Austin Kulasekararaj
austin.kulasekararaj@nhs.net

APPULSE-PNH: oral iptacopan monotherapy demonstrates clinically meaningful hemoglobin increases in patients with paroxysmal nocturnal hemoglobinuria and hemoglobin ≥10 g/dL on anti-C5 therapy

Austin Kulasekararaj[1–3], Flore Sicre de Fontbrune[3,4], Anna Gaya[5], Ilene Weitz[6], David J Kuter[7,8], David J Araten[9,10], Bhumika J Patel[11], Abhay Singh[12], Jun Ho Jang[13], Richard J Kelly[14], Eros Di Bona[15], Michael Loschi[16], Vinod Pullarkat[17], Jörg Schubert[18], Alessandro M Vannucchi[19], Mustafa N Yenerel[20], Régis Peffault de Latour[3,4,21], Navin Mahajan[22], Luca Monaco[22], Tao Ding[23], Tomasz Lawniczek[22], Philippe Ferber[22], Marion Dahlke[22], Antonio M Risitano[3,24,25]

[1]King's College Hospital NHS, London, UK; [2]National Institute for Health and Care Research and Wellcome King's Research Facility, London, UK; [3]The Severe Aplastic Anemia Working Party of the European Society for Blood and Marrow Transplantation; [4]French Reference Center for Aplastic Anemia and Paroxysmal Nocturnal Hemoglobinuria, Paris, France; [5]Hospital Clínic of Barcelona, Barcelona, Spain; [6]USC Norris Cancer Center, Keck-USC School of Medicine, Los Angeles, CA, USA; [7]Massachusetts General Hospital, Boston, MA, USA; [8]Harvard Medical School, Boston, MA, USA; [9]NYU Langone Medical Center, New York, NY, USA; [10]NYU Grossman School of Medicine, New York, NY, USA; [11]Prisma Health Cancer Institute, Greenville, SC, USA; [12]Cleveland Clinic, Cleveland, OH, USA; [13]Samsung Medical Centre, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [14]St James's University Hospital, Leeds, UK; [15]UOC Oncoematologia, AULSS7 Pedemontana, Bassano del Grappa (VI), Italy; [16]Nice University Hospital, Cote d'Azur University, Nice, France; [17]City of Hope Medical Center, Duarte, CA, USA; [18]Dresden University Medical School, Dept. of Hematology, Cellular Therapy and Medical Oncology, Dresden Germany; [19]Azienda Ospedaliera Universitaria Careggi, University of Florence, Florence, Italy; [20]Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey; [21]Assistance Publique Hôpitaux de Paris, Université Paris Cité, Paris, France; [22]Novartis Pharma AG, Basel, Switzerland; [23]China Novartis Institutes For Biomedical Research Co. Ltd, Shanghai, China; [24]AORN Moscati, Avellino, Italy; [25]University of Naples Federico II, Naples, Italy

Scan to obtain the slides

https://tinyurl.com/KulasekararajS183

Oral presented at the European Hematology Association 2025 congress, held in Milan, Italy and virtually on 12–15 June 2025

Disclosures

- **Consulting fees:** Alexion (AstraZeneca Rare Disease), Arrowhead, NovoNordisk, Samsung and Silence Therapeutics
- **Payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events:** Alexion (AstraZeneca Rare Disease), Amgen, Celgene/Bristol Myers Squibb, Janssen, Novartis, Pfizer, Ra Pharma/Union Chimique Belge, Roche and Sobi
- **Support for attending meetings and/or travel:** Alexion (AstraZeneca Rare Disease), Roche and Sobi
- **Participation on a data monitoring safety board or advisory board:** Agios, Alexion (AstraZeneca Rare Disease), Amgen, Apellis, Biocryst, Celgene/Bristol Myers Squibb, Geron, Janssen, Novartis, Pfizer, Regeneron, Roche and Sobi

Oral presented at the European Hematology Association 2025 congress, held in Milan, Italy and virtually on 12–15 June 2025

In PNH, impaired complement regulation due to CD55 and CD59 deficiencies leads to IVH[1–3]

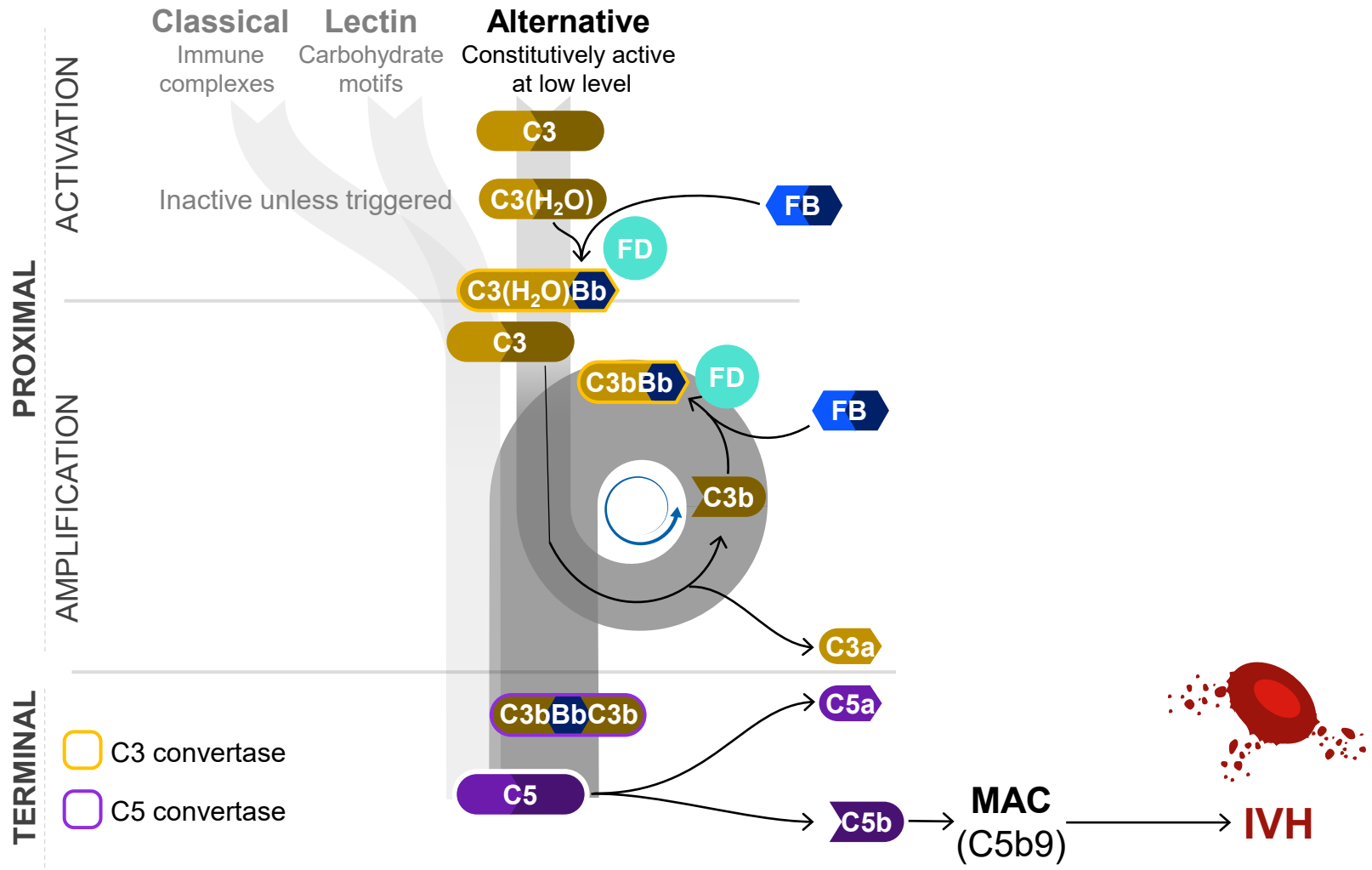


Figure created based on information from multiple sources.[1,4–6] C, complement component; CD, cluster of differentiation; FB, factor B; FD, factor D; GPI, glycosylphosphatidylinositol; IVH, intravascular hemolysis; MAC, membrane attack complex; PNH, paroxysmal nocturnal hemoglobunuria; RBC, red blood cell

