNH patients not treated with C5i within three months prior to screening, with haemoglobin level below lower limit of normal (LLN) (male: < 13.6	Pegcetacoplan s.c. 1080 mg twice weekly or every 3 days up to end of the RCP	Supportive care E.g., transfusions, corticosteroids and supplements (iron, folate, and vitamin B12)	Transfusion avoidance Fatigue (FACIT-Fatigue score) Stabilisation of haemoglobin Normalisation of LDH Safety Quality of life (EORTC QLQ- C30, global health score)	All of the following outcomes were assessed at 26 weeks **Primary efficacy endpoint** Number of subjects who achieved haemoglobin stabilization from baseline up to week 26 *The haemoglobin stabilization was defined as avoidance of a > 1 g/dL decrease in haemoglobin*

Trial name, NCT identifier and reference	Study design	Study duration	Dates of study	Patient population	Intervention	Comparator	Relevant for PICO in treatment guideline	Outcomes and follow-up period
nocturnal hemoglobinuria. Blood Adv 7:2468–2478. [3]				g/dL, female: < 12.0 g/dL)				*concentration from Baseline in the absence of transfusion through Week 26* Change From Baseline in LDH Concentration At Week 26 **Secondary efficacy endpoints** Number of subjects with a haemoglobin response in the absence of transfusions Change from baseline in ARC Change from baseline in haemoglobin concentration Percentage of subjects who received transfusion or decrease of haemoglobin > 2 g/dL from baseline Percentage of subjects with transfusion avoidance Number of pRBC units transfused from baseline through week 26

Trial name, NCT identifier and reference	Study design	Study duration	Dates of study	Patient population	Intervention	Comparator	Relevant for PICO in treatment guideline	Outcomes and follow-up period
								Change from baseline in FACIT-Fatigue Scale Score Percentage of subjects with haemoglobin normalization levels Percentage of subjects With LDH normalization Change from baseline in EORTC QLQ-C30 Scores Change from baseline in Linear Analog Scale Assessment (LASA) Score Percentage of subjects with ARC normalization Number of subjects with failure of haemoglobin stabilization Time to first pRBC transfusion
MAIC-analysis NICE (2023) Single Technology Appraisal	A MAIC of data from APPOINT-PNH and Study 301	As for APPOINT-PNH and Study 301	As for APPOINT-PNH and Study 301	As for APPOINT-PNH and Study 301	APPOINT-PNH: Iptacopan p.o. See APPOINT-	APPOINT-PNH: N/A	Transfusion avoidance Fatigue (FACIT-Fatigue score) Normalisation of LDH	At 168 days for APPOINT-PNH and 183 days for Study 301 the following outcomes were assessed:

Trial name, NCT identifier and reference	Study design	Study duration	Dates of study	Patient population	Intervention	Comparator	Relevant for PICO in treatment guideline	Outcomes and follow-up period
Iptacopan for treating paroxysmal nocturnal haemoglobinuria [ID6176] Document B: Company evidence submission. 67–70. [10]					PNH above for dose Study 301: Ravulizumab i.v. See Study 301 above for dose	Study 301 Eculizumab i.v. See study 301 above for dose		Transfusion avoidance Fatigue (FACIT-Fatigue score) Normalisation of LDH
APPLY-PNH NCT04558918 Peffault de Latour R, et al (2024) Oral Iptacopan Monotherapy in Paroxysmal Nocturnal Hemoglobinuria. New England Journal of Medicine	Randomised phase 3 open label, active comparator-controlled study	8-week screening period followed by a 24-week (168 days) RCP and a 24-week extension period, where all patients were treated with iptacopan	Start: 25/01/2021 Completion: 06/03/23 Data cut-off 26/09/22	PNH patients on a stable C5i treatment with residual anemia (Mean haemoglobin level < 10 g/dL)	Iptacopan p.o. 200 mg twice daily	Eculizumab i.v. every 2 weeks or Ravulizumab i.v. every 8 weeks For both C5i's the patients continued the regimen they were on at study entry	Transfusion avoidance Fatigue (FACIT-Fatigue score) Stabilisation of haemoglobin Safety	All of the following outcomes were assessed at 168 days. **Primary efficacy endpoint** Marginal proportion of participants with sustained increase in haemoglobin levels from baseline of ≥ 2 g/dL in the absence of RBC transfusions Marginal proportion (expressed as percentages) of participants with sustained haemoglobin levels of ≥ 12 g/dL in the absence of RBC transfusions

Trial name, NCT identifier and reference	Study design	Study duration	Dates of study	Patient population	Intervention	Comparator	Relevant for PICO in treatment guideline	Outcomes and follow-up period
390:994–1008 [1]								Percentage of patients meeting haematological response criterion after the start of iptacopan treatment Number of patients not requiring RBC transfusions after the start of iptacopan treatment Change from baseline in haemoglobin at visit day 336 Change from baseline in FACIT-Fatigue questionnaire at day 336 Adjusted annualized clinical BTH rate after the start of iptacopan treatment Adjusted annualized MACEs rate after the start of iptacopan treatment **Secondary efficacy endpoints** Marginal proportion of participants who remain free from transfusions

Trial name, NCT identifier and reference	Study design	Study duration	Dates of study	Patient population	Intervention	Comparator	Relevant for PICO in treatment guideline	Outcomes and follow-up period
								Change from baseline in haemoglobin between day 126 and 168 Change from baseline in FACIT-Fatigue questionnaire in the RCP Change from baseline in ARC in the RCP Ratio to baseline in Log-transformed LDH in the RCP Adjusted annualized clinical BTH rate in the RCP Adjusted annualized MACEs rate in the RCP
PEGASUS NCT03500549 Hillmen P, et al (2021) Pegcetacoplan versus Eculizumab in Paroxysmal Nocturnal	Randomised phase 3 open label, active comparator-control	A 4-week run-in phase followed by a 16-week RCP, followed by a 32-week period where all patients received open-	Start: 14/06/2018 Completion: 13/08/20 Data cut-off 14/11/19	PNH patients with haemoglobin levels lower than 10.5 g/dL despite eculizumab therapy	Pegcetacoplan s.c. During a 4-week run-in phase, all the patients continued to receive their current dose of	Eculizumab i.v. Patients in the comparator group received their current dose of eculizumab with the addition of	Transfusion avoidance Fatigue (FACIT-Fatigue score) Stabilisation of haemoglobin Safety	All of the following outcomes were assessed at 16 weeks. **Primary efficacy endpoint** LS mean change from baseline to week 16 in Haemoglobin level during the RCP *Baseline was the average of measurements recorded before*

Trial name, NCT identifier and reference	Study design	Study duration	Dates of study	Patient population	Intervention	Comparator	Relevant for PICO in treatment guideline	Outcomes and follow-up period
Hemoglobinuria. New England Journal of Medicine 384:1028–1037. [4]		label pegcetacoplan			eculizumab with the addition of twice-weekly pegcetacoplan (1080 mg). After the run-in phase, patients received monotherapy with pegcetacoplan for 16 weeks (RCP) Subsequently all patients received open-label pegcetacoplan in a 32-week period	twice-weekly subcutaneous pegcetacoplan (1080 mg) during the run-in phase. During the 16-week RCP, patients received monotherapy with eculizumab. Subsequently all patients continued to receive eculizumab in addition to pegcetacoplan for the first 4 weeks of the 32-week open-label period		*taking the first dose of pegcetacoplan, which included local and central laboratory values during the screening period. Analysis excluded data before the RCP and was censored for transfusions* **Secondary efficacy endpoints** Percentage of subjects who did not require a transfusion (transfusion avoidance) during the RCP LS mean change from baseline to week 16 in ARC during the RCP LS mean change from baseline to week 16 in LDH level during the RCP LS mean change from baseline to week 16 in FACIT-Fatigue scale score during the RCP Percentage of subjects who achieved a haemoglobin

Trial name, NCT identifier and reference	Study design	Study duration	Dates of study	Patient population	Intervention	Comparator	Relevant for PICO in treatment guideline	Outcomes and follow-up period
								response in the absence of transfusions at week 16 Percentage of subjects who achieved reticulocyte normalization in the absence of transfusions at week 16 Percentage of subjects who achieved haemoglobin normalization in the absence of transfusions at week 16 LS mean change from baseline to week 16 in indirect bilirubin level during the RCP LS mean change from baseline to week 16 in haptoglobin level during the RCP LS mean change from baseline to week 16 in LASA scores during the RCP LS mean change from baseline to week 16 in EORTC QLQ-C30 scores during the RCP

Trial name, NCT identifier and reference	Study design	Study duration	Dates of study	Patient population	Intervention	Comparator	Relevant for PICO in treatment guideline	Outcomes and follow-up period
								Total number of pRBC units transfused during the RCP Mean change from baseline to week 48 in haemoglobin level during the treatment period Mean change from week 17 to week 48 in haemoglobin level during the open-label period Mean Change From Baseline to Week 48 in ARC During the Treatment Period Mean change from week 17 to week 48 in ARC during the open-label period Mean change from baseline to week 48 in LDH level during the treatment period Mean change from week 17 to week 48 in LDH Level during the open-label period Mean change from baseline to week 48 in FACIT-Fatigue scale

Trial name, NCT identifier and reference	Study design	Study duration	Dates of study	Patient population	Intervention	Comparator	Relevant for PICO in treatment guideline	Outcomes and follow-up period
								score during the treatment period Mean change from week 17 to week 48 in FACIT-Fatigue scale score during the open-label period Mean change from baseline to week 48 in LASA scores during the treatment period Mean change from week 17 to week 48 in LASA scores during the open-label period Mean change from baseline to week 48 in QLQ-C30 Scores during the treatment period Mean change from week 17 to week 48 in QLQ-C30 scores during the open-label period Total number of pRBC units transfused during the open-label period

Trial name, NCT identifier and reference	Study design	Study duration	Dates of study	Patient population	Intervention	Comparator	Relevant for PICO in treatment guideline	Outcomes and follow-up period
ITC Peffault de Latour RP, et al (2025) Anchored Indirect Treatment Comparison Finds Comparable Effects of Pegcetacoplan and Iptacopan in Paroxysmal Nocturnal Haemoglobinuria. Eur J Haematol. https://doi.org/10.1111/ejh.14422 [12]	An anchored ITC of data from APPLY-PNH and PEGASUS	As for APPLY-PNH and PEGASUS	As for APPLY-PNH and PEGASUS	As for APPLY-PNH and PEGASUS	APPLY-PNH: Iptacopan p.o. 200 mg twice daily PEGASUS: Pegcetacoplan s.c. 1080 mg twice weekly	APPLY-PNH: Eculizumab i.v. or ravulizumab i.v. For doses see APPLY-PNH above PEGASUS: Eculizumab i.v. For dose see PEGASUS above	Fatigue (FACIT-Fatigue score)	APPLY-PNH: the following outcomes were assessed at 168 days (24 weeks) and PEAGSUS: the following outcomes were assessed at 16 weeks Change from baseline in haemoglobin (g/dL) Change from baseline in ARC Change from baseline in LDH-level (IU/L) Change from baseline in FACIT-Fatigue score

Abbreviations: ARC, absolute reticulocyte count; BTH, breakthrough haemolysis; C5i, complement 5 inhibitor; Ci, complement inhibitor; EORTC QLQ-C30, European Organization of Research and Treatment of Cancer 30-item Core Quality of Life Questionnaire; FACIT, Functional Assessment of Chronic Illness Therapy; ITC; indirect treatment comparison; LASA, linear analog scale assessment; LDH, lactate dehydrogenase; LDH-N, normalisation of LDH levels; LLN, lower limit of normal; LS, least squares; MAVE, major adverse vascular event; MAIC, matching-adjusted indirect comparison; NICE, National Institute for Health and Care Excellence; pRBC, packed red blood cell;RBC, red blood cells; RPC, randomised controlled period; ULN, upper limit of normal.

5. Clinical question

The clinical question in the treatment guideline for PNH [5] is:

"Are there clinically significant differences between the drugs for the treatment of complement inhibitor-naive patients with paroxysmal nocturnal haemoglobinuria?"

In addition, the guideline includes a section with considerations regarding switch between drugs.

This application focuses on the treatment of Ci-naïve patients, but as discussed at a dialogue meeting with the secretariat, it also includes data on patients with residual anemia despite C5i treatment in section 6 of this application.

5.1 Efficacy of iptacopan compared to eculizumab, ravulizumab and pegcetacoplan for Ci-naïve patients with PNH

5.1.1 Relevant studies

The following studies are included in this comparison for Ci-naïve PNH patients: APPOINT-PNH (iptacopan)[1], Study 301 (ravulizumab vs. eculizumab) [2]and PRINCE (pegcetacoplan vs. supportive care) [3]. All studies are listed in Table 3 above.

5.1.2 Comparability of studies

The three studies were published between 2019 and 2024. APPOINT-PNH is a single arm study with iptacopan, Study 301 and PRINCE are randomised controlled trials (RCTs), with comparisons of ravulizumab vs. eculizumab and pegcetacoplan vs. supportive care, respectively. The duration of the treatment period was 26 weeks for APPOINT-PNH, and 24 weeks for Study 301 and PRINCE.

5.1.3 Comparability of patients across studies and with Danish patients eligible for treatment

The number of participants by treatment arm in the studies varies from 18 in PRINCE (standard treatment arm) to 125 in Study 301 (ravulizumab arm). The mean age was between 42.1 and 46.2 years across the studies, and time from PNH diagnosis was between 3.4 and 4.7 years. In all studies, there is a slight predominance of male patients (52-58%).

Regarding ethnicity, the majority of patients in all studies except the eculizumab arm in Study 301 are Asians, with a proportion ranging from 47.1% to nearly 90% among patients who received standard treatment in the PRINCE study.

In general, baseline parameters were at similar levels in APPOINT and PRINCE with regard to body mass index (BMI) (23.2-24.7 kg/m^2) and FACIT-Fatigue score (32.8-37.1) (not recorded in Study 301).

While all patients in APPOINT-PNH were required to have haemoglobin < 10 g/dL at baseline, and all patients in PRINCE were required to have less than the LLN at the screening visit, Study 301 only required patients to have at least one PNH-related symptom at study entry. Anaemia (haemoglobin < 10 g/dL) was only one of the eligible symptoms, and therefore non-anaemic patients could also be included in Study 301.

Patients in the three studies were between 42.1 and 46.2 years old at study entry, and time from diagnosis was between 3.4 and 4.7 years. There was a slight predominance of male patients (52-58%). A Danish register study, which included patients from 2005-2021 showed a mean age in the PNH population of 48.6 years, with a 6 year-follow up from PNH diagnosis and equal distribution between gender. However, for the subgroup of patients treated with C5i's, the mean age was 44.8, and 58% were male. The C5i-treated patient population in Denmark thus seems similar to the populations in the clinical studies [13].

Table 4 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety. Ci-naïve population

	APPOINT-PNH [1]	**Study 301** [2]		**PRINCE** [3]	
	Iptacopan N=40	**Ravulizumab N=125**	**Eculizumab N=121**	**Pegcetacoplan N=35**	**Supportive care* N=18**
Age, years: mean (SD or range)	42.1 (15.9)	44.8 (15.2)	46.2 (16.2)	42.3 (22-67)	49.1 (20-74)
Sex, female: n(%)	17 (42)	60 (48)	52 (43)	16 (45.7)	8 (44.4)
Race, n (%)					
White	12 (30)	43 (34.4)	51 (42.1)	0	0
Asian	27 (68)	72 (57.6)	57 (47.1)	23 (65.7)	16 (88.9)
Black	1 (2)	2 (1.6)	4 (3.3)	2 (5.7)	0
Weight, kg, mean (SD)		68.2 (15.6)	69.2 (14.9)		
Height, cm, mean (SD)		166.3 (9.0)	166.2 (10.7)		
BMI, kg/m^2, mean (SD)	24.7 (3.3)	-	-	24.0 (4.4)	23.2 (2.9)
Time since diagnosis, years (SD or range)	4.7 (5.5)	3.8 (0-41)	3.9 (0-34)	3.4 (0.1-27.0)	4.7 (0.1-15.1)

	APPOINT-PNH [1]	Study 301 [2]		PRINCE [3]	
	Iptacopan N=40	Ravulizumab N=125	Eculizumab N=121	Pegcetacoplan N=35	Supportive care* N=18
Red cell transfusions, 6 months prior, n (%)	28 (70)				
≥ 4 transfusions, previous 12 months, n (%)				14(40.0)	10 (55.6)
> 14 RBC units, previous 12 months, n (%)		23 (18.4)	22 (18.2)		
History of aplastic anaemia, n (%)	16 (40)	-	-	5 (14.3)	5 (27.8)
History of MAVE, n (%)	5 (12)	17 (13.6)	26 (20.7)	-	-
Haemoglobin, g/dL, mean (SD)	8.2 (1.1)	-	-	9.4 (1.4)	8.7 (0.8)
LDH U/L, mean (SD)	1698.8 (683.3)	1633.5 (778.8)	1578.3 (727.1)	2151 (909.4)	1945.9 (1003.7)
Total bilirubin µmol/L, mean (SD)	28.7 (14.9)	-	-	39.4 (20.5)	35.5 (15.0)
ARC x10^{-9}/L, mean (SD)	154.3 (63.7)	-	-	230 .2 (81.0)	180.3 (109.1)

	APPOINT-PNH [1]	Study 301 [2]		PRINCE [3]	
	Iptacopan N=40	**Ravulizumab N=125**	**Eculizumab N=121**	**Pegcetacoplan N=35**	**Supportive care* N=18**
FACIT-Fatigue score, mean (SD)	32.8 (10.2)	Not reported	Not reported	36.3 (10.7)	37.1 (9.3)

*Supportive care in PRINCE was e.g. transfusions, corticosteroids and supplements (iron, folate, and vitamin B12). Abbreviations: ARC, absolute reticulocyte count; BMI, body mass index; FACIT, Functional Assessment of Chronic Illness Therapy; LDH, lactate dehydrogenase; MAVE, major adverse vascular event; RBC, red blood cells; SD, standard deviation.

5.2 Comparative analysis of efficacy and safety

5.2.1 Efficacy and safety – results per study

Based on the treatment guideline for PNH by the DMC, the following outcomes are included in the sections below: Transfusion avoidance, Fatigue, Stabilisation of Haemoglobin, Normalisation of LDH, Quality of Life and Safety.

5.2.1.1 APPOINT-PNH

APPOINT-PNH was a single arm study with iptacopan. A total of 40 patients entered the study and all patients completed the treatment period of 24 weeks [1].

The definition of outcomes, methods of analysis and results are described below. The results are consistent with those presented in the European Public Assessment Report (EPAR) [14].

Transfusion avoidance

Transfusion avoidance was defined as the marginal proportion (expressed as percentage) of participants who did not require transfusions between Day 14 and Day 168.

The term 'marginal proportion' can be interpreted as the population average probability of being a responder. The 95% CI was obtained using the bootstrap method.

Of the 40 patients treated with iptacopan, no patients received or met either criterion for receiving a transfusion between days 14 and 168; estimated percentage, 98% (95% CI, 92-100) [1].

Fatigue

Change from baseline in FACIT-Fatigue scores as mean of visits between Day 126 and Day 168 was assessed in the study.

Change from baseline was analyzed using a Mixed Model for Repeated Measures (MMRM) which includes age (indicator variable of age ≥ 45 years), sex, history of transfusion (yes/no) prior to study treatment, visit, and baseline FACIT-Fatigue score as fixed effects, along with the interaction between visit and baseline FACIT-Fatigue score.

In the APPOINT-PNH trial, the adjusted least squares (LS) mean change from baseline in the FACIT-Fatigue score was 10.8 points (95% CI, 8.7 to 12.8) [1]

Stabilisation of haemoglobin

Stabilisation of haemoglobin (responder) was defined as achieving an increase from baseline in haemoglobin levels of ≥ 2 g/dL on three out of four measurements between Day 126 and 168 of the core treatment period, without requiring red blood cells (RBC) transfusions between Day 14 and Day 168.

The term 'marginal proportion' can be interpreted as the population average probability of being a responder. Results incorporated a method to handle missing data using multiple imputation.

A total of 31 of the 33 evaluable patients in the APPOINT-PNH trial had an increase in haemoglobin level of at least 2 g/dL from baseline without red-cell transfusions; estimated percentage, 92% (95% CI, 82 to 100); a response could not be unequivocally established for 7 of the patients, owing to partial missing data between days 126 and 168 [1]

Normalisation of LDH

Normalisation of LDH was not an endpoint in APPOINT-PNH, however the proportion of patients having LDH levels that were no greater than 1.5 times the upper limit of normal (ULN) range at 24 weeks was 95% [1].

Quality of life

Patients reported EORTC QLQ- C30 scores at every visit. Change from baseline in patient reported scores for EORTC QLQ- C30 global health cores was presented for Day 168.

Descriptive statistics were applied. At each time point, only patients with a value at both baseline and at that time point were included.

Average change in EORTC QLQ- C30 global health score from baseline to day 168 was recorded in 37 patients in APPOINT-PNH, with the average change from baseline being 25.1 points (SD 18.72) at day 168 [15].

Safety findings

A total of 37 patients (92%) experienced at least one AE during the 24-week treatment period, with the most frequently reported AE being headache, reported in 28% of patients. Other AEs reported included Covid-19 infection (15%), upper respiratory tract infection (12%), diarrhea, nausea, abdominal pain and dizziness.

Four patients (10%) experienced a SAE; Covid-19 infection, cataract, type 2 diabetes and bacterial pneumonia, respectively. Regarding the bacterial pneumonia no causative organism was identified, and it was not suspected by the investigator to be related to iptacopan. No deaths were noted, and no AEs led to treatment discontinuation [1].

5.2.1.2 Study 301

Study 301 was a phase 3, open-label study which assessed the non-inferiority of ravulizumab to eculizumab in Ci–naive adults with PNH. A total of 246 patients were randomised 1:1 to receive ravulizumab (n=125) or eculizumab (n=121) for 183 days (26 weeks) [2].

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.

All 125 patients in the ravulizumab arm completed the 183-day (26-week) treatment period. In the eculizumab arm two out of 121 patients discontinued treatment, one due to physician's decision and one withdrew consent.

The definition of outcomes, methods of analysis and results are described below. Note that Study 301 only required patients to have at least one PNH-related symptom at study entry. Anaemia (haemoglobin < 10 g/dL) was only one of the eligible symptoms, and therefore non-anaemic patients could also be included in Study 301, in contrast to APPOINT-PNH and PRINCE, where patients had to be anaemic to be enrolled.

Transfusion avoidance

The proportion who achieved transfusion avoidance, was defined as the proportion who remained transfusion-free and did not need transfusion until day 183.

The absolute difference effect estimate is a calculated estimate. The end point was evaluated as the proportion of patients achieving the end point, computed as a weighted combination of differences between the treatment groups within the 2 randomization stratifications, using Mantel-Haenszel tests. The stratified Newcombe method was used to calculate 95% CIs. Stratification factors were: observed stratification groups of pRBC/whole blood units transfused in the 1 year prior to first dose of study drug and screening LDH levels..

Ninety-two of 125 patients (73.6%) receiving ravulizumab and 80 of 121 patients (66.1%) receiving eculizumab avoided transfusion, with a between-group difference of 6.8 %-points (95% CI, -4.66 to 18.14; Post hoc noninferiority p-value (P_{inf}) < 0.0001). The lower bound of the 95% CI was greater than the protocol-specified non-inferiority margin of -20% [2]

Fatigue

Mean change of FACIT-Fatigue score from baseline to day 183 was assessed in the study. Non-inferiority margin was based on the lower bound of the 95% CI. Non-inferiority margin was -5.

