Dual Inhibition and Innovation: How Are We Redefining the PNH Patient Journey?

Dupla Proteção e Inovação: Como Estamos Redefinindo a Jornada do Paciente com HPN?

Dra. Morag Griffin

Material destinado a profissionais habilitados a prescrever e dispensar medicamentos.
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AstraZeneca

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Disclosures

- Lecture fees/honoraria: Pfizer, Alexion, Sobi, Amgen, Novartis,
- Consultancy: Regeneron
- Advisory board: Pfizer, Alexion, Sobi, Amgen, Novartis, Omeros

Patient case

26-year-old man

2005-2010 ***Dec.2015*** ***Dec.2016***

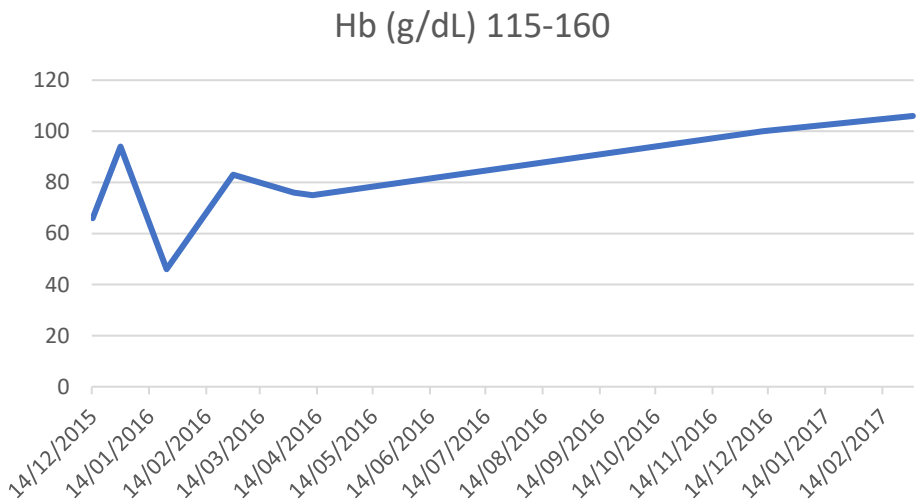
Transfusions

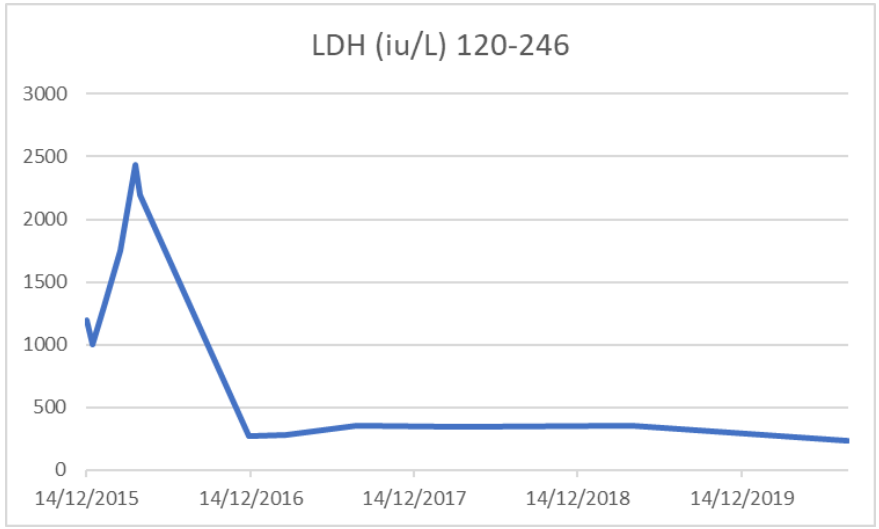
Eculizumab

- Haemoglobinuria – considered trauma related
- GI symptoms
- Appendicectomy; exploratory laparotomy

- 5 hospital admissions on arrival to UK
- Hb 66g/l, WCC 3 x10*9/l, plt 126 x10*9/l, retics 145; LDH 1747 IU/L (ULN 250IU/L)
- Ferritin 23ug/l – commenced replacement

- Referred to haematology for transfusions…
- Hb 83g/l; retics 144z10*9/l; LDH 1747 IU/l (ULN 250)
- Diagnosed with PNH
- Vaccinated





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Epidemiology of PNH: A rare disease[1-6]

Incidence and prevalence

- PNH is a rare disease
- Incidence is estimated to range from 0.08 to 0.35 per 100,000 person-years[1,2]
- Prevalence is estimated to range from 12 to 13 per million people[3]

Demographic characteristics

PNH can occur in any sex or any ethnic, geographical, or age group[4]

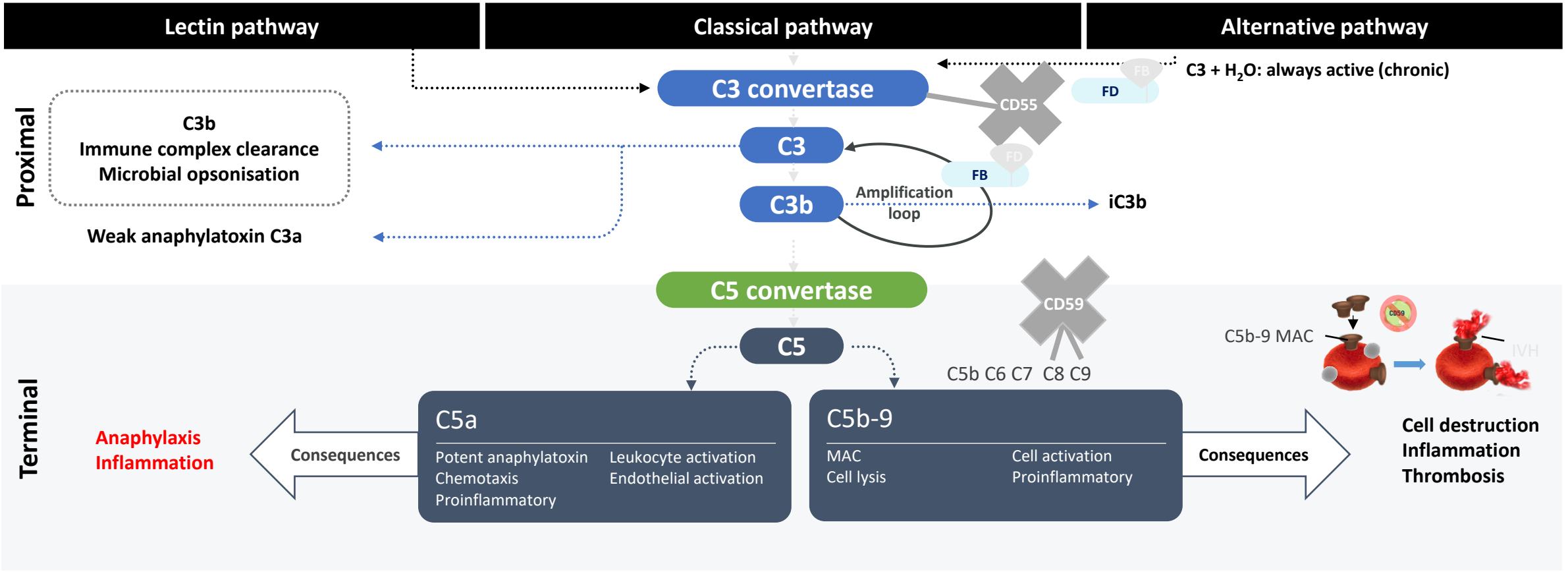
- Men and women are similarly affected[5]
- Median age at onset is approximately 40 years[5]
- Paediatric cases (< 18 years of age) are uncommon, with various studies suggesting that the rate is **10% or less** of reported PNH cases[6]

PNH, paroxysmal nocturnal haemoglobinuria.