1. Brodsky RA. *Blood* 2014;124:2804–11; 2. Hill A *et al. Nat Rev Dis Primers* 2017;3:170281; 3. Ruiz-Arguelles A, Llorente L. *Autoimmun Rev* 2007;6:155–61; 4. Ricklin D *et al. Nat Immunol* 2010;11:785–97; 5. Merle NS *et al. Front Immunol* 2015;6:262; 6. Innate immunity. In: Janeway CA Jr *et al.* Immunobiology. 5th ed. New York, NY: Garland Science, 2001

Oral presented at the European Hematology Association 2025 congress, held in Milan, Italy and virtually on 12–15 June 2025

Anti-C5 treatment can lead to the emergence of EVH[1–4]

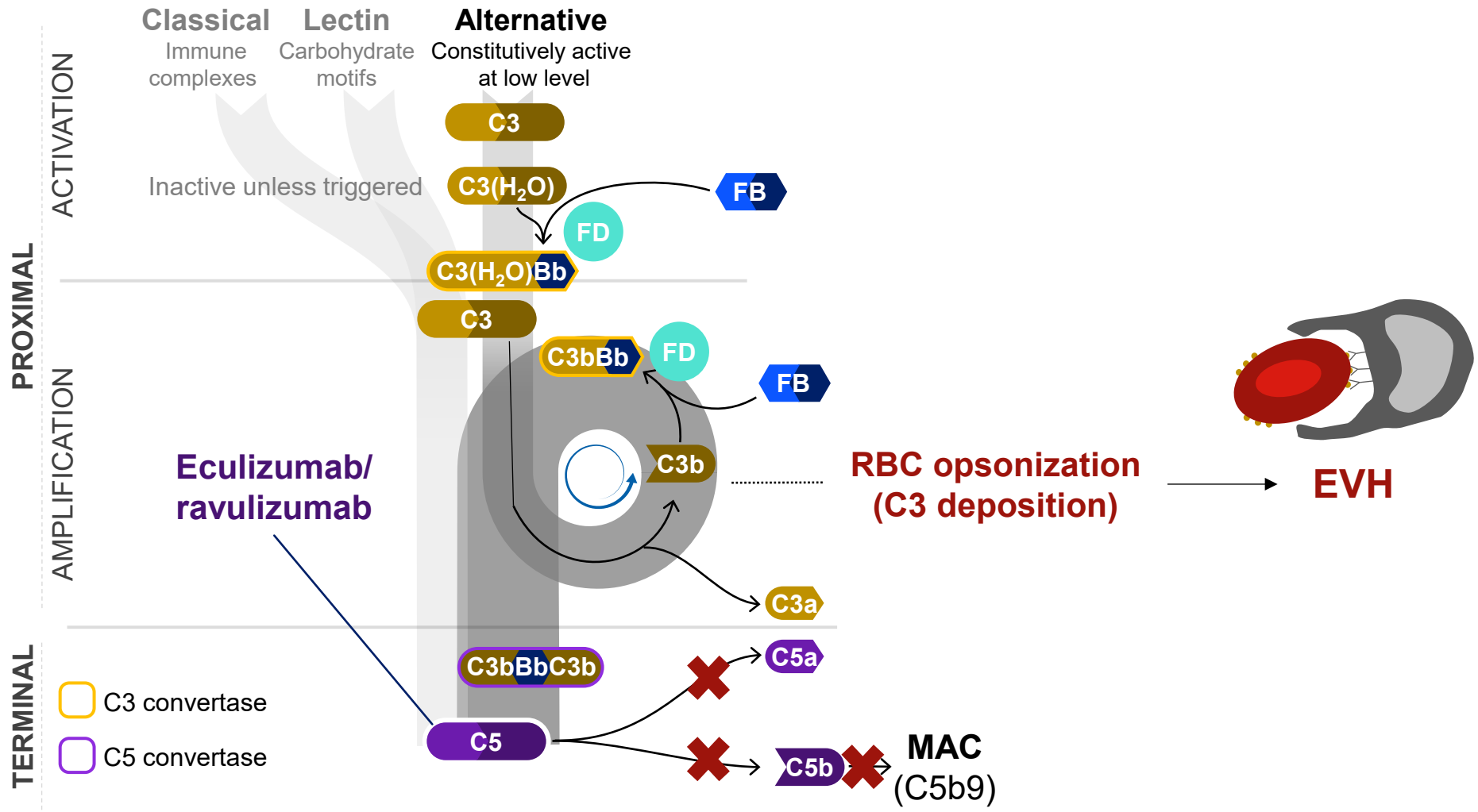


Figure created based on information from multiple sources[3,5–7]
EVH, extravascular hemolysis

1. Risitano AM *et al. Front Immunol* 2019;10:1157; 2. Risitano AM *et al. Blood* 2009;113:4094–100; 3. Brodsky RA *Blood* 2014;124:2804–11; 4. Hill A *et al. Nat Rev Dis Primers* 2017;3:170281;
5. Ricklin D *et al. Nat Immunol* 2010;11:785–97; 6. Merle NS *et al. Front Immunol* 2015;6:262; 7. Innate immunity. In: Janeway CA Jr *et al.* Immunobiology. 5th ed. New York, NY: Garland Science, 2001

Oral presented at the European Hematology Association 2025 congress, held in Milan, Italy and virtually on 12–15 June 2025

Iptacopan targets factor B to selectively block alternative pathway C3 convertase activation and achieve comprehensive hemolysis control[1–3]