The adjusted LS mean change from baseline in the FACIT-Fatigue score was 7.07 points (95% CI, 5.55 to 8.60) for ravulizumab and 6.40 points (95% CI, 4.45 to 7.96) for eculizumab.

LS mean difference in change in FACIT-Fatigue score was 0.67 points (95% CI, -1.21 to 2.55; P_{inf} < 0.0001) [2]

Stabilisation of haemoglobin

Stabilisation of haemoglobin was defined as avoidance of a > 2 g/dL drop in haemoglobin level in the absence of transfusions from baseline to day 183.

The absolute difference effect estimate is a calculated estimate. The end point was evaluated as the proportion of patients achieving the end point, computed as a weighted combination of differences between the treatment groups within the 2 randomization

stratifications, using Mantel-Haenszel tests. The stratified Newcombe method was used to calculate 95% CIs. Stratification factors were: observed stratification groups of pRBC/whole blood units transfused in the 1 year prior to first dose of study drug and screening LDH levels. .

The proportion of patients who achieved stabilisation of haemoglobin was 68.0% (95% CI, 59.82 to 76.18) in the ravulizumab group vs. 64.5% (95% CI, 55.93 to 72.99) in the eculizumab group. The difference in rate was 2.9 %-points (95%CI, -8.80 to 14.64) [2].

Normalisation of LDH

Haemolysis control as measured by LDH normalization (ULN, 246 U/L) from day 29 to 183 was a co-primary endpoint in Study 301. Non-inferiority margin was based on the lower bound of the 95% CI. Non-inferiority margin was -20%.

The adjusted prevalence of LDH normalization was 53.6% (95% CI, 45.9 to 61.2) for the ravulizumab group and 49.4% (95% CI 41.7 to 49.4) for the eculizumab group; the adjusted Odds Ratio (OR) for comparison of ravulizumab vs. eculizumab was 1.19 (95% CI, 0.80 to 1.77; $P_{inf} < 0.0001$). The lower bound of the 95% CI was greater than the protocol-specified non-inferiority margin of 0.39 [2].

Quality of life

The average change in EORTC QLQ- C30 global health score from baseline to day 183 was recorded in Study 301, with an average change from baseline of 13.2 points (SD 21.4) for 124 patients in the ravulizumab group and 12.9 points (SD 21.8) in the eculizumab group. No statistics are presented [2].

Safety findings

A total of 110 patients (88.0%) in the ravulizumab group and 105 patients (86.8%) in the eculizumab group experienced at least one AE during the 183-days (26 weeks) treatment period, with the most frequently reported AE being headache in both groups (36.0% and 33.1% in the ravulizumab and eculizumab groups, respectively).

Eleven patients (8.8%) in the ravulizumab group and 9 patients (7.4%) in the eculizumab group experienced a SAE; Covid-19 infection, cataract, type 2 diabetes and bacterial pneumonia, respectively. Regarding the bacterial pneumonia no causative organism was identified, and it was not suspected by the investigator to be related to iptacopan. No deaths were noted during the 183-day treatment period, and no AEs led to treatment discontinuation. One patient in the eculizumab group died of lung cancer during the extension phase of the study, considered as unrelated to the treatment by the investigator [2].

5.2.1.3 PRINCE

PRINCE was a phase 3, randomised, multicenter, open-label, controlled study to evaluate the efficacy and safety of pegcetacoplan vs. control (supportive care only, e.g., blood transfusions, corticosteroids, and supplements) in Ci–naive patients with PNH. A total of

53 patients were randomised 2:1 to receive pegcetacoplan (n=35) or supportive care only (n=18) for 26 weeks [3].

Patients randomly assigned to the control group continued supportive care but could escape to pegcetacoplan treatment if their haemoglobin level decreased ≥ 2 g/dL below their baseline measurement or if they had a qualifying thromboembolic event secondary to PNH.

Co-primary and secondary efficacy end points were evaluated with the intent-to-treat analysis set; all patients were analyzed based on their original treatment group, and patients who escaped to pegcetacoplan treatment were set as missing in the control group. Patients who escaped from the control group were considered non-responders.

Pegcetacoplan safety was evaluated using the safety analysis set, with patients categorized into 2 groups: (1) overall pegcetacoplan, which included all patients who received ≥ 1 dose of pegcetacoplan after being randomly assigned to the pegcetacoplan group and those who escaped the control group while receiving pegcetacoplan and (2) patients in the control group who received supportive care only throughout the study or before escape.

Over a median of 10.2 weeks (range, 5.3-21.0 weeks), 11 control patients escaped to pegcetacoplan treatment after a qualifying event; none of the qualifying events were PNH-related thrombosis. All escape patients completed the study on pegcetacoplan treatment until week 26.

Three patients did not complete the trial. One pegcetacoplan-treated patient was lost to follow-up, and 2 patients died (1 in each group).

The definition of outcomes, methods of analysis and results are described below.

Transfusion avoidance

The proportion of patients who achieved transfusion avoidance, defined as no transfusions until week 26 was assessed in PRINCE.

The absolute difference effect estimate is a calculated estimate. The number and percentage of patients with transfusion avoidance was computed and compared between treatment groups using a stratified Cochran-Mantel-Haenszel χ^2 test, and the stratified Miettinen-Nurminen method was used to determine treatment difference in percentages and 95% Cis...

Thirty-two of 35 patients (91.4%) receiving pegcetacoplan and one of 18 patients (5.6%) in the control, supportive care only-group achieved transfusion avoidance through week 26, with a between-group difference of 72.4 %-points (95% CI, 55.8 to 89.0), $p < 0.001$ [3].

Fatigue

Mean change of FACIT-Fatigue score from baseline to week 26 was assessed in the study.

All statistical testing was performed at the 5% level of significance (two-sided). Continuous endpoints were analyzed using an analysis of covariance model with a multiple imputation approach for handling missing data. Continuous endpoint summary values included mean, median, range, SD, and SE.

The adjusted LS mean change from baseline in the FACIT-Fatigue score was 7.8 points (SE 1.2) for pegcetacoplan and 3.3 points (SE 2.1) for the control group, with a difference between groups of 4.5 points (-0.2 to 9.2), p=0.0610 [3].

Stabilisation of haemoglobin

Stabilisation of haemoglobin was defined as avoidance of a > 1 g/dL drop in haemoglobin level in the absence of transfusions from baseline to week 26.

The absolute difference effect estimate is a calculated estimate. The number and percentage of patients with hemoglobin stabilization was computed and compared between treatment groups using a stratified Cochran-Mantel-Haenszel χ^2 test, and the stratified Miettinen-Nurminen method was used to determine treatment difference in percentages and 95% CIs..

The proportion of patients who achieved stabilisation of haemoglobin was 85.7% in the pegcetacoplan group vs. none in the control. The difference was 73.1 %-points (95%CI, 57.2 to 89.0), P < 0.0001 [3].

Normalisation of LDH

The proportion with LDH normalisation (< 226 U/L) at week 26 in the absence of blood transfusions was assessed in PRINCE.

The absolute difference effect estimate is a calculated estimate The number and percentage of patients with transfusion avoidance was computed and compared between treatment groups using a stratified Cochran-Mantel-Haenszel χ^2 test, and the stratified Miettinen-Nurminen method was used to determine treatment difference in percentages and 95% CIs.

The proportion of patients with LDH normalization was 65.7% in the pegcetacoplan group vs. none in the control group. The difference was 55.9 %-points (95% 36.8 to 75.0), P < 0.0001) [3].

Quality of life

The average change in EORTC QLQ- C30 global health score from baseline to week 26 was recorded in PRINCE.

All statistical testing was performed at the 5% level of significance (two-sided). Continuous end points were analyzed using an analysis of covariance model with a multiple imputation approach for handling missing data. Continuous end point summary values included mean, median, range, SD, and SE.

The mean change from baseline was 18.9 points (SD 2.9) in the pegcetacoplan group vs. -2,9 points (SD 5.7) in the control group. The difference was 21.8 points (95% CI 9.4 to 34.2), P=.0006 [3].

Safety findings

A total of 33 patients (71.1%) in the pegcetacoplan group and 12 patients (66.7%) in the control group experienced at least one AE during the 26-week treatment period. Pegcetacoplan-related events occurred in 13 patients (28.3%).

The most common AEs in pegcetacoplan group were injection site reactions (30.4%), infections (19.6%, none were serious), and hypersensitivity (19.6%). Hyperkalemia was seen in 13.0%, dizziness in 10.9%, fever in 8.7% and ecchymosis, arthralgia, and headache in 6.5%, respectively.

SAEs were experienced in 4 patients (8.7%) in the pegcetacoplan group (none considered related to pegcetacoplan) vs. 3 patients (16.7%) in the control group. No AEs led to discontinuation. Two patients died, 1 in each study group; both deaths were considered by investigators to be unrelated to treatment [3].

5.2.2 Qualitative description of safety data

All studies reported data on AEs. The results for APPOINT-PNH [1], Study 301 [2], and PRINCE [3] are shown in Table 5 and described below.

The proportion of patients experiencing an AE was 67% for supportive care and 72% for pegcetacoplan in the PRINCE study, 87% for eculizumab and 88% for ravulizumab in Study 301 and 92% for iptacopan in APPOINT-PNH. The studies indicated that the AEs were generally mild or moderate.

The proportion of patients experiencing an SAE was 10% for iptacopan and ranged from 7.4% for the eculizumab arm in Study 301 to 16.7% for the supportive care arm in the PRINCE study.

In the PRINCE study, there were two deaths, one in each study arm. Both cases were assessed as not being related to the treatment. No deaths were reported in APPOINT-PNH or Study 301.

There were three MAVEs in Study 301, two in the ravulizumab arm and one in the eculizumab arm. No MAVE were reported in APPOINT-PNH or PRINCE.

In Study 301, there was one patient in the eculizumab arm who stopped treatment due to an AE. No treatment discontinuations due to AEs occurred in APPOINT-PNH or PRINCE.

The most frequently reported AE in APPOINT-PNH was headache, reported in 28% of patients. Other AEs reported included Covid-19 infection (15%), upper respiratory tract infection (12%), diarrhea, nausea, abdominal pain and dizziness. The most common AE in Study 301 was headache (36.0% and 33.1% in the ravulizumab and eculizumab arms, respectively). Other AEs included upper respiratory tract infection, joint pain, dizziness, fever, and hypokalemia.

The most common AEs in the pegcetacoplan arm of the PRINCE study included hypokalemia, dizziness, fever, headache, and joint pain. Additionally, injection-related reactions were frequent among patients treated with pegcetacoplan (30.4%).

None of the studies had cases of meningococcal infection.

APPOINT-PNH reported other serious infections in two patients, one patient had Covid-19, and one had lobar pneumonia of bacterial etiology, for which no causative organism was identified and which resolved with antibiotic treatment. Study 301 reported other serious infections in 1.6% of patients in the ravulizumab group and 3.3% of patients in the eculizumab group. There were no serious infections in the PRINCE study [1, 5].

In conclusion, the safety profiles for the Ci's, including iptacopan, are generally comparable and manageable.

Table 5 Overview of adverse events for Ci-naïve patients

	APPOINT-PNH [1]	**Study 301** [2]		**PRINCE** [3]	
Treatment	**Iptacopan** (N = 40)	**Ravulizumab** (N = 125)	**Eculizumab** (N = 121)	**Pegcetacoplan** (N = 46)*	**Supportive care** (N = 18)
Any AE, n (%)	37 (92.5)	110 (88.0)	105 (86.8)	33 (71.7)	12 (66.7)
SAE in total, n (%)	4 (10.0)	11 (8.8)	9 (7.4)	4 (8.7)	3 (16.7)
Deaths in total, n (%)**	0	0	0	1 (2.2)	1 (5.6)
MAVE in total, (%)	0	2 (1.6)	1 (0.8)	0	NR
Withdrawal due to an AE, n (%)	0	0	1 (0.8)	0	0
Covid-19 infection, n (%)	6 (15.0)	-	-	NR	NR
Headache, n (%)	11 (27.5)	45 (36.0)	40 (33.1)	3 (6.5)	0
Upper respiratory tract infection, n (%)	5 (12.5)	13 (10.4)	7 (5.8)	NR	NR
Serious infections. n (%)	1 (2.5)	2 (1.6)	4 (3.3)	0	0
Arthralgia, n (%)	0	8 (6.4)	8 (6.6)	3 (6.5)	0
Dizziness, (%)	1 (2.5)	9 (7.2)	7 (5.8)	5 (10.9)	0
Fever, n (%)	NR	6 (4.8)	13 (10.7)	4 (8.7)	0

	APPOINT-PNH [1]	Study 301 [2]		PRINCE [3]	
Treatment	**Iptacopan** (N = 40)	**Ravulizumab** (N = 125)	**Eculizumab** (N = 121)	**Pegcetacoplan** (N = 46)*	**Supportive care** (N = 18)
Hypokalemia. n (%)	NR	6 (4.8)	6 (5.0)	6 (13.0)	2 (11.1)
Infusion related reaction, n (%)	NR	NR	NR	NR	NR
Injection related reaction, n (%)	NR	NR	NR	14 (30.4)	NR

*Includes the 35 patients randomised to pegcetacoplan and additional 11 patients who crossed over from eculizumab to pegcetacoplan. Omfatter de oprindelige 35 patienter randomiseret til pegcetacoplan og yderligere 11 patienter. der krydsede over fra eculizumab til pegcetacoplan. **None of the reported deaths were considered to be realted to treatment. Abbreviations: AE, adverse event; MAVE, major adverse vascular event; NR, not reported; SAE, seious adverse event.

5.2.3 Differences in definitions of outcomes between studies

The definitions of the outcomes for the studies included are shown in Table 6 below.

Table 6 Definition of outcomes by study

Study	Outcome definition	Differences in definitions
Transfusion avoidance		
APPOINT-PNH Peffault de Latour et al, 2024 [1]	Proportion not receiving red-cell transfusions and not meeting the protocol-specified criteria for transfusion between days 14 and 168	Definitions are similar except for the time observed, and that APPOINT-PNH requires protocol specified criteria being met for getting a transfusion
Study 301 Lee et al., 2019 [2]	The proportion who achieved transfusion independence, defined as the proportion who remained transfusion-free and did not need transfusion until day 183*	
PRINCE Wong et al, 2023 [3]	The proportion who achieved transfusion independence, defined as no transfusions until week 26	
Fatigue		
APPOINT-PNH Peffault de	Mean change* of FACIT-Fatigue score from baseline to week 24	Similar definitions, except for the time observed (24-26 weeks)

Study	Outcome definition	Differences in definitions
Latour et al, 2024 [1]		
Study 301 Lee et al., 2019 [2]	Mean change* of FACIT-Fatigue score from baseline to day 183	
PRINCE Wong et al, 2023 [3]	Mean change* of FACIT-Fatigue score from baseline to week 26	
Stabilisation of haemoglobin		
APPOINT-PNH Peffault de Latour et al, 2024 [1]	The proportion with an increase in haemoglobin of ≥ 2 g/dL in the absence of transfusions from baseline to day 168	Outcomes definitions differ significantly as APPOINT-PNH requires an increase in haemoglobin on ≥ 2 g/dL whereas the definitions in Study 301 and PRINCE required avoidance of a drop of > 2 g/dL and > 1 g/dl, respectively. Results are presented narratively in the comparative analysis
Study 301 Lee et al., 2019 [2]	The proportion with avoidance of a > 2 g/dL drop in haemoglobin level in the absence of transfusions from baseline to day 183	
PRINCE Wong et al, 2023 [3]	The proportion with avoidance of a > 1 g/dL drop in haemoglobin level in the absence of transfusions from baseline to week 26	
Normalisation of LDH		
APPOINT-PNH Peffault de Latour et al, 2024 [1]	The proportion of patients having LDH levels that were no greater than 1.5 times ULN range at 24 weeks	Level of LDH defining normalization differs between studies. Results are presented narratively in the comparative analysis
Study 301 Lee et al, 2019 [2]	The proportion with haemolysis control measured as LDH normalization (ULN, 246 U/L) from day 29 to 183	
PRINCE Wong et al, 2023 [3]	The proportion with LDH normalization (< 226 U/L) at week 26 in the absence of blood transfusions	
Quality of life		

Study	Outcome definition	Differences in definitions
APPOINT-PNH Peffault de Latour et al, 2024 [1]	Average change in EORTC QLQ- C30 *global health score* from baseline to day 168	Similar definitions, except for the time observed (24-26 weeks)
Study 301 Lee et al, 2019 [2]	Average change in EORTC QLQ- C30 *global health score* from baseline to day 183	
PRINCE Wong et al, 2023 [3]	Average change* in EORTC QLQ- C30 *global health score* from baseline to week 26	

*Least squares mean change. Abbreviations: EORTC QLQ-C30, European Organization of Research and Treatment of Cancer 30-item Core Quality of Life Questionnaire; FACIT, Functional Assessment of Chronic Illness Therapy; LDH, lactate dehydrogenase, ULN, upper limit of normal.

5.2.4 Method of synthesis

As stated in the guideline, the strongest evidence base for comparisons of interventions is direct comparisons in RCTs. There are no direct comparative studies that include all medications, and it is not meaningful to connect the studies in a network or use other indirect comparisons. Therefore, the evidence review is based on naive comparisons of the medications, e.g., narrative comparisons.

This is in line with the method used in the treatment guideline for PNH and was discussed at the dialogue meeting with the DMC secretariat.

In addition, based on discussions with the DMC secretariat, data from a MAIC including APPOINT-PNH and Study 301 will be presented. The MAIC was submitted to and evaluated by NICE [10], and includes two of the five outcomes from the treatment guideline (transfusion avoidance and fatigue). The MAIC is described in detail in Appendix C.

5.2.5 Results from the comparative analysis

The following outcomes are compared narratively: Transfusion avoidance, Fatigue and Stabilisation of haemoglobin, Normalisation of LDH and Quality of life. An overview of the results is shown in Table 7.

More details for each of the outcomes are provided in Table 8, Table 9, Table 10, Table 11 and Table 12 below.

Table 7 Results from the comparative analysis of iptacopan vs. eculizumab, ravulizumab and pegcetacoplan for Ci-naïve PNH patients. Narrative comparison

Outcome measure	Iptacopan (N=40) [1, 15]	Eculizumab (N=121) [2]	Ravulizumab (N=125) [2]	Pegcetacoplan (N=35) [3]	Results
Proportion of patients with Transfusion avoidance, % (95% CI)	98 (92 to 100)	66.1 (57.7 to 74.6)	73.6 (65.9 to 81.3)	91.4	The results indicate that iptacopan reduces the need for transfusions to the same extent as pegcetacoplan, and numerically more than eculizumab and ravulizumab, however the difference vs. pegcetacoplan does not exceed the minimal clinically relevant difference of 20 %-points as defined by DMC [5]
Fatigue (Change from baseline in FACIT-fatigue score, points (95%CI)/SE	10.8 (8.7 to 12.8)	6.4 (4.9 to 8.0)	7.1 (5.6 to 8.6)	7.8 SE:1.2	The average change in the FACIT-Fatigue score was numerically higher for iptacopan than for pegcetacoplan, ravulizumab, and eculizumab. However, the differences do not exceed the minimal clinically relevant difference of 5 points as defined by DMC [5]
Proportion of patients with Stabilisation of hemoglobin, % (95% CI)	92 (82 to 100)	64.5 (55.9 to 73.0)	68.0 (59.8 to 76.2)	85.7	Of note, the definition of the outcome differs significantly between studies. A numerically higher proportion of patients treated with iptacopan achieved stabilisation of haemoglobin vs. with ravulizumab, eculizumab and pegcetacoplan, however, the difference vs. pegcetacoplan does not exceed the minimal clinically relevant difference of 20 %-points as defined by DMC [5]
Proportion of patients with Normalisation of LDH, % (95% CI)	95	49.4 (41.7 to 57.0)	53.6 (45.7 to 61.2)	65.7	A numerically higher proportion of patients treated with iptacopan achieved normalisation of LDH vs. ravulizumab, eculizumab and pegcetacoplan, and the differences vs ravulizumab, eculizumab, and pegcetacoplan exceeded

Outcome measure	Iptacopan (N=40) [1, 15]	Eculizumab (N=121) [2]	Ravulizumab (N=125) [2]	Pegcetacoplan (N=35) [3]	Results
					the minimal clinically relevant difference of 20 %-points as defined by DMC [5]
Change from baseline in EORTC QLQ-C30 *global health score,* points SD/SE	25.1 SD 18.72	12.9 SD 21.8	13.2 SD 21.4	18.9 SE 2.9	The average change in EORTC QLQ-C30 global health score was numerically higher for iptacopan vs. ravulizumab, eculizumab and pegcetacoplan. However, the difference vs. pegcetacoplan does not exceed the minimal clinically relevant difference of 10 points as defined by DMC [5]

This table is based on Table 3 in section 5.2.4 in the DMC template for applications, and has been adjusted to include a narrative comparison vs. more than one comparator. Narrative comparion was discussed at a dialogue meeting with DMC.
Abbreviations: CI, confidence interval; DMC, Danish Medicines Council; FACIT, Functional Assessment of Chronic Illness Therapy; LDH, lactate dehydrogenase; SD, standard deviation; SE, standard error.

5.2.5.1 Transfusion avoidance

All the included studies had results regarding the efficacy endpoint of transfusion independence, which had approximately the same definition in all the studies. Results are shown in Table 8.

Table 8 Results for the outcome Transfusion avoidance

Study	Comparison	Definition of outcome	Estimate, % (95 % CI)	Difference (95 % CI)
APPOINT-PNH [1]	iptacopan	Proportion not receiving red-cell transfusions on not meeting the protocol-specified criteria for transfusion between days 14 and 168	98 (92 to 100)	NA
Study 301 [2]	ravulizumab vs. eculizumab	The proportion who achieved transfusion independence, defined as the proportion who remained transfusion-free and did not need transfusion until day 183	73.6 (65.9 to 81.3) vs. 66.1 (57.7 to 74.6)	Absolute difference: 7.5 Calculated absolute difference: 6.8 (-4.7 to 18.1)
PRINCE [3]	pegcetacoplan vs. supportive care	The proportion who achieved transfusion independence, defined as no transfusions until week 26	91.4 vs. 5.6	Absolute difference: 85.8 Calculated absolute difference: 72.4 (55.8 to 89.0) p < 0.0001
MAIC-analysis [10]	Iptacopan vs. ravulizumab or eculizumab	See APPOINT-PNH and Study 301	78.6 73.5 66.1	 OR = 1.32 (0.47 to 3.73) P=0.6011 OR = 1.88 (0.67 to 5.28) P=0.2281

Abbreviations: CI, confidence interval; MAIC, matched-adjusted indirect comparison; NA, not applicable; OR, odds ratio.

The proportion of patients achieving transfusion independence on iptacopan was 98% (95%CI, 92 to 100), and as such higher than for ravulizumab and eculizumab (respectively 73.6% and 66.1%), and in the same range as for pegcetacoplan (91.4%).

The MAIC analysis with iptacopan vs. ravulizumab or eculizumab showed a higher proportion of patients achieving transfusion independence on iptacopan (78.6%) both vs. ravulizumab (73.5%, OR = 1.32 (95% CI, 0.47 to 3.73)) and vs. eculizumab 66.1% OR = 1.88, however the differences were not statistically significant.

The results indicate that iptacopan reduces the need for transfusions to the same extent as pegcetacoplan, and numerically more than eculizumab and ravulizumab, however the results are not statistically significant.

5.2.5.2 Fatigue

There were results from all studies regarding fatigue, and the efficacy endpoint was defined in the same way. The results are shown in Table 9.

