Adding new dimensions to proximal inhibition

Transforming paroxysmal nocturnal haemoglobinuria (PNH) management

Paroxysmal nocturnal haemoglobinuria:
A disease at the crossroads of somatic mutations, clonal expansion and immunity

Florence, Italy

3 October 2024, 16:30-17:00 CET

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Date of preparation: September 2024

Disclaimer & **important information**

- This presentation serves educational purposes and is intended to provide information and stimulate discussion on selected topics in paroxysmal nocturnal haemoglobinuria.
- The intent is not to provide medical or any other type of advice.
- All treatment decisions should be up to the discretion of the healthcare provider and the patient, as each patients' situation may vary.
- This scientific event is a non-promotional activity sponsored by Sobi and the speaker is being compensated for her/his involvement.
- This presentation includes information on Sobi products.
- The content, discussion, and answers reflect the personal opinion of the speaker and may not represent those of Sobi.
- No identifiable patient-specific information is included.
- Pegcetacoplan ▼ is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.
- Pegcetacoplan is authorised as monotherapy in the treatment of adult patients with PNH who have haemolytic anaemia. Pegcetacoplan is only reimbursed in Italy for the treatment of adult patients with PNH who have haemoglobin <10.5 g/dL after treatment with a C5 inhibitor for at least 3 months

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Here with you today

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Disclosures

Research support (to institute)	Celgene/BMS, Novartis
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Scientific advisory board	Agios, Alexion, Amgen, Biocryst, Celgene/BMS, Novartis, Pfizer, Regeneron, Roche, Sobi

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Untreated PNH is associated with **multiple clinical symptoms and life-threatening complications***

Kidney dysfunction[1-3]
Associated with increased mortality risk[3,4]

Up to 65%

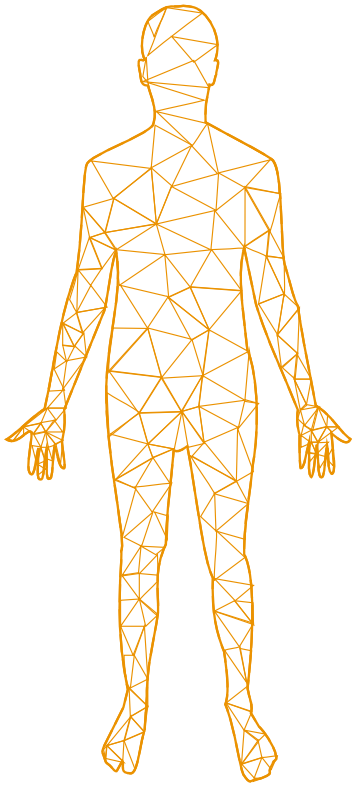
Pulmonary hypertension[5,6]

Up to 47%

Thrombosis[7-10]
Leading cause of death in PNH patients†

Up to 44%

Cardiovascular events[1]
Cause of death in ~20% of PNH patients



Up to 96% — **Fatigue**[10-12]

Up to 94% — **Anaemia**[4,10]

Up to 66% — **Dyspnoea**[10-12]

Up to 50% — **Haemoglobinuria**[4,10,13]

Smooth muscle dystonia[14]
- Abdominal pain (up to **57%**)[10-12]
- Erectile dysfunction (up to **47%**)[10,11]
- Dysphagia (up to **41%**)[10,11]

The percentages indicate the proportion of patients that manifest the symptom.
Colour gradients indicate the range of proportions reported by the references.

* In patients not treated with a complement inhibitor, e.g. eculizumab. † Of patients with known cause of death. PNH, paroxysmal nocturnal haemoglobinuria.

1. Socié et al. *Intern Med J* 2016 **2.** Hillmen et al. *Am J Hematol* 2010 **3.** Jang et al. *J Korean Med Sci* 2016 **4.** Nishimura et al. *Medicine* 2004 **5.** Hill et al. *Br J Haematol* 2010 **6.** Hill et al. *Br J Haematol* 2012 **7.** Hillmen et al. *N Engl J Med* 1995 **8.** Devalet et al. *J Extracell Vesicles* 2014 **9.** Hill et al. *Blood* 2013 **10.** Kelly et al. *Blood* 2024 **11.** Meyers et al. *Blood* 2007 **12.** Mitchell et al. *SM Clin Med Oncol* 2017 **13.** Parker et al. *Blood* 2005 **14.** Hill et al. *Nat Rev Dis Primers* 2017.

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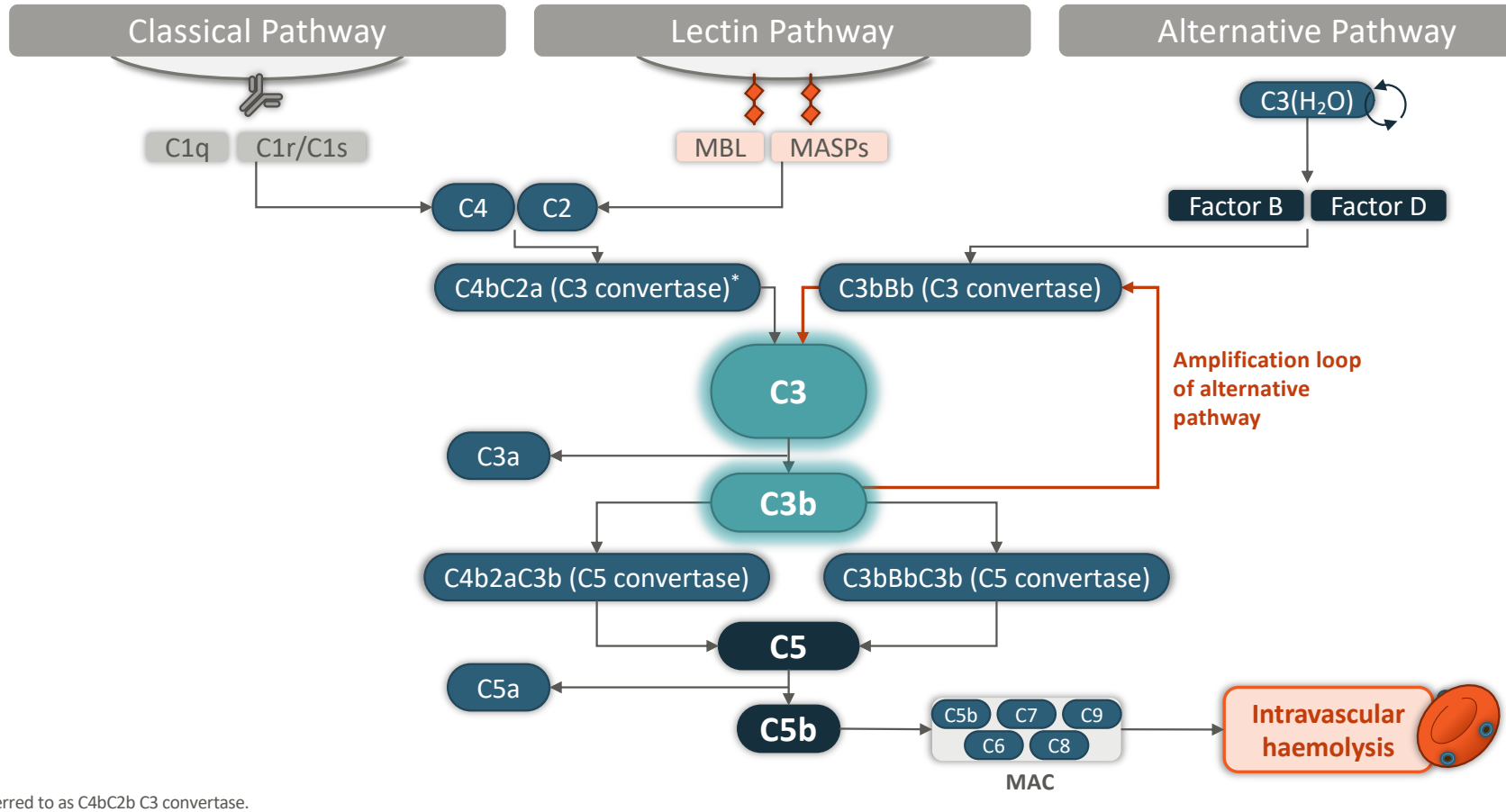
Complement activation in **untreated PNH**[1]



* Also referred to as C4bC2b C3 convertase.
MAC, membrane attack complex; MASPs, mannose-binding lectin-associated proteases; MBL, mannose-binding lectin; PNH, paroxysmal nocturnal hemoglobinuria.
1. Hillmen et al. *Int J Mol Sci* 2024. Figure adapted from Hillmen et al. *Int J Mol Sci* 2024 (CC BY 4.0).