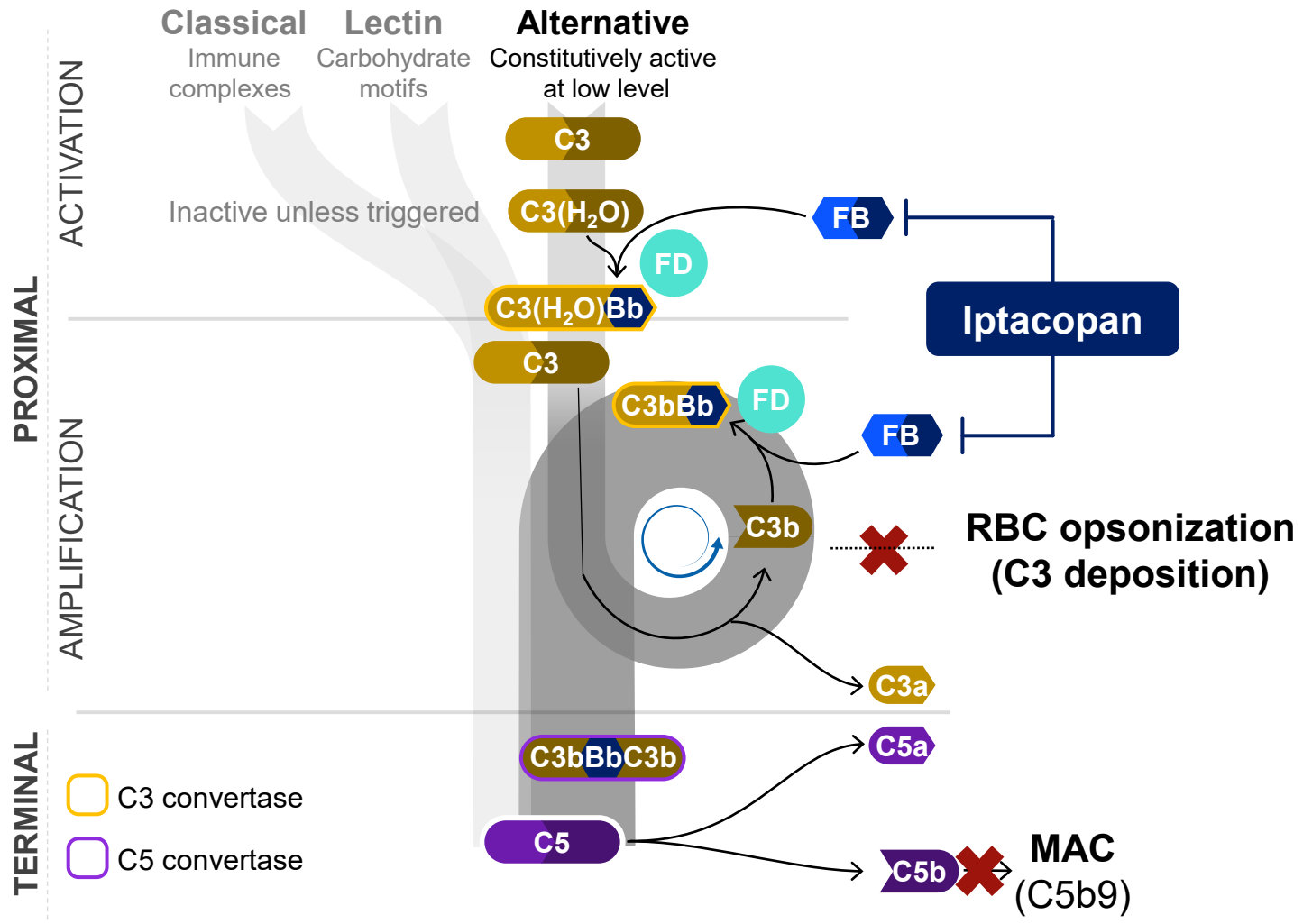


Figure created based on information from multiple sources[3–6]

1. Schubart A *et al. Proc Natl Acad Sci U S A* 2019;116:7926–31; 2. Risitano AM *et al. Lancet Haematol* 2021;8:e344–54; 3. Brodsky RA *Blood* 2014;124:2804–11; 4. Ricklin D *et al. Nat Immunol* 2010;11:785–97; 5. Merle NS *et al. Front Immunol* 2015;6:262; 6. Innate immunity. In: Janeway CA Jr *et al.* Immunobiology. 5th ed. New York, NY: Garland Science, 2001

Oral presented at the European Hematology Association 2025 congress, held in Milan, Italy and virtually on 12–15 June 2025

Patients with PNH who achieve Hb ≥10 g/dL with anti-C5 therapy may have ongoing EVH and experience a substantial QoL burden

Oral iptacopan monotherapy has demonstrated efficacy and safety in:

- **Complement inhibitor-naïve** patients with **Hb <10 g/dL and LDH >1.5 × ULN** (APPOINT-PNH)[1,2]
- **Anti-C5-experienced** patients with **Hb <10 g/dL** (APPLY-PNH)[1,2]

APPULSE-PNH evaluated the efficacy and safety of oral iptacopan monotherapy in anti-C5-treated patients with Hb ≥10 g/dL who:

- May have **ongoing EVH** (indicated by increased ARC and C3d+ PNH RBCs)[3–5]
- May remain **anemic** according to WHO guidelines* resulting in **fatigue**, **impaired QoL** and an increased risk of **serious complications**[6–10]
- Require **hospital visits** every 2 or 8 weeks for **IV anti-C5 infusions**[11]

*Hb <12 and <13 g/dL for adult women and men, respectively

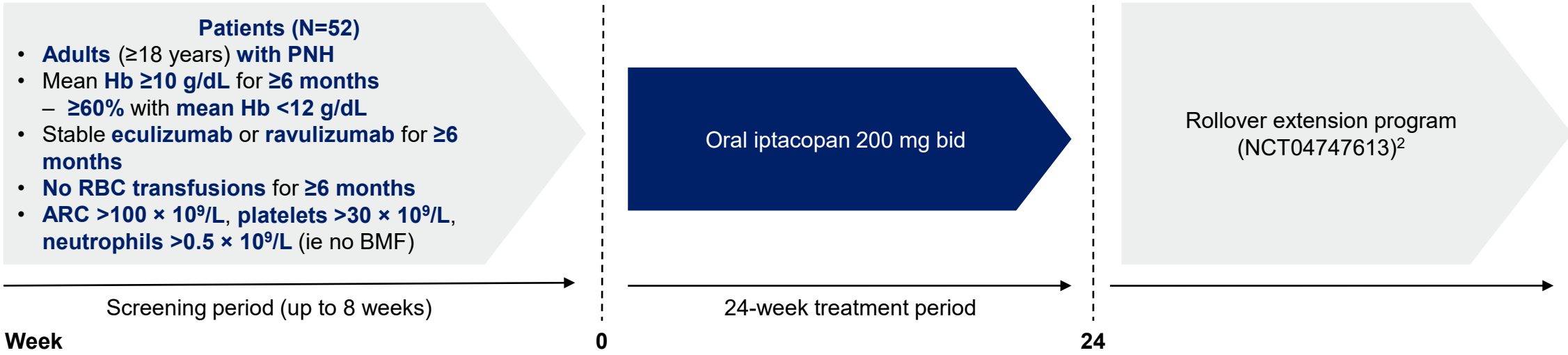
ARC, absolute reticulocyte count; Hb, hemoglobin; IV, intravenous; LDH, lactate dehydrogenase; QoL, quality of life; ULN, upper limit of normal; WHO, World Health Organization

1. Peffault de Latour R *et al. N Engl J Med* 2024;390:994–1008; 2. Risitano AM *et al. Lancet Haematol* 2025;12:e414–30; 3. Risitano AM *et al. Front Immunol* 2019;10:1157; 4. Debureaux P-E *et al. Bone Marrow Transplant* 2021;56:2600–2; 5. Risitano AM *et al. Blood* 2009;113:4094–100; 6. World Health Organization. Guideline on haemoglobin cutoffs to define anaemia in individuals and populations. Available at: https://www.who.int/publications/i/item/9789240088542 (accessed June 2025); 7. Bektas M *et al. J Manag Care Spec Pharm* 2020;26:S8–14; 8. Young NS *et al. Semin Hematol* 2009;46:S1–16; 9. Dingli D *et al. Ann Hematol* 2022;101:251–63; 10. Panse J *et al. HemaSphere* 2024;8(S1):4998–9; 11. Levy AR *et al. Blood* 2019;134:4803

Oral presented at the European Hematology Association 2025 congress, held in Milan, Italy and virtually on 12–15 June 2025

APPULSE-PNH was a single-arm, open-label, multicenter, Phase IIIb trial

APPULSE-PNH (NCT05630001) study design[1]



Primary endpoint:
adjusted mean change from baseline in Hb
using the mean of four visits between Day 126 and 168

Non-inferiority of iptacopan after switch from anti-C5 therapy to be concluded if **lower bound of 95% CI >−1 g/dL** (**primary objective**)

Hierarchical testing

Superiority of iptacopan after switch from anti-C5 therapy to be concluded if **lower bound of 95% CI >0 g/dL** (**key secondary objective**)

bid, twice daily; BMF, bone marrow failure; CI, confidence interval

1. ClinicalTrials.gov. NCT05630001. Available at: https://clinicaltrials.gov/study/NCT05630001 (accessed June 2025);
2. ClinicalTrials.gov. NCT04747613. Available at: https://clinicaltrials.gov/study/NCT04747613 (accessed June 2025)

Oral presented at the European Hematology Association 2025 congress, held in Milan, Italy and virtually on 12–15 June 2025