Table 9 Results for the outcome Fatigue

Study	Comparison	Definition of outcome	Estimate (95 % CI)	Difference (95 % CI)
APPOINT-PNH [1]	Iptacopan	Mean change* of FACIT-Fatigue score from baseline to week 24	10.8 (8.7 to 12.8)	NA
Study 301 [2]	ravulizumab vs. eculizumab	Mean change* of FACIT-Fatigue score from baseline to day 183	7.1 (5.6 to 8.6) vs. 6.4 (4.9 to 8.0)	Absolute difference: 0.7 (-1.2 to 2.6)
PRINCE [3]	pegcetacoplan vs. supportive care	Mean change* of FACIT-Fatigue score from baseline to week 26	7.8 (SE: 1.2) vs. 3.3 (SE: 2.1)	Absolute difference: 4.5 (-0.2 to 9.2) p = 0.0610
MAIC-analysis [10]	Iptacopan** ravulizumab or eculizumab	See APPOINT-PNH and Study 301	10.85 (7.23 to 14.47) 7.07 (5.55 to 8.60) 6.40 (4.84 to 7.96)	 3.78 (-1.38 to 8.94) P=0.1514 4.45 (-0.72 to 9.62) P=0.0918

*Least squares mean change, **APPOINT-PNH results using Study 301 endpoint definitions and population adjusted to balance with Study 301 on age (means and SD), proportion of males, transfusion free 12 months prior, baseline LDH (mean and SD) and history of MAVE.. Abbreviations: CI, confidence interval; FACIT, Functional Assessment of Chronic Illness Therapy; LDH, lactate dehydrogenase; MAVE, major adverse vascular event; MAIC, matched-adjusted indirect comparison; NA, not applicable; SD, standard deviation.

The average change in the FACIT-Fatigue score was higher for iptacopan 10.8 (95%CI 8.7 to 12.8) than for pegcetacoplan 7.8 (SE: 1.2), ravulizumab 7.1 (95%CI 5.6 to 8.6) and eculizumab 6.4 (95%CI 4.9 to 8.0). The MAIC showed similar results for iptacopan vs. ravulizumab and eculizumab, however the differences were not statistically significant,

respectively 3.78 points (95%CI -1.38 to 8.94), P=0.1514 for ravulizumab and 4.45 points (95%CI -0.72 to 9.62), P=0.0918 for eculizumab.

5.2.5.3 Stabilisation of haemoglobin

All studies reported results regarding the efficacy endpoint of haemoglobin stabilisation. The efficacy endpoint was defined differently. In APPOINT-PNH it was defined as an increase in haemoglobin of ≥ 2 g/dl, whereas it was defined as an avoidance of a drop in haemoglobin levels of > 1 g/dL in PRINCE and > 2 g/dL in Study 301. It should also be considered that non-anemic patients could be included in Study 301 in contrast to what was the case for APPOINT-PNH and PRINCE. Results are shown in Table 10.

Table 10 Results for the outcome Stabilisation of haemoglobin

Study	Comparison	Definition of outcome	Estimate, % (95 % CI)	Difference (95 % CI)
APPOINT-PNH [1]	iptacopan	The proportion with an increase in haemoglobin of ≥ 2 g/dL in the absence of transfusions from baseline to day 168	92 (82 to 100)	NA
Study 301 [2]	ravulizumab vs. eculizumab	The proportion with avoidance of a > 2 g/dL drop in haemoglobin level in the absence of transfusions from baseline to day 183	68.0 (59.8 to 76.2) vs. 64.5 (55.9 to 73.0)	Absolute difference: 3.5 Calculated absolute difference: 2.9 (-8.8 to 14.6)
PRINCE [3]	pegcetacoplan vs. supportive care	The proportion with avoidance of a > 1 g/dL drop in haemoglobin level in the absence of transfusions from baseline to week 26	85.7 vs. 0	Absolute difference: 85.7 Calculated absolute difference: 73.1 (57.2 to 89.0) p < 0.0001

Abbreviations: CI, confidence interval; NA, not applicable.

Haemoglobin stabilisation was achieved by 92% (95% CI, 82 to 100) of patients treated with iptacopan. For pegcetacoplan haemoglobin stabilisation was achieved by 85.7%, and for ravulizumab and eculizumab the numbers were 68.0% (95% CI, 59.8 to 76.2), and 64.5% (95% CI, 55.9 to 73.0), respectively. As the definition of the outcome differs between studies, and no statistical analysis demonstrated a difference between iptacopan and the comparators, the efficacy of iptacopan may be considered to be similar to the comparators.

5.2.5.4 Normalisation of LDH

All studies had results for the efficacy endpoint of LDH normalization, but the definitions were not entirely consistent. Especially the definition in APPOINT-PNH differs substantially, by accepting levels up to 1.5 times the ULN range. Results are shown in Table 11.

Table 11 Results for the outcome Normalisation of LDH

Study	Comparison	Definition of outcome	Estimate, % (95 % CI)	Difference (95 % CI)
APPOINT-PNH [1]	iptacopan	The proportion of patients having LDH levels that were no greater than 1.5 times the ULN range at 24 weeks	95	NA
Study 301 [2]	ravulizumab vs. eculizumab	The proportion with haemolysis control measured as LDH normalization (ULN, 246 U/L) from day 29 to 183	53.6 (45.9 to 61.2) vs. 49.4 (41.7 to 57.0)	Absolute difference: 4.2 Relative difference: OR: 1.2 (0.8 to 1.8)
PRINCE [3]	pegcetacoplan vs. supportive care	The proportion with LDH normalization (< 226 U/L) at week 26 in the absence of blood transfusions	65.7 vs. 0	Absolute difference: 65.7 Calculated absolute difference: 55.9 (36.8 to 75.0) p < 00001

Abbreviations: CI, confidence interval; LDH, lactate dehydrogenase; NA, not applicable; OR, odds ratio; ULN, upper limit of normal.

Due to the difference in definition of the outcome it is difficult to compare across studies. In the APPOINT-PNH study 95% of the iptacopan-treated patients achieved the outcome, which is more than for pegcetacoplan (65.7%), ravulizumab (53.6%, 95%CI 45.9 to 61.2) and eculizumab (49.4%, 95%CI 41.7 to 57.0). However, it would also be expected to be higher (with similar efficacy) because it included responses between normal and 1.5 times the upper level of normal LDH levels.

5.2.5.5 Quality of life

There was information on quality of life, defined as the average change from baseline to day 183 and week 26 measured using the EORTC QLQ-C30 global health score, in Study 301 and PRINCE. Results from APPOINT-PNH measured on day 168 are data on file. Results are shown in Table 12.

Table 12 Results for the outcome Quality of life

Study	Comparison	Definition of outcome	Estimate (95 % CI)	Difference (95 % CI)
APPOINT-PNH* [1]	iptacopan	Average change in EORTC QLQ-C30 *global health score* from baseline to day 168	25.1 (SD 18.72)	NA
Study 301 [2]	ravulizumab vs. eculizumab	Average change in EORTC QLQ-C30 *global health score* from baseline to day 183	13.2 (SD 21.4) vs. 12.9 (SD 21.8)	Absolute difference: 0.3
PRINCE [4]	pegcetacoplan vs. supportive care	Average change** in EORTC QLQ-C30 *global health score* from baseline to week 26	18.9 (SE 2.9) vs. -2.9 (SE 5.7)	Absolute difference: 21.8 (9.4 to 34.2)

* Data on file,**Least squares mean change. Abbreviations: CI, confidence interval; EORTC QLQ-C30, European Organization of Research and Treatment of Cancer 30-item Core Quality of Life Questionnaire; NA, not applicable; SE, standard error; SD, standard deviation.

The average change in EORTC QLQ-C30 global health score was 25.1 (SD 18.72) for iptacopan, 18.9 (SE 2.9) for pegcetacoplan, 13.2 (SD 21.4) ravulizumab and 12.9 (SD 21.8) for eculizumab. Thus, both iptacopan and pegcetacoplan lead to an increased quality of life compared to ravulizumab and eculizumab.

5.2.6 Conclusion

Based on the results described above iptacopan seems to have similar efficacy in Ci-naive PNH patient as the comparators eculizumab, ravulizumab and pegcetacoplan.

6. Considerations regarding switch between drugs

This section concerns PNH patients with residual anemia despite treatment with C5i's. Treatment of these patients was not addressed as a clinical question in the treatment guideline; however, it was discussed in section *4.3 Considerations regarding switch between the medicinal products*.

At a dialogue meeting with the DMC secretariat, it was discussed that it is relevant to compare iptacopan with pegcetacoplan for the treatment of PNH patients with residual anemia despite treatment with C5i's.

6.1 Efficacy of iptacopan compared to pegcetacoplan for PNH patients with residual anemia despite treatment with C5i's

6.1.1 Relevant studies

The following studies are included in this comparison for PNH patients with residual anemia despite treatment with C5i's: APPLY-PNH (iptacopan vs. eculizumab/ravulizumab) [1], and PEGASUS (pegcetacoplan vs. eculizumab) [3]. In addition, an anchored ITC [12] of iptacopan and pegcetacoplan with data from APPLY-PNH and PEGASUS is included. Both studies and the ITC are listed in Table 3 above.

6.1.2 Comparability of studies

The two studies APPOINT-PNH and PEGASUS were published in 2024 and 2021. Both studies are RCTs, however APPOINT-PNH had a duration of 24 weeks whereas PEGASUS had a duration of 16 weeks.

In addition, there is some lack of similarity between the C5 inhibitor comparator arms of APPLY-PNH and PEGASUS, given the PEGASUS run-in period during which patients randomised to eculizumab also received pegcetacoplan for 4 weeks, before switching back to eculizumab monotherapy. In the APPLY-PNH study, patients randomised to the C5i arm continued the same C5i treatment as prior to the trial, as monotherapy (without addition of iptacopan at any time).

6.1.3 Comparability of patients across studies and with Danish patients eligible for treatment

The patients baseline characteristics were similar in the two studies, see Table 13 below.

Patients in the two studies were between 47.3 and 51.7 years old at study entry and they have previously been treated with a C5i for 3.3 to 4.3 years. There was a slight predominance of female patients (56-69%). A Danish register study, which included patients from 2005-2021 showed that for the subgroup of patients treated with C5i's, the mean age was 44.8, and 58% were male. Considering that the patients in APPOINT-PNH and PEGASUS had already been treated with C5i's for 3-4 years, the Danish patient

population eligible for treatment after C5i's seems to be in the same age range as the populations in the clinical studies [13].

Table 13 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety for patients with residual anemia despite C5i-treatment

	APPLY-PNH [1]		PEGASUS [4]	
	Iptacopan n=62	Eculizumab/Ravulizumab n=35	Pegcetacoplan n=41	Eculizumab n=39
Age, years: mean (SD or range)	51.7 (16.9)	49.8 (16.7)	50.2 (19-81)	47.3 (23-78)
Sex, female: n (%)	24 (69)	43 (69)	27 (66)	33 (56)
Race, n (%)				
White	48 (77)	26 (74)	24 (59)	25 (64)
Asian	12 (19)	7 (20)	5 (12)	7 (18)
Black	2 (3)	2 (6)	2 (5)	0
BMI, kg/m^2, mean (SD)	24.9 (5.0)	26.9 (6.3)	26.7 (4.3)	25.9 (4.3)
Time since diagnosis, years (SD or range)	11.9 (9.8)	13.5 (10.9)	6.0 (1-31)	9.7 (1-38)
Mean duration of prior treatment with C5i, years (SD or range)	3.8 (3.6)	4.2 (3.9)	4.4 (0.4-17.1)	3.4 (0.3-13.8)
Prior C5i treatment, n (%)				
Eculizumab	40 (65)	23 (66)	41 (100)	39 (100)
Ravulizumab	22 (35)	12 (34)	0	0
Red cell transfusions, 6 months prior, n (%)	21 (60)	35 (56)		
≥ 4 transfusions, previous 12 months, n (%)			21 (51)	23 (59)

	APPLY-PNH [1]		PEGASUS [4]	
	Iptacopan n=62	Eculizumab/Ravulizumab n=35	Pegcetacoplan n=41	Eculizumab n=39
History of aplastic anemia, n (%)	9 (15)	5 (14)	11 (27)	9 (23)
Haemoglobin, g/dL, mean (SD)	8.9 (0.7)	8.9 (0.9)	8.69 (1.08)	8.68 (0.89)
LDH U/L, mean (SD)	269.1 (70.1)	272.7 (84.8)	257.5 (97.6)	308.6 (284.8)
Total bilirubin µmol/L, mean (SD)	31.6 (30.5)	31.8 (20.3)	42.5 (31.5)	40.5 (26.6)
ARC $x10^{-9}$/L, mean (SD)	193.2 (83.6)	190.6 (80.9)	217.5 (75.0)	216.2 (69.1)
FACIT-Fatigue score, mean (SD)	34.7 (9.8)	30.8 (11.5)	32.2 (11.4)	31.6 (12.5)

Abbreviations: ARC, absolute reticulocyte count; BMI, body mass index; C5i, complement 5 inhibitor; FACIT, Functional Assessment of Chronic Illness Therapy; LDH, lactate dehydrogenase; SD, standard deviation.

6.2 Comparative analysis of efficacy and safety

6.2.1 Efficacy and safety – results per study

Based on the treatment guideline for PNH by the DMC, the following outcomes are included in the sections below: Transfusion avoidance, Fatigue, Stabilisation of haemoglobin and Safety.

6.2.1.1 APPLY-PNH

APPLY-PNH was a randomised, controlled study with an 8-week screening period, a 24-week core treatment period, and a 24-week extension period. Patients were randomly assigned in an 8:5 ratio to receive oral iptacopan monotherapy or to continue C5i therapy. Randomisation was stratified according to C5i therapy (eculizumab or ravulizumab) and whether a red-cell transfusion had been received in the preceding 6 months (yes or no). Iptacopan was administered by the patients at a dose of 200 mg twice daily in both trials; C5i therapy was administered intravenously according to the therapy received (i.e., every 2 weeks for patients receiving eculizumab and every 8 weeks for patients receiving ravulizumab).

Efficacy and safety were assessed in all the patients. The APPLY-PNH trial was designed to show the superiority of iptacopan over C5i therapy; the overall type I error was controlled at the one-sided 2.5% level. A total of 97 patients were randomised in the study, 62 were treated with iptacopan and 35 continued their C5i treatment. One patient in the iptacopan arm discontinued treatment due to pregnancy.

APPLY-PNH was conducted during the Covid-19 pandemic. Missing haemoglobin data were imputed based on pattern mixture model [16].

The definition of outcomes, methods of analysis and results are described below. Normalisation of LDH was not an outcome in APPLY-PNH. The results are consistent with those presented in the EPAR [14] , except for transfusion avoidance, where the EPAR states that 60 of 62 patients achieved this outcome vs. 59 of 62 patients in the publication [1].

Transfusion avoidance

Transfusion avoidance was defined as the marginal proportion (expressed as percentage) of participants who did not require transfusions between Day 14 and Day 168.

Differences in estimated proportions were assessed with the use of a logistic-regression model with a Firth correction that adjusted for treatment and randomisation strata and with baseline covariates (i.e., sex, age ≥ 45 years, and haemoglobin level of ≥ 9 g/dL at baseline) as factors.

Between days 14 and 168 of the APPLY-PNH trial, 59 of 62 patients who received iptacopan and 14 of 35 patients who received C5i met the criteria for transfusion avoidance: estimated percentages, 95% (95% CI, 88 to 100) and 26% (95% CI, 12 to 42), respectively. The difference was 69 %-points (95% CI, 51 to 84), P < 0.001 [1].

Fatigue

Change from baseline in FACIT-Fatigue scores as mean of visits between Day 126 and Day 168 was assessed in the study.

Change from baseline was analyzed using a MMRM which includes age (indicator variable of age ≥ 45 years), sex, history of transfusion (yes/no) prior to study treatment, visit, and baseline FACIT-Fatigue score as fixed effects, along with the interaction between visit and baseline FACIT-Fatigue score as interaction.

In the APPLY-PNH trial, the adjusted LS mean change from baseline in the FACIT-Fatigue score (ranging from 0 to 52, with higher scores indicating less fatigue) was 8.6 points (95% CI, 6.7 to 10.5) for iptacopan and 0.3 points (95% CI, −2.2 to 2.8) for C5i's. The difference was 8.3 points (95% CI, 5.3 to 11.3), P < 0.001) [1].

Stabilisation of haemoglobin

Stabilisation of haemoglobin (responder) was defined as achieving an increase from baseline in haemoglobin levels of ≥ 2 g/dL on three out of four measurements between Day 126 and 168 of the core treatment period without requiring red-cell transfusions between Day 14 and Day 168.

Differences in estimated proportions were assessed with the use of a logistic-regression model with a Firth correction that adjusted for treatment and randomisation strata and with baseline covariates (i.e., sex, age ≥ 45 years, and haemoglobin level of ≥ 9 g/dL at baseline) as factors.

A total of 51 of 60 evaluable patients who received iptacopan (a response could not be unequivocally established for 2 of the 62 patients assigned to the iptacopan group owing to partial missing data between days 126 and 168) had an increase in the haemoglobin level of at least 2 g/dL from baseline without red-cell transfusions, as compared with none of the 35 patients who received C5i therapy; estimated percentages, 82% (95% CI, 73 to 90) and 2% (95% CI, 1 to 4), respectively. The difference was 80 %-points (95% CI, 71 to 88), P < 0.001) [1].

Safety findings

A total of 51 patients (82%) in the iptacopan group and 28 patients (80%) in the eculizumab/ravulizumab group experienced at least one AE during the 24 week treatment period. Non-SAEs that occurred more frequently with iptacopan than with C5i were headache (in 16% of patients with iptacopan vs. 3% of patients with C5i), diarrhea (in 15% vs. 6%), nasopharyngitis (in 11% vs. 6%), and nausea (in 10% vs. 3%). Coronavirus disease 2019 (Covid-19; in 8% vs. 26%) and BTH (in 3% vs. 17%) occurred more frequently with C5i's.

SAEs were reported in 10% of the patients who received iptacopan and in 14% of the patients who received C5i treatment. No meningococcal or pneumococcal infections were reported in either treatment group. Two patients had serious infections caused by Pseudomonas aeruginosa, an encapsulated bacterium: one patient in the iptacopan group

had a urinary tract infection and one patient in the C5i group had bacterial arthritis leading to sepsis. No deaths were noted during the 24-week treatment period, and no AEs led to treatment discontinuation. One patient discontinued iptacopan because of pregnancy [1]

6.2.1.2 PEGASUS

PEGASUS was a phase 3 open-label, controlled trial to assess the efficacy and safety of pegcetacoplan as compared with eculizumab in adults with PNH and haemoglobin levels lower than 10.5 g/dL despite eculizumab therapy. The trial treatment period consisted of three parts (Fig. 1). During a 4-week run-in phase, all the patients continued to receive their current dose of eculizumab with the addition of twice-weekly pegcetacoplan (1080 mg), which the patients administered themselves subcutaneously. After the run-in phase, patients were randomly assigned, in a 1:1 ratio, to monotherapy with pegcetacoplan or eculizumab for 16 weeks (randomised, controlled period). This period was followed by a 32-week period in which all patients received open-label pegcetacoplan. Randomisation was stratified according to the number of pRBC transfusions patients had received during the 12 months before screening (< 4 or ≥ 4) and the platelet count at screening (< 100,000 or ≥ 100,000 cells × 109 per liter) [4].

Efficacy and safety were assessed in all the patients. The trial was designed to have 90% power (using a two-sided test at the 5% level of significance) to detect a significant difference in primary endpoint between the two treatment groups, assuming a treatment difference in haemoglobin of 1 g/dL with an SD for the change from baseline of 1.2 g/dl. Three patients in the pegcetacoplan group discontinued treatment due to BTH [4].

The definition of outcomes, methods of analysis and results are described below. Normalisation of LDH was not an outcome in PEGASUS.

Transfusion avoidance

Transfusion avoidance was defined as the proportion of patients who did not require a transfusion during the randomised, controlled period (to week 16).

The risk difference in percentage and 95% CI were calculated based on Miettinen-Nurminen method.

Over the 16-week randomised, controlled period, 35 of 41 patients (85%) in the pegcetacoplan group were transfusion-free, whereas only 6 of 39 patients (15%) in the eculizumab group were transfusion-free. The difference was 63 %-points (95% CI, 48 to 77), P < 0.001 [4].

Fatigue

Change from baseline to week 16 in FACIT-Fatigue score was assessed in the study.

Analysis was a between-treatment-group comparison using an MMRM. The difference between pegcetacoplan and eculizumab LS mean changes from Baseline at Week 16 was calculated along with its 2-sided 95% CI and associated P-value from the MMRM model for the intention-to-treat (ITT) set, censored for transfusions [4].

The adjusted LS mean change from baseline in the FACIT-Fatigue score (ranging from 0 to 52, with higher scores indicating less fatigue) was 9.2 points SE ±1.6) for pegcetacoplan and -2.7 points (SE±2.8) for eculizumab. The difference was 11.9 points (95% CI, 5.49 to 18.25) [4].

Stabilisation of haemoglobin

Stabilisation of haemoglobin (responder) was defined as the proportion with normalization of haemoglobin in the absence of transfusions from baseline to week 16.

The difference in percentage and 95% CI are calculated based on stratified Miettinen-Nurminen method stratified by randomisation factor so it is not a direct difference of two reporting groups [4].

A total of 41 patients (34.1%) who received pegcetacoplan achieved normalized haemoglobin in the absence of transfusions from baseline to week 16 vs. none in the eculizumab treated group. Adjusted risk difference was 30.4 %-points (95% CI, 14.9 to 45.9) [4].

Safety findings

AEs that occurred during treatment were recorded in 36 patients (88%) receiving pegcetacoplan and in 34 (87%) receiving eculizumab. The most common AEs in the pegcetacoplan and eculizumab groups were injection-site reactions (37% vs. 3%), diarrhea (22% vs. 3%), BTH (10% vs. 23%), headache (7% vs. 23%), and fatigue (5% vs. 15%).

The incidence of serious AEs was similar in the two groups, with events reported in 7 patients (17%) receiving pegcetacoplan and in 6 (15%) receiving eculizumab.

Infections were reported in 12 patients (29%) in the pegcetacoplan group and in 10 (26%) in the eculizumab group. Meningitis was not reported in either treatment group. One case of sepsis was reported during the run-in period and was considered by the principal investigator to be unrelated to the initiation of pegcetacoplan treatment. No patient had a thrombotic event, and no deaths occurred during the trial. Three patients withdrew from the pegcetacoplan group, all due to BTH [4].

6.2.2 Qualitative description of safety data

AEs were reported in both APPLY-PNH and PEGASUS. The results from the two studies are shown in Table 14 and described below [1, 4].

The proportions of patients experiencing an AE was 82% for iptacopan and 80% for eculizumab/ravulizumab in APPLY-PNH and 88% for pegcetacoplan and 87% for eculizumab in PEGASUS. The studies indicated that the AEs were generally mild or moderate.

The proportions of patients experiencing an SAEs were 10% for iptacopan and 14% for eculizumab/ravulizumab in APPLY-PNH and 17% for pegcetacoplan and 15% for eculizumab in PEGASUS.

No deaths were reported in any of the studies.

There was one MAVE (transient ischaemic attack) in the iptacopan arm in APPLY-PNH, considered by the investigator to be unrelated to iptacopan. No MAVE was reported for PEGASUS.

In PEGASUS, three patients in the pegcetacoplan arm stopped treatment due to an AE (all due to BTH), whereas all patients in the eculizumab arm, and all patients in APPLY-PNH completed the randomised, controlled phase.