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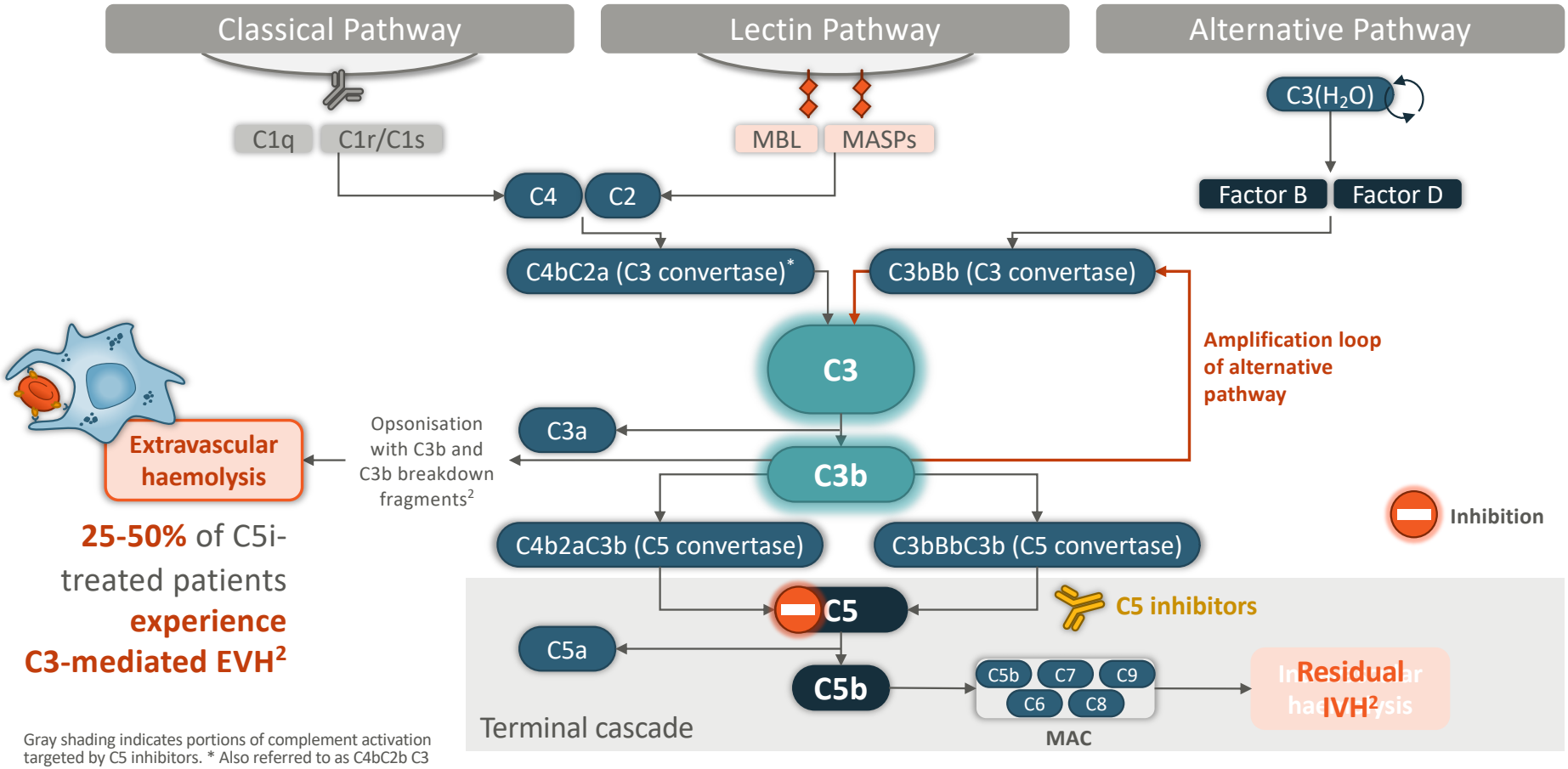
C5 inhibition effectively **blocks IVH** but **allows for EVH to emerge**[1]



25-50% of C5i-treated patients **experience C3-mediated EVH**[2]

Gray shading indicates portions of complement activation targeted by C5 inhibitors. * Also referred to as C4bC2b C3 convertase. C5i, C5 inhibitor; EVH, extravascular haemolysis; IVH, intravascular haemolysis; MAC, membrane attack complex; MASPs, mannose-binding lectin–associated proteases; MBL, mannose-binding lectin; PNH, paroxysmal nocturnal hemoglobinuria. **1.** Hillmen et al. *Int J Mol Sci* 2024 **2.** Risitano et al. *Front Immunol* 2019. Figure adapted from Hillmen et al. *Int J Mol Sci* 2024 (CC BY 4.0).

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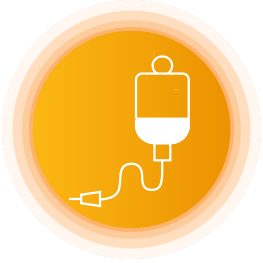
Many PNH patients treated with **C5 inhibitors have unmet needs**[*,1-11]

Ongoing anaemia

~63-91%

of patients have **sub-normal haemoglobin**[2-7]

Transfusion requirements



~18-35%

of patients remain **transfusion dependent**[2-5,8-11]

Fatigue and diminished QoL

~61-89%

of patients continue to **report fatigue**[5-7]

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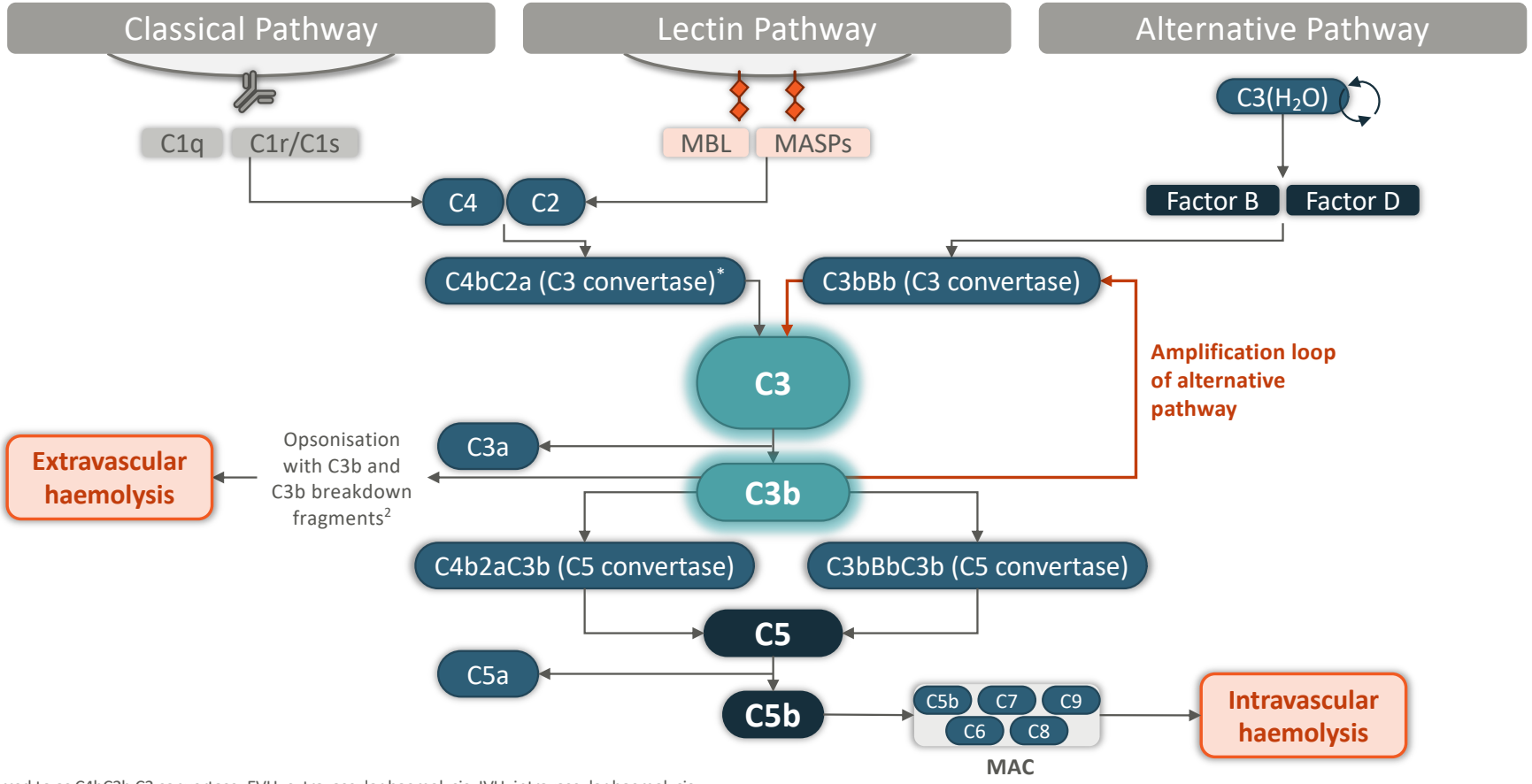
* Based on expert reviews, retrospective studies and patient survey studies. PNH, paroxysmal nocturnal haemoglobinuria; QoL, quality of life.