Demographics, baseline disease characteristics and disposition

Characteristic	Iptacopan 200 mg bid (N=52)
Mean age, years (SD)	46.0 (13.7)
Female, n (%)	20 (38.5)
Race, n (%) White Asian Not reported/unknown	 35 (67.3) 4 (7.7) 13 (25.0)
Mean time since diagnosis, years (SD)	10.8 (7.5)
Prior anti-C5 treatment, n (%) Ravulizumab Eculizumab	 46 (88.5) 6 (11.5)
Mean duration of prior anti-C5,* years (SD)	3.5 (3.2)
Hb ≥12 g/dL, n (%)	20 (38.5)
Mean Hb, g/dL (SD)	11.87 (1.32)
Mean ARC, 10^9/L (SD)	154.84 (76.16)
Mean LDH, U/L (SD)	226.8 (69.1)

Characteristic	Iptacopan 200 mg bid (N=52)
Mean FACIT-Fatigue score, (SD)	38.9 (9.4)
Mean PNH clone size (SD) Total RBC (type II + III) Granulocyte Monocyte	 51.7 (30.6) 82.2 (16.0) 80.2 (19.5)

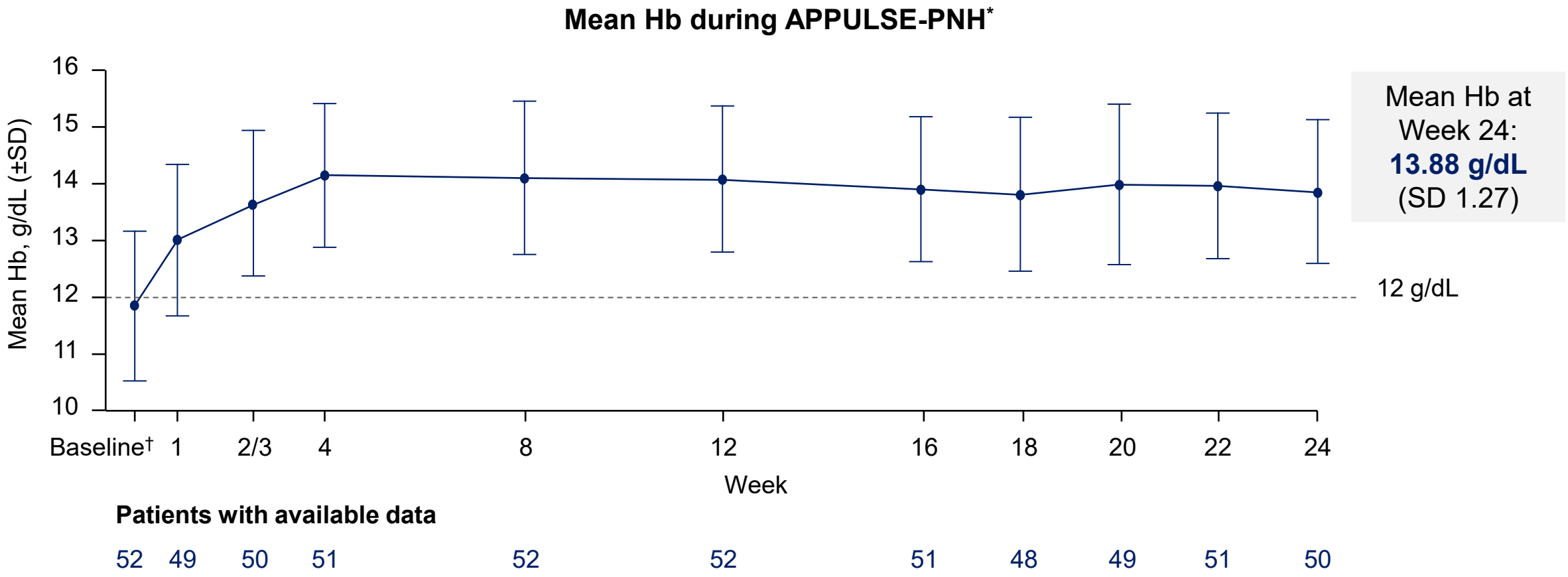
- **98.1%** (51/52) of patients **completed** the study
  - One discontinued on Day 104 because of a non-serious TEAE of palpitations
- Mean **relative dose intensity**† was **99.9%** (SD 0.28)

Characteristic	Baseline Hb <12 g/dL (N=32)	Baseline Hb ≥12 g/dL (N=20)
Mean Hb, g/dL (SD)	11.08 (0.5)	13.13 (1.2)
Mean ARC, 10^9/L (SD)	165.27 (75.61)	138.16 (75.92)
Mean LDH, U/L (SD)	223.6 (75.5)	211.3 (55.5)

*Stable regimen; †Ratio across all patients of received dose intensity versus planned dose intensity of 400 mg per day (administered as 200 mg bid)
FACIT, Functional Assessment of Chronic Illness Therapy; SD, standard deviation; TEAE, treatment-emergent adverse event

Oral presented at the European Hematology Association 2025 congress, held in Milan, Italy and virtually on 12–15 June 2025

Iptacopan monotherapy led to rapid normalization of mean Hb levels



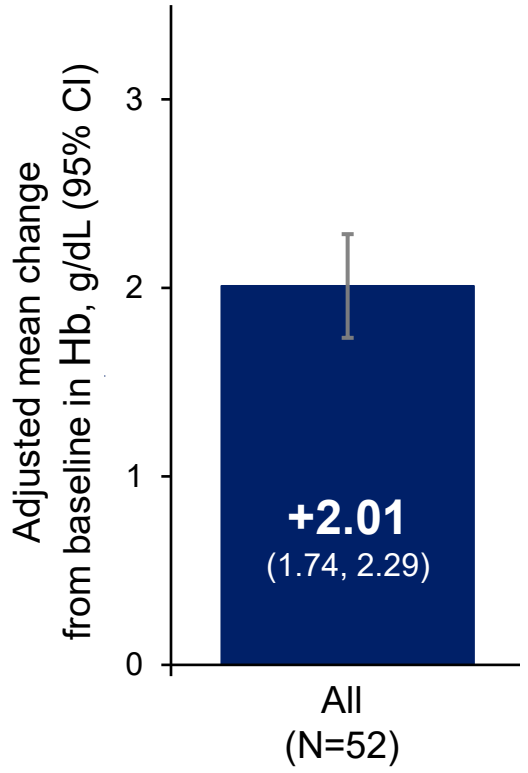
Mean Hb at Week 24: **13.88 g/dL** (SD 1.27)

*At each visit, only patients with a value at both baseline and that visit are included. On-treatment period for iptacopan is from the date of the first dose until 7 days after the date of the last dose;
†Mean baseline Hb: 11.87 (SD 1.32) g/dL

Oral presented at the European Hematology Association 2025 congress, held in Milan, Italy and virtually on 12–15 June 2025