1. Richards SJ, *et al. Eur J Haematol*. 2021;107(2):211–218; 2. Hansen DL, *et al. Clin Epidemiol*. 2020;12:497–508; 3. Jalbert JJ, *et al. Blood* 2019;34(S1):3407; 4. Schrezenmeier H, *et al. Haematologica*. 2014;99(5):922–929;
5. Brodsky RA. In: Hoffman R, *et al.*, eds. *Hematology: Basic Principles and Practice*. Seventh edition. Elsevier; 2018:415–424; 6. Ware RE, *et al. N Engl J Med*. 1991;325(14):991–996.

The complement pathway and its role in PNH and IVH[1–8]

PNH is a disease of impaired terminal complement regulation[9–11]

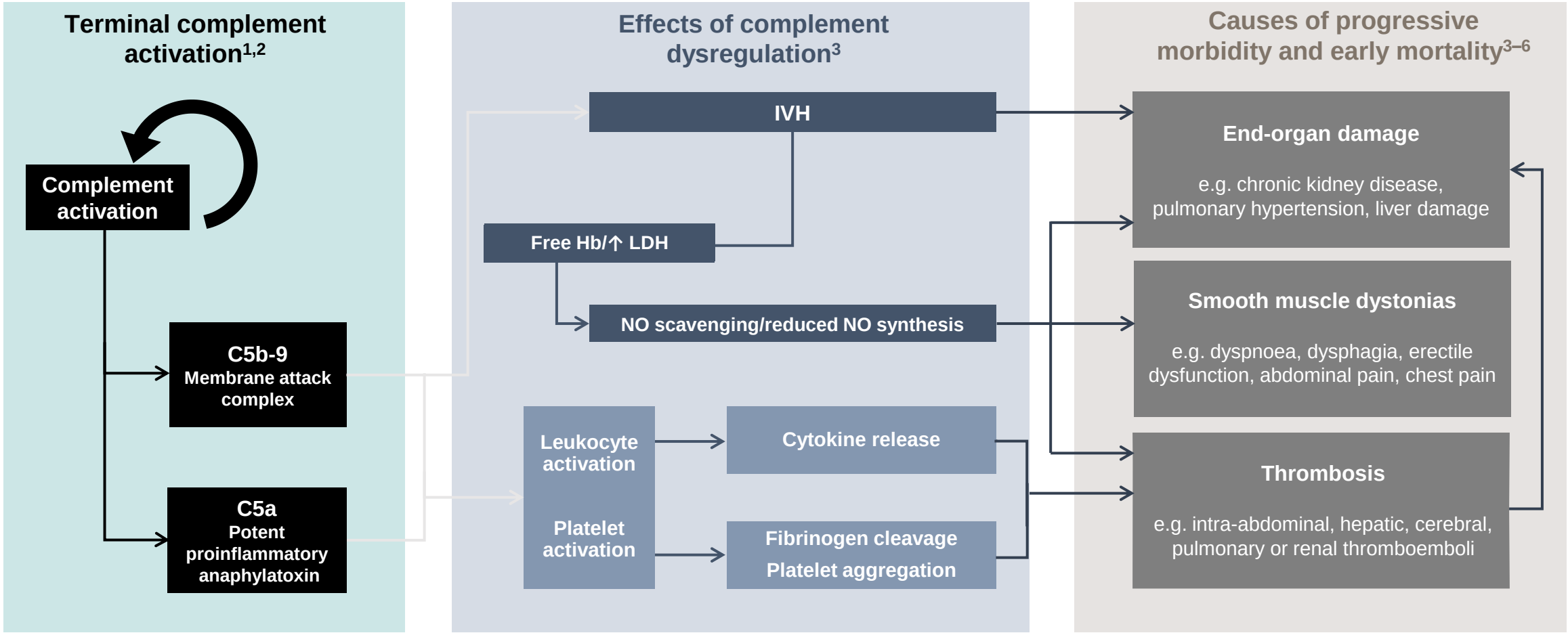


Adaptado de: Kelly R, et al. *Ther Clin Risk Manag*. 2009;5:911–921

C3, complement component 3; C5, complement component 5; FB, factor B; FD, factor D; IVH, intravascular haemolysis; MAC, membrane attack complex; PNH, paroxysmal nocturnal haemoglobinuria.

1. Kelly R, et al. *Ther Clin Risk Manag*. 2009;5:911–921; 2. Hill A, et al. *Nat Rev Dis Primers*. 2017;3:17028; 3. Notaro R, Sica M. *Semin Hematol*. 2018;55:130–135; 4. Ricklin D, et al. *Nat Rev Nephrol*. 2018;14(1):26–47; 5. Walport MJ. *N Engl J Med*. 2001;344:1058–1066; 6. Olutogun T, et al. *Blood Transfus*. 2015;13:363–369; 7. Murphy K, Weaver C. In: *Janeway's Immunobiology*. 9th ed. Garland Science/Taylor & Francis Group LLC; 2016:37–76; 8. Merle NS et al. *Front Immunol*. 2015;6:262; 9. Brodsky RA. *Blood*. 2014;18(124):2804–2811; 10. Hill A, et al. *Blood*. 2013;25(121):4985–4996; 11. Risitano AM, et al. *Immunol Rev*. 2023;313:262–278

IVH is a consequence of uncontrolled terminal complement activation in PNH[1]



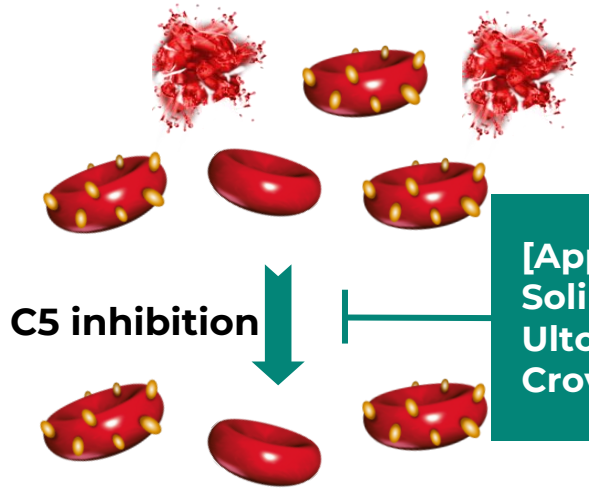
AP, anchor protein; GPI, glycosyl phosphatidylinositol; IVH, intravascular haemolysis; PNH, paroxysmal nocturnal haemoglobinuria.

1. Hill A, et al. *Blood*. 2013;25(121):4985–4996; 2. Kelly R, et al. *Ther Clin Risk Manag*. 2009;5:911–21; 3. Rother RP, et al. *JAMA*. 2005;293:1653–62; 4. Brodsky RA. Hematology: Basic Principles and Practices. 4th ed. Philadelphia, PA: Elsevier Churchill Livingstone; 2005:419–427; 5. Bessler M, Hiken J. *Hematology Am Soc Hematol Educ Program*. 2008:104–110; 6. Devos T, et al. *Eur J Haematol*. 2018;101:737–749.

BLOCKING TERMINAL COMPLEMENT ACTIVATION

C5 inhibitor Ultomiris® is the current standard of care in patients diagnosed with PNH where available[1]

- Reduce **IVH**[2,3]
- Reduce transfusions[2]
- Improve symptoms[2,3]
- Reduce thrombotic events[2,3]
- Reduce organ damage[2,3]
- Improve morbidity[2,3]
  - LDH normalization was achieved during the initial evaluation period and maintained through 2 years in the open-label extension of the 301 and 302 studies of Ultomiris®[4]



IVH is the major contributor to morbidity associated with PNH
All PNH treatments need to achieve IVH inhibition

IVH, intravascular hemolysis; **LDH**, lactate dehydrogenase; **PNH**, paroxysmal nocturnal hemoglobinuria.

1. Kulasekararaj AG, et al. *Ther Adv Hematol*. 2022;13. doi:10.1177/20406207221091046 **2.** Hillmen P, et al. *Br J Haematol*. 2013;162(1):62-73. **3.** Kulasekararaj A, et al. *HemaSphere*. 2023;7(S3):1427-1428.
4. Kulasekararaj A, et al. *Eur J Haematol.* 2022;109(2):205-214. **5.** Brodsky RA. Paroxysmal nocturnal hemoglobinuria. In: Hoffman R, et al, eds. 2005:419- 427. **6.** Hill A, et al. *Br J Haematol*. 2007;137(3):181-192.
7. Sharma VR. *Clin Adv Hematol Oncol*. 2013;11(9):2-8.