1. Risitano et al. *Front Immunol* 2019 **2.** de Fontbrune et al. *Hematology* 2022 **3.** Risitano et al. *Blood* 2009 **4.** Kelly et al. *Blood* 2024 **5.** Dingli et al. *Ann Hematol* 2022
6. Matos et al. ISPOR EU 2021 **7.** Panse et al. *Eur J Haematol* 2022 **8.** Brodsky *Blood* 2014 **9.** Peffault de Latour et al. *Blood* 2015 **10.** Luzzatto et al. *F1000Res* 2016 **11.** Hillmen et al. *Br J Haematol* 2013.

Proximal inhibition effectively blocks **IVH and EVH in patients with PNH**[1]



* Also referred to as C4bC2b C3 convertase. EVH, extravascular haemolysis; IVH, intravascular haemolysis;
MAC, membrane attack complex; MASPs, mannose-binding lectin–associated proteases; MBL, mannose-binding lectin; PNH, paroxysmal nocturnal hemoglobinuria.

1. Hillmen et al. *Int J Mol Sci* 2024. Figure adapted from Hillmen et al. *Int J Mol Sci* 2024 (CC BY 4.0).

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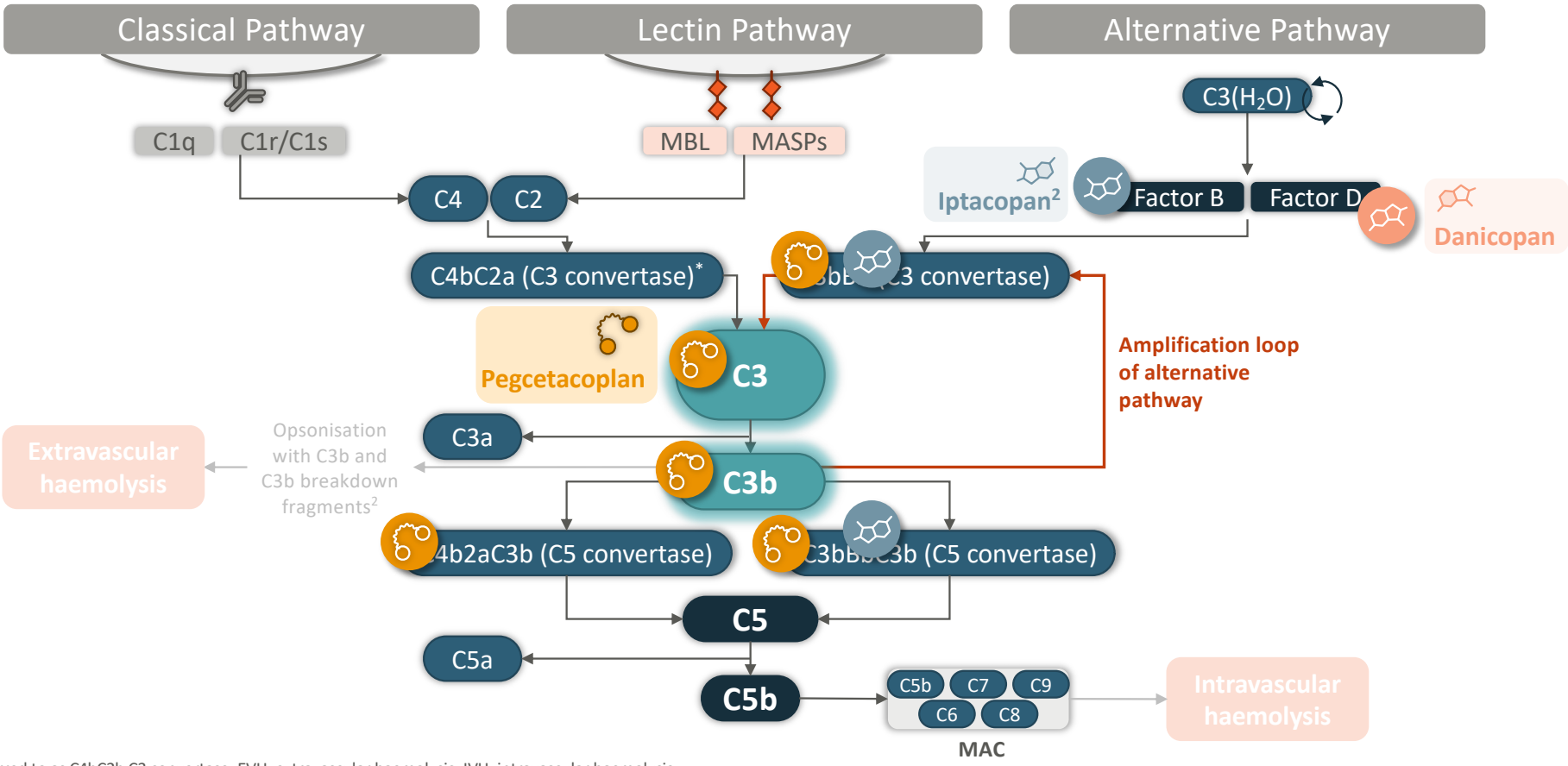

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1. Hillmen et al. *Int J Mol Sci* 2024 **2.** Schubart et al. *Proc Natl Acad Sci* 2019. Figure adapted from Hillmen et al. *Int J Mol Sci* 2024 (CC BY 4.0).

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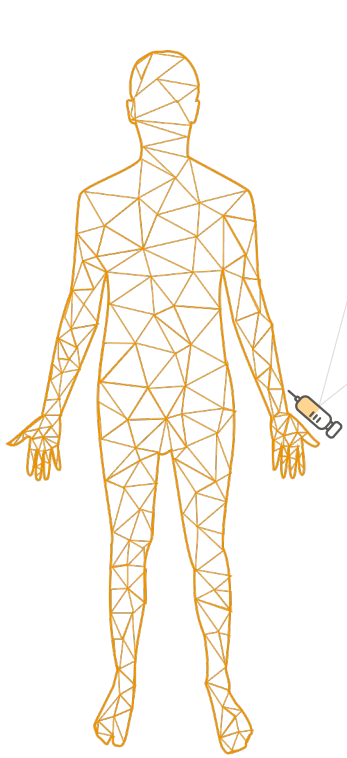
The ability to therapeutically **block EVH** enables **improvement in a broad range of disease markers**[1]



Qualitative comparison of routine laboratory assessments for PNH (based on expert opinion)[1]

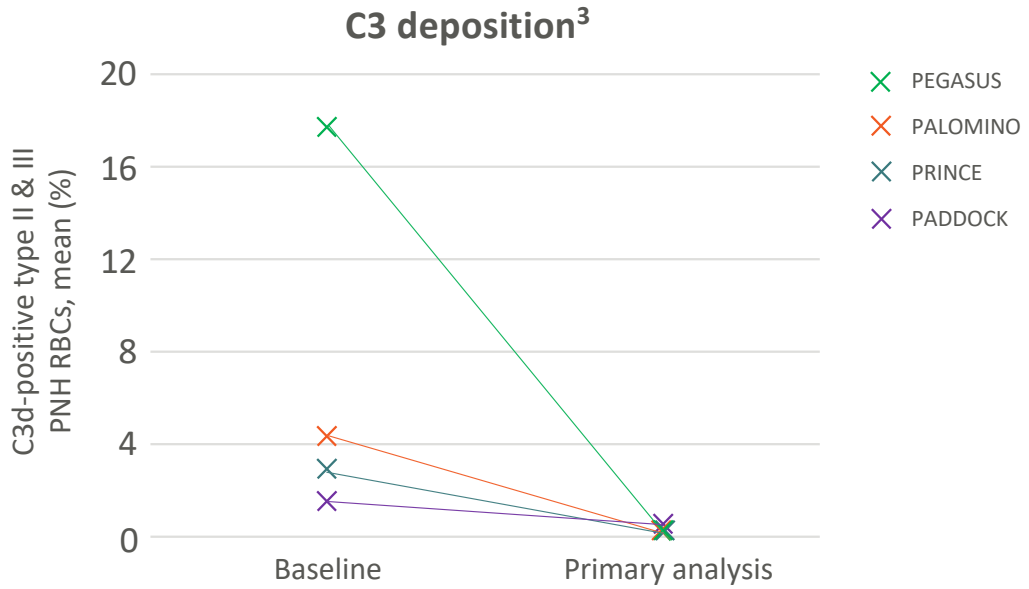
Parameter	Marker for	Levels in untreated PNH patients	Effect of C5 inhibition	Effect of proximal inhibition
LDH	IVH	High	Highly reduced / normalised	Highly reduced / normalised
Bilirubin	EVH, and to a lesser extent, IVH	High	Slightly reduced	Highly reduced / normalised
Haemoglobin	Clinical response	Low	Moderately increased	Highly increased / normalised
ARC	IVH, EVH, and BM reserve/function or degree of BMF	High*	Slightly to moderately reduced	Highly reduced / normalised
Haptoglobin	IVH and EVH	Low	Moderately increased	Moderately increased
PNH RBC clone size	IVH and EVH	Low	Slightly to moderately increased	Highly increased

* High assuming no bone marrow failure.