The most frequently reported AE for iptacopan, (n=62), in APPLY-PNH was headache (16%), diarrhea (15%), nasopharyngitis (11%) and nausea (10%). In addition, arthralgia, covid-19 infection and urinary tract infection were reported in 8%, respectively; abdominal pain, increase in LDH level and dizziness were reported in 6%, respectively and upper respiratory tract infection and BTH were reported in 3%, respectively.

The most frequently reported AE for pegcetacoplan, (n=41), in PEGASUS was diarrhea (22%), abdominal pain (10%), and haemolysis (10%). Further, asthenia, back pain, pain in arms or legs, headache and hypertension were reported in 7%, respectively; fatigue, pyrexia, nausea, and viral upper respiratory tract infection were reported in 5% respectively and dizziness, dyspnea and anxiety were reported in one patient each (2%). Additionally, injection-related reactions were frequent among patients treated with pegcetacoplan (37%).

None of the studies had cases of meningococcal infection.

In APPLY-PNH, two patients had serious infections caused by Pseudomonas aeruginosa, an encapsulated bacterium: one patient in the iptacopan group had a urinary tract infection and one patient in the C5i group had bacterial arthritis leading to sepsis. No serious infections were reported for PEGASUS.

In conclusion, apart from injection-related reactions and numerically more events of BTH with pegcetacoplan, the safety profiles for iptacopan and pegcetacoplan are generally comparable and manageable in patients with residual anemia despite Ci5 treatment, when considering the relatively low number of patients in the treatment arms.

Table 14 Overview of adverse events for patients with residual anemia despite Ci5 treatment during randomised, controlled period

	APPLY-PNH [1]		**PEGASUS** [4]	
Treatment	**Iptacopan** (N = 62)	**Ravulizumab or Eculizumab** (N = 35)	**Pegcetacoplan** (N = 41)	**Eculizumab** (N = 39)
Any AE, n (%)	51 (82)	28 (80)	36 (88)	34 (87)
SAE in total, n (%)	6 (10)	5 (14)	7 (17)	6 (15)

	APPLY-PNH [1]		PEGASUS [4]	
Treatment	**Iptacopan** (N = 62)	**Ravulizumab or Eculizumab** (N = 35)	**Pegcetacoplan** (N = 41)	**Eculizumab** (N = 39)
Deaths in total, n (%)**	0	0	0	0
Withdrawal due to an AE, n (%)	0*	0	3 (7)	0
MAVE in total, (%)	1 (2)**	0	NR	NR
BTH	2 (3)	6 (17)	4 (10)	9 (23)
Covid-19 infection	5 (8)	9 (26)	-	-
Headache, n (%)	10 (16)	1 (3)	3 (7)	9 (23)
Fatigue, n (%)	NR	NR	2 (5)	6 (15)
Upper respiratory tract infection, n (%)***	2 (3)	3 (9)	2 (5)	2 (5)
Serious infections. n (%)****	1 (2)	1 (3)	NR	NR
Arthralgia, n (%)	5 (8)	1 (3)	NR	NR
Diarrhea, n (%)	9 (15)	2 (6)	9 (22)	1 (3)
Abdominal pain, n (%)	4 (6)	1 (3)	5 (12)	4 (10)
Dizziness, (%)	4 (6)	0	1 (2)	4 (10)
Fever, n (%)	2 (3)	3 (9)	2 (5)	2 (5)
Injektion relateret reaction, n (%)	NR	NR	15 (37)	1 (3)

Note: the follow-up time was 24 weeks for APPLY and 16 weeks for PEGASUS. *One patient withdrew from treatment because of pregnancy, **A transient ischaemic attack. The investitator did not consider it related to iptacopan, ***In PEGASUS viral upper respiratory tract infectons were recorded, ****No meningococcal or pneumococcal infections were recorded for either study. Abbreviations: AE, adverse event; BTH, breakthrough haemolysis; MAVE, major adverse vascular event; NR, not reported; SAE, serious adverse event.

6.2.3 Differences in definitions of outcomes between studies

Table 15 Definition of outcomes by study

Study	Outcome definition	Differences in definitions
Transfusion avoidance		
APPLY-PNH [1]	The proportion not receiving red-cell transfusions and not meeting the protocol-specified criteria for transfusion between days 14 and 168	Definitions are similar except for the time observed, and that APPOINT-PNH requires protocol specified criteria being met for getting a transfusion
PEGASUS [4]	The proportion of patients who did not require a transfusion during the randomised, controlled period (to week 16)	
Fatigue		
APPLY-PNH [1]	Mean change* of FACIT-Fatigue score from baseline to week 24	Similar definitions, except for the time observed (16 and 24)
PEGASUS [4]	Mean change* of FACIT-Fatigue score from baseline to week 16	
Stabilisation of haemoglobin		
APPLY-PNH [1]	The proportion with an increase in haemoglobin of ≥ 2 g/dL in the absence of transfusions from baseline to day 168	Outcomes definitions differ significantly as APPLY-PNH requires an increase in haemoglobin on ≥ 2 g/dL and PEGASUS requires normalization of haemoglobin. Results are presented narratively in the comparative analysis
PEGASUS [12]	The proportion with normalization of haemoglobin in the absence of transfusions from baseline to week 16	

*Least squares mean. Abbreviations: FACIT, Functional Assessment of Chronic Illness Therapy.

6.2.4 Method of synthesis

As for the comparisons for Ci-naïve PNH patients, the evidence review is based on naive comparisons of the medications, e.g., narrative comparisons.

Comparison of efficacy in PNH patients with residual anemia despite treatment with C5i's was not addressed as a clinical question in the treatment guideline for PNH but considered in section *4.3 Considerations regarding switch between the medicinal products* [5]. Novartis expects that the conclusions from the comparison in the application will be included in section 4.3, when the treatment guideline is updated. Thus, an ITC would not add additional value compared to a narrative comparison.

A very recently published paper (accepted 21 March 2025) [12] presents the results of an anchored ITC between iptacopan and pegcetacoplan, based on APPLY-PNH and PEGASUS. It includes one of the five outcomes from the treatment guideline (fatigue), which will also be included in the narrative comparison. The ITC is described in detail in Appendix C.

6.2.5 Results from the comparative analysis

The following outcomes are compared narratively: Transfusion avoidance, Fatigue and Stabilisation of haemoglobin. An overview of the results is shown in Table 16.

More details for each of the outcomes are provided in Table 17, Table 18 and Table 19 below.

Table 16 Results from the comparative analysis of iptacopan vs. pegcetacoplan in PNH patients with residual anaemia despite C5i treatment. Narrative comparison

Outcome measure	Iptacopan (N=62) [1]	Pegcetacoplan (N=41) [4]	Results
Proportion of patients with Transfusion avoidance, % (95% CI)	95 (88 to 100)	85	The efficacy of iptacopan and pegcetacoplan appears to be similar. The difference between iptacopan and pegcetacoplan does not exceed the minimal clinically relevant difference of 20 %-points as defined by DMC [5]
Fatigue (Change from baseline in FACIT-fatigue score; points (95% CI)/SE	8.6 (6.7 to 10.5)	9.2 SE±	The efficacy of iptacopan and pegcetacoplan appears to be similar. The difference between iptacopan and pegcetacoplan does not exceed the minimal clinically relevant difference of 5 points as defined by DMC [5]
Proportion of patients with Stabilisation of haemoglobin; % (95% CI)	82 (73 to 90)	34.1	The definition of Stabilisation of haemoglobin differs significantly, thus a comparison is not feasible

This table is based on Table 3 in section 5.2.4 in the DMC template for applications, and has been adjusted to include a narrative comparison. Narrative comparion was discussed at a dialogue meeting with DMC.
Abbreviations: CI, confidence interval; DMC, Danish Medicines Council; FACIT, Functional Assessment of Chronic Illness Therapy; SE, standard error.

6.2.5.1 Transfusion avoidance

Both APPLY-PNH and PEGASUS included the efficacy endpoint of transfusion independence, which had approximately the same definition. Results are shown in Table 17.

Table 17 Results for the outcome Transfusion avoidance

Study	Comparison	Definition of outcome	Estimate, % (95 % CI)	Difference (95 % CI)
APPLY-PNH [1]	iptacopan vs. C5i therapy (eculizumab or ravulizumab)	The proportion not receiving red-cell transfusions on not meeting the protocol-specified criteria for transfusion between days 14 and 168	95 (88 to 100) vs. 26 (12 to 42)	Absolute difference: 69 (51 to 84) p < 0.001
PEGASUS [4]	pegcetacoplan vs. eculizumab	The proportion of patients who did not require a transfusion during the randomised, controlled period (to week 16)	85 vs. 15	Absolute difference: 63 (48 to 77) p < 0.001

Abbreviations: C5i, complement 5 inhibitor; CI, confidence interval.

The proportion of patients achieving transfusion independence on iptacopan in APPLY-PNH was 95% (95%CI, 88 to 100) at week 24. For pegcetacoplan, 85% of patients in PEGASUS achieved transfusion independence at week 16. With the relatively low number of patients in the studies, as well as the lack of statistical comparison, the efficacy of iptacopan and pegcetacoplan in PNH patients with residual anemia despite treatment with C5i´s seem to be similar.

6.2.5.2 Fatigue

Both APPLY-PNH and PEGASUS have results regarding fatigue, and the efficacy endpoint was defined in the same way. The results are shown in Table 18.

Table 18 Results for the outcome Fatigue

Study	Comparison	Definition of outcome	Estimate (95 % CI)	Difference (95 % CI)
APPLY-PNH [1]	iptacopan vs. C5i therapy (eculizumab or ravulizumab)	Mean change* of FACIT-Fatigue score from baseline to week 24	8.6 (6.7 to 10.5) vs. 0.3 (-2.2 to 2.8)	Absolute difference: 8.3 (5.3 to 11.3) p < 0.001
PEGASUS [4]	pegcetacoplan vs. eculizumab	Mean change* of FACIT-Fatigue score from baseline to week 16	9.2 (SE±1.6) vs. -2.7 (SE±2.8)	Absolute difference: 11.9 (5.5 to 18.3)
ITC [12]	Iptacopan vs. pegcetacopan	See APPLY-PNH and PEGASUS	See APPLY-PNH and PEGASUS	Absolute difference: -3.57 (−12.73 to 5.60). NS

*Least squares mean change. Abbrevieations: C5i, complement 5 inhibitor, CI, confidence interval; FACIT, Functional Assessment of Chronic Illness Therapy; NS: not statistically significant; SE, standard error.

The mean change from baseline in FACIT-Fatigue score at 24 weeks was 8.6 points for patients on iptacopan in APPLY-PNH. The mean change from baseline in FACIT-Fatigue score at 16 weeks for patients treated with pegcetacoplan in PEGASUS was 9.2 points (SE±1.6). The results seem similar, which is confirmed in an ITC [12]. More details on the ITC can be found in Appendix D.

6.2.5.3 Stabilisation of haemoglobin

Both APPLY-PNH and PEGASUS reported results regarding the efficacy endpoint of haemoglobin stabilisation. However, the efficacy endpoint was defined differently. In APPLY-PNH it was defined as an increase in haemoglobin of ≥ 2 g/dl, whereas it was defined as normalisation of haemoglobin in the absence of transfusions from baseline to week 16 in PEGASUS. Results are shown in Table 19.

Table 19 Results for the outcome Stabilisation of haemoglobin

Study	Comparison	Definition of outcome	Estimate, % (95 % CI)	Difference (95 % CI)
APPLY-PNH [1]	iptacopan vs. C5i therapy (eculizumab or ravulizumab)	The proportion with an increase in haemoglobin of ≥ 2 g/dL in the absence of transfusions from baseline to day 168	82 (73 to 90) vs. 2 (1 to 4)	Absolute difference: 80 (72 to 88) p < 0.001
PEGASUS [4]	pegcetacoplan vs. eculizumab	The proportion with normalization of haemoglobin in the absence of transfusions from baseline to week 16	34.1 vs. 0	Absolute difference: 34.1

Abbreviations: C5i, complement 5 inhibitor; CI, confidence interval.

The proportion of patients achieving stabilisation of haemoglobin on iptacopan in APPLY-PNH was 82% (95%CI, 75 to 90) at week 24. For pegcetacoplan, 34.1% of patients in PEGASUS achieved stabilisation of haemoglobin at week 16. Both iptacopan and pegcetacoplan achieved better results than C5i´s in patients with residual anemia despite treatment with C5i`s, however as the definitions in the two studies differ significantly, no conclusions can be made regarding efficacy of iptacopan vs. pegcetacoplan.

6.2.6 Conclusion

Based on the results described above iptacopan seems to have similar efficacy in PNH patients with anemia despite C5i treatment.

6.2.7 Additional information on switch from C5i

Results from APPULSE-PNH (NCT05630001), were recently presented at the EHA 2025 congress, and provide more information on efficacy and safety after switching from C5i's to iptacopan.

APPULSE-PNH was a phase 3B, multinational, multicenter, single-arm, open-label study to evaluate the efficacy and safety of twice-daily oral iptacopan monotherapy in adults with PNH who were switched from C5i therapies (eculizumab or ravulizumab).

Participants enrolled were required to be on a stable regimen with C5i therapies for at least 6 months prior to screening with average haemoglobin ≥ 10g/dL and no red blood cell transfusions in this period.

The trial enrolled 52 patients who were treated with iptacopan 200 mg p.o. twice daily for 24 weeks; 88.5% switched from ravulizumab and 11.5% from eculizumab.

No patients required RBC transfusions between day 1 and 168. Proportion of patients with haemoglobin ≥ 12 g/dL between day 126 and 168 was 92.7% (95% CI 84.6, 98.1). Adjusted mean (95% CI) change from baseline in FACIT-Fatigue was +4.29 (1.74, 6.85). There were no new safety findings, and no patients had clinical breakthrough hemolysis, major adverse vascular events or died.

More information can be found in the EHA congress abstract [17, 18].

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Appendix A. Main characteristics of studies included

A.1 Main characteristics of APPOINT-PNH

Table 20 Main characteristic of APPOINT-PNH. Source: [1, 19]

Trial name: APPOINT-PNH	**NCT number: NCT04820530**
Objective	The purpose of the APPOINT-PNH trial was to determine whether iptacopan is efficacious and safe for the treatment of PNH patients who were naïve to Ci therapy.
Publications – title, author, journal, year	Peffault de Latour R, Röth A, Kulasekararaj AG, et al. Oral Iptacopan Monotherapy in Paroxysmal Nocturnal Hemoglobinuria. N Engl J Med. 2024;390(11):994-1008. doi:10.1056/NEJMoa2308695. PMID: 38477987.
Study type and design	The APPOINT-PNH trial was a multicenter, single-arm, open-label trial, which was comprised of an 8-week screening period, a 24-week core treatment period and a 24-week extension treatment period. The core treatment period was defined from day 1 to day 168 and was used for the primary efficacy analyses. Eligible PNH patients with haemolysis (LDH > 1.5 ULN) and anemia (haemoglobin < 10 g/dL), who were naive to Ci therapy, including C5i treatment, received iptacopan monotherapy at a dose 200 mg orally twice daily.
Sample size (n)	The APPOINT-PNH trial began on July 19, 2021 (data-cutoff date, November 2, 2022); 40 patients who had not undergone Ci therapy (out of 52 who underwent screening) received iptacopan for 24 weeks. Adherence to the iptacopan regimen, assessed according to the mean relative dose intensity, was 99.4% in the APPOINT-PNH trial.
Main inclusion criteria	• Male and female participants ≥ 18 years of age with a diagnosis of PNH confirmed by high-sensitivity flow cytometry with RBCs and white blood cells clone size ≥ 10% • Mean haemoglobin level < 10 g/dL • LDH > 1.5 x ULN • Vaccination against Neisseria meningitidis infection is required prior to the start of study treatment • If not received previously, vaccination against Streptococcus pneumoniae and Haemophilus influenzae infections should be given.

Trial name: APPOINT-PNH	NCT number: NCT04820530
Main exclusion criteria	• Prior treatment with a Ci, including anti-C5 antibody • Known or suspected hereditary complement deficiency • History of haematopoietic stem cell transplantation • Patients with laboratory evidence of bone marrow failure (reticulocytes < $100x10^9$/L; platelets < $30x10^9$/L; neutrophils < $0.5x10^9$/L). • Active systemic bacterial, viral (incl. COVID-19) or fungal infection within 14 days prior to study drug administration. • History of recurrent invasive infections caused by encapsulated organisms, e.g. meningococcus or pneumococcus. • Major concurrent comorbidities including but not limited to severe kidney disease (e.g., dialysis), advanced cardiac disease (e.g., New York Heart Association (NYHA) class IV heart failure), severe pulmonary disease (e.g., severe pulmonary hypertension (World Health Organization (WHO) class IV)), or hepatic disease (e.g., active hepatitis) that in the opinion of the investigator precludes participant's participation in the study.
Intervention	The trial included an 8-week screening period, a 24-week core treatment period, and a 24-week extension period. Iptacopan was administered by the patients at a dose of 200 mg twice daily in the trial.
Comparator(s)	The trial was a single-arm trial.
Follow-up time	The study duration for the primary analysis was 24 weeks. Assessment of primary endpoints was assessed between days 126 and 168 with day 1 being the day of the first dose.
Primary, secondary and exploratory endpoints	**Primary efficacy endpoint** • Marginal Proportion of Participants With Sustained Increase in Haemoglobin Levels From Baseline of ≥ 2 g/dL in the Absence of RBC Transfusions ○ Sustained increase in haemoglobin levels (responder) is defined as an increase from baseline in haemoglobin levels of ≥ 2 g/dL on three out of four measurements between Day 126 and 168 of the core treatment period, without requiring RBC transfusions between Day 14 and Day 168. **Secondary efficacy endpoints** • Marginal proportion (expressed as percentage) with sustained haemoglobin levels of ≥ 12 g/dL in the absence of RBC transfusions

- Marginal proportion of participants who remain free from transfusions
- Change from baseline in haemoglobin levels in the core treatment period
- Percent change from baseline in LDH between day 126 and day 168
- Adjusted annualized clinical BTH rate in the core treatment period
- Change from baseline in ARC
- Change from baseline in FACIT-Fatigue score
- Adjusted annualized MACEs rate in the core treatment period

Other efficacy endpoints

- Percentage of patients meeting haematological response criteria irrespective of RBC transfusions
- Marginal proportion (expressed as percentage) of patients not receiving and not requiring RBC transfusions
- Change from baseline in haemoglobin levels
- Change from baseline in LDH at visit day 336
- Adjusted annualized clinical BTH rate after the start of LNP023 treatment
- Change from baseline in ARC at day 336
- Change from baseline in FACIT-fatigue score
- Adjusted annualized MACEs rate after the start of LNP023 treatment

Exploratory efficacy endpoints

- Haematological parameters (including RBCs and haptoglobin), bilirubin levels, number and units of pRBC transfusions, and PNH signs and symptoms collected between days 1 and 168
- Change in patient-reported outcomes score for the Patient Global Impression of Severity questionnaire, EORTC QLQ-C30, and EuroQol – 5 Dimensions– 5 Level (EQ-5D-5L) questionnaire collected between days 1 and 168
- Percentage of C3d-positive RBCs collected between days 1 and 168 (to detect C3-positive RBCs, whole blood samples were analyzed by flow cytometry and antiC3d biotin antibody [Quidel, clone C3D] was used to assess C3 deposition on PNH RBCs)
- Type I, II, and III RBCs and PNH population size (in red and white blood cells) collected between days 1 and 168

Trial name: APPOINT-PNH	NCT number: NCT04820530
	• Pharmacokinetic parameters of iptacopan • Patient responses to a semi-structured interview focusing on the patient's experience with their symptoms, particularly fatigue • Proportion of patients with stabilized haemoglobin, defined as avoidance of a ≥ 2 g/dL decrease in haemoglobin level from baseline between days 126 and 168 (in the absence of pRBC transfusions between days 14 and 168 **Endpoints included in this application:** • Marginal proportion of participants with sustained increase in haemoglobin levels from baseline of ≥ 2 g/dL in the absence of RBC transfusions • Average change in EORTC QLQ- C30 global health score from baseline to day 168 • The proportion of patients having LDH levels that were no greater than 1.5 times the ULN range at 24 weeks • Marginal proportion of participants who remain free from transfusions • Change from baseline in FACIT-Fatigue score • Percent change from baseline in LDH between day 126 and day 168 (included in the MAIC, only. See Appendix C.)
Method of analysis	The primary end point was assessed by means of derivation of an estimated proportion (the simple proportion of persons who had a response from multiple imputed data sets), with 95% CI computed with the use of bootstrap analysis. The lower boundary of the two-sided 95% CI was compared with a prespecified threshold of 15%, which was derived by indirectly estimating haemoglobin responses in two trials of C5 inhibitors. Estimated proportions reflect the probability that the end-point criteria were met in the trial populations. Secondary endpoints, haemoglobin ≥ 12 g/dL (in absence of RBC transfusion) and transfusion avoidance were analyzed by means of standardized marginal proportions derived similarly to the estimation applied to the primary endpoint. Changes from baseline in the secondary endpoints were analyzed using repeated measures models that adjusted for covariates of age (categorical), sex, transfusion dependency, visit, baseline and interaction of visit and baseline value. Rates of MAVEs and clinical BTH were estimated using the Wilson method.
Subgroup analyses	None.
Other relevant information	None.

A.2 Main characteristics of Study 301

Table 21 Main characteristic of Study 301. Source: [2, 20]

Trial name: Study 301	**NCT number: NCT02946463**
Objective	The purpose of the Study 301 (ALXN1210-PNH-301) trial was to assess the noninferiority of ravulizumab compared to eculizumab in adult participants with PNH who had never been treated with a Ci (treatment-naïve).
Publications – title, author, journal, year	Lee JW, Sicre de Fontbrune F, Wong Lee Lee L, et al. Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study. Blood. 2019;133(6):530-539. doi:10.1182/blood-2018-09-876136. PMID: 30510080. Schwartz CE, Stark RB, Borowiec K, Nolte S, Myren KJ. Norm-based comparison of the quality-of-life impact of ravulizumab and eculizumab in paroxysmal nocturnal hemoglobinuria. Orphanet J Rare Dis. 2021 Sep 15;16(1):389. doi: 10.1186/s13023-021-02016-8. Schrezenmeier H, Kulasekararaj A, Mitchell L, Sicre de Fontbrune F, Devos T, Okamoto S, Wells R, Rottinghaus ST, Liu P, Ortiz S, Lee JW, Socie G. One-year efficacy and safety of ravulizumab in adults with paroxysmal nocturnal hemoglobinuria naive to complement inhibitor therapy: open-label extension of a randomized study. Ther Adv Hematol. 2020 Oct 24;11:2040620720966137. doi: 10.1177/2040620720966137. eCollection 2020. Ishiyama K, Nakao S, Usuki K, Yonemura Y, Ikezoe T, Uchiyama M, Mori Y, Fukuda T, Okada M, Fujiwara SI, Noji H, Rottinghaus S, Aguzzi R, Yokosawa J, Nishimura JI, Kanakura Y, Okamoto S. Results from multinational phase 3 studies of ravulizumab (ALXN1210) versus eculizumab in adults with paroxysmal nocturnal hemoglobinuria: subgroup analysis of Japanese patients. Int J Hematol. 2020 Oct;112(4):466-476. doi: 10.1007/s12185-020-02934-6. Epub 2020 Aug 31. Brodsky RA, Peffault de Latour R, Rottinghaus ST, Roth A, Risitano AM, Weitz IC, Hillmen P, Maciejewski JP, Szer J, Lee JW, Kulasekararaj AG, Volles L, Damokosh AI, Ortiz S, Shafner L, Liu P, Hill A, Schrezenmeier H. Characterization of breakthrough hemolysis events observed in the phase 3 randomized studies of ravulizumab versus eculizumab in adults with paroxysmal nocturnal hemoglobinuria. Haematologica. 2021 Jan 1;106(1):230-237. doi: 10.3324/haematol.2019.236877.
Study type and design	The Study 301 trial is a phase 3, multicenter, randomised, active-controlled, open-label study conducted in 123 centers in 25 countries. The study consisted of a 4-week screening period and a 26-week RCP to evaluate the efficacy and safety of ravulizumab vs. eculizumab, followed by an extension period of up to 5 years, during which all

Trial name: Study 301		NCT number: NCT02946463
	patients receive ravulizumab. Patients were stratified into 6 groups based on transfusion history (0, 1-14, or >14 units of pRBCs in the 1 year before the first dose of study drug) and LDH screening level (1.5 to < 3 times the ULN or ≥ 3X ULN). Patients within each of the 6 groups were randomly assigned in a 1:1 ratio to receive ravulizumab or eculizumab.	
Sample size (n)	Of 285 patients screened for eligibility, 246 were randomised to ravulizumab (n = 125) or eculizumab (n = 121); 244 patients completed the 26-week treatment period (ravulizumab, n = 125; eculizumab, n = 119. Overall, 99.2% of patients received all planned infusions of study medication.	
Main inclusion criteria	• Male or female ≥ 18 years of age • PNH diagnosis confirmed by documented by high-sensitivity flow cytometry • Presence of 1 or more of the following PNH-related signs or symptoms within 3 months of screening: • Fatigue, haemoglobinuria, abdominal pain, shortness of breath (dyspnea), anemia (haemoglobin < 10 g/dL), history of a MACE (including thrombosis), dysphagia, or erectile dysfunction; or history of (pRBC transfusion due to PNH • LDH level ≥ 1.5 times the ULN at screening • Documented meningococcal vaccination not more than 3 years prior to, or at the time of, initiating study treatment • Female participants of childbearing potential must use highly effective contraception starting at screening and continuing until at least 8 months after the last dose of ravulizumab • Willing and able to give written informed consent and comply with study visit schedule. Eligibility criteria for roll-over cohort: • All participants regardless of age, who are currently receiving ALXN1210 IV in an ongoing ALXN1210 study in patients with PNH • Participants must be willing and able to give written informed consent and to comply with all Extension study visits and procedures, including the use of any data collection device(s) to directly record patient data • Females of childbearing potential and male patients with female partners of childbearing potential must use highly effective contraception continuing until at least 8 months after the last dose of ravulizumab.	