Effects of Complement C5 Blockade by Eculizumab in PNH long term data[1-8]

- Reduction of hemolysis
- Reduction of transfusion requirement
- Improvement in anemia
- Reduction in organ damage: pHTN3, renal function
- Reduction in D-Dimer and thromboembolic complications
- Improvement in platelet count in some patients
- Improved pregnancy outcomes
- Risk of meningococcal infection

[h]

Table I. Most frequently reported AEs (by MedDRA preferred term) in patients with PNH.

	Spontaneous number of AEs per 100 PY		Solicited number of AEs per 100 PY		Total
MedDRA preferred term	Serious	Nonserious	Serious	Nonserious	
Haemoglobin decreased	2·4	0·9	12·7	3·4	19·4
Fatigue	0·4	1·7	1·6	3·9	17·6
Pyrexia	1·6	0·9	3·9	3·3	9·7
Headache	0·6	1·0	1·4	6·2	9·2
Haemolysis	2·7	0·5	3·5	2·3	9·0
Dyspnoea	0·5	0·6	1·8	4·3	7·2
Abdominal pain	0·7	0·6	2·1	3·7	7·1
Platelet count decreased	0·6	0·5	3·7	2·2	7·1
Transfusion	0·6	0	5·0	0·2	5·8

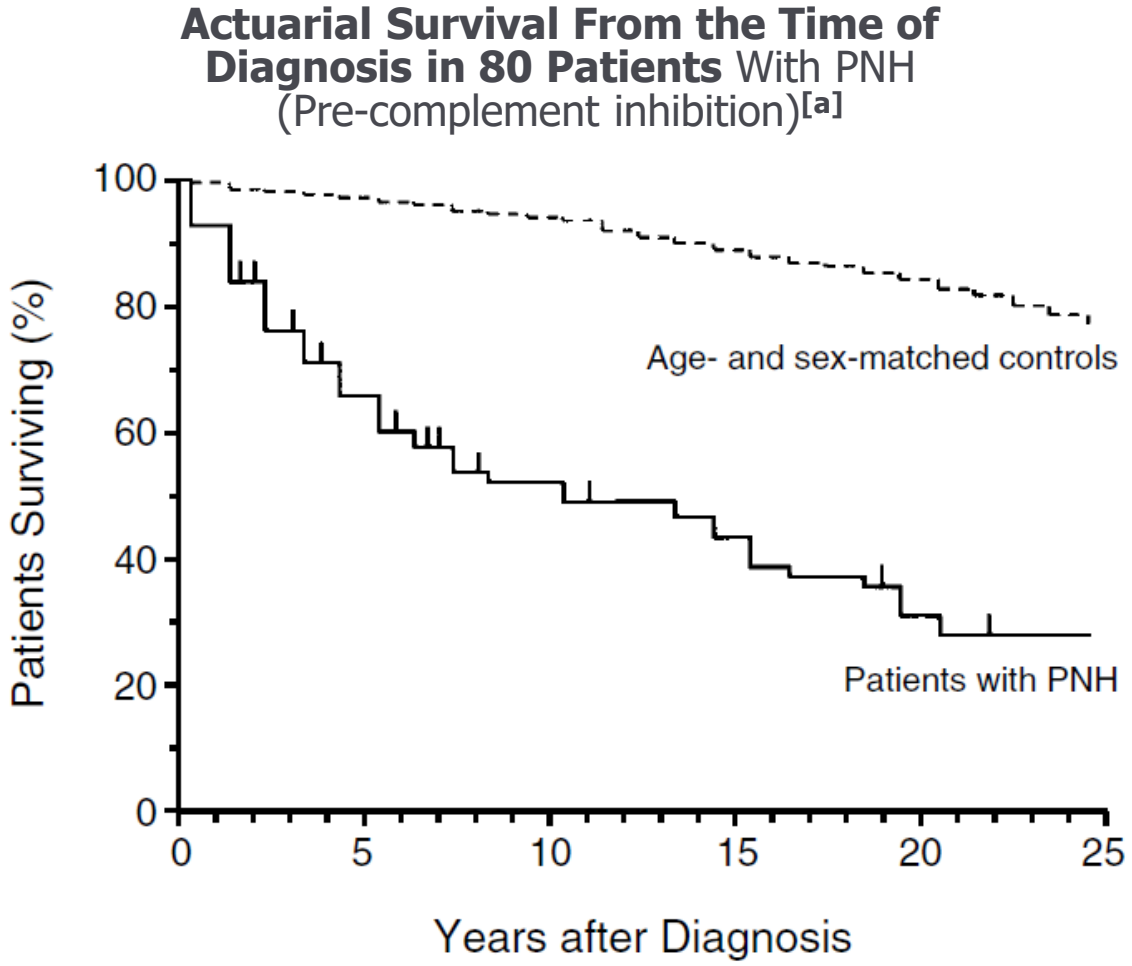
Incidence rates are expressed as per 100 PY.

AEs, adverse events; MedDRA, Medical Dictionary for Regulatory Activities; PNH, paroxysmal nocturnal haemoglobinuria; PY, patient-years.

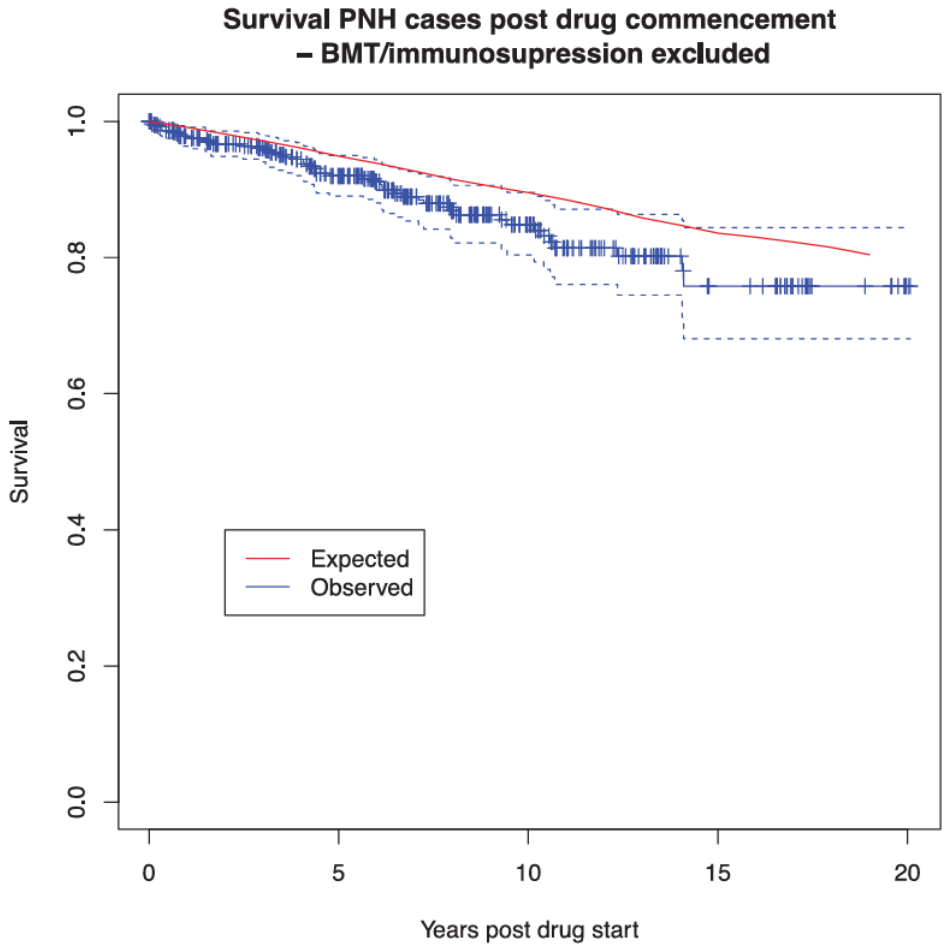
pHTN: pulmonary hypertension

1. Hillmen P, et al. Blood. 2007;110:4123-4128; 2. Brodsky RA, et al. Blood. 2008;111:1840-1847; 3. Hill A, et al. Br J Haematol. 2010;149:414-245; 4. Hillmen P, et al. Am J Hematol. 2010;85:553-559; 5. Hillmen P, et al. Br J Haematol. 2013;162:62-73; 6. Weitz IC, et al. Thromb Res. 2012;130:361-368; 7. Kelly RJ, et al. N Engl J Med 2015; 373:1032-1039; 8. Socié G, et al. Br J Haematol. 2019;185:297-310.