ARC, absolute reticulocyte count; BM, bone marrow; BMF, bone marrow failure; EVH, extravascular haemolysis; IVH, intravascular haemolysis; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal haemoglobinuria; QoL, quality of life; RBC, red blood cell. **1.** Kulasekararaj et al. *Blood Rev* 2023.

Decline in C3 deposition following pegcetacoplan treatment **highlights blockade of EVH**[1-3]

In clinical trials*, C3 deposition on **PNH RBCs declined rapidly** upon treatment to become almost completely abrogated



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Pegcetacoplan **prevents** the **C3b-mediated opsonisation of PNH RBCs, blocking** the pathway to **EVH**

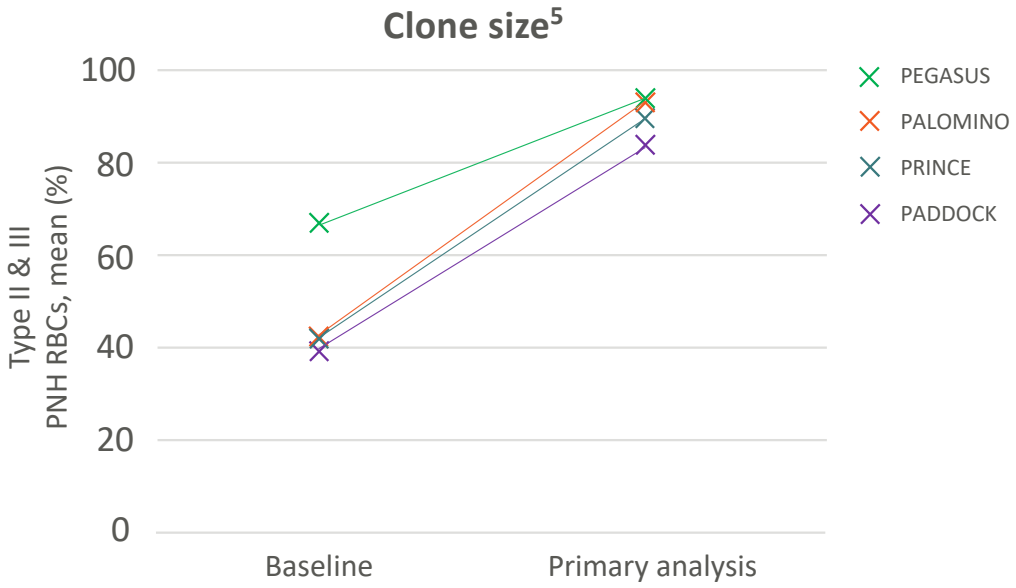
* Patients in PADDOCK, PALOMINO and PRINCE were complement inhibitor-naïve, while PEGASUS enrolled patients with suboptimal response to complement C5 inhibitor treatment. Primary analysis for PADDOCK and PALOMINO occurred at Day 365, for PRINCE occurred at Week 26, and for PEGASUS occurred at Week 16 of pegcetacoplan treatment.

EVH, extravascular haemolysis; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell.

1. Wong et al. *Ann Hematol* 2022 **2.** Peffault de Latour et al. *Lancet Haematol* 2022 **3.** Horneff et al. *Int J Mol Sci* 2024. Figure adapted from Horneff et al. *Int J Mol Sci* 2024 (CC BY 4.0).

Increase in RBC clone size following pegcetacoplan treatment **indicates effective protection from haemolysis**[1-5]

PNH RBC **clone sizes increased substantially** upon pegcetacoplan therapy in complement inhibitor-naïve and C5 inhibitor-treated patients[2-5]*



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PNH RBCs experience a **broad level of protection from haemolysis**, from both IVH and EVH[2-6]

* Patients in PADDOCK, PALOMINO and PRINCE were complement inhibitor-naïve, while PEGASUS enrolled patients with suboptimal response to complement C5 inhibitor treatment. Primary analysis for PADDOCK and PALOMINO occurred at Day 365, for PRINCE occurred at Week 26, and for PEGASUS occurred at Week 16 of pegcetacoplan treatment.

EVH, extravascular haemolysis; IVH, intravascular haemolysis; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell.

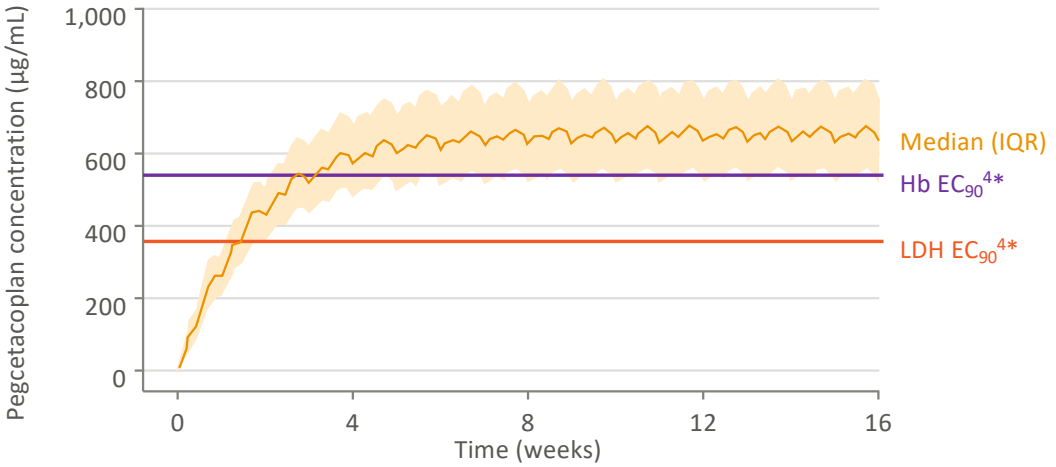
1. Risitano et al. *Semin Immunol* 2022 **2.** Wong et al. *Ann Hematol* 2022 **3.** Peffault de Latour et al. *Lancet Haematol* 2022 **4.** Hillmen et al. *N Engl Med J* 2021 **5.** Horneff et al. *Int J Mol Sci* 2024 **6.** Wong et al. *Blood Adv* 2023. Figure adapted from Horneff et al. *Int J Mol Sci* 2024 (CC BY 4.0).

Pegcetacoplan shows **linear pharmacokinetics and minimal peak to trough variation at steady state**[1-5]

*Pharmacokinetic properties of pegcetacoplan**

- $t_{1/2}$ is **8.6 days** with **steady-state serum concentrations** being achieved within **4 to 6 weeks** after the first dose with twice weekly dosing in PNH patients[1,2]
- In PEGASUS, **change of mean trough pegcetacoplan concentration** was **<10% between any 2 scheduled visits** from Week 2 to 16[2]

Predicted exposure among adults with PNH receiving pegcetacoplan 1,080 mg SC BIW[3,4]



Dose adjustment

The pegcetacoplan dosing regimen may be changed to **1,080 mg every third day** if LDH >2× ULN[1]

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At steady state, **population PK modelling** predicts that a **single dose delayed for up to 96 hours would not meaningfully affect pegcetacoplan serum concentration or LDH levels**.[5] This suggests **occasional deviation** from the recommended administration routine is **unlikely to have safety implications**

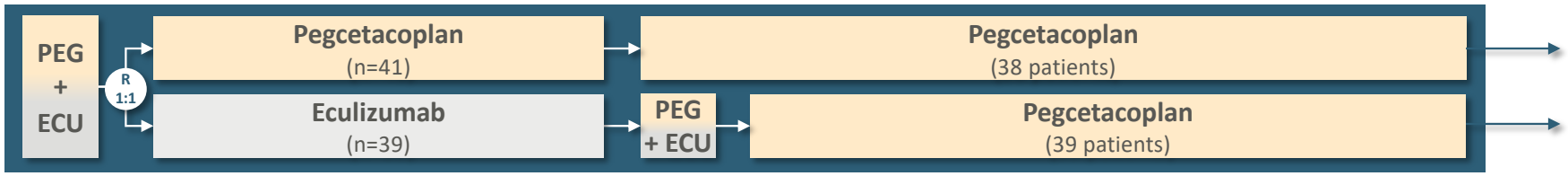
* Following BIW SC dosing at 1,080 mg.

BIW, twice-weekly; EC_{90}, concentration of pegcetacoplan producing 90% of maximal response; Hb, haemoglobin; IQR, interquartile range; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal haemoglobinuria; SC, subcutaneous; $t_{1/2}$, half-life; ULN, upper limit of normal.