APPULSE-PNH met its primary and key secondary objectives

Adjusted mean change from baseline* in Hb
between Day 126 and 168†



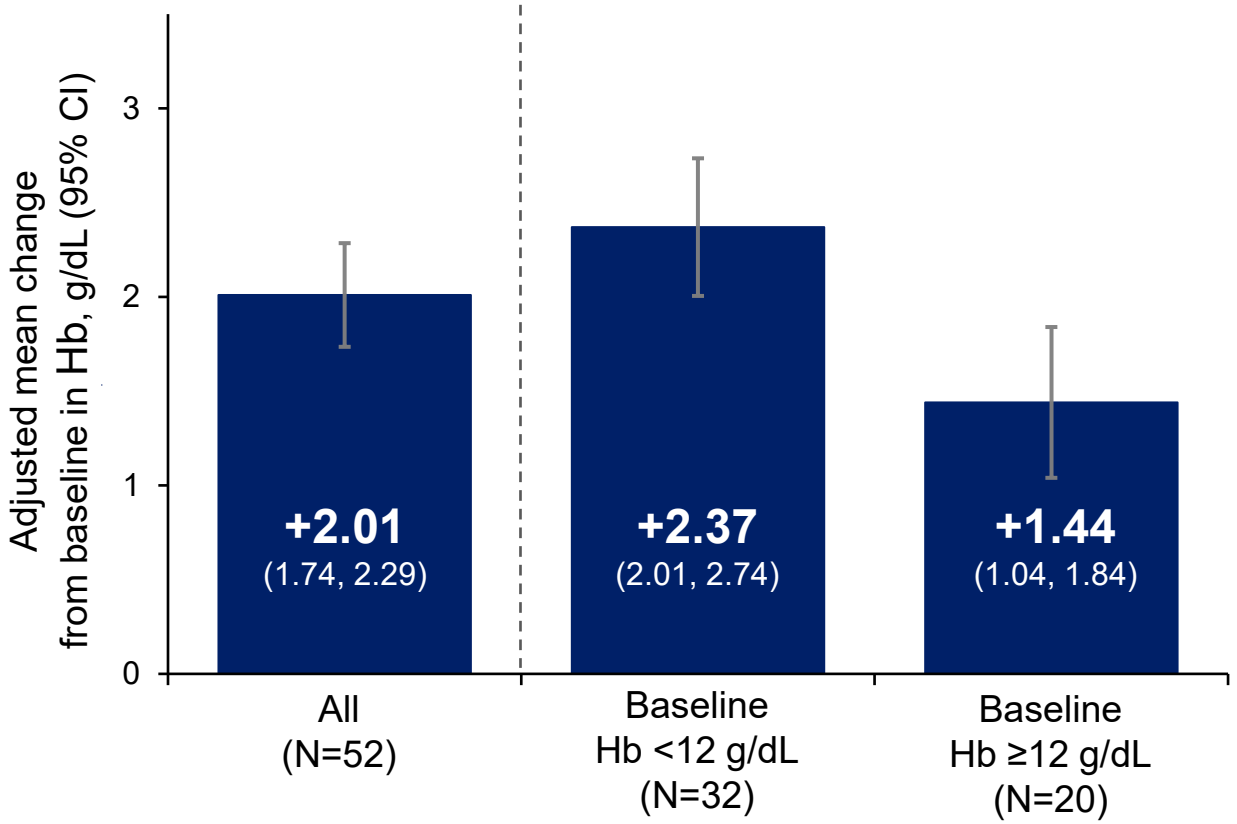
Iptacopan was
non-inferior (*P*<0.0001)‡
and **superior (*P*<0.0001)**‡
after switch from anti-C5 therapy

*Mean baseline Hb: 11.87 (SD 1.32) g/dL; †Analyzed using a a repeated measures model that adjusted for covariates; ‡Assessed using predefined thresholds (lower bound of 95% CI >−1 for inferiority and >0 g/dL for superiority). *P* values were one-sided and unadjusted

Oral presented at the European Hematology Association 2025 congress, held in Milan, Italy and virtually on 12–15 June 2025

APPULSE-PNH met its primary and key secondary objectives

Adjusted mean change from baseline* in Hb
between Day 126 and 168†



*Mean baseline Hb: 11.87 (SD 1.32) g/dL; †Analyzed using a a repeated measures model that adjusted for covariates; ‡Assessed using predefined thresholds (lower bound of 95% CI >−1 for inferiority and >0 g/dL for superiority). *P* values were one-sided and unadjusted

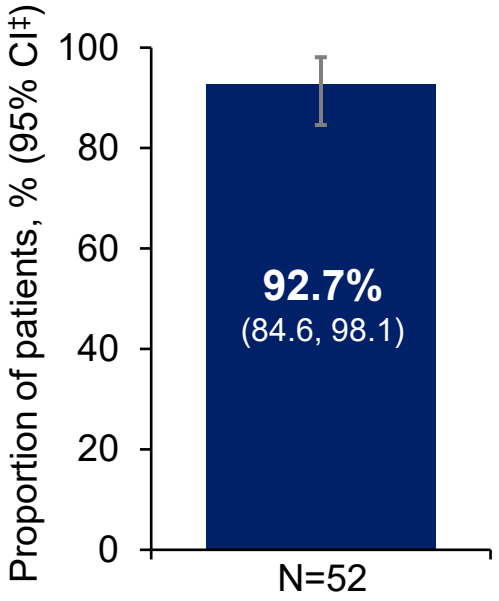
Oral presented at the European Hematology Association 2025 congress, held in Milan, Italy and virtually on 12–15 June 2025

During APPULSE-PNH, most patients achieved Hb ≥12 g/dL and all patients remained transfusion free

At **baseline**, **38.5%** patients (20/52) had **Hb ≥12 g/dL** in the absence of RBC transfusions 6 months prior to screening

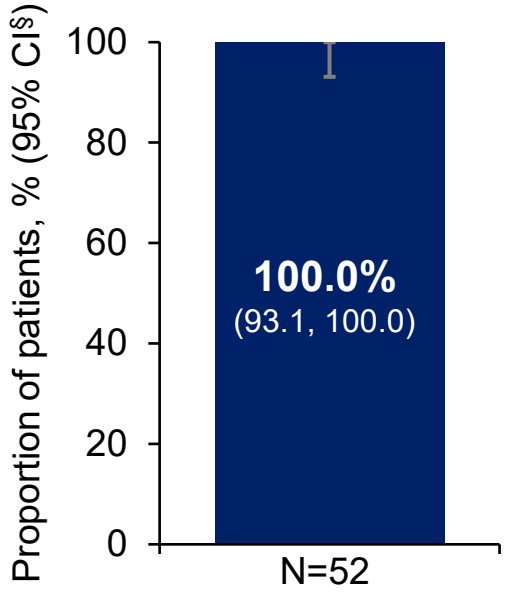
Patients achieving Hb ≥12 g/dL
between Day 126 and 168* in the absence of RBC transfusions between Day 1 and 168†

48/51 patients with non-missing data*



RBC transfusion avoidance
between Day 1 and 168†

52/52 patients



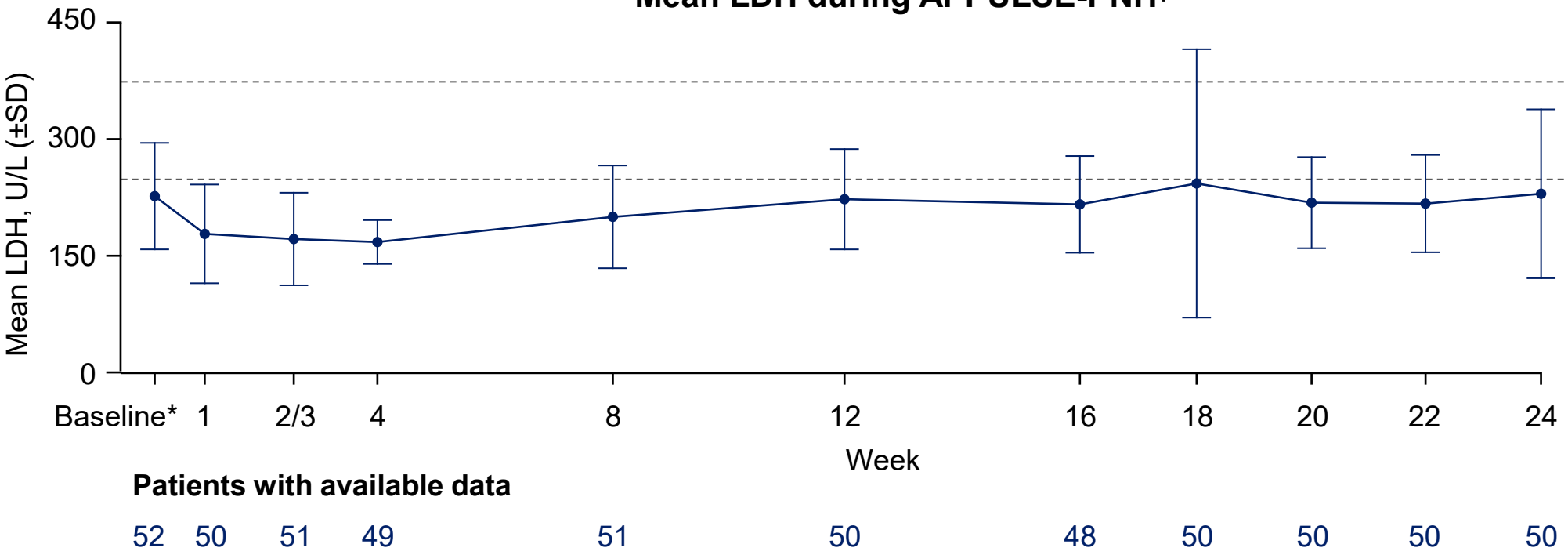
*≥3 of 4 scheduled assessments; †Neither meeting the criteria for administration of an RBC transfusion nor receiving an RBC transfusion; ‡Calculated using bootstrap method; §Calculated using Wilson's method