Long-Term Clinical Benefits of Terminal Complement Inhibition in Patients With PNH[1,2]



Adaptado de: Hillmen P, et al. N Engl J Med. 1995;333:1253-1258



Adaptado de: Kelly R, et al. Blood 2023;2023021762

1. Hillmen P, et al. N Engl J Med. 1995;333:1253-1258; 2.Kelly R, et al. Blood 2023;2023021762.

ULTOMIRIS®

(ravulizumabe)

Solução para Diluição para Infusão

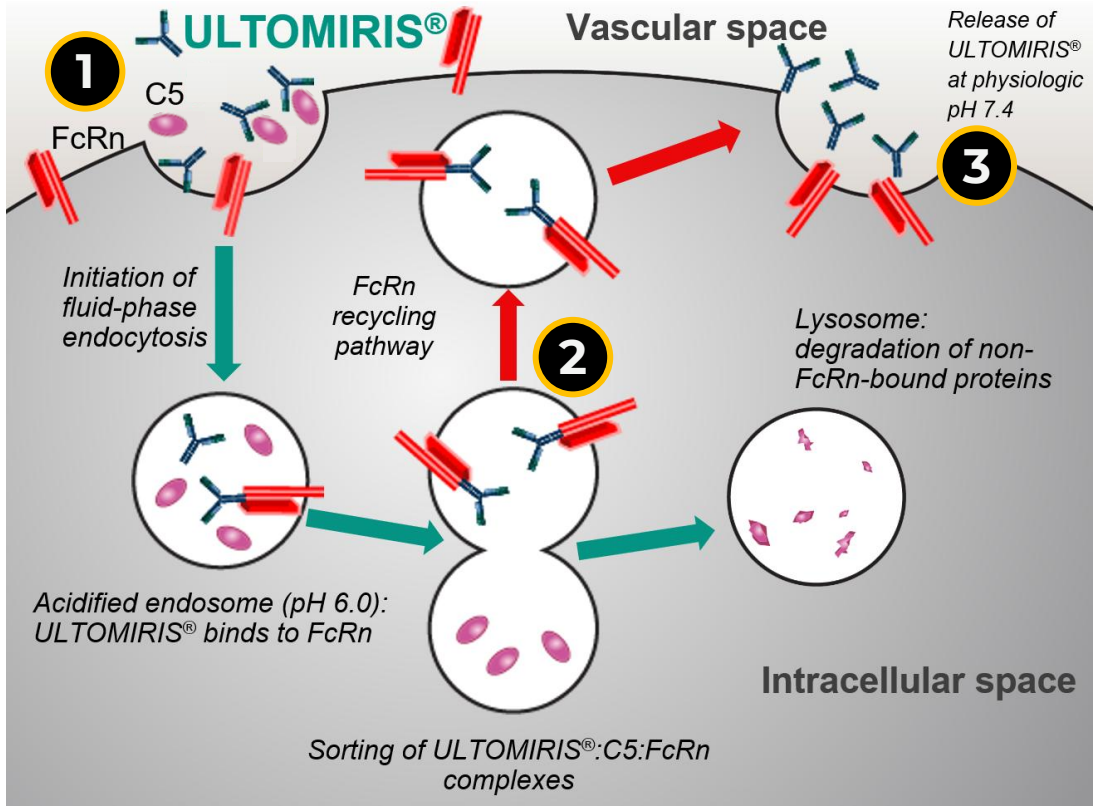
AstraZeneca

Material destinado a profissionais de saúde prescritores ou dispensadores de medicamentos

ULTOMIRIS® has a pharmacodynamic profile that offers immediate, complete and sustained terminal complement inhibition from the first infusion[1–3]

1 ULTOMIRIS® binds to C5 in the blood **to immediately inhibit terminal complement activity**[1]

2 ULTOMIRIS® was designed to allow the antibody* to take part in **multiple rounds of C5 binding** & **neutralisation**[4]



3 Additional improvements were introduced† to **further extend the activity (half-life) of ULTOMIRIS®**[4]

, complement component 5; FcRn, neonatal Fc receptor.

*The antibody dissociates from the C5 once in the endosome and then binds efficiently to FcRn for recycling.[4] †Improvement in FcRn recycling.[4]

†The effects of these improvements were studied and evaluated in a murine model.[4]

1. Ultomiris® (ravulizumabe) Bula do Profissional da Saúde. Bulário Eletrônico. Agência Nacional de Vigilância Sanitária (ANVISA). Disponível em: https://consultas.anvisa.gov.br/#/bulario/q/?numeroRegistro=198110004; 2. Lee JW, et al. *Blood*. 2019;6(133):530–539; 3. Kulasekararaj AG, et al. *Blood*. 2019;6(133):540–549; 4. Sheridan D, et al. *PLoS ONE*. 2018;13:e0195909C5.

ULTOMIRIS® provides you with the reassurance of a well-established efficacy profile[1–7]

Study 301 (N=246)[1*†]

- Phase 3 multicentre, randomised, active-controlled, open-label, non-inferiority study to evaluate the efficacy and safety of ULTOMIRIS® vs SOLIRIS® in treatment-naïve adults with a documented diagnosis of PNH
- Patients were treated with ULTOMIRIS® or SOLIRIS® over a 26-week initial evaluation period

Study 302 (N=195)[2†‡]

- Phase 3 multicentre, randomised, active-controlled, open-label, non-inferiority study to evaluate the efficacy and safety of ULTOMIRIS® vs SOLIRIS® in SOLIRIS®-experienced adult patients with a documented diagnosis of PNH
- Patients were treated with ULTOMIRIS® or SOLIRIS® over a 26-week initial evaluation period

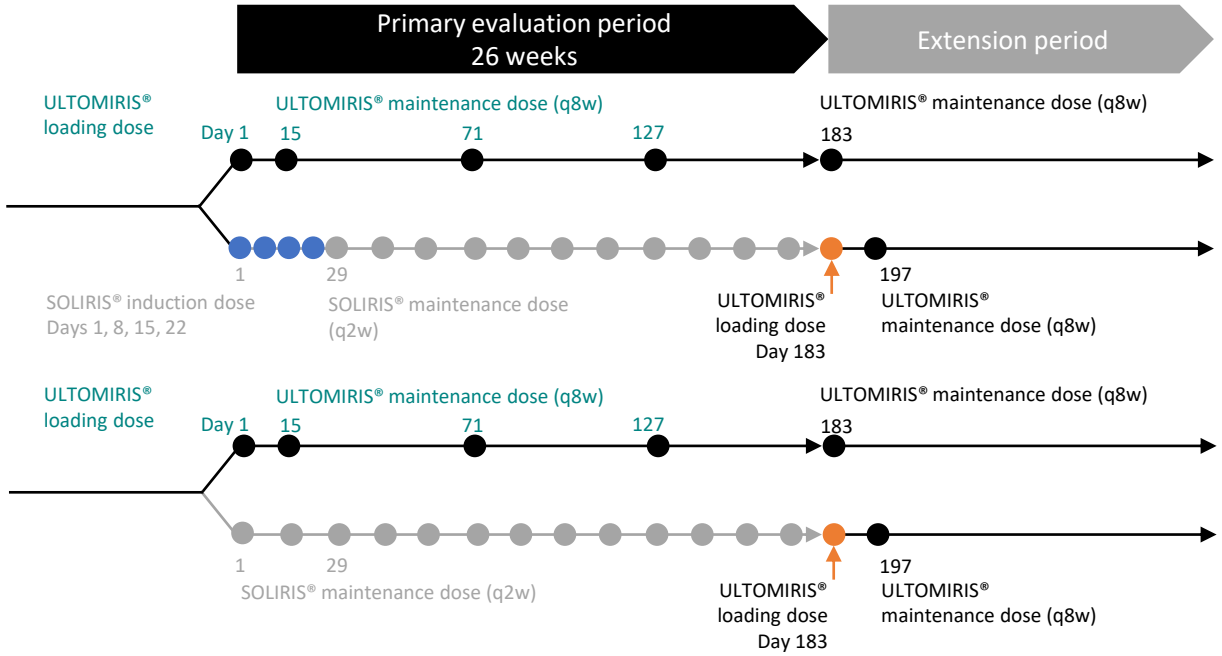


Figure adapted from Peffault de Latour R, et al. 2020.[4]