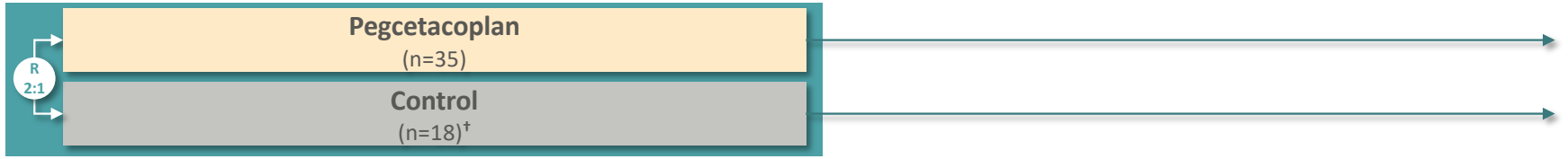
1. Aspaveli SmPC 2024 **2.** Hillmen et al. *N Engl J Med* 2021;suppl **3.** Crass et al. IPIG 2023; oral presentation **4.** Crass et al. IPIG 2023; poster presentation **5.** Horneff et al. *Int J Mol Sci* 2024.

Phase 3 pegcetacoplan trials: **PEGASUS and PRINCE**[1-3]

PEGASUS (C5 inhibitor-experienced adult PNH patients [Hb <10.5 g/dL, stable on ECU ≥3 months])[1,2]



PRINCE (C5 inhibitor-naïve patients*)[3]

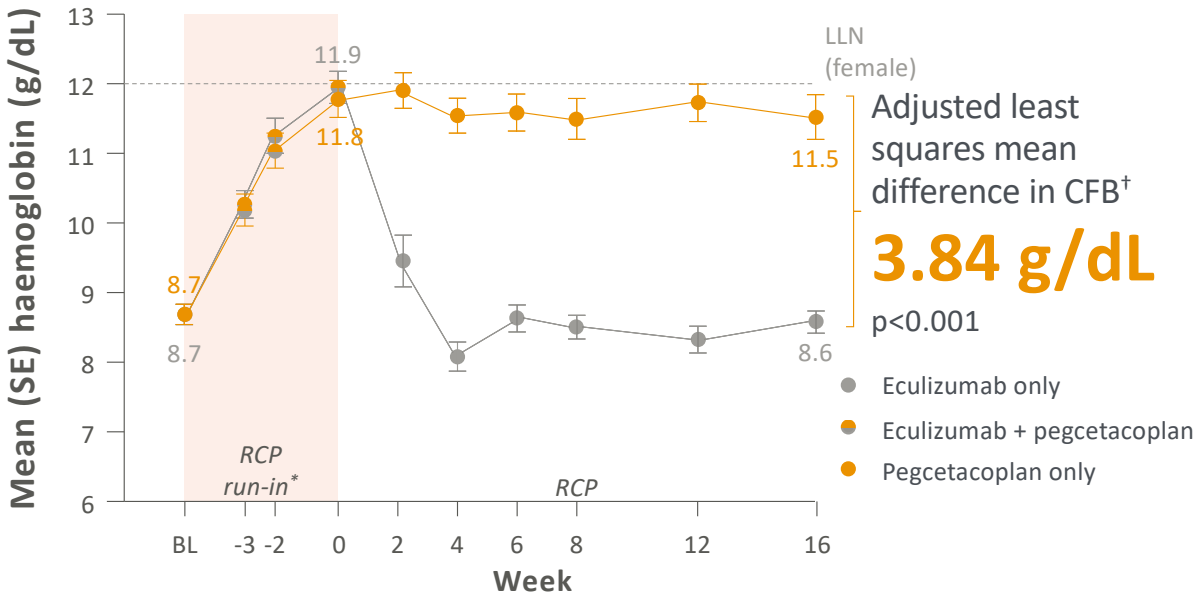


Extension study (optional)[4]

* No C5 inhibitor within 3 months of screening.
† Patients in the PRINCE control arm could escape to the pegcetacoplan arm before the end of the 26 weeks if Hb decreased by ≥2 g/dL from baseline or if they experienced a qualifying thromboembolic event.
ECU, eculizumab; Hb, haemoglobin; OLP; open-label period; PEG, pegcetacoplan; PNH, paroxysmal nocturnal haemoglobinuria; R, randomisation; RCP, randomised controlled period; W, week.
1. Hillmen et al. *N Engl J Med* 2021 2**.** Peffault de Latour et al. *Lancet Haematol* 2022 **3.** Wong et al. *Blood Adv* 2023. **4.** Hoffman et al. ASH 2021; poster 2175.

PEGASUS: **Pegcetacoplan was superior to eculizumab in improving haemoglobin** from baseline to Week 16[1]

Primary endpoint: **Change in haemoglobin**



* Pegcetacoplan run-in periods: 1) before randomisation, for both pegcetacoplan-to-pegcetacoplan and eculizumab-to-pegcetacoplan treatment groups; and 2) before the open-label period, for the eculizumab-to-pegcetacoplan treatment group only. All observed/uncensored for transfusion data. † The LS mean CFB was censored for transfusion events, all values after intercurrent events set to missing.
BL, baseline; CFB, change from baseline; LLN, lower limit of normal; LS, least square; RCP, randomised controlled period; SE, standard error. **1.** Hillmen et al. *N Engl J Med* 2021.

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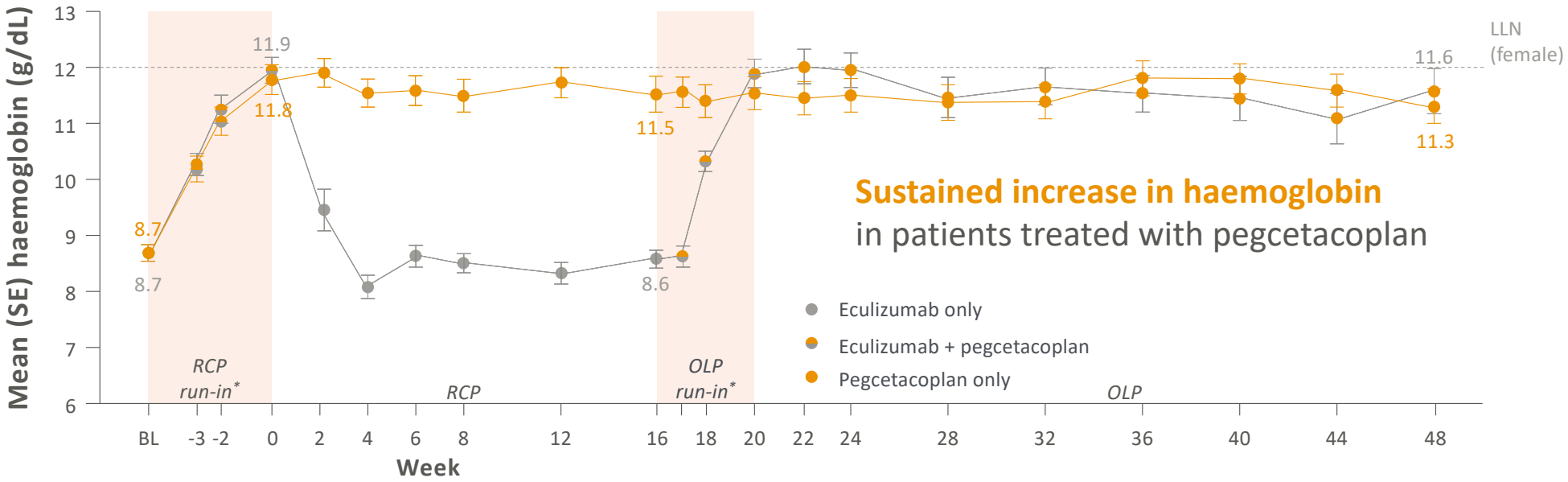
PEGASUS: **Improvements** in haematological and clinical parameters were **maintained up to Week 48**[1,2]

Primary endpoint: **Change in haemoglobin**



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A range of haematological and clinical parameters improved and were maintained up to Week 48, with mean **ARC and LDH levels below** the **ULN, freedom from transfusions in a high number of patients,** and mean **FACIT-Fatigue scores near the general population norm**†[2]

* Pegcetacoplan run-in periods: 1) before randomisation, for both pegcetacoplan-to-pegcetacoplan and eculizumab-to-pegcetacoplan treatment groups; and 2) before the open-label period, for the eculizumab-to-pegcetacoplan treatment group only. All observed/uncensored for transfusion data. † General population norm: 43.6.[3]

ARC, absolute reticulocyte count; BL, baseline; FACIT, Functional Assessment of Chronic Illness Therapy; LDH, lactate dehydrogenase; OLP, open-label period; RCP, randomised controlled period; SE, standard error; ULN, upper limit of normal. **1.** Hillmen et al. *N Engl J Med* 2021 **2.** Peffault de Latour et al. *Lancet Haematol* 2022 **3.** Cella et al. *Cancer* 2002.