Oral presented at the European Hematology Association 2025 congress, held in Milan, Italy and virtually on 12–15 June 2025

Mean LDH remained below the ULN throughout the study

Between Day 126 and 168, the adjusted mean percentage change from baseline in LDH* was **−1.30%** (95% CI −6.56, 4.26),† with a geometric adjusted mean ratio versus baseline* of **0.99** (95% CI 0.93, 1.04)

Mean LDH during APPULSE-PNH‡



Mean LDH at Week 24: **231.1 U/L** (SD 109.0)

Patients with available data

Baseline*	1	2/3	4	8	12	16	18	20	22	24
52	50	51	49	51	50	48	50	50	50	50

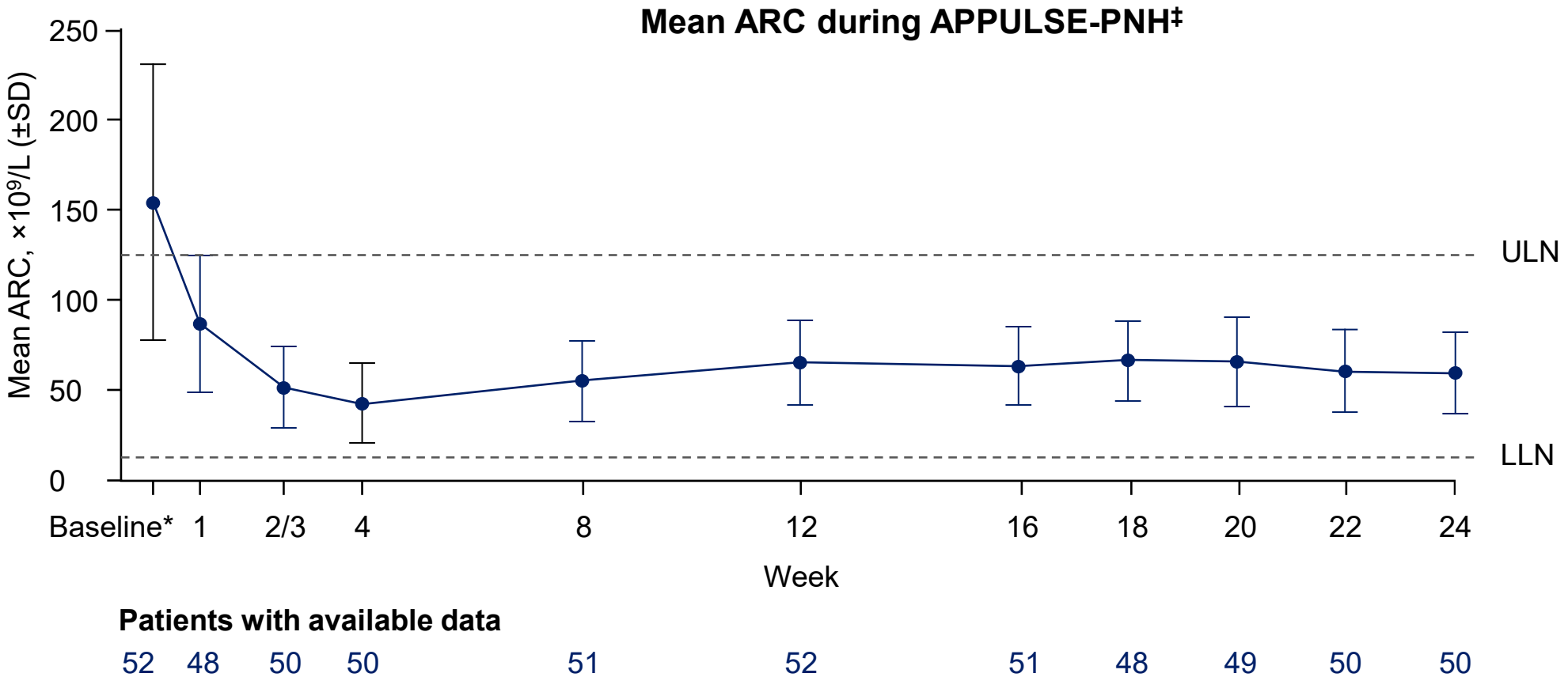
No patients experienced **clinical BTH**§

*Mean baseline LDH: 226.8 (SD 69.1) U/L; †Analyzed using a repeated measures model that adjusted for covariates; ‡At each visit, only patients with a value at both baseline and that visit are included. On-treatment period for iptacopan is from the date of the first dose until 7 days after the date of the last dose; §Clinical BTH was defined as LDH >1.5 × ULN with an increase compared with the last two assessments, together with either a decrease in Hb of ≥2 g/dL or significant clinical PNH-related signs and symptoms
BTH, breakthrough hemolysis

Oral presented at the European Hematology Association 2025 congress, held in Milan, Italy and virtually on 12–15 June 2025

Mean ARC rapidly decreased to within normal range, which was maintained throughout the study

Adjusted mean change from baseline* in ARC between Day 126 and 168 was **−89.19 × 10^9/L** (95% CI −95.47, −82.92)†



Mean ARC at Week 24: **60.40 × 10^9/L** (SD 22.36)

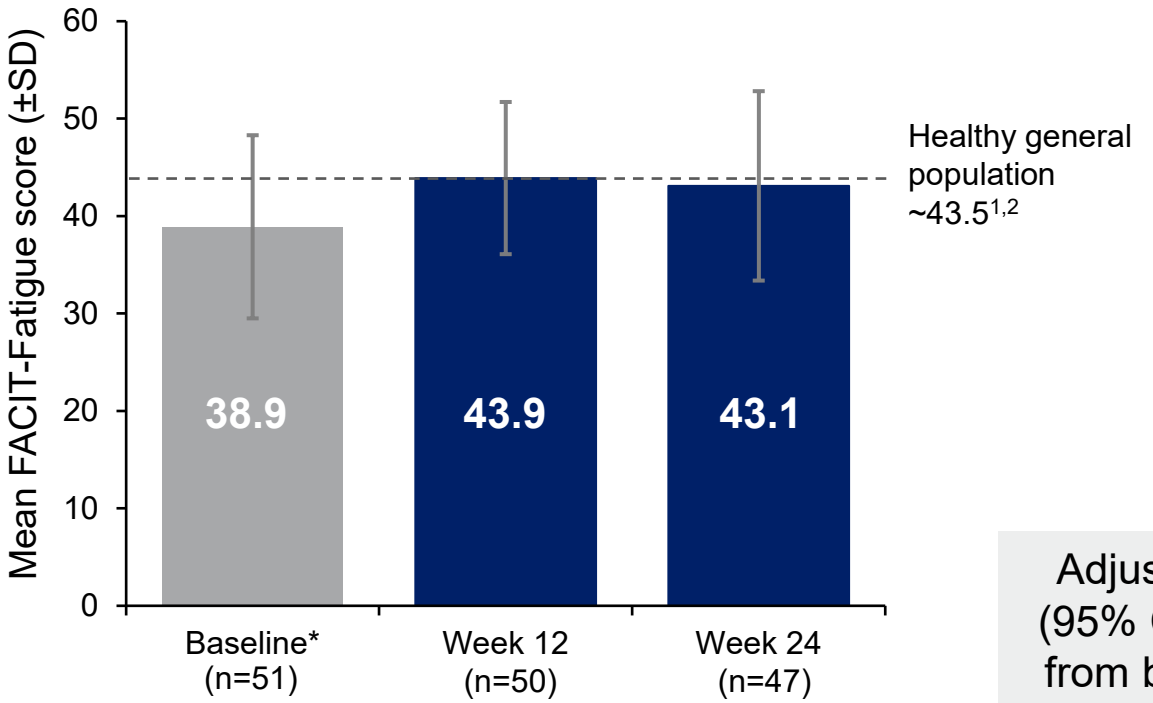
*Mean baseline ARC: 154.84 (SD 76.16) × 10^9/L; †Analyzed using a repeated measures model that adjusted for covariates; ‡At each visit, only patients with a value at both baseline and that visit are included.
On-treatment period for iptacopan is from the date of the first dose until 7 days after the date of the last dose
LLN, lower limit of normal