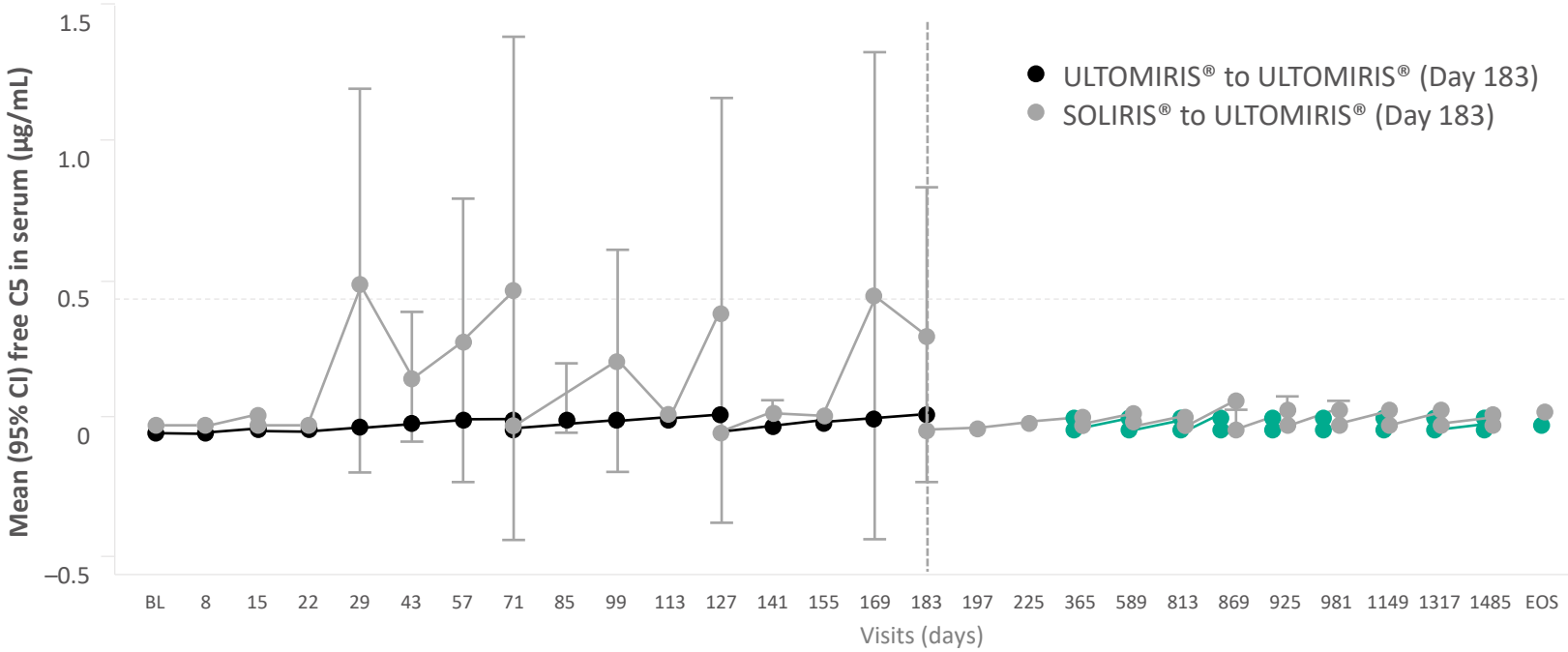
The robust safety and efficacy of ULTOMIRIS® are backed by the largest body of evidence in complement inhibitor-naïve patients with PNH to date[1]

LDH, lactate dehydrogenase; MAVE, major adverse vascular event; P_{inf}, p value for non-inferiority; PNH, paroxysmal nocturnal haemoglobinuria; q8w, every 8 weeks; ULN, upper limit of normal.

1. Lee JW, et al. *Blood*. 2019;133(6):530–539; 2. Kulasekararaj AG, et al. *Blood*. 2019;133(6):540–549; 3. Kulasekararaj AG, et al. *Eur J Haematol*. 2022;3(109):205-214; 4. Peffault de Latour R, et al. *Br J Haematol*. 2020;191:476–485; 5. Ultomiris® (ravulizumabe) Bula do Profissional da Saúde. Bulário Eletrônico. Agência Nacional de Vigilância Sanitária (ANVISA). Disponível em: https://consultas.anvisa.gov.br/#/bulario/q/?numeroRegistro=198110004.; 6. Lee JW, et al. *Blood*. 2019;133(6):530–539. Supplementary data; 7. Kulasekararaj AG, et al. *Blood*. 2019;133(6):540–549. Supplementary data.

ULTOMIRIS® maintained serum free C5 levels below 0.5 µg/mL throughout the dosing interval, and this was demonstrated over long-term follow-up (up to 4 years)[1–3]

- Free C5 levels over time among patients receiving ULTOMIRIS® for up to 4 years (302 study)*†[1]



	BL	8	15	22	29	43	57	71	85	99	113	127	141	155	169	183	197	225	365	589	813	869	925	981	1149	1317	1485	EOS
ULTOMIRIS® to ULTOMIRIS®	97	95	96	95	95	96	96	96	94	93	94	96	96	95	95	95			95	94	77	3	4	54	45	22	23	57
SOLIRIS® to ULTOMIRIS®	98	98	97	96	96	97	97	96	97	96	96	95	95	95	94	94	95	94	92	94	72	2	4	44	34	19	17	54

Figure adapted from Kulasekararaj A, et al. 2023.[1]

Serum free C5 levels below 0.5 µg/mL are associated with complete terminal complement inhibition[2,3]

C5, complement component 5; CI, confidence interval.
*197 patients were randomised to receive ULTOMIRIS® or SOLIRIS® in the initial evaluation period of the 302 study. The cohort entering the open-label extension, and receiving ongoing treatment with ULTOMIRIS®, included 96 patients initially assigned to ULTOMIRIS® and 95 patients initially assigned to SOLIRIS®. Overall ULTOMIRIS® treatment exposure in this cohort was 527.04 patient-years.[1]
†The dotted horizontal line indicates complete free C5 suppression (< 0.5 µg/mL); the vertical horizontal line indicates the ULTOMIRIS® open-label extension period.[1]
1. Kulasekararaj A, Brodsky RA, Griffin M, Röth A, Piatek CI, Ogawa M, et al. P772: LONG-TERM RAVULIZUMAB TREATMENT IN COMPLEMENT INHIBITOR-EXPERIENCED PATIENTS WITH PNH PROVIDES DURABLE CONTROL OF INTRAVASCULAR HEMOLYSIS WITH LOW INCIDENCE OF MAJOR ADVERSE VASCULAR EVENTS AND DEATH. HemaSphere. 2023 Aug 1;7(S3):e6327336–6.2. Lee JW, et al. *Blood*. 2019;6(133):530-539; 3. Kulasekararaj AG, et al. *Blood*. 2019;6(133):540–549.