PRINCE: Pegcetacoplan was **superior to control for the co-primary endpoints**[1]

Haemoglobin stabilisation at Week 26*

Defined as avoidance of ≥1 g/dL decrease in Hb from BL

Pegcetacoplan group	Control group
86%	**0%**
n=30/35	n=0/18

Difference: 73%
(95% CI 57, 89)
p<0.0001†

Change from baseline to Week 26 in LDH levels

LS mean (SE)

Pegcetacoplan group	Control group
-1,871 U/L (±101.0)	**-400 U/L** (±313.0)
n=35	n=18

Difference: -1470
(95% CI –2113, –827)
p<0.0001‡

A range of haematological and clinical parameters improved, with mean **CFB in Hb of +2.9** g/dL, mean **ARC and LDH levels below** the **ULN**, **freedom from transfusions in 91% of patients and mean FACIT-Fatigue scores above the population norm**

* Patients who received a transfusion, escaped from the control group to the pegcetacoplan treatment group, withdrew from study, or were lost to follow-up were categorised as failing to achieve stabilisation or non-responders, respectively. † Stratified Cochran-Mantel-Haenszel χ-square test. ‡ Covariance model with multiple imputation approach for handling missing data.
ARC, absolute reticulocyte count; BL, baseline; CI, confidence interval; CFB, change from baseline; FACIT, Functional Assessment of Chronic Illness Therapy; Hb, haemoglobin; LDH, lactate dehydrogenase; LLN, lower limit of normal; LS, least squares; SE, standard error; ULN, upper limit of normal. **1.** Wong et al. *Blood Adv* 2023.

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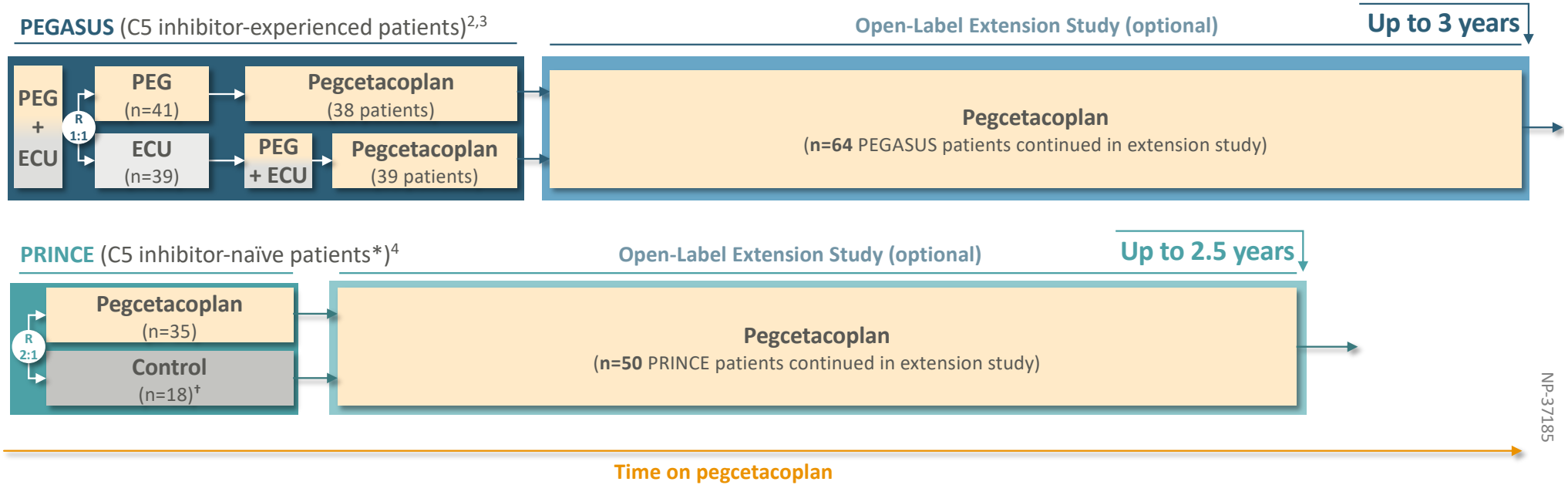
Integrated analysis of PEGASUS and PRINCE and the subsequent **open-label extension study**[1]



Efficacy and safety results reported only for time on pegcetacoplan: Efficacy endpoints from pegcetacoplan initiation and safety endpoints (AEs) from pegcetacoplan monotherapy initiation, through 2.5 years (PRINCE population) and 3 years (PEGASUS population)

* No C5 inhibitor within 3 months of screening.
† Patients in the PRINCE control arm could escape to the pegcetacoplan arm before the end of the 26 weeks if Hb decreased by ≥2 g/dL from baseline or if they experienced a qualifying thromboembolic event.
AEs, adverse events; ECU, eculizumab; PEG, pegcetacoplan; R, randomisation.
1. de Castro et al. ASH 2023; presentation 574 **2.** Hillmen et al. *N Engl J Med* 2021 **3.** Peffault de Latour et al. *Lancet Haematol* 2022 **4.** Wong et al. *Blood Adv* 2023.

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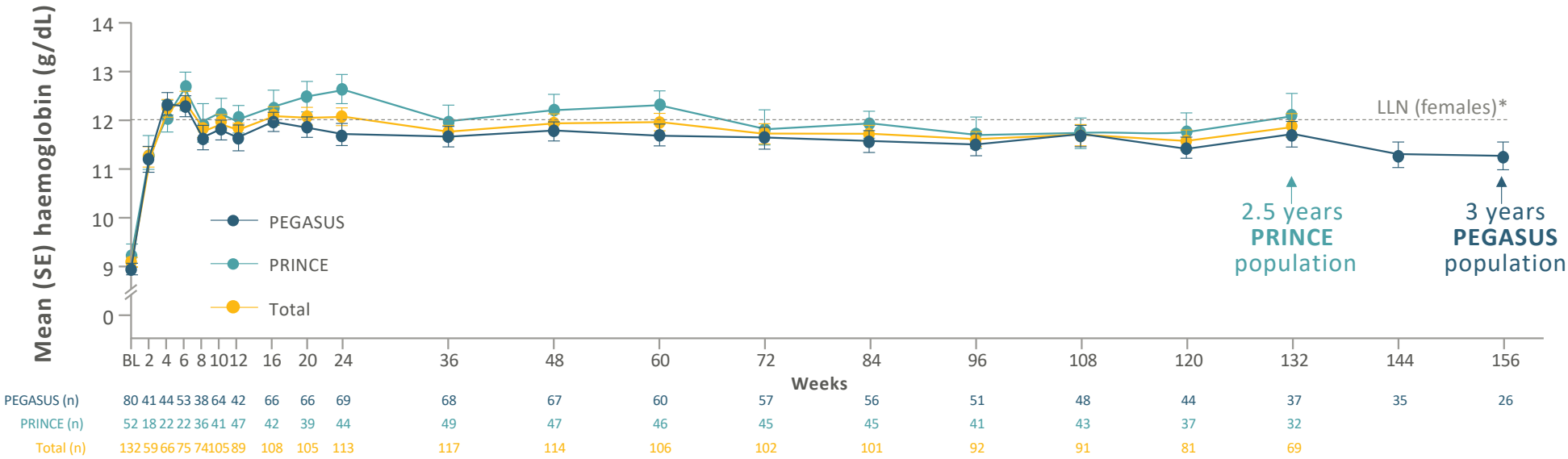
Pegcetacoplan maintained **long-term efficacy for up to 3 years**[1]



ARC and LDH

Mean ARC and LDH were **maintained below the ULN***

FACIT-Fatigue score

Mean FACIT-Fatigue score **maintained close to the general population norm**†

Transfusion avoidance

>70% of **patients avoided transfusions** in **each year** of follow-up

The haemoglobin analysis excluded measures taken within 28 days before pegcetacoplan initiation and those taken within 60 days after the transfusion during pegcetacoplan treatment.
* Normal ranges are per central laboratory; local laboratory values were normalised using central laboratory normal ranges. LLN for Hb: 12 g/dL for females and 13.6 g/L for males.
ULN for ARC: 120 $\times 10^9$ cells/L. ULN for LDH: 226 U/L. † General population norm: 43.6.[2] ARC, absolute reticulocyte count; BL, baseline (at pegcetacoplan initiation);
FACIT, Functional Assessment Of Chronic Illness Therapy; LDH, lactate dehydrogenase; LLN, lower limit of normal; SE, standard error; ULN, upper limit of normal.
1. de Castro et al. ASH 2023; presentation 574 **2.** Cella et al. *Cancer* 2002.