Trial name: Study 301		NCT number: NCT02946463
Main exclusion criteria	• Treatment with a Ci at any time • History of bone marrow transplantation • Body weight < 40 kg • Females who are pregnant, breastfeeding, or who have a positive pregnancy test at screening or Day 1 • Participation in another interventional clinical study or use of any experimental therapy within 30 days before initiation of study drug on Day 1 in this study or within 5 half-lives of that investigational product, whichever is greater • History of or ongoing major cardiac, pulmonary, renal, endocrine, or hepatic disease that, in the opinion of the investigator or sponsor, would preclude participation • Unstable medical conditions (for example, myocardial ischaemia, active gastrointestinal bleed, severe congestive heart failure, anticipated need for major surgery within 6 months of randomisation, coexisting chronic anemia unrelated to PNH).	
Intervention	The intravenous ravulizumab group received a loading dose (2400 mg for patients weighing ≥ 40 to < 60 kg, 2700 mg for patients ≥ 60 kg to < 100 kg, and 3000 mg for patients ≥ 100 kg) on day 1, followed by maintenance doses of ravulizumab (3000 mg for patients ≥ 4 0 to < 60 kg, 3300 mg for patients ≥ 6 0 to < 100 kg, and 3600 mg for patients ≥ 100 kg) on day 15 and every 8 weeks thereafter.	
Comparator(s)	Patients assigned to eculizumab received induction doses of 600 mg on days 1, 8, 15, and 22, followed by maintenance dosing of 900 mg on day 29 and every 2 weeks thereafter per the approved PNH dosing regimen.	
Follow-up time	The study consisted of a 4-week screening period and a 26-week RCP, followed by an extension period of up to 5 years, during which all patients receive ravulizumab.	
Primary, secondary and exploratory endpoints	**Primary efficacy endpoint** • Proportion of participants with normalization of LDH levels ○ LDH is an indicator of intravascular haemolysis that occurs in participants with PNH. A decrease in LDH from above the ULN to below the ULN indicates reduction (improvement) in haemolysis. Normalization of LDH levels (LDH-N) was LDH levels less than or equal to 1 x ULN, from Day 29 through Day 183. The ULN for LDH is 246 U/L. • Percentage of participants who achieved transfusion avoidance	

- Transfusion avoidance was defined as the percentage of participants who remained transfusion free and did not require a transfusion per protocol-specified guidelines through Day 183.

Secondary efficacy endpoints

- Percentage of participants with BTH [Time frame: baseline through day 183]
- Percent change from baseline in LDH levels [Time frame: baseline, day 183]
- Change from baseline in quality of life as assessed by the FACIT-Fatigue [Time frame: baseline, day 183]
- Percentage of participants with stabilized haemoglobin levels [Time frame: baseline through day 183]

Other efficacy endpoints

- Time to first occurrence of LDH normalization
- Total number of pRBC units transfused
- Change in clinical manifestations of PNH
- Change from baseline in the EORTC QLQ-C30, version 3.0
- Proportion of patients experiencing MAVEs (including thrombosis)
- Change in free C5 concentrations.

Endpoints included in this application:

- Percentage of participants with stabilized haemoglobin levels
- Average change in EORTC QLQ- C30 global health score from baseline to day 168
- Proportion of participants with normalization of LDH levels
- Percentage of participants who achieved transfusion avoidance
- Change from baseline in quality of life as assessed by the FACIT-Fatigue
- Percent change from baseline in LDH levels (used in the MAIC, only. See Appendix C.)

Method of analysis	The coprimary endpoint transfusion avoidance was evaluated as the proportion of patients achieving the endpoint, computed as a weighted

Trial name: Study 301	NCT number: NCT02946463
	combination of differences between the treatment groups within the 2 randomisation stratifications, using Mantel-Haenszel tests. The stratified Newcombe method was used to calculate 95% CIs for transfusion avoidance. ORs and 95% CIs for the coprimary end point of LDH normalization were analyzed using a generalized estimating equation approach with first-order autoregressive correlation structure. The model included LDH normalization as the dependent variable and an indicator variable for treatment, history of transfusion (as a categorical variable based on the stratification factor levels), and baseline LDH level (as a continuous variable). The key secondary endpoints were tested in a hierarchical manner if noninferiority was declared for the coprimary end points. If noninferiority was established for all key secondary end points, then superiority was assessed in the following order: BTH, percentage change in LDH, LDH normalization, change in FACIT-Fatigue score, haemoglobin stabilization, and transfusion avoidance. To assess the strength of evidence of the study results, post hoc P values were calculated for testing of noninferiority (P_{inf}) relative to the prespecified noninferiority margins. 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. All analyses were performed using SAS (SAS Institute Inc, Cary, NC), version 9.4, or higher or other validated statistical software.
Subgroup analyses	None.
Other relevant information	None.

A.3 Main characteristics of PRINCE

Table 22 Main characteristic of PRINCE. Source: [3, 21]

Trial name: PRINCE	NCT number: NCT04085601
Objective	The study aimed to evaluate the efficacy and safety of pegcetacoplan in patients with PNH.
Publications – title, author, journal, year	Wong RSM, Navarro-Cabrera JR, Comia NS, et al. Pegcetacoplan controls hemolysis in complement inhibitor-naive patients with

Trial name: PRINCE	NCT number: NCT04085601
	paroxysmal nocturnal hemoglobinuria. Blood Adv. 2023;7(11):2468-2478. doi:10.1182/bloodadvances.2022009129. PMID: 36848639 Del Pozo Martin 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. No abstract available.
Study type and design	The study was a phase 3, randomised, multicenter, open-label, controlled study. It was conducted in 22 centers where Ci's were not approved or widely available (ie, patients were receiving supportive care only for PNH treatment, including transfusions, anticoagulants, corticosteroids, and supplements). The study comprised a ≤ 4-week screening period followed by a 26-week RCP. All subjects who completed RCP rolled over into a separate open-label, long-term extension study (APL2-307) or completed the safety follow-up (34 weeks). Centralized Interactive Response Technology randomly assigned patients using a 2:1 ratio of pegcetacoplan treatment to control (supportive care only). Randomisation was stratified based on the number of pRBC transfusions (< 4 or ≥ 4) received within the 12 months before screening.
Sample size (n)	A total of 53 Ci–naive patients were randomly assigned to pegcetacoplan treatment (n = 35) or continued supportive care (control; n = 18).
Main inclusion criteria	• Be at least 18 years old (inclusive). • Have LDH ≥ 1.5 x ULN at the screening visit. • Have PNH diagnosis, confirmed by high sensitivity flow cytometry (granulocyte or monocyte clone > 10%). • Have haemoglobin less than the LLN at the screening visit. • Have ferritin greater than/equal to the LLN, or total iron binding capacity less than/equal to ULN at the screening visit, based on central laboratory reference ranges. If a subject is receiving iron supplements at screening, the Investigator must ensure that the subject's dose has been stable for 4 weeks prior to screening, and it must be maintained throughout the study. Subjects not receiving iron at screening must not start iron supplementation during the course of the study. • BMI ≤ 35 kg/m2 at the screening visit. • Have a platelet count of > 50,000/mm3 at the screening visit. • Have an absolute neutrophil count > 500/mm3 at the screening visit.

Trial name: PRINCE	NCT number: NCT04085601

Main exclusion criteria	• Treatment with any Ci (eg, eculizumab) within 3 months prior to screening.
	• Hereditary complement deficiency.
	• History of bone marrow transplantation.
	• Concomitant use of any of the following medications is prohibited if not on a stable regimen for the time period indicated below prior to screening:
	  ○ Erythropoietin or immunosuppressants for at least 8 weeks
	  ○ Systemic corticosteroids for at least 4 weeks
	  ○ Vitamin K antagonists (eg, warfarin) with a stable international normalized ratio for at least 4 weeks
	  ○ Iron supplements, vitamin B12, or folic acid for at least 4 weeks
	  ○ Low-molecular-weight heparin for at least 4 weeks.

Intervention	Patients in the intervention arm received subcutaneous infusion of pegcetacoplan 1080 mg twice weekly or every 3 days up to end of the RCP (Week 26). Patients were not allowed to receive treatment with other Cis.
Comparator(s)	Patients in the comparator arm continued to receive supportive care but were not allowed to receive treatment with a Ci unless they qualified for pegcetacoplan escape therapy.
Follow-up time	Primary and secondary efficacy endpoints were reported after the 26-week randomised, controlled period.
Primary, secondary and exploratory endpoints	**Primary efficacy endpoint** • Number of Subjects Who Achieved Haemoglobin Stabilization from baseline up to week 26 ○ The haemoglobin stabilization was defined as avoidance of a > 1 g/dL decrease in haemoglobin concentration from Baseline in the absence of transfusion through Week 26. • Change From Baseline in LDH Concentration At Week 26 **Secondary efficacy endpoints** • Number of Subjects With an Haemoglobin Response in the Absence of Transfusions [Time Frame: Baseline and Week 26] • Change From Baseline in ARC at Week 26 [Time Frame: Baseline and Week 26]

Trial name: PRINCE	NCT number: NCT04085601
	• Change From Baseline in haemoglobin Concentration at Week 26 [Time Frame: Baseline and Week 26] • Percentage of Subjects Who Received Transfusion or Decrease of haemoglobin > 2 g/dL From Baseline [Time Frame: At Week 26] • Percentage of Subjects With Transfusion Avoidance [Time Frame: At Week 26] • Number of pRBC Units Transfused From Baseline Through Week 26 [Time Frame: Up to Week 26] • Change From Baseline in FACIT-Fatigue Scale Score at Week 26 [Time Frame: Baseline and Week 26] • Percentage of Subjects With haemoglobin Normalization Levels at Week 26 [Time Frame: Baseline and Week 26] • Percentage of Subjects With LDH Normalization at Week 26 [Time Frame: At Week 26] • Change From Baseline in EORTC QLQ-C30 Scores at Week 26 [Time Frame: Baseline and Week 26] • Change From Baseline in Linear Analog Assessment (LASA) Scales Score at Week 26 [Time Frame: Baseline and Week 26] • Percentage of Subjects With ARC Normalization [Time Frame: At Week 26] • Number of Subjects With Failure of haemoglobin Stabilization [Time Frame: Up to Week 26] • Time to First pRBC Transfusion [Time Frame: Up to Week 26] **Endpoints included in this application:** • The proportion with avoidance of a > 1 g/dL drop in haemoglobin level in the absence of transfusions from baseline to week 26 • The proportion who achieved transfusion independence, defined as no transfusions until week 26 • Mean change (LS mean change) of FACIT-Fatigue score from baseline to week 26 • The proportion with LDH normalization (< 226 U/L) at week 26 in the absence of blood transfusions • Average change (LS mean change) in EORTC QLQ- C30 global health score from baseline to week 26
Method of analysis	Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). Coprimary and secondary efficacy end points were

Trial name: PRINCE	NCT number: NCT04085601
	evaluated with the intent-to-treat analysis set; all patients were analyzed based on their original treatment group, and patients who escaped to pegcetacoplan treatment were set as missing in the control group. Patients who escaped from the control group were considered nonresponders (ie, patients for whom treatment failed to achieve the first coprimary end point of haemoglobin stabilization). Efficacy data for escape patients were evaluated separately in post hoc analyses. All statistical testing was performed at the 5% level of significance (two-sided), and all point estimates for the comparison between treatment groups were accompanied by adjusted ORs and two-sided 95% CIs. Continuous end points were analyzed using an analysis of covariance model with a multiple imputation approach for handling missing data. Continuous end point summary values included mean, median, range, SD, and SE. Categorical end points were analyzed by tabulating the number and percentage of patients based on the treatment group and comparing them using a stratified Cochran- Mantel-Haenszel $\chi 2$ test. Secondary efficacy end points were tested in a hierarchical manner after statistical significance was reached for the 2 coprimary end points to preserve the type 1 error rate. If a patient received a transfusion during their treatment period, the pretransfusion values for haemoglobin, LDH, ARC, FACIT- Fatigue score, and EORTC QLQ-C30 score were used in the model. Patients were categorized as non-responders for the haematologic stabilization, response, normalization and for clinically meaningful improvements in the FACIT-Fatigue score end points if they received a transfusion until week 26, escaped from the control to the pegcetacoplan group, withdrew from the study before week 26, or were lost to follow-up.
Subgroup analyses	None.
Other relevant information	None.

A.4 Main characteristics of APPLY-PNH

Table 23 Main characteristic of APPLY-PNH. Source: [1, 22]

Trial name: APPLY-PNH	NCT number: NCT04558918
Objective	The purpose of the APPLY-PNH trial in PNH patients presenting with residual anemia despite treatment with C5i's, was to determine whether iptacopan is efficacious and safe for the treatment of PNH compared to C5i treatment.
Publications – title, author, journal, year	Peffault de Latour R, Röth A, Kulasekararaj AG, et al. Oral Iptacopan Monotherapy in Paroxysmal Nocturnal Hemoglobinuria. N Engl J Med.

Trial name: APPLY-PNH	NCT number: NCT04558918
	2024;390(11):994-1008. doi:10.1056/NEJMoa2308695. PMID: 38477987.
Study type and design	The APPLY-PNH trial was a multi-center, randomised, open-label, active comparator-controlled, parallel group study, which was comprised of an 8-week screening period, a 24-week core treatment period and a 24-week extension treatment period. The trial included PNH patients who had received eculizumab or ravulizumab in a stable regimen for at least 6 months before randomisation. Patients were randomly assigned in an 8:5 ratio, by means of an interactive response system, to receive oral iptacopan monotherapy or to continue C5i therapy. Randomisation was stratified according to C5i therapy (eculizumab or ravulizumab) and whether a red-cell transfusion had been received in the preceding 6 months (yes or no). Iptacopan was administered by the patients at a dose of 200 mg twice daily; C5i therapy was administered intravenously according to the therapy received (i.e., every 2 weeks for patients receiving eculizumab and every 8 weeks for patients receiving ravulizumab).
Sample size (n)	The APPLY-PNH trial began on January 25, 2021 (data-cutoff date, September 26, 2022); 97 patients with persistent anemia (out of 125 who underwent screening) received iptacopan (62 patients) or continued C5i therapy (35 patients) for 24 weeks. Adherence to the iptacopan regimen, assessed according to the mean relative dose intensity, was 99.6% in the APPLY-PNH trial.
Main inclusion criteria	• Male and female participants ≥ 18 years of age with a diagnosis of PNH confirmed by high-sensitivity flow cytometry with clone size ≥ 10% • Stable regimen of C5i treatment (either eculizumab or ravulizumab) for at least 6 months prior to randomisation • Mean haemoglobin level < 10 g/dL • Vaccination against Neisseria meningitidis infection is required prior to the start of treatment. • If not received previously, vaccination against Streptococcus pneumoniae and Haemophilus influenzae infections should be given
Main exclusion criteria	• Participants on a stable eculizumab dose but with a dosing interval of 11 days or less or patients on stable ravulizumab dose but with a dosing interval of less than 8 weeks. • Known or suspected hereditary complement deficiency at screening • History of haematopoietic stem cell transplantation

Trial name: APPLY-PNH		NCT number: NCT04558918
	• Patients with laboratory evidence of bone marrow failure (reticulocytes < 100x10E9/L; platelets < 30x10E9/L; neutrophils < 500x10E6/L). • Active systemic bacterial, viral (incl. COVID-19), or fungal infection within 14 days prior to study drug administration • A history of recurrent invasive infections caused by encapsulated organisms, e.g. meningococcus or pneumococcus. • Major concurrent comorbidities including but not limited to severe kidney disease (e.g., eGFR < 30 mL/min/1.73 m^2, dialysis), advanced cardiac disease (e.g., NYHA class IV), severe pulmonary disease (e.g., severe pulmonary hypertension (WHO class IV)), or hepatic disease (e.g., active hepatitis) that in the opinion of the investigator precludes participant's participation in the study.	
Intervention	The trial included an 8-week screening period, a 24-week core treatment period, and a 24-week extension period. Iptacopan was administered by the patients at a dose of 200 mg twice daily; C5i therapy was administered intravenously according to the therapy received (i.e., every 2 weeks for patients receiving eculizumab and every 8 weeks for patients receiving ravulizumab).	
Comparator(s)	Patients were randomly assigned in an 8:5 ratio, by means of an interactive response system, to receive oral iptacopan monotherapy or to continue C5i therapy.	
Follow-up time	The study duration for the primary analysis was 24 weeks. Assessment of primary endpoints was assessed between days 126 and 168 with day 1 being the day of the first dose.	
Primary, secondary and exploratory endpoints	**Primary efficacy endpoint** • Marginal proportion of participants with sustained increase in haemoglobin levels from baseline of ≥ 2 g/dL in the absence of RBC transfusions • Marginal proportion (expressed as percentages) of participants with sustained haemoglobin levels of ≥ 12 g/dL in the absence of RBC transfusions • Percentage of patients meeting haematological response criterion after the start of iptacopan treatment • Number of patients not requiring RBC transfusions after the start of iptacopan treatment • Change from baseline in haemoglobin at visit day 336 • Change from baseline in FACIT-Fatigue questionnaire at day 336	

- Adjusted annualized clinical BTH rate after the start of iptacopan treatment
- Adjusted annualized MACEs rate after the start of iptacopan treatment

Secondary efficacy endpoints

- Marginal proportion of participants who remain free from transfusions
- Change from baseline in haemoglobin between day 126 and 168
- Change from baseline in FACIT-Fatigue questionnaire in the RCP
- Change from baseline in ARC in the RCP
- Ratio to baseline in Log-transformed LDH in the RCP
- Adjusted annualized clinical BTH rate in the RCP
- Adjusted annualized MACEs rate in the RCP

Other efficacy endpoints

- Change from baseline in ARC at day 336
- Ratio to baseline in Log-transformed LDH at visit day 336

Exploratory efficacy endpoints

- Haematological parameters (including RBCs and haptoglobin), bilirubin levels, number and units of transfusions, and PNH signs and symptoms collected between days 1 and 168
- Change in patient-reported outcomes score for the EORTC QLQ-C30 and EQ-5D-5L questionnaire collected between days 1 and 168
- Percentage of C3d-positive RBCs collected between days 1 and 168 (to detect C3-positive RBCs, whole blood samples were analyzed by flow cytometry and antiC3d biotin antibody [Quidel, clone C3D] was used to assess C3 deposition on PNH RBCs)
- Type I, II, and III RBCs and PNH population size (in red and white blood cells) collected between days 1 and 168
- Pharmacokinetic parameters of iptacopan

Trial name: APPLY-PNH	NCT number: NCT04558918
	• Patient responses to a semi-structured interview focusing on the patient's experience with their symptoms, particularly fatigue **Endpoints included in this application:** • Marginal proportion of participants with sustained increase in haemoglobin levels from baseline of ≥ 2 g/dL in the absence of RBCtransfusions • Marginal proportion of participants who remain free from transfusions • Change from baseline in FACIT-Fatigue questionnaire in the RCP
Method of analysis	The APPLY-PNH trial was designed to show the superiority of iptacopan over C5i therapy; the overall type I error was controlled at the one-sided 2.5% level. Superiority was determined with the use of a sequentially rejective testing procedure to adjust for multiplicity in the primary and secondary end points. Unadjusted one-sided P values are shown for endpoints in which superiority was shown. The primary end points in the APPLY-PNH trial were assessed by calculation of ORs, estimated (or marginal) proportions, and differences in estimated proportions with the use of a logistic-regression model with a Firth correction that adjusted for treatment and randomisation strata and with baseline covariates (i.e., sex, age ≥ 45 years, and haemoglobin level of ≥ 9 g/dL at baseline) as factors.
Subgroup analyses	None.
Other relevant information	None.

A.5 Main characteristics of PEGASUS

Table 24 Main characteristic of PEGASUS. Source: [4, 23]

Trial name: PEGASUS	NCT number: NCT03500549
Objective	The purpose of the PEGASUS trial was to evaluate the efficacy and safety of APL-2 in patients with PNH.
Publications – title, author, journal, year	Hillmen P, Szer J, Weitz I, et al. Pegcetacoplan versus Eculizumab in Paroxysmal Nocturnal Hemoglobinuria [published correction appears in N Engl J Med. 2024 Mar 14;390(11):1060. doi: 10.1056/NEJMx240003.].