ULTOMIRIS® provided rapid control of LDH level (<1.5× ULN), and this was sustained for up to 4 years[1,2]

- LDH levels over time among patients receiving ULTOMIRIS® for up to 4 years (302 study)*†[1]

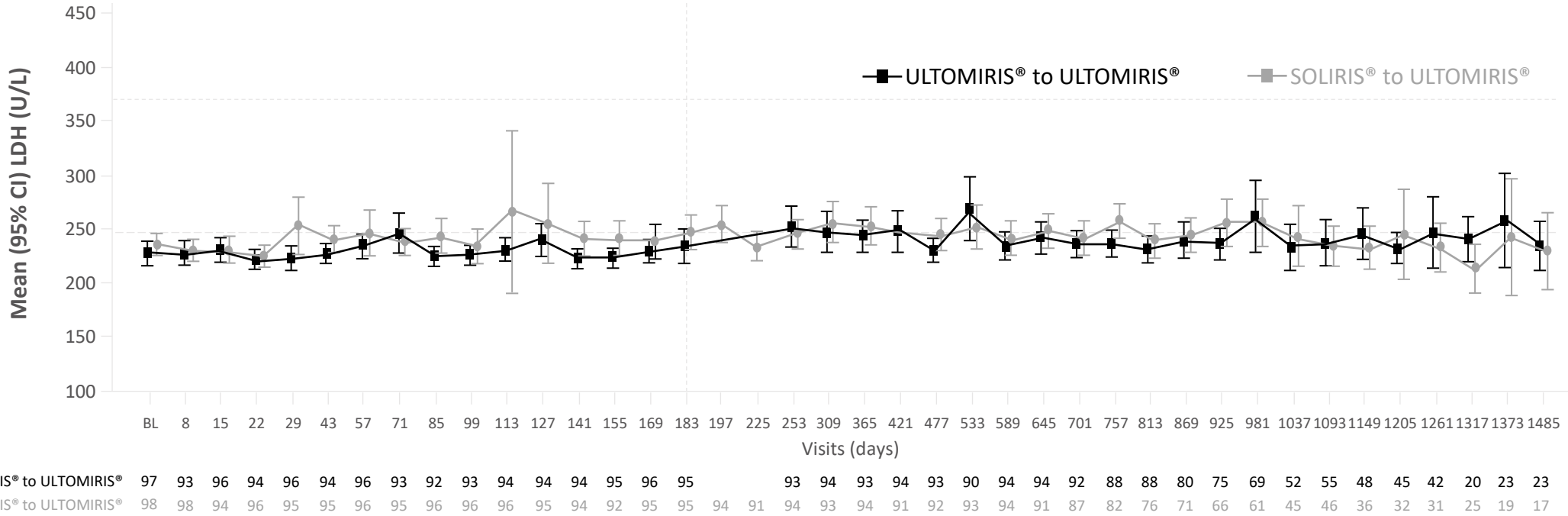


Figure adapted from Kulasekararaj A, et al. 2023.[1]

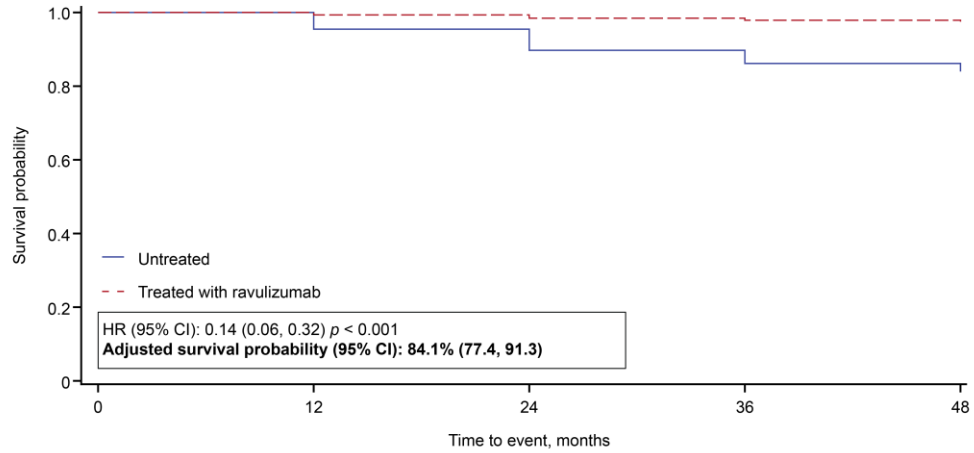
The majority of patients treated with ULTOMIRIS® (~93% [178/192]) were free of breakthrough IVH through 4 years[1]

C5, complement component 5; CI, confidence interval; LDH, lactate dehydrogenase; ULN, upper limit of normal.
*197 patients were randomised to receive ULTOMIRIS® or SOLIRIS® in the initial evaluation period of the 302 study. The cohort entering the open-label extension, and receiving ongoing treatment with ULTOMIRIS®, included 96 patients initially assigned to ULTOMIRIS® and 95 patients initially assigned to SOLIRIS®. Overall ULTOMIRIS® treatment exposure in this cohort was 527.04 patient-years.[1]
†The dashed horizontal line indicates 1 × ULN (246 U/L) and the dotted horizontal line indicates 1.5 × ULN (369 U/L); the vertical horizontal line indicates the ULTOMIRIS® open-label extension period.[1]
1. Kulasekararaj A, Brodsky RA, Griffin M, Röth A, Piatek CI, Ogawa M, et al. P772: LONG-TERM RAVULIZUMAB TREATMENT IN COMPLEMENT INHIBITOR-EXPERIENCED PATIENTS WITH PNH PROVIDES DURABLE CONTROL OF INTRAVASCULAR HEMOLYSIS WITH LOW INCIDENCE OF MAJOR ADVERSE VASCULAR EVENTS AND DEATH. HemaSphere. 2023 Aug 1;7(S3):e6327336–6.; 2. Schrezenmeier H, et al. *Ther Adv Hematol.* 2020;11:2040620720966137.

Long-Term Follow-up of Study 301 and Comparisons with Patients of the International PNH Registry

- Outcomes for up to 6 yrs in C5 inhibitor-naïve pts with PNH from study 301
  - Comparison with survival with untreated patients of the International PNH Registry
- 246 inhibitor-naïve pts with PNH & LDH level ≥ 1.5 × ULN & at least one sign or symptom of PNH) randomized to receive ravulizumab or eculizumab
- Data were available for 244/246 patients
  - At baseline, all 246 patients had LDH levels > 1.5 × ULN
  - At 26 weeks: 87.1% achieved LDH levels ≤ 1.5 × ULN, maintained in 79.3% at last follow-up
- MAVE:
  - At baseline, 17.1% of patients had a history of MAVEs (MAVE rate: 3.4 per 100 patient-years)
  - Proportion of ravulizumab-treated patients who experienced MAVEs:
    - n = 11 [4.5%]: 13 events, MAVE rate: 1.4 per 100 Patient years
- Prior to randomization 24.8% of patients did not need transfusions; increasing at 26 weeks to 73.6% and was maintained in 53.9% of patients for the entire OLE
- 33 patients (13.4%) discontinued ravulizumab treatment during the entire study period
  - Death (n = 8), pt choice (n = 7), physician decision (n = 5), pregnancy (n = 4), AE (n = 3), lost to follow-up (n = 1) and other (n = 5)

Figure 1. Adjusted survival analysis of ravulizumab-treated and untreated patients with PNH



Covariates included in the final adjusted model include age at PNH diagnosis, sex and transfusion history at baseline.
CI, confidence interval; HR, hazard ratio; PNH, paroxysmal nocturnal hemoglobinuria.