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Treatment-emergent adverse events for up to 3 years were **as expected** in adults with PNH[1]

TEAEs*, n (%)	PEGASUS population (N=80)	PRINCE population (N=52)	Total population (N=132)
Any TEAE	79 (98.8)	50 (96.2)	129 (97.7)
Considered related to pegcetacoplan	43 (53.8)	17 (32.7)	60 (45.5)
Serious TEAEs	**43 (53.8)**	**23 (44.2)**	**66 (50.0)**
Considered related to pegcetacoplan	5 (6.3)	1 (1.9)	6 (4.5)
Leading to pegcetacoplan discontinuation	16 (20.0)	1 (1.9)	17 (12.9)
Leading to death†	**1 (1.3)**	**3 (5.8)**	**4 (3.0)**
Considered related to pegcetacoplan	0	0	0
TEAEs of special interest			
Hypersensitivity	27 (33.8)	16 (30.8)	43 (32.6)
Any infection	63 (78.8)	35 (67.3)	98 (74.2)
Sepsis	4 (5.0)	2 (3.8)	6 (4.5)
Meningitis	0	0	0
Thrombosis	3 (3.8)	0	3 (2.3)
Breakthrough haemolysis‡	23 (28.8)	16 (30.8)	39 (29.5)

Most AEs of infections were mild to moderate and **non-serious**

Thrombotic events occurred in the context of multiple **associated comorbidities** (n=2) or after **discontinuation** (n=1)

No new safety concerns were identified through up to 3 years of follow-up

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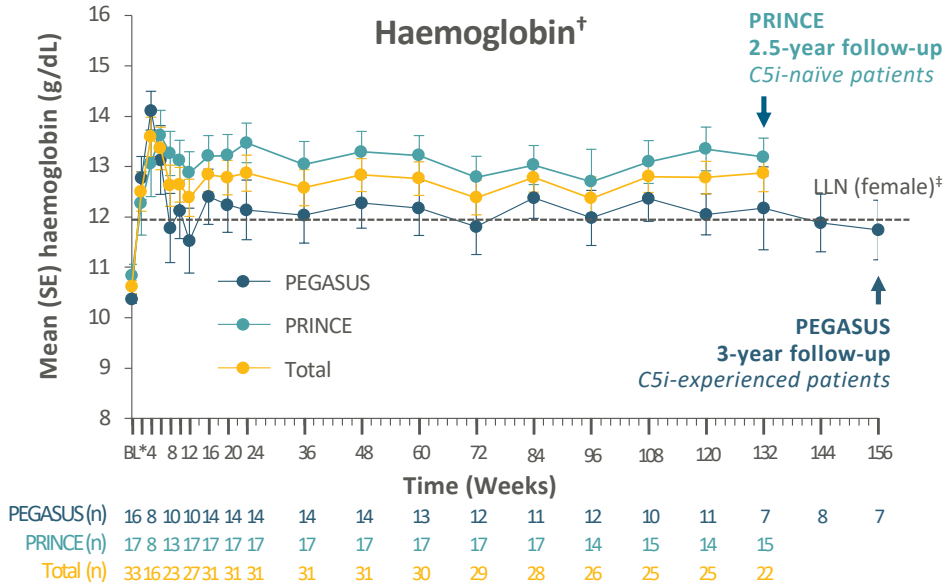
* TEAE: AEs with a start date on or after the first dose of monotherapy pegcetacoplan or if it has a start date before the date of the first dose of pegcetacoplan but increases in severity on or after the date of the first dose of drug. AEs measured through 2.5 years (PRINCE) and 3 years (PEGASUS). Did not include AEs occurring more than 8 weeks after the last dose of pegcetacoplan. Patients with multiple occurrences of an AE were counted only once.
† COVID-19 (PEGASUS); septic shock, sudden cardiac death, and gastrointestinal haemorrhage with hypovolemic shock (PRINCE); all were deemed unrelated to pegcetacoplan.
‡ Clinically-significant (as reported by investigators) and laboratory-confirmed events. AE, adverse event; PNH, paroxysmal nocturnal haemoglobinuria; TEAE, treatment-emergent adverse event.
1. de Castro et al. ASH 2023; presentation 574.

Improvement in haematologic parameters maintained **for up to 3 years in patients with baseline Hb ≥10.0 g/dL[1]**

33 patients in total (PRINCE, 17 patients; PEGASUS, 16 patients)



Improvement in mean **haemoglobin** was maintained for **up to 2.5 (PRINCE) and 3 (PEGASUS) years**

Median LDH decreased rapidly and stabilised below the ULN, and **mean ARC decrease below the ULN** was sustained†

Rapid **increases in mean FACIT-Fatigue scores**† approaching the **general population norm**§ which were largely **maintained long-term**

Pegcetacoplan's safety profile‖ was **consistent** with previously reported data, with **no new safety signals**

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Data cut off 31/01/2023. * Baseline was defined as the time of pegcetacoplan initiation, regardless of when this occurred in the Phase 3 trials. † In the absence of transfusions. ‡ Haemoglobin LLN (female): 12 g/dL.
§ FACIT-Fatigue score US population norm: 43.6.[2] . ‖ With SAEs in 14 patients (42%; 0 related to PEG), serious treatment-emergent AEs of infection in 8 patients (24%; 0 related to PEG), no meningococcal infections and 3 cases of thrombosis, and no AEs leading to death. 2 patients discontinued due to 3 AEs (sepsis and diffuse large B-cell lymphoma[1 patient]; and haemolysis [1 patient]).
AE, adverse event; ARC, absolute reticulocyte count; BL, baseline; C5i, C5 inhibitor; FACIT, Functional Assessment of Chronic Illness Therapy; Hb, haemoglobin; LDH, lactate dehydrogenase; LLN, lower limit of normal; PEG, pegcetacoplan; SAE, serious adverse event; SE, standard error; ULN, upper limit of normal. **1.** Panse et al. EHA 2024; Poster P816 **2.** Cella *Cancer* 2002.

PNH patients with a **history of AA** derived **benefit from treatment** with pegcetacoplan

Post-hoc analysis in **PNH** patients with and without **a history of AA** from PEGASUS and PRINCE

Mean change from baseline in haemoglobin, g/dL

PEGASUS[1]

	History of AA (n=7)	No history of AA (n=26)
Week 48	+1.7	+2.7

PRINCE*[2]

	History of AA (n=5)	No history of AA (n=28)
Week 6	+3.0	+2.7

Similar outcome patterns in Ci naïve patients and patients with insufficient response to C5 inhibition with or without history of AA[1,2]

Rapid decrease in LDH levels in PRINCE and **low levels** maintained in PEGASUS

Most patients in both groups (>70%) **achieved transfusion avoidance**

Clinically important differences (≥5 points)[3] in **FACIT-Fatigue** in both groups

Pegcetacoplan's overall safety profile for patients with a history of AA is **consistent** with that of patients with no history of AA[1,2]

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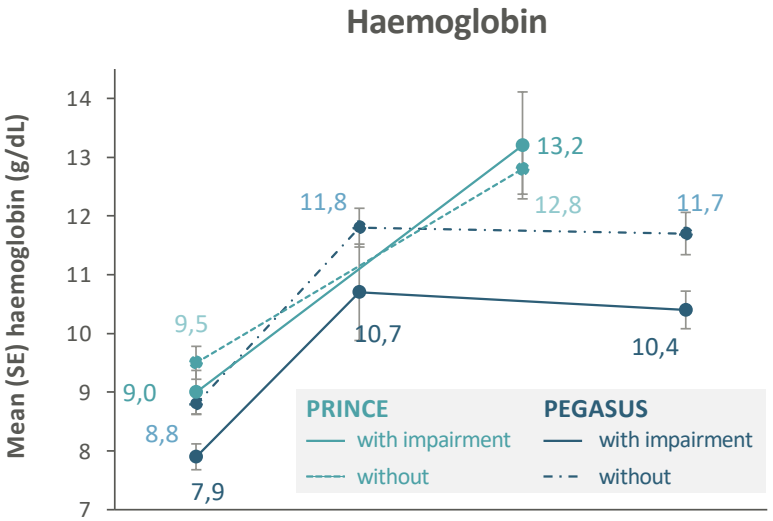
* Haemoglobin was assessed at Week 6 when the steady state of pegcetacoplan was reached and before the first patient escaped from the control arm to pegcetacoplan therapy.
AA, aplastic anaemia; Ci, complement inhibitor; FACIT, Functional Assessment of Chronic Illness Therapy; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal haemoglobinuria.
1. Usuki et al. JSH 2022; oral presentation OS2-5C-2 **2.** Bogdanovic et al. EHA 2023; poster 794 **3.** Cella et al. *J Patient Rep Outcomes* 2023.

PNH patients with **impaired bone marrow function** derived **benefit from treatment** with pegcetacoplan

Post-hoc analysis in PNH patients with and without **impaired bone marrow function at baseline** from PEGASUS and PRINCE



Week	BL	16	26	48
Number of patients analysed				
PRINCE, with impairment	7	-	5	-
without	28	-	24	-
PEGASUS, with impairment	5	3	-	3
without	36	32	-	25

Treatment outcomes followed similar patterns for patients with and without impaired bone marrow function

- **Rapid decrease** and stabilisation in **LDH** levels in PRINCE and mean levels **below the ULN** in both studies
- Mean **ARC** levels decreased **below the ULN**
- **Most patients** in both groups **achieved transfusion avoidance**

ARC, absolute reticulocyte count; BL, baseline; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal haemoglobinuria; SE, standard error; ULN, upper limit of normal.