Oral presented at the European Hematology Association 2025 congress, held in Milan, Italy and virtually on 12–15 June 2025

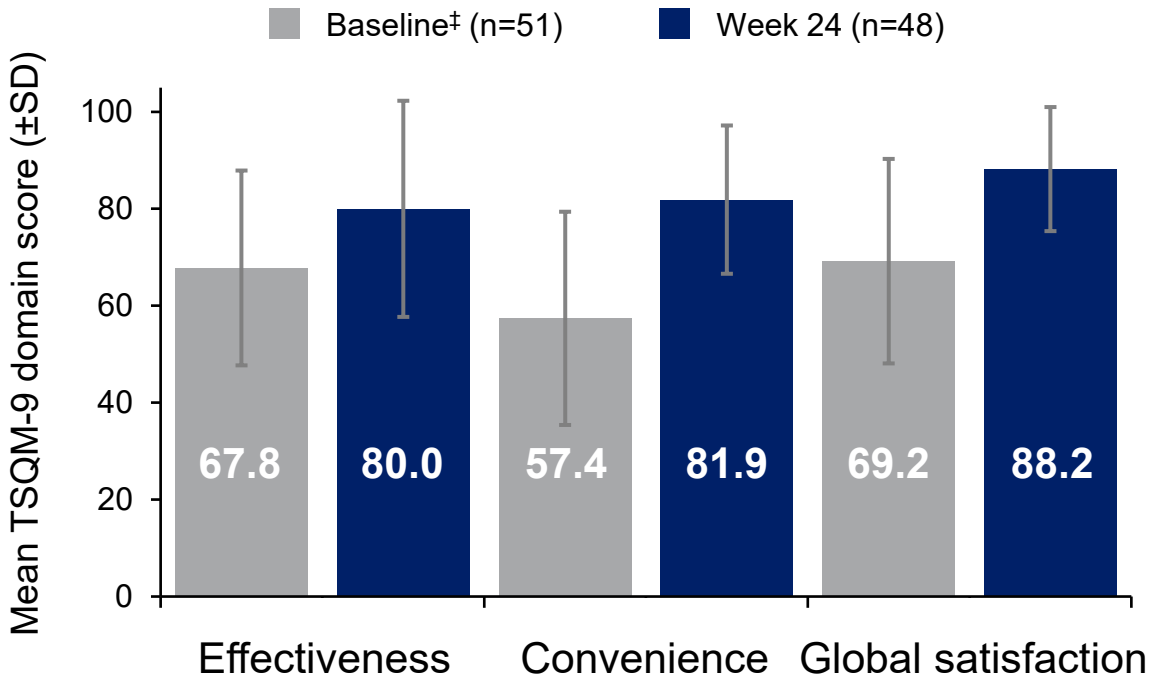
Mean FACIT-Fatigue and TSQM-9 domains scores improved

Adjusted mean change from baseline* in FACIT-Fatigue score at Day 168 was **+4.29** (95% CI 1.74, 6.85)†

Mean FACIT-Fatigue score during APPULSE-PNH



Mean TSQM-9 scores during APPULSE-PNH



Adjusted mean (95% CI) change from baseline:†,‡	Effectiveness	Convenience	Global satisfaction
	+12.54 (5.58, 19.49)	**+23.86** (17.62, 30.10)	**+18.53** (12.87, 24.19)

*Mean baseline FACIT-Fatigue score: 38.9 (SD 9.4); †Analyzed using a repeated measures model that adjusted for covariates;
‡Mean (SD) baseline scores in the TSQM-9 effectiveness, convenience and global satisfaction domains were 67.8 (20.1), 57.4 (22.0) and 69.2 (21.1), respectively
TSQM-9, Treatment Satisfaction Questionnaire for Medication – 9 items

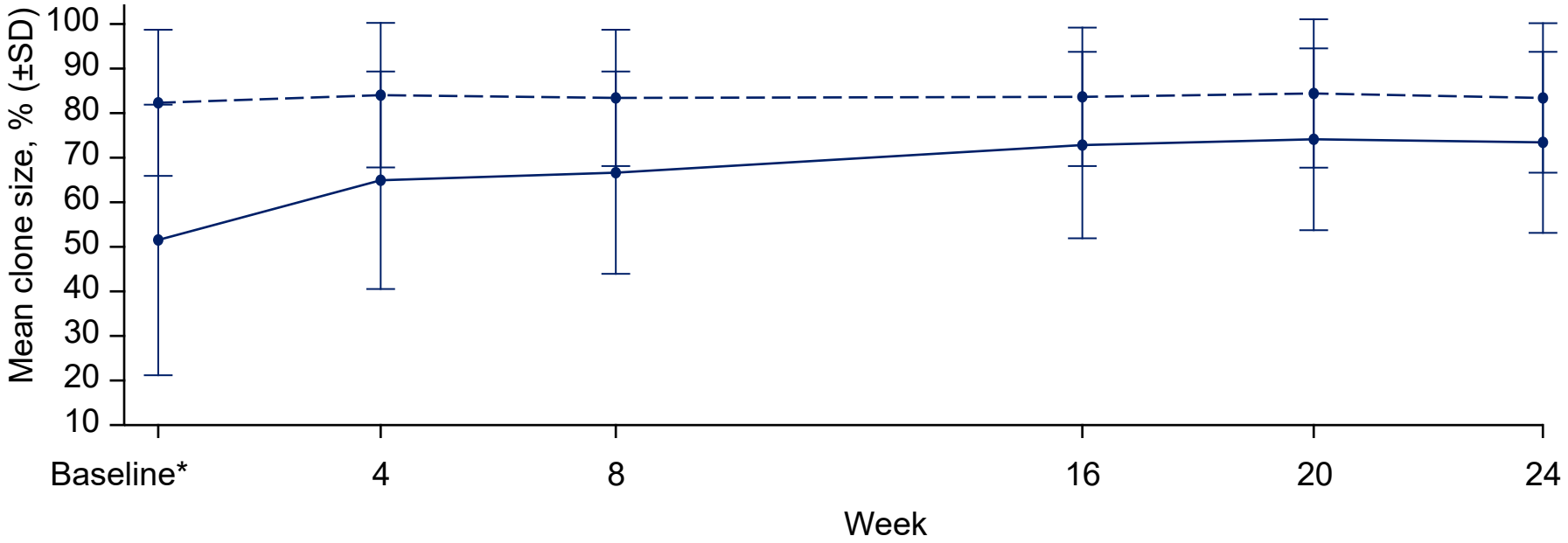
1. Cella D *et al. Cancer* 2002;94:528–38; 2. Montan I *et al. Value Health* 2018;21:1313–21