Ravulizumab associated with an adjusted survival of 84.1% at 4 years (HR [95%CI]: 0.14 (0.06, 0.32), p < 0.001)

Mortality was 3.5-fold lower than that observed in untreated PNH registry patients

Kulasekararaj A, Brodsky R, Schrezenmeier H, Griffin M, Röth A, Piatek C, et al. Ravulizumab demonstrates long-term efficacy, safety and favorable patient survival in patients with paroxysmal nocturnal hemoglobinuria. Annals of Hematology. 2025 Jan 22;

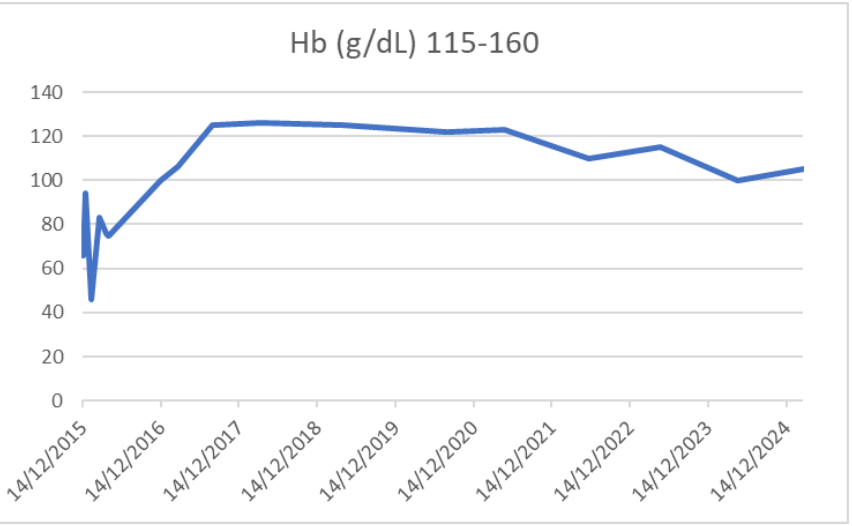
Patient case

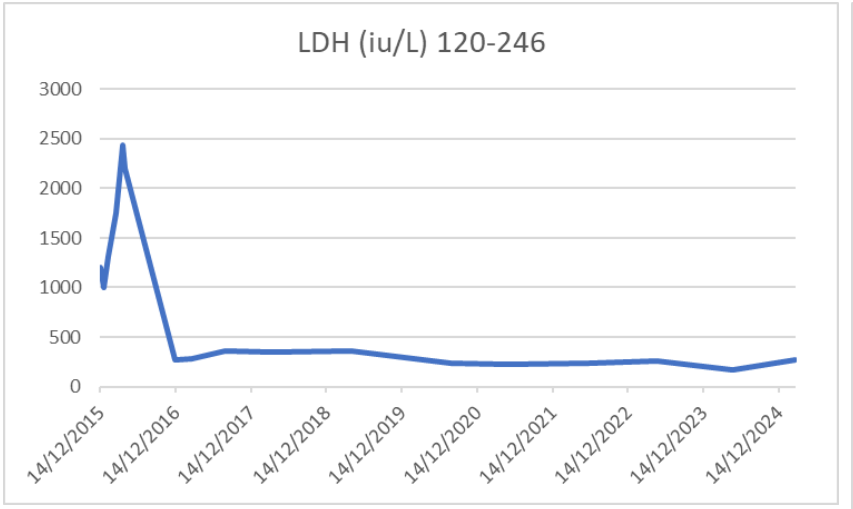
26-year-old man

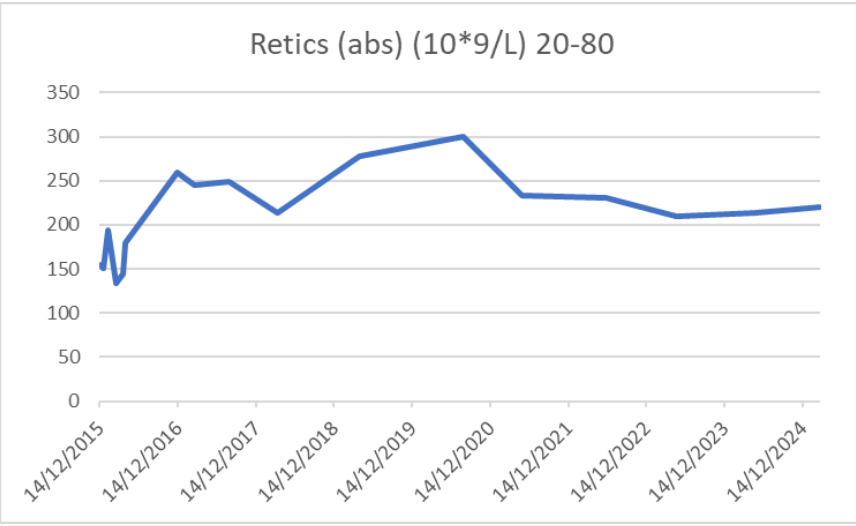
- 5 hospital admissions on arrival to UK
- Hb 66g/l, WCC 3 x10*9/l, plt 126 x10*9/l, retics 145; LDH 1747 IU/L (ULN 250IU/L)
- Ferritin 23ug/l – commenced replacement

- Referred to haematology for transfusions…
- Hb 83g/l; retics 144z10*9/l; LDH 1747 IU/l (ULN 250)
- Diagnosed with PNH
- Vaccinated

- Much improved
- Keen to switch to ravulizumab
- Transitioned well, no issues





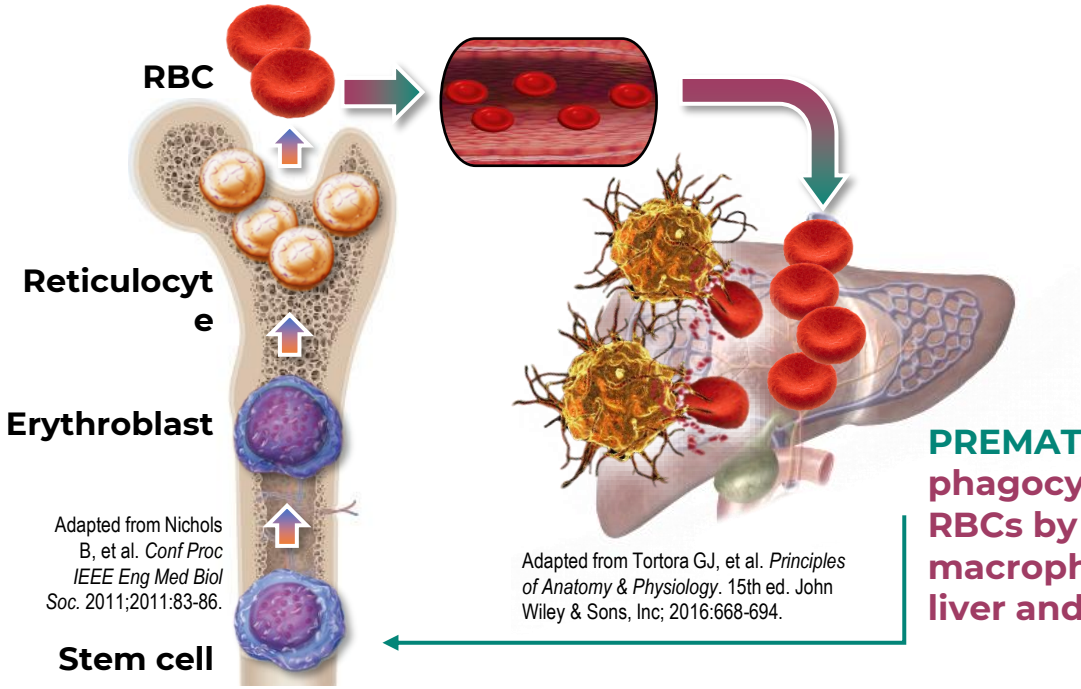


Author Slide – Dr. Morag Griffin

CLINICALLY SIGNIFICANT EVH

- **EVH is a mechanistic consequence of treatment with C5 inhibitors Soliris® and Ultomiris® [1,2]**
- Caused by **ongoing C3 deposition on surviving yet defective red blood cells**
  - Rendering them susceptible to **phagocytosis in the liver or spleen** as they are no longer destroyed by IVH
- There is no agreed upon definition or characterization of the clinical relevance of EVH[3]
- **If the EVH is clinically significant, this may be addressed with proximal inhibition[4,5]**

RBC lifespan in circulation is REDUCED[6]



PREMATURE phagocytosis of RBCs by macrophages in liver and spleen[1,6]

Erythropoiesis[7]

This process stimulates new RBC production, but may result in anemia if production cannot keep up with destruction[8]

BTH, breakthrough hemolysis; **csEVH,** clinically significant extravascular hemolysis; **EVH**, extravascular hemolysis; **IVH,** intravascular hemolysis; **PNH**, paroxysmal nocturnal hemoglobinuria; **RBC**, red blood cell.