Trial name: PEGASUS	NCT number: NCT03500549
	N Engl J Med. 2021;384(11):1028-1037. doi:10.1056/NEJMoa2029073. PMID: 33730455. Peffault de Latour RP, Szer J, Weitz IC, Roth A, Hochsmann B, Panse J, Usuki K, Griffin M, Kiladjian JJ, de Castro CM, Nishimori H, Ajayi T, Al-Adhami M, Deschatelets P, Francois C, Grossi F, Risitano AM, Hillmen P. Pegcetacoplan versus eculizumab in patients with paroxysmal nocturnal haemoglobinuria (PEGASUS): 48-week follow-up of a randomised, open-label, phase 3, active-comparator, controlled trial. Lancet Haematol. 2022 Sep;9(9):e648-e659. doi: 10.1016/S2352-3026(22)00210-1. Cella D, Sarda SP, Hsieh R, Fishman J, Hakimi Z, Hoffman K, Al-Adhami M, Nazir J, Cutts K, Lenderking WR. Changes in hemoglobin and clinical outcomes drive improvements in fatigue, quality of life, and physical function in patients with paroxysmal nocturnal hemoglobinuria: post hoc analyses from the phase III PEGASUS study. Ann Hematol. 2022 Sep;101(9):1905-1914. doi: 10.1007/s00277-022-04887-8. Epub 2022 Jul 23. Hakimi Z, Wilson K, McAughey E, Pochopien M, Wojciechowski P, Toumi M, Knight C, Sarda SP, Patel N, Wiseman C, de Castro NP, Nazir J, Kelly RJ. The cost-effectiveness, of pegcetacoplan compared with ravulizumab for the treatment of paroxysmal nocturnal hemoglobinuria, in a UK setting. J Comp Eff Res. 2022 Sep;11(13):969-985. doi: 10.2217/cer-2022-0076. Epub 2022 Jul 7. Bhak RH, Mody-Patel N, Baver SB, Kunzweiler C, Yee CW, Sundaresan S, Swartz N, Duh MS, Krishnan S, Sarda SP. Comparative effectiveness of pegcetacoplan versus ravulizumab in patients with paroxysmal nocturnal hemoglobinuria previously treated with eculizumab: a matching-adjusted indirect comparison. Curr Med Res Opin. 2021 Nov;37(11):1913-1923. doi: 10.1080/03007995.2021.1971182. Epub 2021 Sep 3.
Study type and design	The PEGASUS trial is a 48-week, phase 3, randomised, multicenter, open-label, active-comparator–controlled trial of the efficacy and safety of pegcetacoplan as compared with eculizumab in patients with PNH and a haemoglobin level of less than 10.5 g/dL despite treatment with eculizumab. The trial treatment period consisted of three parts. During a 4-week run-in phase, all the patients continued to receive their current dose of eculizumab with the addition of twice-weekly pegcetacoplan (1080 mg), which the patients administered themselves subcutaneously. After the run-in phase, patients were randomly assigned, in a 1:1 ratio, to monotherapy with pegcetacoplan or eculizumab for 16 weeks (randomised, controlled period). This period was followed by a 32-week period in which all patients received open-label pegcetacoplan. Randomisation was stratified according to the number of pRBC transfusions patients had received during the 12 months before screening (< 4 or ≥ 4) and the platelet count at screening (< 100,000 or ≥ 100,000 cells $\times 10^9$ per liter).

Trial name: PEGASUS	NCT number: NCT03500549
Sample size (n)	Of 102 patients screened, 80 (49 women and 31 men) met the entry criteria and were enrolled across 44 centers; 41 patients were randomly assigned to receive pegcetacoplan and 39 to receive eculizumab during the 16-week randomised, controlled period. All 39 patients assigned to receive eculizumab completed the 16 weeks of therapy; 3 of the 41 patients in the pegcetacoplan group discontinued therapy before week 16 owing to BTH. The trial was conducted from June 2018 through November 2019.
Main inclusion criteria	• At least 18 years of age • Primary diagnosis of PNH confirmed by high-sensitivity flow cytometry • On treatment with eculizumab. Dose of eculizumab must have been stable for at least 3 months prior to the Screening Visit • Haemoglobin < 10.5 g/dL at the Screening Visit • ARC > 1.0x ULN at the Screening Visit • Platelet count of > 50,000/mm3 at the Screening Visit • Absolute neutrophil count > 500/mm3 at the Screening Visit • Vaccination against Neisseria meningitides types A, C, W, Y and B, Streptococcus pneumoniae and Haemophilus influenzae Type B either within 2 years prior to Day 1 dosing, or within 14 days after starting treatment with APL-2 • Women of child-bearing potential must have a negative pregnancy test at the Screening and Day -28 Visit (Run-in Period) and must agree to use protocol defined methods of contraception for the duration of the study and 90 days after their last dose of study drug • Males must agree to use protocol defined methods of contraception and agree to refrain from donating sperm for the duration of the study and 90 days after their last dose of study drug • Willing and able to give informed consent • Willing and able to self-administer APL-2 (administration by caregiver will be allowed) • Have a BMI ≤ 35.0 kg/m2 Cardiac eligibility criteria: • 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

Trial name: PEGASUS		NCT number: NCT03500549
	• Myocardial infarction, coronary artery bypass grafting. , coronary or cerebral artery stenting and /or angioplasty, stroke, cardiac surgery, or hospitalization for congestive heart failure within 3 months or greater than Class 2 Angina Pectoris or NYHA Heart Failure Class > 2 • QTcF > 470 ms, PR > 280 ms • Mobitz II 2nd degree Atrioventricular Block, 2:1 Atrioventricular Block, High Grade Atrioventricular Block, or Complete Heart Block unless the patient has an implanted pacemaker or implantable cardiac defibrillator with backup pacing capabilities • 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 one week prior to the first dose of study medication (must have a repeat screening electrocardiogram after one week of prophylactic antibiotics with QTcF < 470 ms)	
Main exclusion criteria	• Active bacterial infection that has not resolved within 14 week of Day -28 (first dose of APL-2) • Receiving iron, folic acid, vitamin B12 and erythropoietin, unless the dose is stable, in the 4 weeks prior to Screening • Hereditary complement deficiency • History of bone marrow transplantation • History or presence of hypersensitivity or idiosyncratic reaction to compounds related to the investigational product or s.c. administration • Participation in any other investigational drug trial or exposure to other investigational agent within 30 days or 5 half-lives (whichever is longer) • Currently breast-feeding women • Inability to cooperate or any condition that, in the opinion of the investigator, could increase the subject's risk of participating in the study or confound the outcome of the study	
Intervention	During a 4-week run-in phase, all the patients continued to receive their current dose of eculizumab with the addition of twice-weekly pegcetacoplan (1080 mg), which the patients administered themselves subcutaneously. After the run-in phase, patients in the intervention group received monotherapy with pegcetacoplan for 16 weeks (RCP).	

Trial name: PEGASUS	NCT number: NCT03500549
	Subsequently all patients received open-label pegcetacoplan in a 32-week period.
Comparator(s)	Patients in the comparator group received their current dose of eculizumab with the addition of twice-weekly subcutaneous pegcetacoplan (1080 mg) during the run-in phase. During the 16-week RCP, patients in the comparator group received monotherapy with eculizumab. Subsequently all patients received open-label pegcetacoplan in a 32-week period. Patients who received eculizumab during the 16-week RCP continued to receive eculizumab in addition to pegcetacoplan for the first 4 weeks of the open-label period.
Follow-up time	Primary and secondary efficacy endpoints were reported after the 16-week RCP. Secondary efficacy endpoints are reported after 48 weeks.
Primary, secondary and exploratory endpoints	**Primary efficacy endpoint** • LS mean change from baseline to week 16 in Haemoglobin level during the RCP ○ Baseline was the average of measurements recorded before taking the first dose of pegcetacoplan, which included local and central laboratory values during the screening period. Analysis excluded data before the RCP and was censored for transfusions. **Secondary efficacy endpoints** • Percentage of subjects who did not require a transfusion (transfusion avoidance) during the RCP • LS mean change from baseline to week 16 in ARC during the RCP • LS mean change from baseline to week 16 in LDH level during the RCP • LS mean change from baseline to week 16 in FACIT-Fatigue scale score during the RCP • Percentage of subjects who achieved a haemoglobin response in the absence of transfusions at week 16 • Percentage of subjects who achieved reticulocyte normalization in the absence of transfusions at week 16 • Percentage of subjects who achieved haemoglobin normalization in the absence of transfusions at week 16 • LS mean change from baseline to week 16 in indirect bilirubin level during the RCP • LS mean change from baseline to week 16 in haptoglobin level during the RCP

Trial name: PEGASUS	NCT number: NCT03500549

- LS mean change from baseline to week 16 in LASA scores during the RCP
- LS mean change from baseline to week 16 in EORTC QLQ-C30 scores during the RCP
- Total number of pRBC units transfused during the RCP
- Mean change from baseline to week 48 in haemoglobin level during the treatment period
- Mean change from week 17 to week 48 in haemoglobin level during the open-label period
- Mean Change From Baseline to Week 48 in ARC During the Treatment Period
- Mean change from week 17 to week 48 in ARC during the open-label period
- Mean change from baseline to week 48 in LDH level during the treatment period
- Mean change from week 17 to week 48 in LDH Level during the open-label period
- Mean change from baseline to week 48 in FACIT-Fatigue scale score during the treatment period
- Mean change from week 17 to week 48 in FACIT-Fatigue scale score during the open-label period
- Mean change from baseline to week 48 in LASA scores during the treatment period
- Mean change from week 17 to week 48 in LASA scores during the open-label period
- Mean change from baseline to week 48 in QLQ-C30 Scores during the treatment period
- Mean change from week 17 to week 48 in QLQ-C30 scores during the open-label period
- Total number of pRBC units transfused during the open-label period

Endpoints included in this application:

- The proportion with normalization of haemoglobin in the absence of transfusions from baseline to week 16
- The proportion of patients who did not require a transfusion during the RCP(to week 16)
- Mean change (LS mean change) of FACIT-Fatigue score from baseline to week 16

Trial name: PEGASUS	NCT number: NCT03500549
Method of analysis	The between-group comparison for the primary end point was performed with the use of a MMRM, with baseline haemoglobin as a continuous variable, time point as a categorical variable, and treatment group, stratification variables, and time-by-treatment interaction as fixed effects. Transfusions were considered to be intercurrent events that could confound the results, and data after the first transfusion were censored. To control for a type 1 error, the key secondary end points were tested for noninferiority in the following hierarchical manner if superiority was declared for the primary end point: the proportion of patients who did not require a transfusion during the randomised, controlled period, followed by change from baseline to week 16 in ARC, LDH level, and FACIT–F score. Analyses were also conducted with all observed data considered (with no censoring of post-transfusion data).
Subgroup analyses	A subgroup analysis was performed by number of pretrial transfusions in the previous 12 months before screening; < 4 or ≥ 4 transfusions.
Other relevant information	None.

Appendix B. Efficacy results per study

B.1 Results of APPOINT-PNH

Table 25 Results of APPOINT-PNH

Results of APPOINT-PNH (NCT04820530)											
				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		
Marginal proportion of participants with sustained increase in haemoglobin levels from baseline of ≥ 2 g/dL in the absence of red blood cell transfusions	Iptacopan (single arm)	40	92% (82-100)	NA	NA	NA	NA	NA	NA	Sustained increase in haemoglobin levels (responder) is defined as an increase from baseline in haemoglobin levels of ≥ 2 g/dL on three out of four measurements between Day 126 and 168 of the core treatment period, without requiring RBC transfusions between Day 14 and Day 168. The term 'marginal proportion' can be interpreted as the population average probability of being a responder. Results incorporated a method to handle missing data using multiple imputation.	[1, 19]

Results of APPOINT-PNH (NCT04820530)											
				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		
Marginal proportion of participants who remain free from transfusions	Iptacopan (single arm)	40	98% (92-100)	NA	NA	NA	NA	NA	NA	Transfusion avoidance was analyzed by means of standardized marginal proportions derived similarly to the estimation applied to the primary endpoint.	[1, 19]
The proportion of patients having LDH levels that were no greater than 1.5 times the ULN range at 24 weeks	Iptacopan (single arm)	40	95%	NA	NA	NA	NA	NA	NA	Not specified Changes from baseline in the secondary endpoints were analyzed using repeated measures models that adjusted for covariates of age (categorical), sex, transfusion dependency, visit, baseline and interaction of visit and baseline value.	[1, 19]
Change From Baseline in FACIT-Fatigue Score	Iptacopan (single arm)	40	10.8 points (8.7 to 12.8)	NA	NA	NA	NA	NA	NA	Change from baseline in FACIT-Fatigue scores as mean of visits between Day 126 and Day 168. Change from baseline was analyzed using a MMRM which includes age (indicator variable of age ≥ 45 years), sex, history of transfusion (yes/no) prior to study treatment, visit, and baseline FACIT-	[1, 19]

Results of APPOINT-PNH (NCT04820530)											
				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		
										Fatigue score as fixed effects, along with the interaction between visit and baseline FACIT-Fatigue score.	
Average change in EORTC QLQ- C30 global health score from baseline to day 168	Iptacopan (single arm)	37	25.1 points (SD 18.72)	NA	NA	NA	NA	NA	NA	Patients reported EORTC QLQ- C30 scores at every visit. Change from baseline in patient reported scores for EORTC QLQ-C30 global health cores were presented for Day 168. Descriptive statistics were applied. At each time point, only patients with a value at both baseline and at that time point were included.	Data on file [15]

Abbreviations: CI, confidence interval; EORTC QLQ-C30, European Organization of Research and Treatment of Cancer 30-item Core Quality of Life Questionnaire; FACIT, Functional Assessment of Chronic Illness Therapy; LDH, lactate dehydrogenase; MMRM, Mixed Model for Repeated Measures; NA, not applicable; N, number of patients; RBC, red blood cells; ULN, upper limit of normal.

B.2 Results of Study 301

Table 26 Results of Study 301

Results of Study 301 (NCT02946463)											
				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**		
Proportion of participants with normalization of LDH levels	Ravulizumab	125	53.6% (45.9-61.2)	4.3 %-points	NA	NA	OR: 1.19	0.80-1.77	P_{inf} < 0.0001	LDH-N was analyzed using a generalized estimating equation approach. The model included the following terms: treatment group, history of transfusion (as a categorical variable based on the stratification factor levels), and baseline LDH level (as a continuous variable). Noninferiority margin was based on the lower bound of the 95% CI for the OR of ravulizumab versus eculizumab for LDH normalization being greater than an OR of 0.39.	[2, 20]
	Eculizumab	121	49.4% (41.7-57.0)								
Percentage of participants who achieved transfusion avoidance	Ravulizumab	125	73.6% (65.87-81.33)	6.8 %-points	-4.66-18.14	P_{inf} < 0.0001	NA	NA	NA	The absolute difference effect estimate is a calculated estimate. The end point was evaluated as the proportion of patients achieving the end point, computed as a weighted combination of differences between the treatment groups within the 2 randomization stratifications, using Mantel-Haenszel tests.	[2, 20]
	Eculizumab	121	66.1% (57.68-74.55)								

Results of Study 301 (NCT02946463)											
				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**		
										The stratified Newcombe method was used to calculate 95% CIs. Stratification factors were: observed stratification groups of pRBC/whole blood units transfused in the 1 year prior to first dose of study drug and screening LDH levels.	
Change from baseline in quality of life as assessed by the FACIT-Fatigue	Ravulizumab	125	7.07 points (5.55-8.60)	0.67 points	-1.21-2.55	P_{inf} < 0.0001	NA	NA	NA	Noninferiority margin was based on the lower bound of the 95% CI. Noninferiority margin was -5.	[2, 20]
	Eculizumab	121	6.40 points (4.85-7.96)								

Results of Study 301 (NCT02946463)											
				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**		
Percentage of participants with stabilized haemoglobin levels	Ravulizumab	125	68.0% (59.82-76.18)	2.9 %-points	-8.80-14.64	P_{inf} < 0.0001	NA	NA	NA	The absolute difference effect estimate is a calculated estimate. The end point was evaluated as the proportion of patients achieving the end point, computed as a weighted combination of differences between the treatment groups within the 2 randomization stratifications, using Mantel-Haenszel tests. The stratified Newcombe method was used to calculate 95% CIs. Stratification factors were: observed stratification groups of pRBC/whole blood units transfused in the 1 year prior to first dose of study drug and screening LDH levels.	[2, 20]
	Eculizumab	121	64.5 (55.93-72.99)								
Average change in EORTC QLQ- C30 global health score from baseline to day 183	Ravulizumab	124	13.2 points (SD: 21.4)	0.3 points	NA	NA	NA	NA	NA	Not specified	[2, 20]
	Eculizumab	118	12.9 points (SD: 21.8)								

Results of Study 301 (NCT02946463)												
				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**			

Abbreviations: CI, confidence interval; EORTC QLQ-C30, European Organization of Research and Treatment of Cancer 30-item Core Quality of Life Questionnaire; FACIT, Functional Assessment of Chronic Illness Therapy; LDH, lactate dehydrogenase; LDH-N, normalization of LDH levels; MMRM, Mixed Model for Repeated Measures; NA, not applicable; N, number of patients; P_{inf}, post hoc noninferiority p-value.

B.3 Results of PRINCE

Table 27 Results of PRINCE

Results of PRINCE (NCT04085601)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
The proportion with avoidance of a > 1 g/dL drop in haemoglobin level in the absence of transfusions from baseline to week 26	Pegcetacoplan	35	85.7%	73.1 %-points	57.2-89.0	< 0.0001	NA	NA	NA	The absolute difference effect estimate is a calculated estimate. The number and percentage of patients with hemoglobin stabilization was computed and compared between treatment groups using a stratified Cochran-Mantel-Haenszel χ^2 test, and the stratified Miettinen-Nurminen method was used to determine treatment difference in percentages and 95% CIs.	[3, 21]
	Supportive Care	18	0%								

Results of PRINCE (NCT04085601)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
The proportion who achieved transfusion independence, defined as no transfusions until week 26	Pegcetacoplan	35	91.4%	72.4 %-points	55.8-89.0	< 0.0001	NA	NA	NA	The absolute difference effect estimate is a calculated estimate. The number and percentage of patients with transfusion avoidance was computed and compared between treatment groups using a stratified Cochran-Mantel-Haenszel χ^2 test, and the stratified Miettinen-Nurminen method was used to determine treatment difference in percentages and 95% CIs.	[3, 21]
	Supportive Care	18	5.6%								
Mean change (LS mean change) of FACIT-Fatigue score from baseline to week 26	Pegcetacoplan	35	7.8 points (SE: 1.2)	4.5 points	-0.2-9.2	0.061	NA	NA	NA	All statistical testing was performed at the 5% level of significance (two-sided). Continuous end points were analyzed using an analysis of covariance model with a multiple imputation approach for handling missing data. Continuous end point summary	[3, 21]
	Supportive Care	18	3.3 points (SE: 2.1)								

Results of PRINCE (NCT04085601)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										values included mean, median, range, SD, and SE.	
The proportion with LDH normalization (< 226 U/L) at week 26 in the absence of blood transfusions	Pegcetacoplan	35	65.7%	55.9 %-points	36.8 – 75.0	< 0.0001	NA	NA	NA	The absolute difference effect estimate is a calculated estimate. The number and percentage of patients with LDH normalization was computed and compared between treatment groups using a stratified Cochran-Mantel-Haenszel χ^2 test, and the stratified Miettinen-Nurminen method was used to determine treatment difference in percentages and 95% CIs.	[3, 21]
	Supportive Care	18	0%								

Results of PRINCE (NCT04085601)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Average change (LS mean change) in EORTC QLQ- C30 global health score from baseline to week 26	Pegcetacoplan	35	18.9 points (SE: 2.9)	21.8 points	9.4-34.2	0.0006	NA	NA	NA	All statistical testing was performed at the 5% level of significance (two-sided). Continuous end points were analyzed using an analysis of covariance model with a multiple imputation approach for handling missing data. Continuous end point summary values included mean, median, range, SD, and SE.	[3, 21]
	Supportive Care	18	-2.9 points (SE: 5.7)								

Abbreviations: CI, confidence interval; EORTC QLQ-C30, European Organization of Research and Treatment of Cancer 30-item Core Quality of Life Questionnaire; FACIT, Functional Assessment of Chronic Illness Therapy; LDH, lactate dehydrogenase; LS, least square; NA, not applicable; N, number of patients; OR, odds ratio; SD, standard deviation; SE, standard error.

B.4 Results of APPLY-PNH

Table 28 Results of APPLY-PNH

Results of APPLY-PNH (NCT04558918)											
				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**		
Marginal proportion of participants with sustained increase in haemoglobin levels from baseline of ≥ 2 g/dL in the absence of red blood cell transfusions	Iptacopan	62	82.3% (73.4-90.2)	80.2 %-points	71.2-87.6	< 0.001	NA	NA	NA	Time frame: Baseline, haemoglobin between Day 126 and Day 168 and absence of transfusions between Day 14 and Day 168. Differences in estimated proportions were assessed with the use of a logistic-regression model with a Firth correction that adjusted for treatment and randomisation strata and with baseline covariates (i.e., sex, age ≥ 45 years, and haemoglobin level of ≥ 9 g/dL at baseline) as factors.	[1, 22]
	C5i	35	2.0% (1.1-4.0)								

Results of APPLY-PNH (NCT04558918)											
				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		
Marginal proportion of participants who remain free from transfusions	Iptacopan	62	94.8% (88.1-100.0)	68.9 %-points	51.4-83.9	< 0.001	NA	NA	NA	Time frame: Between Day 14 and Day 168. Transfusion avoidance was analyzed using conditional logistic regression (for calculation of the OR and P value), which was conditioned on the stratum within which patients were randomised, and included the covariates of treatment, sex, age (indicator of age ≥ 45 years), and an indicator variable of baseline haemoglobin ≥ 9 g/dL.	[1, 22]
	C5i	35	25.9 (11.6-42.4)								
Change from baseline in FACIT-Fatigue questionnaire in the randomised treatment period	Iptacopan	62	8.6 points (6.7-10.5)	8.29 points	5.3-11.3	< 0.001	NA	NA	NA	Time frame: Baseline, mean of visits between Day 126 and Day 168. The mean difference was estimated using a MMRM with two-sided unadjusted p-value.	[1, 22]
	C5i	33	0.3 points (-2.2-2.8)								

Abbreviations: C5i, complement 5 inhibitor; CI, confidence interval; FACIT, Functional Assessment of Chronic Illness Therapy; NA, not applicable; MMRM, Mixed Model for Repeated Measures; N, number of patients.

B.5 Results of PEGASUS

Table 29 Results of PEGASUS

Results of PEGASUS (NCT03500549)											
				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**		
The proportion with normalization of haemoglobin in the absence of transfusions from baseline to week 16	Pegcetacoplan	41	34.1%	30.4 %-points	14.9-45.9	NA	NA	NA	NA	The difference in percentage and 95% CI is calculated based on stratified Miettinen-Nurminen method stratified by randomisation factor so it is not a direct difference of two reporting groups.	[4, 23]
	Eculizumab	39	0%								
The proportion of patients who did not require a transfusion during the randomised, controlled period (to week 16)	Pegcetacoplan	41	85%	63 %-points	48 - 77	< 0.001	NA	NA	NA	The risk difference in percentage and 95% CI is calculated based on Miettinen-Nurminen method.	[4, 23]
	Eculizumab	39	15%								

Results of PEGASUS (NCT03500549)											
				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**		
Mean change (LS mean change) of FACIT-Fatigue score from baseline to week 16	Pegcetacoplan	41	9.2 points (SE±1.6)	11.9 points	5.49-18.25	NA	NA	NA	NA	Analysis was a between-treatment-group comparison using an MMRM. The difference between pegcetacoplan and eculizumab LS mean changes from Baseline at Week 16 was calculated along with its 2-sided 95% CI and associated P-value from the MMRM model for the ITT set, censored for transfusions.	[4, 23]
	Eculizumab	39	-2.7 points (SE±2.8)								

Abbreviations: CI, confidence interval; FACIT, Functional Assessment of Chronic Illness Therapy; ITT, intention to treat; LS, least square; MMRM, , Mixed Model for Repeated Measures; N, number of patients; NA, not applicable; SE, standard error.

Appendix C. Comparative analysis of efficacy

The comparative analyses in this application are narratively, and presented in Table 30 and Table 31 below. In addition more details are presented in sections 5.2.5 and 6.2.5.

In addition, two ITCs have been included in this application. One MAIC conducted for the Ci-naïve population and one anchored ITC conducted for the residual anemia despite C5i treatment population. The ITCs are described in detail in the following section.