Oral presented at the European Hematology Association 2025 congress, held in Milan, Italy and virtually on 12–15 June 2025

Mean PNH RBC clone size increased to become similar to mean PNH granulocyte clone size

Mean change from baseline* in total PNH RBC clone size† (exploratory endpoint) at Day 168 was **+22.2%** (SD 16.2)

Mean total PNH RBC† and granulocyte clone size during APPULSE-PNH‡



Mean total PNH RBC† clone size at Week 24: **73.9%** (SD 20.4)

Patients with available data

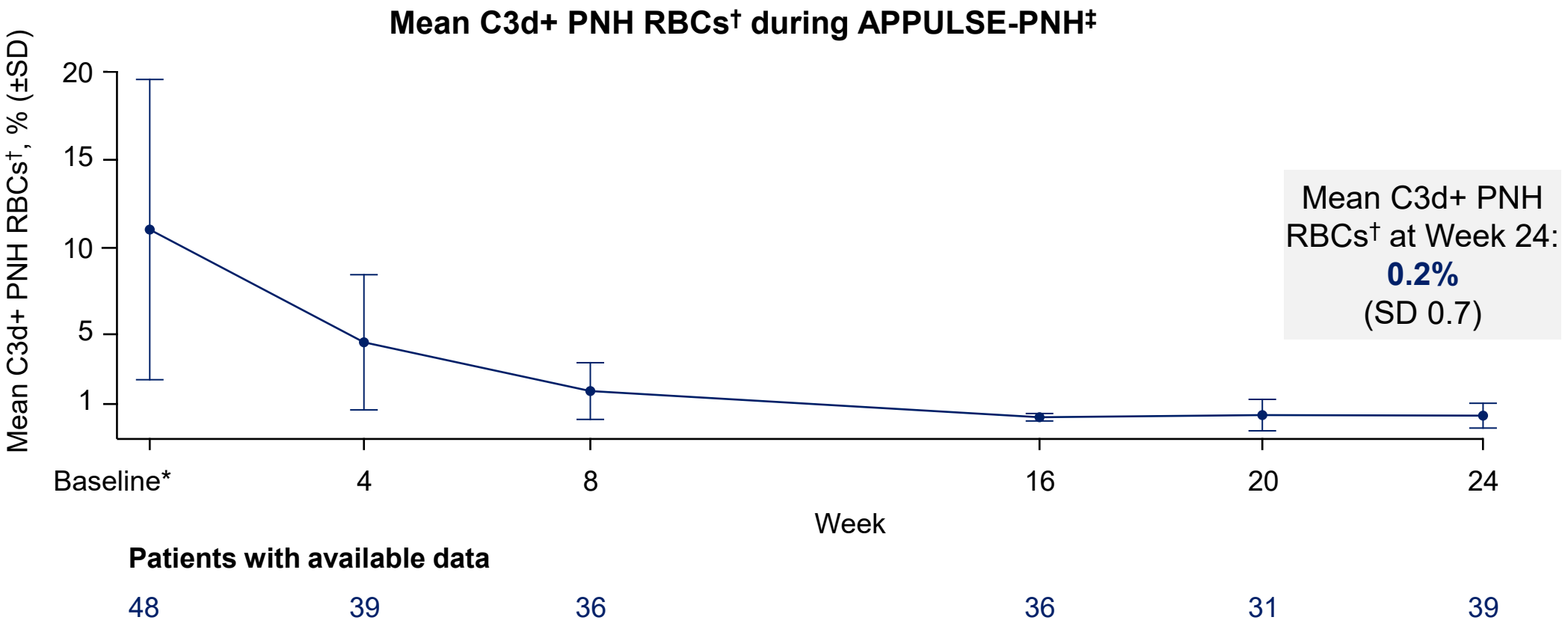
	Baseline*	4	8	16	20	24
—— PNH RBCs	49	44	41	45	46	46
– – PNH granulocytes	48	43	39	43	43	45

*Among the 46 patients who had available data at both baseline and Week 24 (mean baseline total PNH RBC clone size for these patients: 51.7% [SD 31.5]); †Type II + type III PNH RBCs; ‡At each visit, only patients with a value at both baseline and that visit are included

Oral presented at the European Hematology Association 2025 congress, held in Milan, Italy and virtually on 12–15 June 2025

Mean C3 deposition reduced to negligible levels by Week 16

Mean change from baseline* in C3d+ PNH RBCs† (exploratory endpoint) at Day 168 was **–11.6%** (SD 9.3)



*Among the 39 patients who had available data at both baseline and Week 24 (mean baseline C3d+ PNH RBCs for these patients: 11.8% [SD 9.2]); †Type II + type III PNH RBCs that were C3d+; ‡At each visit, only patients with a value at both baseline and that visit are included

Oral presented at the European Hematology Association 2025 congress, held in Milan, Italy and virtually on 12–15 June 2025

Iptacopan monotherapy was well tolerated with no new safety findings

Safety event, n (%)	Iptacopan 200 mg bid (N=52)
Any TEAE	44 (84.6)
Mild/moderate/severe TEAEs	27 (51.9)/15 (28.8)/2 (3.8)
Most common TEAEs*	
Headache	9 (17.3)
Diarrhea	6 (11.5)
Nasopharyngitis	6 (11.5)
Nausea	6 (11.5)
Serious TEAEs	2 (3.8)
Bacterial pneumonia	1 (1.9)
Pyrexia†	1 (1.9)
Traumatic subdural hematoma†	1 (1.9)
Iptacopan-related serious TEAEs	0
Deaths	0

No patients experienced a **MAVE** (secondary efficacy endpoint)

- **42.3%** (22/52) of patients had TEAEs in the **infections and infestations** system organ class
  - Infections likely caused by **encapsulated bacteria** were **bacterial pneumonia** (1.9%; 1/52) and **otitis media** (3.8%; 2/52)
- **One patient discontinued** iptacopan on Day 104 because of a **non-serious** TEAE of **palpitations** reported as suspected to be **related to iptacopan**

*Occurring in ≥10% of patients; †The serious TEAEs of pyrexia and traumatic subdural hematoma occurred concurrently in the same patient
MAVE, major adverse vascular event

Oral presented at the European Hematology Association 2025 congress, held in Milan, Italy and virtually on 12–15 June 2025

Conclusions

- In **anti-C5-experienced** patients with **Hb ≥10 g/dL**, **iptacopan** was **superior** after switch from anti-C5 therapy in **change from baseline in Hb**
- Iptacopan enabled **most patients** to achieve **Hb ≥12 g/dL** and **all patients** to maintain **transfusion independence**
- **Targeting factor B** with iptacopan **controlled anti-C5-induced EVH** while **maintaining IVH control**
- Patients also reported **improvements in fatigue** and **treatment satisfaction** scores
- Iptacopan was **well tolerated** with **no clinical BTH**, **MAVEs** or **new safety findings**[1,2]

Results from APPULSE-PNH and previous trials establish **oral iptacopan monotherapy** as a **potentially practice-changing** treatment capable of inducing **improvements in Hb to normal/near normal levels** by providing **comprehensive hemolysis control**[1,2]

1. Peffault de Latour R *et al. N Engl J Med* 2024;390:994–1008; 2. Risitano AM *et al. Lancet Haematol* 2025;12:e414–30

Oral presented at the European Hematology Association 2025 congress, held in Milan, Italy and virtually on 12–15 June 2025

Acknowledgments

- We thank the patients, their families, the investigators and staff at participating study sites
- This study was sponsored by Novartis
- We thank Jake Stoddart MRes, from AMICULUM, who provided medical writing support funded by Novartis Pharmaceuticals Corporation in accordance with Good Publication Practice 2022 guidelines

Scan to obtain the slides

https://tinyurl.com/KulasekararajS183