1. Szer et al. *Int J Mol Sci* 2024. Figure adapted from Szer et al. *Int J Mol Sci* 2024 (CC BY 4.0).

Real-world evidence **further confirmed the efficacy and favourable safety profile of pegcetacoplan**[1-11]

RWE in Europe and the US **confirmed the efficacy and safety of pegcetacoplan** in PNH with improvements in a broad range of haematological and clinical outcomes compared to baseline

- ↑ Increased haemoglobin
- ⇄ Improved/ maintained LDH
- ↓ Decreased ARC
- ↓ Decreased transfusions
- ↑ Improved QoL and high treatment satisfaction*

RWE supports pegcetacoplan's **favourable benefit-risk profile**

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* Based on physician and patient assessments.

ARC, absolute reticulocyte count; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal haemoglobinuria; QoL, quality of life; RWE, real-world evidence.

1. Wilson et al. *Eur J Haematol* 2023 **2.** Wilson et al. EBMT 2023; poster P258 **3.** Fishman et al. AMCP Nexus 2023; poster D4 **4.** Fishman et al. *Blood* 2023 **5.** Fishman et al. ISPOR 2023; poster C033 **6.** Fishman et al. SOHO 2023; poster MDS355 **7.** Vallejo et al. EHA 2024; Poster P1917 **8.** Griffin et al. *Am J Hematol* 2024 **9.** Desai et al. SOHO 2022; poster MDS278 **10.** Desai et al. *Blood* 2022 **11.** Desai et al. Blood 2022.

Pegcetacoplan improved or maintained control over **haematological parameters**[1,2]

Haemoglobin

23 PNH patients in Spain received PEG* in a real-world setting[1]

+ 3.0 g/dL median change
4 weeks after PEG initiation

48 PNH patients treated with PEG* in the **UK and France**[2]

+ 2.2 g/dL mean change
3 months after PEG initiation (n=41†)

LDH levels below the ULN were achieved and/or maintained and **ARC** decreased below the ULN[‡,1,2]
Need for transfusions was **reduced**, while **QoL** and **treatment satisfaction improved**[§1]

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* Patients switched to pegcetacoplan from previous complement inhibitor treatment. † Patients with paired data available. ‡ Spain: Median LDH and ARC; UK/France: Mean LDH and ARC. § Based on physician and patient assessments.
ARC, absolute reticulocyte count; LDH, lactate dehydrogenase; PEG, pegcetacoplan; PNH, paroxysmal nocturnal haemoglobinuria; QoL, quality of life; ULN, upper limit of normal.

1. Vallejo et al. EHA 2024; Poster P1917 **2.** Griffin et al. *Am J Hematol* 2024.

Real-world evidence supports pegcetacoplan's **favourable benefit-risk profile**

Safety in real-world studies[1,2]

Real world studies have reported a **favourable safety profile** for pegcetacoplan

Pegcetacoplan was **well tolerated**

BTH events have been reported, but were **manageable** with most patients **remaining on pegcetacoplan**

Events reported with pegcetacoplan in the **post-marketing setting** and across **7 clinical trials**[3]

Low thrombotic event rate similar to that of C5i

626 patient-years in the **post-marketing setting***,†

0.32‡ **thrombotic events/ 100 PY**[2]

2 events

409 patient-years in the **clinical trial setting***,§

1.22 **thrombotic events/ 100 PY**

5 events in 4 patients, none of which were deemed related to pegcetacoplan, and all resolved

No encapsulated meningococcal infections

1,127 patient-years in the **combined post-marketing**† and **clinical trial**§ settings[3,4]

0 **encapsulated meningococcal infections**

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* As of November 2023 in the post-marketing setting and November 2022 in clinical trials. † Exposure and events reported through pharmacovigilance and post-marketing distribution programs in the United States, Europe, and the rest of the world. ‡ In comparison, the reported rate of venous thrombotic events is approximately 0.1–0.2 per 100 PY in the general population of the United States and Europe.[5]
§ Exposure and events were assessed during the completed clinical trial, throughout the ongoing, long-term, rollover, open-label, and extension trial. BTH, breakthrough haemolysis; C5i, C5 inhibitor; PY, patient-years.
1. Vallejo et al. EHA 2024; Poster P1917 **2.** Griffin et al. *Am J Hematol* 2024 **3.** Kelly et al. *Res Pract Thromb Haemost* 2024
4. Panse et al. EHA 2024; Poster P838 **5.** Lutsey et al. *Nat Rev Cardiol* 2023.

COMPLETE: **Phase 4 real-world study initiated in 2023**[1,2]

A single-arm, multicentre observational study to evaluate the real-world effectiveness of pegcetacoplan in patients with PNH

Patients

- PNH patients ≥18 years
- Started pegcetacoplan ≤12 months before enrolment or are prescribed pegcetacoplan at enrolment

Study overview

- ~200 patients at 70 sites in Europe, the Middle East, Canada, and Australia
- Prospective observation period of 2 years
- Retrospective treatment data for up to 12 months before pegcetacoplan start

Endpoints

Primary endpoint:

- Change in Hb level after 6 months of pegcetacoplan treatment

Secondary endpoints:

- Change in LDH, ARC, bilirubin, haptoglobin and ferritin
- Hb ≥12 g/dL and increase in Hb level of ≥2 g/dL
- RBC transfusions and acute hemolytic events
- Patient-reported QoL scores
- Treatment satisfaction
- Healthcare resource use

As the COMPLETE study progresses, additional data will expand our understanding of real-world effectiveness of pegcetacoplan

ARC, absolute reticulocyte count; Hb, haemoglobin; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal haemoglobinuria; QoL, quality of life; RBC, red blood cell.
1. clinicaltrials.gov NCT05776472. **2.** Peffault de Latour EHA 2023; abstract PB2064.

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Key takeaways

Key takeaways

C5 inhibitors can **control IVH** but symptoms may persist due to emerging **EVH** and **residual IVH**, highlighting the **unmet needs** that remain for patients with PNH[1-13]

Pegcetacoplan's mechanism of action addresses both the **proximal and terminal complement cascade** dysregulation[13,14]

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EVH, extravascular haemolysis; IVH, intravascular haemolysis; PNH; paroxysmal nocturnal haemoglobinuria.

1. Hillmen et al. *N Engl J Med* 1995 **2.** Kelly et al. *Blood* 2024 **3.** Risitano et al. *Front Immunol* 2019 **4.** de Fontbrune et al. *Hematology* 2022 **5.** Risitano et al. *Blood* 2009 **6.** Dingli et al. *Ann Hematol* 2022 **7.** Matos et al. ISPOR EU 2021 **8.** Panse et al. *Eur J Haematol* 2022 **9.** Brodsky *Blood* 2014 **10.** Peffault de Latour et al. *Blood* 2015 **11.** Luzzatto et al. *F1000Res* 2016 **12.** Hillmen et al. *Br J Haematol* 2013 **13.** Hillmen et al. *Int J Mol Sci* 2024 **14.** de Castro et al. *Am J Hematol* 2020.

Key takeaways

In the Phase 3 studies, **pegcetacoplan improved** haematological and clinical **outcomes** and was **well tolerated**[1-3]

Efficacy and **safety** observed in the parent studies were **maintained for up to 3 years**, both in the overall population[4] and the **subpopulation of patients with haemoglobin ≥10 g/dL** at baseline[5]

Post-hoc analyses of PEGASUS and PRINCE indicated that PNH patients **with a history of AA** or **with impaired bone marrow function** can **benefit from pegcetacoplan treatment**[6-8]

AA, aplastic anaemia; PNH, paroxysmal nocturnal haemoglobinuria.

1. Hillmen et al. *N Engl J Med* 2021 **2.** Peffault de Latour et al. *Lancet Haematol* 2022 **3.** Wong et al. *Blood Adv* 2023 **4.** de Castro et al. ASH 2023; presentation 574 **5.** Panse et al. EHA 2024; Poster P816
6. Bogdanovic et al. EHA 2023; poster 794 **7.** Usuki et al. JSH 2022; oral presentation OS2-5C-2 4. **8.** Szer et al. *Int J Mol Sci* 2024.

Key takeaways

Pegcetacoplan **improved a broad range of haematological and clinical outcomes** in **real-world studies**[1,2] and demonstrated a **favourable safety profile**[1,3]

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1. Vallejo et al. EHA 2024; Poster P1917 **2.** Griffin et al. *Am J Hematol* 2024 **3.** de Castro et al. *Blood* 2023.

Adding new dimensions to proximal inhibition

Transforming paroxysmal nocturnal haemoglobinuria (PNH) management

Q&A

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We value your feedback

Evaluation

Please **scan the QR code** using your phone or tablet device to **fill in** the evaluation

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Thank you