C.1 Iptacopan compared to eculizumab, ravulizumab, and pegcetacoplan in Ci-naïve PNH patients

Table 30 Narrative comparison of iptacopan vs. eculizumab, ravulizumab and pegcetacoplan in Ci-naïve PNH patients

Outcome	Studies included in the analysis	Iptacopan	Eculizumab	Ravulizumab	Pegcetacoplan	Results	Method used for quantitative synthesis
Proportion of patients with Transfusion avoidance, % (95% CI)	APPOINT-PNH Study 301 PRINCE [1–3]	98 (92 to 100)	66.1 (57.7 to 74.6)	73.6 (65.9 to 81.3)	91.4	The results indicate that iptacopan reduces the need for transfusions to the same extent as pegcetacoplan, and numerically more than eculizumab and ravulizumab, however the difference vs. pegcetacoplan does not exceed the minimal clinically relevant difference of 20 %-points as defined by DMC [5]	Narrative comparison
Fatigue (Change from baseline in FACIT-fatigue score, points (95% CI)/SE	APPOINT-PNH Study 301 PRINCE [1–3]	10.8 (8.7 to 12.8)	6.4 (4.9 to 8.0)	7.1 (5.6 to 8.6)	7.8 SE:1.2	The average change in the FACIT-Fatigue score was numerically higher for iptacopan than for pegcetacoplan, ravulizumab, and eculizumab. However, the differences do not exceed the minimal clinically relevant difference of 5 points as defined by DMC [5]	Narrative comparison
Proportion of patients with Stabilisation of	APPOINT-PNH Study 301	92 (82 to 100)	64.5 (55.9 to 73.0)	68.0 (59.8 to 76.2)	85.7	Of note, the definition of the outcome differs significantly between studies. A numerically higher proportion of patients achieved stabilisation of haemoglobin vs. with ravulizumab, eculizumab and pegcetacoplan, however, the difference vs.	Narrative comparison

Outcome	Studies included in the analysis	Iptacopan	Eculizumab	Ravulizumab	Pegcetacoplan	Results	Method used for quantitative synthesis
hemoglobin, % (95% CI)	PRINCE [1–3]					pegcetacoplan does not exceed the minimal clinically relevant difference of 20 %-points as defined by DMC [5]	
Proportion of patients with Normalisation of LDH, % (95% CI)	APPOINT-PNH Study 301 PRINCE [1–3]	95	49.4 (41.7 to 57.0)	53.6 (45.7 to 61.2)	65.7	A numerically higher proportion of patients achieved normalisation of LDH vs. ravulizumab, eculizumab and pegcetacoplan, and the differences vs ravulizumab, eculizumab, and pegcetacoplan exceeded the minimal clinically relevant difference of 20 %-points as defined by DMC [5]	Narrative comparison
Change from baseline in EORTC QLQ-C30 *global health score,* points SD/SE	APPOINT-PNH Study 301 PRINCE [2, 3, 15]	25.1 SD 18.72	12.9 SD 21.8	13.2 SD 21.4	18.9 SE 2.9	The average change in EORTC QLQ-C30 global health score was numerically higher for iptacopan vs. ravulizumab, eculizumab and pegcetacoplan. However, the difference vs. pegcetacoplan does not exceed the minimal clinically relevant difference of 10 points as defined by DMC [5]	Narrative comparison

This table is based on Table 6 in appendix C in the DMC template for applications, and has been adjusted to include a narrative comparison vs. more than one comparator. Narrative comparion was discussed at a dialogue meeting with DMC.
Abbreviations: CI, confidence interval; DMC, Danish Medicines Council; FACIT, Functional Assessment of Chronic Illness Therapy; LDH, lactate dehydrogenase; SD, standard deviation; SE, standard error.

C.2 Iptacopan compared to pegcetacoplan in patients with residual anemia despite treatment with C5i's

Table 31 Narrative comparison of iptacopan vs. pegcetacoplan in patients with residual anaemia despite treatment with C5i's

Outcome	Studies included in the analysis	Iptacopan	Pegcetacoplan	Results	Method used for quantitative synthesis
Proportion of patients with Transfusion avoidance, % (95% CI)	APPLY-PNH PEGASUS [1, 4]	95 (88 to 100)	85	The efficacy of iptacopan and pegcetacoplan appears to be similar. The difference between iptacopan and pegcetacoplan does not exceed the minimal clinically relevant difference of 20 %-points as defined by DMC [5]	Narrative comparison
Fatigue (Change from baseline in FACIT-fatigue score; points (95% CI)/SE	APPLY-PNH PEGASUS [1, 4]	8.6 (6.7 to 10.5)	9.2 SE±	The efficacy of iptacopan and pegcetacoplan appears to be similar. The difference between iptacopan and pegcetacoplan does not exceed the minimal clinically relevant difference of 5 points as defined by DMC [5]	Narrative comparison
Proportion of patients with Stabilisation of haemoglobin; % (95% CI)	APPLY-PNH PEGASUS [1, 4]	82 (73 to 90)	34.1	The definition of Stabilisation of haemoglobin differs significantly, thus a comparison is not feasible	Narrative comparison

This table is based on Table 6 in appendix C in the DMC template for applications, and has been adjusted to include a narrative comparison vs. more than one comparator. Narrative comparion was discussed at a dialogue meeting with DMC.
Abbreviations: CI, confidence interval; DMC, Danish Medicines Council; FACIT, Functional Assessment of Chronic Illness Therapy; SE, standard error.

C.3 Matching-adjusted indirect comparison (MAIC): Ci-naïve population

As previously discussed with the DMC secretariat, this application presents an ITC, which also was included in the application for iptacopan to NICE in the UK [10]. In the ITC, the efficacy of iptacopan is informed by the single-arm trial APPOINT-PNH while Study 301 was included as the comparator study. Study 301, a recent pivotal trial for ravulizumab in PNH, was a RCT in Ci-naïve patients that compared ravulizumab with eculizumab [2].

C.3.1 ITC methods summary

Given that APPOINT-PNH was a single-arm trial, a population-adjusted unanchored ITC was conducted, leveraging individual patient data (IPD) for iptacopan from APPOINT-PNH and published summary-level data for ravulizumab and eculizumab from Study 301[2]. The analysis followed the general approach outlined by the NICE Decision Support Unit Technical Support Document 18 for population-adjustment [24]. No patients were excluded from the APPOINT-PNH dataset due to a high degree of overlap in study eligibility criteria; the difference in haemoglobin inclusion criteria could not be addressed since Study 301 included a broader population. IPD from APPOINT-PNH were reweighted using entropy balancing [25] to adjust for differences between the APPOINT-PNH and Study 301 populations. The adjustment factors (age, sex, % transfusion free in prior 12 months, baseline LDH, history of MAVE) were validated by UK clinicians [26]. Baseline haemoglobin could not be included in the reweighting since the analysis did not converge.

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

C.3.2 Study characteristics comparison

A summary of APPOINT-PNH and Study 301 key study characteristics is provided in the table below.

Table 32 Key study characteristics for APPOINT-PNH and Study 301

	APPOINT-PNH	Study 301
Study dates	2021-2022	2016-2018
Intervention(s)	Iptacopan (N=40)	Ravulizumab (N=125) Eculizumab (N=121)

	APPOINT-PNH	Study 301
Population	≥ 18 years of age PNH diagnosis LDH > 1.5 × ULN Haemoglobin < 10 g/dL Naïve to Cis	≥ 18 years of age PNH diagnosis LDH ≥ 1.5 × ULN Body weight ≥ 40 kg PNH-related sign or symptom† Naïve to Cis
Outcomes reported which could be used for ITC	Outcomes aligned with comparator study	% change from baseline in LDH Transfusion avoidance Change from baseline in FACIT-Fatigue
Study duration	Primary analysis: 24 weeks	Primary analysis: 26 weeks
Study used for	Iptacopan data for unanchored ITC	Comparator data for unanchored ITC

† fatigue, hemoglobinuria, abdominal pain, dyspnoea, anaemia (haemoglobin levels < 10 g/dL), or history of MAVEs (including thrombosis), dysphagia, erectile dysfunction, or history of packed RBC transfusion because of PNH; Abbreviations: C5i, complement 5 inhibitor; FACIT, Functional Assessment of Chronic Illness Therapy; ITC, indirect treatment comparison; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal hemoglobinuria; ULN, upper limit of normal.

C.3.3 Patient characteristics comparison

A comparison of APPOINT-PNH and Study 301 patient characteristics is provided in the table below.

Table 33 Comparison of patient characteristics in APPOINT-PNH and Study 301

Trial	Intervention	Mean age (SD), years	Female, n (%)	Mean haemoglobin (SD), g/dL	Mean LDH (SD), U/L	Mean platelets (SD), $x10^9$/L	Mean ARC (SD), $x10^9$/L	Mean FACIT-Fatigue score (SD)	Transfusion free, 12 months prior, n (%)	History of aplastic anemia, n (%)	History of MAVE, n (%)
APPOINT-PNH	IPT (N=40)	42.1 (15.85)	17 (42.5)	8.16 (1.09)	1,698.8 (683.33)	159.4 (61.09)	154.33 (63.67)	32.78 (10.17)	13 (32.5)	16 (40)	5 (12.50)
Study 301	RAV (N=125)	44.8 (15.2)	60 (48.0)	9.41 (1.46)	1,633.5 (778.8)	NR	NR	NR	23 (18.4)	NR	17 (13.6)
	ECU (N=121)	46.2 (16.2)	52 (43.0)	9.59 (1.71)	1,578.3 (727.1)	NR	NR	NR	21 (17.4)	NR	25 (20.7)

Abbreviations:ARC, absolute reticulocyte count; ECU, eculizumab; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy – Fatigue; IPT, iptacopan; LDH, lactate dehydrogenase; MAVE, major adverse vascular event; NR, not reported; RAV, ravulizumab; SD, standard deviation.

C.3.4 Trial results comparison

A comparison of APPOINT-PNH and Study 301 trial results for the outcomes analysed in the ITC are provided in the table below.

Table 34 Comparison of trial results from APPOINT-PNH and Study 301

Trial	Intervention	Analysis timepoint	Change from baseline in LDH, % or in U/L	Transfusion avoidance, n (%)	Mean change from baseline in FACIT-Fatigue
APPOINT-PNH	IPT (N=40)	Week 24	% change: -83.55 (95% CI: -84.90, -82.08); Change in U/L: -1,424.4	40 (100)	10.75 (95% CI: 8.66, 12.84)
Study 301	RAV (N=125)	Week 26	% change: -76.84 (95% CI: -79.96, -73.73)	92 (73.6)	7.07 (95% CI: 5.55, 8.60)
	ECU (N=121)	Week 26	% change: -76.02 (95% CI: -79.20, -72.83)	80 (66.1)	6.40 (95% CI: 4.85, 7.96)

Abbreviations: CI, confidence interval; ECU, eculizumab; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy – Fatigue; ITC, indirect treatment comparison; IPT, iptacopan; LDH, lactate dehydrogenase; RAV, ravulizumab.

C.3.5 ITC methods

C.3.5.1 Data processing

The IPD from APPOINT-PNH were pre-processed before conducting the ITC vs. Study 301 as follows:

- Dropping of off-support cases from APPOINT-PNH IPD dataset:
  - The analysis is based on the assumption of common support that is there is sufficient overlap in the characteristics of the patients from both studies being compared to estimate the weights adequately.
  - Study eligibility criteria for Study 301 were similar to APPOINT-PNH (Table 35). Therefore, it was not necessary to drop patients from the APPOINT-PNH dataset prior to the reweighting.

Table 35 Overview of Key Eligibility Criteria in APPOINT-PNH and Study 301

Key Eligibility Criteria	APPOINT-PNH	Study 301	Similarity
Age	> 18	>18	
Platelet count	≥ 30 × 10^9/L	≥ 30 × 10^9/L	
History of transfusion	No restrictions in study entry	Enrollment of patients without a history of transfusion was capped at 20%	

Key Eligibility Criteria	APPOINT-PNH	Study 301	Similarity
Body weight	No restrictions in study entry	≥ 40 kg	
Hemoglobin	< 10 g/dL	Included as PNH-related symptoms	

Green = trials are similar; Yellow = trials are different; can be addressed by ITC; Red = trials are different; cannot be addressed by ITC. Abbreviations: ITC, indirect treatment comparison; PNH, paroxysmal nocturnal haemoglobinuria.

- Balancing of pre-treatment marginal distributions (% or mean and SDs) between APPOINT-PNH with the Study 301 population.
    - Entropy balancing was implemented using the *ebal* package for R [27]. Entropy balancing is mathematically identical to weights derived using the method of moments [25].
    - For the population-adjusted ITC using Study 301, the adjustment included five key factors validated by UK clinicians [26] : age, mean (SD); sex, % male; % transfusion free 12 months prior; baseline LDH, mean (SD); % with history of MAVE.
    - Other candidate prognostic factors considered for the ITC with Study 301 but not included in the reweighting were: baseline haemoglobin (did not converge- provisional univariate analysis resulted in an effective sample size (ESS) after balancing on mean baseline haemoglobin = 5; ESS after balancing on mean and SD baseline haemoglobin = 2); number of units pRBC 6 months prior (% transfusion free used as a proxy); baseline reticulocytes (not reported for Study 301) and % with ongoing aplastic anaemia (not reported for Study 301).

Imbalances in pre-treatment characteristics between APPOINT-PNH and Study 301 were summarized using the absolute value of the standardized mean difference (SMD) [28] and balance before and after reweighting were classified as small differences (SMD < 0.10), moderate differences (0.10 ≤ SMD < 0.20), or substantial differences (SMD ≥ 0.20). The ESS is calculated as:

$$= \frac{\left(\sum_{i=1}^{n} w_i\right)^2}{\sum_{i=1}^{n} w_i^2}$$

where n is total number of patients and w_i is the weight for patient i as derived from entropy-balancing function.

C.3.5.2 Endpoint alignment

The ITC of APPOINT-PNH vs. Study 301 were conducted for efficacy outcomes available from both trials: Change from baseline in LDH, transfusion avoidance, and change from

baseline in FACIT-Fatigue score. ITC for haemoglobin outcomes were not feasible, since these were not reported from Study 301. Where definitions of endpoints differed, APPOINT-PNH results were reassessed to match definitions of Study 301, to the extent possible. This included including transfusions from Day 1 onwards, rather than from Day 14 as specified in APPOINT-PNH, in the analysis of the transfusion avoidance outcome. Due to the longer study duration of Study 301 (26 weeks) compared to APPOINT-PNH (24 weeks), a full adjustment of analysis time frames was not feasible; APPOINT-PNH data up to Day 168 was compared to Study 301 data up to Day 183. Details are provided in Table 36.

Table 36 Comparison of outcomes in APPOINT-PNH and Study 301

	Study 301 [2]	**APPOINT-PNH** [15]	**Can emulate the definition of the comparator trial with APPOINT-PNH data?**
Change from baseline in LDH			
Definition of endpoint	Percent change from baseline to Day 183 in LDH	Percent change (log transformed) from baseline in LDH as a mean of visits between Days 126 and 168	Partially – Rederive percentage change in LDH from Day 1 to Day 168 to approximate Study 301 definition
Definition of baseline	If a Day 1 assessment is missing, the screening assessment will be used as the baseline assessment	The mean of the two measurements taken during screening. In patients who received a transfusion after the first confirmatory measurement, the baseline is the first measurement	Yes
Handling of missing values	NR	Values observed within 30 days of transfusion or after treatment discontinuation are set to missing and imputed according to hypothetical estimand	Unable to emulate comparator definition. Missing values are assumed to be treated similarly between trials.
Statistical model	MMRM	MMRM	Yes
Covariates included in model	Treatment Transfusion history (> 14 units 12 months prior) Screening LDH (≥ 3 x ULN vs. 1.5 to < 3 ULN)	History of transfusion (6 months prior) Age Sex	Yes

	Study 301 [2]	APPOINT-PNH [15]	Can emulate the definition of the comparator trial with APPOINT-PNH data?
	Study visit Study visit x treatment Baseline LDH	Study visit Baseline LDH Study visit × baseline LDH	
Covariance structure	NR	Unstructured	Assume unstructured
Transfusion avoidance			
Definition of endpoint	Proportion of patients who remain transfusion-free and do not require a transfusion as per protocol-specified guidelines through Day 183 (Week 26)	Proportion of patients who did not receive and did not meet the criteria for transfusion between Day 14 to Day 168	Partially – Rederive transfusion avoidance from Day 1 to Day 168 to approximate Study 301 definition
Threshold for transfusion	Haemoglobin value of ≤ 9 g/dL with signs or symptoms of sufficient severity to warrant a transfusion Haemoglobin value of ≤ 7 g/dL regardless of presence of clinical signs or symptoms	Haemoglobin between < 7 and ≤ 9 g/dL (<6 and ≤ 8 g/dL for Chinese population) with signs/symptoms of sufficient severity to warrant a transfusion Haemoglobin ≤ 7 g/dL (≤ 6g/dL for patients in China), regardless of presence of clinical signs	Partially – Study 301 did not specify additional requirements for Chinese patients
Change from baseline in FACIT-Fatigue score			
Definition of endpoint	Change from baseline to Day 183 in FACIT-Fatigue score	Change from baseline in FACIT-Fatigue as a mean of visits between Days 126 and 168	Rederive change from baseline in FACIT-Fatigue from Day 1 to Day 168 to approximate timeframe in Study 301
Definition of baseline	If a Day 1 assessment is missing, the screening assessment will be used as the baseline assessment	The mean of the two measurements taken during screening. In patients who received a transfusion after the first confirmatory measurement, the baseline is the first measurement	Yes

	Study 301 [2]	APPOINT-PNH [15]	Can emulate the definition of the comparator trial with APPOINT-PNH data?
Handling of missing values	NR	Values observed within 30 days of transfusion or after treatment discontinuation are set to missing and imputed according to hypothetical estimand	Unable to emulate comparator definition. Missing values is assumed to be treated similarly between trials
Statistical model	MMRM	MMRM	Yes
Covariates included in model	Treatment Transfusion history (> 14 units 12 months prior) Screening LDH (≥ 3 x ULN vs. 1.5 to < 3 ULN) Study visit Study visit x treatment Baseline FACIT-Fatigue	History of transfusion (6 months prior) Age Sex Study visit Baseline FACIT-Fatigue Study visit × baseline FACIT-Fatigue	Yes
Covariance structure	NR	Unstructured	Assumed Unstructured

Abbreviations: FACIT, Functional Assessment of Chronic Illness Therapy; LDH, lactate dehydrogenase; MMRM, mixed model for repeated measures, NR, not reported, ULN, upper limit of normal.

C.3.5.3 Estimation of treatment outcomes

Continuous longitudinal outcomes: For change from baseline in LDH, the APPOINT-PNH endpoint was rederived as the percentage change in LDH from Day 1 to Day 168 to approximate Study 301 definition which was change from baseline up to Day 183. Then estimates were derived by fitting a MMRM to the reweighted IPD from APPOINT-PNH. Treatment, baseline LDH, stratification variables (transfusion history, screening LDH), study visit, and study visit × treatment were used as variables in the model to emulate the model specification used in Study 301. The treatment effect between iptacopan and ravulizumab and between iptacopan and eculizumab was then derived as the difference between the adjusted mean change from baseline for iptacopan and the published adjusted mean of pooled Study 301 population. The variance of the adjusted mean for iptacopan was derived using the Kenward-Roger method and that of ravulizumab or eculizumab was derived from the published 95% CI for the adjusted mean. A similar estimation was conducted for change from baseline in FACIT-Fatigue scores.

Binary efficacy outcomes: For transfusion avoidance, the APPOINT-PNH endpoint was rederived as transfusion avoidance from Day 1 to Day 168 to approximate Study 301

definition (through to Day 183). Estimates were then derived with an intercept-only logistic regression model fitted to the reweighted IPD for APPOINT-PNH. The estimated intercept was used as an estimate of the weighted log odds of remaining transfusion-free. Robust SEs for the log odds were estimated using the sandwich estimator via the R package 'sandwich'. An estimate of the log OR for iptacopan vs. ravulizumab and eculizumab was derived as the difference between the weighted log odds for iptacopan and the estimated log odds for ravulizumab and eculizumab based on published transfusion events from Study 301. The 95% CI for the log OR was derived using the sum of variances for the log odds for iptacopan and ravulizumab and eculizumab. Point estimates and 95% CIs were transformed to the OR scale for reporting. An OR > 1 implies greater odds of remaining transfusion-free for iptacopan versus ravulizumab or eculizumab.

Results were reported using point estimates (mean difference, OR) and 95% CIs for each analysis. Nominal significance was ascertained using a two-tailed p-Value of < 0.05. All analyses were conducted using R, largely adapted from code presented in the NICE Evidence Synthesis Technical Support Document Series [29].

C.3.6 Results

C.3.6.1 Comparison of pre-treatment characteristics before and after weighting

A comparison of APPOINT-PNH patient characteristics before and after reweighting to balance baseline characteristics with the Study 301 population is presented in Table 37. Reweighting reduced the ESS from 40 to 31 patients. Of note is the difference in baseline haemoglobin between trials (unweighted SMD: 0.983; weighted SMD: 1.127); adjusting for the difference was not possible as the analysis failed to converge.

Table 37 Comparison of baseline characteristics between Study 301 and APPOINT-PNH, before and after weighting

Baseline Characteristics	Study 301	APPOINT-PNH Unweighted		APPOINT-PNH Weighted†	
	N = 246	N = 40	SMDs	ESS = 31	SMDs
Age, years: mean (SD)	45.5 (15.7)	42.1 (15.8)	0.216	45.5 (15.7)	0.000
LDH, U/L: mean (SD)	1,606.4 (752.7)	1,698.8 (683.3)	0.129	1,606.4 (684.7)	0.000
Transfusion free, 12 months prior: n (%)	44 (17.9%)	13 (32.5%)	0.342	17.8%	0.000
History of MAVE, n (%)	42 (17.1%)	5 (12.5%)	0.129	17.1%	0.001
Sex, male: n (%)	134 (54.5%)	23 (57.5%)	0.061	54.5%	0.001

Baseline Characteristics	Study 301	APPOINT-PNH Unweighted		APPOINT-PNH Weighted†	
	N = 246	N = 40	SMDs	ESS = 31	SMDs
Weight, kg: mean (SD)	68.7 (15.2)	70.1 (12.7)	0.100	68.6 (12.3)	0.005
Height, cm: mean (SD)	166.2 (9.8)	168.2 (9.1)	0.208	167.1 (9.0)	0.100
Race, white: n (%)	94 (38.2%)	12 (30%)	0.174	28.4%	0.210
Haemoglobin, g/dL: mean (SD)	9.5 (1.6)	8.15 (1.09)	0.983	7.9 (1.2)	1.127
Baseline FACIT-Fatigue score: mean (SD)	NR	32.8 (10.2)	NA	32.3 (10.0)	NA
Reticulocyte count: mean (SD), per mm^3	NR	154,325 (63,666)	NA	143,231 (609,11)	NA

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

†Reweights APPOINT-PNH data to balance with Study 301 on age (means and SD), proportion of males, LDH level at baseline (mean and SD), transfusion free 12 months prior, and history of MAVE;

Abbreviations: ESS, effective sample size; FACIT, Functional Assessment of Chronic Illness Therapy; LDH, lactate dehydrogenase; MAVE, major adverse vascular event; NA, not applicable; NR, not reported; SD, standard deviation; SMD, standardised mean difference.

C.3.6.2 Overview of ITC results

Table 38 presents a summary of the ITC results of APPOINT-PNH vs. Study 301. Iptacopan-treated patients had a significantly greater reduction in LDH from baseline compared with ravulizumab or eculizumab (mean difference < 0). Results for the transfusion avoidance and change from baseline in FACIT-Fatigue outcomes were not statistically significant, while the point estimates favoured iptacopan over ravulizumab or eculizumab for both outcomes.

Table 38 Overview of results for iptacopan vs. ravulizumab or eculizumab in the Ci-naïve population

	Transfusion avoidance	% change from baseline in LDH	Change from baseline in FACIT-Fatigue score
Iptacopan (ESS=31†)	78.6%	% change from baseline = –85.08	Change from baseline =10.85 (95% CI 7.23, 14.47)

	Transfusion avoidance	% change from baseline in LDH	Change from baseline in FACIT-Fatigue score
		(95% CI –87.84, –82.32)	
Ravulizumab (N=125)	73.5%	% change from baseline = –76.84 (95% CI –79.96, –73.73)	change from baseline = 7.07 (95% CI 5.55, 8.60)
Eculizumab (N =121)	66.1%	% change from baseline = –76.02 (95% CI –76.20, –72.83)	change from baseline = 6.40 (95% CI 4.85, 7.96)
Iptacopan (ESS=31†) vs. ravulizumab (N=125)	OR = 1.32 (95% CI 0.47, 3.73) p=0.6011	MD = –8.24 (95% CI –13.28, –3.20) p=0.0013	MD = 3.78 95% CI –1.38, 8.94 p=0.1514
Iptacopan (ESS=31†) vs. eculizumab (N =121)	OR = 1.88 (95% CI 0.67, 5.28) p=0.2281	MD = –9.06 (95% CI –14.14, –3.98) p=0.0005	MD = 4.45 (95% CI –0.72, 9.62), p=0.0918

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

C.3.6.3 Uncertainties of ITC of APPOINT-PNH vs. Study 301

Due to the single-arm design of APPOINT-PNH, only an unanchored ITC was feasible. In addition, study inclusion criteria differed with regards to presence of anaemia. While all patients in APPOINT-PNH were required to have haemoglobin < 10 g/dL at baseline, Study 301 only required patients to have at least one PNH-related symptom at study entry. Anaemia (haemoglobin < 10 g/dL) was only one of the eligible symptoms, and therefore non-anaemic patients could also be included in Study 301. This difference is reflected in mean (SD) haemoglobin at baseline of 9.5 (1.6) g/dL in Study 301 vs. 8.15 (1.09) g/dL in APPOINT-PNH before population adjustments; weighting the APPOINT-PNH population to align with Study 301 on other characteristics further increased the difference (APPOINT-PNH 7.9 [1.2] g/dL after weighting). Due to non-convergence, the difference in baseline haemoglobin could not be adjusted for, and results of associated outcomes should be interpreted with caution.

C.4 Anchored indirect treatment comparison: Residual anaemia despite C5i treatment population

To inform the assessment of iptacopan in the population of patients with residual anaemia despite C5i treatment, an anchored ITC was included in this application. The ITC was conducted by Peffault de Latour et al. and was recently published in European Journal of Haematology (March 2025) [12].

In the absence of gold standard head-to-head evidence from RCTs, an evaluation through ITC is a pragmatic solution. The ITC conducted by Peffault de Latour et al. evaluates the efficacy between pegcetacoplan and iptacopan for the treatment of PNH in patients on stable doses of C5i with persistently low haemoglobin levels [12].

C.4.1 Materials and Methods

The ITC was based on the PEGASUS study and the APPLY-PNH study (both described in detail in Appendix A). Patient level data from PEGASUS were used to document the efficacy of pegcetacoplan, and published outcomes data from APPLY-PNH were used to document the efficacy of iptacopan [12].

C.4.2 Outcomes

PEGASUS and APPLY-PNH differed by definitions of the primary endpoints (Table 39) and RCP durations (i.e., end of study (EOS) was week 16 for PEGASUS and week 24/day 168 for APPLY-PNH). The primary efficacy endpoint of PEGASUS was change-from-baseline to week 16 EOS in haemoglobin level [4]. The primary efficacy endpoint of APPLY-PNH was the proportion of patients who achieved a sustained increase between day 126 and day 168 EOS in haemoglobin levels of ≥ 2 g/dL from baseline in the absence of RBC transfusions (between day 14 and day 168 EOS), and a sustained increase (between day 126 and day 168 EOS) in haemoglobin levels to ≥ 12 g/dL, in the absence of RBC transfusions (between day 14 and day 168 EOS) (Table 39) [1].

Given the differences in designs between PEGASUS and APPLY-PNH, it was not possible to compare outcomes on the primary effect measures reported in each study. Hence, the analysis evaluated outcomes for a selection of secondary measures, including mean haemoglobin level, mean ARC, mean LDH level and mean FACIT-Fatigue overall score. Moreover, as deemed more reliable than interim data for each visit, the analysis used mean change-from-baseline to respective EOS periods, which provided a more complete data set [12].

Outcomes data for the APPLY-PNH study were obtained from published graphical results plotted at each visit for the above parameters [1]. As a standard approach employed when individual patient or numerical data are not available [30, 31] the figures allowed digitalisation of graphs to estimate numerical results, with all graphs digitalised using Inkscape Software for vector graphics. Results were available for both the iptacopan and reference arms, with corresponding SD at respective visits and number of patients. For consistency, crude changes from baseline to EOS were calculated for PEGASUS based on available data regarding the secondary outcomes. These changes were then indirectly

compared with data digitalised from the figures reported in the APPLY-PNH, ensuring a standardized methodology across the trials [12].

Notably, differences in study design also made it unfeasible to conduct ITC on the outcome of BTH events. Firstly, in PEGASUS, the definition of BTH was not protocol-defined but reported by investigators as AEs [4]. Whereas APPLY-PNH collected BTH data as a pre-defined endpoint, based on meeting one of the two clinical criteria: a decrease in haemoglobin level of ≥ 2 g/dL or PNH symptoms of gross haemoglobinuria, haemolytic crisis, dysphagia, or any other clinically significant sign or symptom associated with PNH, in addition to elevated LDH level (> 1.5 × ULN) [1].

Table 39 Comparison of study endpoints reported in APPLY-PNH and PEGASUS

Endpoints		Arm	Proportion of patients	Summary statistic (95% CI)	Comparative statistic (95% CI)	Comment
			n/M[a]	**Marginal proportion (% [95% CI])**	**Difference in marginal proportion (% [95% CI])**	
Primary	Response defined as increase from baseline in haemoglobin of ≥ 2 g/ dL[c] in the absence of RBC transfusions[d]	Iptacopan	51/60	82.3% (73.4, 90.2)	80.3% (71.3, 87.6)	Comparison not feasible:[i] Outcome assessed as sustained response with follow-up longer than in PEGASUS
		C5i	0/35	2.0% (1.1, 4.1)		
	Response defined as haemoglobin level ≥ 12 g/ dL in the absence of RBC transfusions[d]	Iptacopan	42/60	68.8% (58.3, 78.9)	67.0% (56.3, 76.9)	Proportions calculated with logistic regression model of unknown structure
		C5i	0/35	1.8% (0.9, 4.0)		
Secondary	RBC transfusion avoidance[d]	Iptacopan	60/62	96.4% (90.7, 100.0)[e]	70.3% (52.6, 84.9)[e]	Comparison not feasible:[i] Outcome assessed as sustained response with follow-up greater than in PEGASUS
		C5i	14/35	26.1 (12.4, 42.7)[e]		Proportions calculated with logistic regression model of unknown structure
			M/N[f]	**Adjusted mean change-from-baseline (95% CI)**	**Adjusted mean difference in change-from-baseline (95% CI)**	
Secondary	Change-from-baseline in haemoglobin (g/dL)[c],[g]	Iptacopan	62/62	+3.59 (3.32, 3.86)	+3.63 (3.18, 4.08)	Comparison not feasible:[i]
		C5i	30/35	−0.04 (−0.42, 0.35)		

Endpoints		Arm	Proportion of patients	Summary statistic (95% CI)	Comparative statistic (95% CI)	Comment
	Change-from-baseline in FACIT-Fatigue score[c,b]	Iptacopan	62/62	+8.59 (6.72, 10.47)	+8.29 (5.28, 11.29)	Outcome assessed at follow-up greater than in PEGASUS
		C5i	31/33	+0.31 (−2.20, 2.81)		
	Change-from-baseline in ARC (10^9/L)[c,h]	Iptacopan	62/62	−115.89 (−126.49, −105.30)	−116.26 (−132.17, −100.36)	Outcomes assessed with repeated measures model, adjusting for covariates
		C5i	35/35	+0.37 (−13.03, 13.77)		
	Ratio to baseline in log- transformed LDH (U/L)[c,k]	Iptacopan	62/62	0.96 (0.90, 1.03)	1.15 (−10.18, 11.32)	Comparison not feasible:[l] Outcome assessed at follow-up greater than in PEGASUS No information regarding statistical methods used
		C5i	35/35	0.98 (0.89, 1.07)		
			n/N[j]	**Adjusted annual rate (% [95% CI])**	**Rate ratio (95% CI)**	
Secondary	Rate of clinical BTH[l]	Iptacopan	2/62	0.07 (0.02, 0.31)	0.10	Too few events in the active group
		C5i	6/35	0.67 (0.26, 1.72)	(0.02, 0.61)	
	Rate of MAVEs	Iptacopan	1/62	0.03 (0.00, 0.25)	Not estimable	
		C5i	0/35	0		

Abbreviations: ARC, absolute reticulocyte count; BTH: Breakthrough haemolysis; CI, confidence interval; Ci5, complement 5 inhibitor; D, day; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy–Fatigue; N, overall number of patients; RBC, red blood cell.

[a]n, number of patients with response, M, number of patients with evaluable/non-missing data.

[b]Mean (SD) baseline FACIT-Fatigue scores were 34.7 (9.8) and 30.8 (11.5) in the iptacopan and Ci5 arms, respectively.
[c]Assessed between D126 and 168.
[d]Between days 14 and 168.
[e]The prespecified methodology for handling of missing data may have underestimated transfusion avoidance in the C5i arm, so a post hoc sensitivity analysis was conducted using a different approach. In this analysis, marginal proportions (95% CI) were 96.7% (91.3, 100.0) versus 38.9% (23.1, 55.8) for iptacopan and C5i, respectively ($p < 0.0001$).
[f]M, number of patients with evaluable/non-missing data, N, overall number of patients.
[g]Excluding values within 30 days of RBCT. Mean (SD) baseline haemoglobin levels were 8.93 (0.70) and 8.85 (0.90) g/dL in the iptacopan and C5i arms, respectively.
[h]Mean (SD) baseline ARCs were 193.2 (83.6) and 190.6 (80.9) × 10^9/L in the iptacopan and C5i arms, respectively.
[i]Given the differences in design, duration and statistical methods between PEGASUS and APPLY-PNH, the comparison of the primary effect measures reported in each study was not feasible.
[j]n=number of patients with at least one event, N=overall number of patients.
[k]Mean (SD) baseline LDH levels were 269.1 (70.1) and 272.7 (84.8) UL in the iptacopan and C5i arms, respectively.
[l]Events that met the protocol-specified criteria for clinical breakthrough haemolysis.

C.4.3 Statistical Analysis

The ITC employed an anchored approach, whereby both studies are required to share a common reference arm; in both, the PEGASUS and APPLY-PNH trials, patients in the reference groups received C5i. However, eculizumab was the reference C5i treatment in PEGASUS, and general C5i's (comprising ravulizumab or eculizumab) was the reference treatment in APPLY-PNH. The validity of the anchored approach used in the ITC, however, rested on the results of the head-to-head 302 RCT (NCT04201262) comparing ravulizumab versus eculizumab in C5i treatment-experienced patients with PNH [32], the study indicated no significant differences between both treatments. The outcomes justified the assumption that both, eculizumab and ravulizumab share a group effect of C5i, confirming that the reference groups from the PEGASUS and APPLY-PNH trials could be considered similar enough to serve as the comparator. This subsequently enabled use of Bucher's indirect comparison due to the robustness, reproducibility, and high transparency of this method [33].

C.4.3.1 Confirmatory Simulated Treatment Comparison (STC)

A STC between pegcetacoplan and iptacopan served as the sensitivity analysis to assess the robustness of the results from the Bucher method. By accounting for between-trial differences in baseline characteristics, STC is one of the techniques recommended by NICE to minimize the risk of bias within indirect comparisons [29].

C.4.4 Results

C.4.4.1 Baseline Data

Overall baseline characteristics of the populations in the PEGASUS and APPLY-PNH studies were broadly comparable, with 35% of patients in APPLY-PNH receiving ravulizumab (. By treatment arm, mean × 10^9/L (SD) baseline ARC was slightly higher (217.0 [71.7]) for the pegcetacoplan arm in PEGASUS than for the iptacopan arm in APPLY-PNH (192.3 [82.3]). On FACIT-Fatigue, mean (SD) baseline score was slightly higher in the iptacopan arm than the pegcetacoplan arm, although within the APPLY-PNH trial itself, the difference in mean baseline FACIT-Fatigue scores between the iptacopan arm (34.7 [9.8]) and C5i arm (30.8 [11.5]) was not statistically significant [1]. In PEGASUS, the difference in mean baseline FACIT-Fatigue scores between the pegcetacoplan arm (32.2 [11.4]) and C5i arm (31.6 [12.5]) also was not significant [4].

Table 40 Comparison of baseline data from APPLY-PNH and PEGASUS

			APPLY-PNH		PEGASUS	
Parameter	**Iptacopan 200 mg bid (N = 62)**	**C5i (N = 35)**	**Overall (N = 97)**	**Pegcetacoplan (N = 41)**	**Eculizumab (N = 39)**	**Overall (N = 80)**
Mean age	51.7	49.8	51.0	50.2	47.3	48.2
Years (SD)	(16.9)	(16.7)	(16.8)	(16.3)	(15.8)	(15.9)
Female n (%)	43 (69.4)	24 (68.6)	67 (69.1)	27 (66)	22 (56)	49 (61)
Time since diagnosis years (SD)	11.9 (9.8)	13.6 (10.9)	12.5 (10.2)	8.7 (11.7)	11.7 (9.6)	10.2 (8.6)
C5i:						
Eculizumab, n (%)	40 (64.5)	23 (65.7)	63 (64.9)	41 (100)	39 (100)	80 (100)
Ravulizumab, n (%)	22 (35.5)	12 (34.3)	34 (35.1)	—	—	—
Mean duration, years (SD)	3.8 (3.5)	4.2 (3.9)	4.0 (3.6)	5.1 (4.29)	4.8 (3.64)	4.95 (3.97)
Received RBC transfusions, n (%)	35 (56.5)	21 (60.0)	56 (57.7)	29 (70.7)	25 (64.1)	54 (67.5)
Mean baseline haemoglobin g/dL (SD)	8.9 (0.7)	8.9 (0.9)	8.9 (0.8)	8.69 (1.08)	8.68 (0.89)	8.68 (0.98)
Mean baseline LDH U/L (SD)	269.1 (70.1)	272.7 (84.8)	270.4 (75.3)	257.5 (97.6)	308.6 (284.8)	282 (211)
Baseline LDH > 1.5 × ULN n (%)	4 (6.5)	3 (8.6)	7 (7.2)	—	—	—
Mean baseline ARC, 10^{9} /L (SD)	193.2 (83.6)	190.6 (80.9)	192.3 (82.3)	217.5 (75.0)	216.2 (69.1)	217 (71.7)

			APPLY-PNH		PEGASUS	
Parameter	Iptacopan 200 mg bid (N = 62)	C5i (N = 35)	Overall (N = 97)	Pegcetacoplan (N = 41)	Eculizumab (N = 39)	Overall (N = 80)
Mean baseline FACIT-Fatigue score (SD)	34.7 (9.8)	30.8 (11.5)	—	32.2 (11.4)	31.6 (12.5)	—

Abbreviations: ARC, absolute reticulocyte count; BID, twice a day; C5i, complement 5-inhibitor; LDH, lactate dehydrogenase; RBC, red blood cell; SD, standard deviation; ULN, upper limit of normal.

C.4.4.2 Clinical Efficacy and Patient-Reported Outcomes

The anchored ITC did not demonstrate any significant mean differences [95% CI] in change from baseline to EOS between pegcetacoplan and iptacopan across any endpoint:

- Haemoglobin Level (pegcetacoplan versus iptacopan: −0.49 g/dL [−1.78, 0.80]).
- ARC (pegcetacoplan versus iptacopan: −34.41 × 10^9/L [−90.02, 21.21]).
- LDH level (pegcetacoplan versus iptacopan: –115.16 U/L [−244.40, 14.01]).
- FACIT-Fatigue score (pegcetacoplan versus iptacopan: 3.57 [−5.60, 12.73]).

The regression-based STC produced results consistent with the Bucher analyses on both point estimates and CIs.

C.4.5 Discussion

The anchored ITC conducted by Peffault de Latour et al. applied the best available trial data and pointed only to some slight numeric differences in comparative effectiveness between the two treatments. There was no evidence of significant differences in mean change from baseline to respective EOS visits for any clinical or fatigue-related endpoints between the iptacopan arm compared with the pegcetacoplan arm. Confirmatory STC analyses underscored the findings [12].

As a key analytic strength, this study used an anchored ITC approach which preserved the randomised feature of both trials and cancelled the impact of unbalanced prognostic factors, some of which were known and others unknown. Hence, the rigour applied in the present analysis may explain the difference in findings from this study in comparison with another previously presented ITC which did not use an anchored approach [34].

Due to differences in study protocols, it was not suitable to conduct a comparison in the current analysis between BTH events associated with pegcetacoplan and iptacopan. Specifically, haemolytic events in PEGASUS were collected based on reported AEs [4], whereas in APPLY-PNH [1], BTH was explicitly defined in the protocol. During the 24-Week RCP of APPL- PNH, two patients treated with iptacopan experienced a BTH event according to per protocol definitions and there were no discontinuations due to BTH. In PEGASUS, four patients had reported AEs of haemolysis during the 16-week RCP; three of these patients discontinued [4].

The second consideration for this present work is that the evaluation of iptacopan data required digitalisation of graphed data and imputation of SD for mean change-from-baseline values, along with an assumption of a normal distribution of the data. Therefore, the precision of data extraction depended on the quality of respective published figures, and hence, results should be interpreted with caution due to incomparable risks in respective control groups. With this limitation notwithstanding, it is possible to conclude that the present analysis indicates there is no evidence for significant differences between pegcetacoplan and iptacopan for the treatment of PNH in C5i-experienced patients [12]

C.4.6 Conclusion

The findings of ITC conducted by Peffault de Latour et al. support a conclusion that pegcetacoplan and iptacopan have similar efficacy based on key PNH-specific trial parameters. In the absence of significant differences in clinical outcomes evaluated through ITC, decision-making across treatment options must also rely upon individualised patient-related factors as well as clinician confidence, based on longevity of clinical data and supportive real-world usage and outcomes [12].

Appendix D. Literature searches for the clinical assessment. N/A

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

As agreed with the DMC at the dialogue meeting, a systematic literature search is not applicable for the present application.

Table 41 Bibliographic databases included in the literature search. N/A

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

Abbreviations:

Table 42 Other sources included in the literature search. N/A

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

Abbreviations:

Table 43 Conference material included in the literature search. N/A

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

Abbreviations:

D.1.2 Search strategies

Not applicable. No literature search has been performed.

Table 44 of search strategy table for [name of database]. N/A

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

D.1.3 Systematic selection of studies

Not applicable. No literature search has been performed.

Table 45 Inclusion and exclusion criteria used for assessment of studies. N/A

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population		
Intervention		
Comparators		
Outcomes		
Study design/publication type		
Language restrictions		

Table 46 Overview of study design for studies included in the technology assessment. N/A

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Study 1						
Study 2						

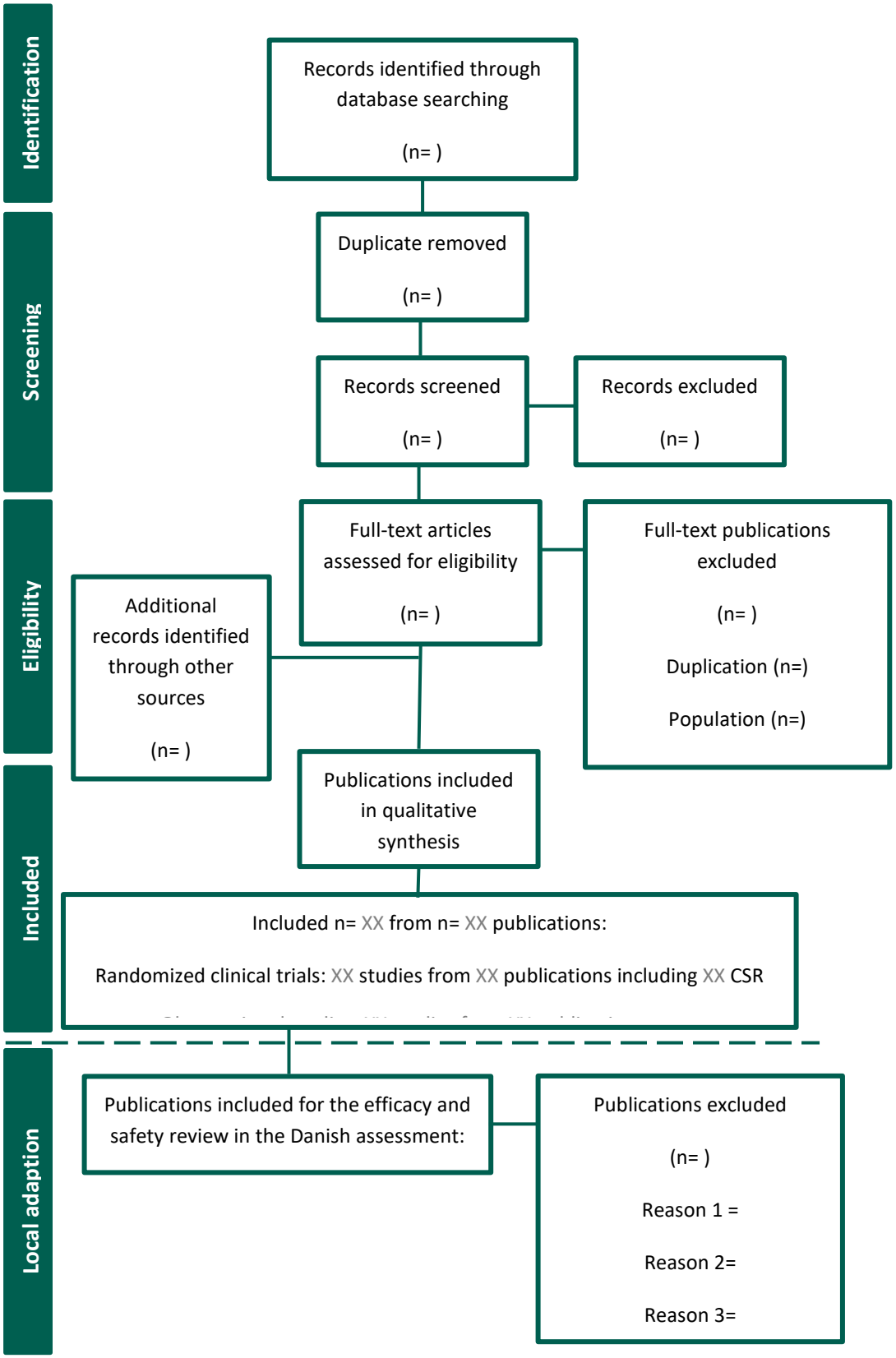
D.1.4 Quality assessment

[Describe strengths and weaknesses of the literature search performed.]

D.1.5 Unpublished data

[The quality of any unpublished data must be specifically addressed and a publication plan for unpublished data must be submitted].

Example of PRISMA diagram. The diagram is editable and may be used for recording the records flow for the literature searches and for the adaptation of existing SLRs.



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