1. Risitano AM, et al. *Blood.* 2009;113(17):4094-4100. **2.** Hill A, et al. *Nat Rev Dis Primers.* 2017;3:17028. doi:10.1038/nrdp.2017.28 **3**. Shammo J, et al. *J Blood Med*. 2022;13:425-437. **4.** Kulasekararaj AG, et al. *Am J Hematol*. 2021;96(7):E232-E235. **5.** Lee JW, et al. *HemaSphere*. 2023;7(S3):1424-1426. **6.** Dhaliwal G, et al. *Am Fam Phys*. 2004;69(11):2599-2606. **7.** Nichols B, et al. *Conf Proc IEEE Eng Med Biol Soc*. 2011;2011:83-86. **8**. Tortora GJ, et al. *Principles of Anatomy & Physiology*. 15th ed. John Wiley & Sons, Inc; 2016:668-694. **9.** Notaro R, Luzzatto L. *N Engl J Med.* 2022;3878(2):160-166. **10.** Hillmen P, et al. *N Engl J Med.* 2021;384(11):1028-1037. **11.** Griffin M, et al. *Blood.* 2023;141(1):116-120.

cs-EVH is not considered life-threatening[1]

Hb[1,2]

- RBCs are destroyed faster than they are created, resulting in anaemia

Absolute reticulocyte count[2,3]

- Replace destroyed RBCs
- More accurate marker of EVH than LDH

- Anaemia[2,4]
- Fatigue[4]
- Dyspnea[4]
- Possible need for transfusion[1,3]

Patients with cs-EVH are not at increased risk of PNH-specific, life-threatening complications such as IVH and thrombosis[1,5]

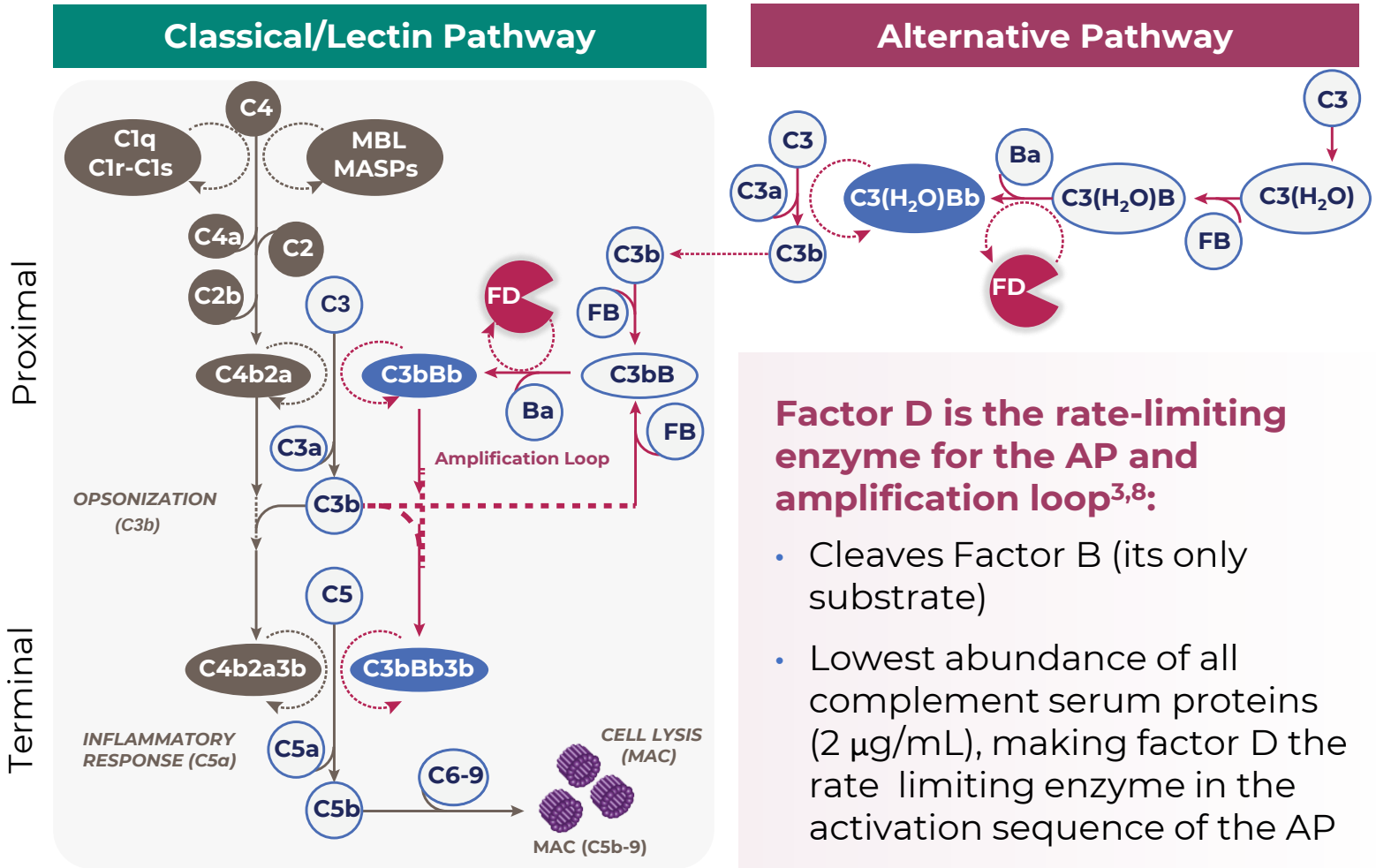
cs-EVH; clinically significant extravascular haemolysis; Hb, haemoglobin; LDH, lactate dehydrogenase; RBC, red blood cell.

1. Hill A, et al. *Nat Rev Dis Primers*. 2017;(3):17028; 2. Brodsky RA. In: Hoffman R, et al, eds. *Hematology: Basic Principles and Practices*. 6th ed. Livingstone; 2013:415–424; 3. McKinley CE, et al. *Blood*. 2017;130 (suppl 1): 3471;4. Dhaliwal G, et al. *Am Fam Phys*. 2004;69(11):2599–2606; 5. Kulasekararaj AG, et al. *Ther Adv Hematol*. 2022;(13):20406207221091046.

UPSTREAM COMPLEMENT INHIBITION

- Alternative pathway inhibition may reduce early activation of complement on the surface of PNH RBCs, preventing csEVH[1,2]
- **Factor D** is a critical control point in the alternative pathway, proximal of the hemolysis effector molecules[3,4]

Simplified Complement Pathway[3,5-7]



Shaded box represents a cell or tissue surface (solid phase)

Factor D is the rate-limiting enzyme for the AP and amplification loop[3,8]:

- Cleaves Factor B (its only substrate)
- Lowest abundance of all complement serum proteins (2 µg/mL), making factor D the rate limiting enzyme in the activation sequence of the AP

AP, alternative pathway; **csEVH**, clinically significant extravascular hemolysis; **PNH**, paroxysmal nocturnal hemoglobinuria; **RBCs**, red blood cells.

1. Risitano A, et al. *Front Immunol.* 2019;10:1157. doi: 10.3389/fimmu.2019.01157 **2.** Lee JW, et al. *HemaSphere.* 2023;7(S3):1424-1426. **3.** Barratt J and Weitz I. *Front Immunol*. 2021;12:712572. doi:10.3389/fimmu.2021.712572 **4.** Lee JW, et al. *Expert Rev Clin* Pharmacol. 2022;15(7):851-861. **5.** Merle NS, et al. *Front Immunol*. 2015;6:262. doi:10.3389/fimmu.2015.00262. **6.** Kenawy H, et al. *Front Immunol.* 2015;6:215. doi:10.3389/fimmu.2015.00215. **7.** Yuan X, et al. *Haematologica*. 2017;102:466-475.**8.** Schreiber RD, et al. *Proc. Nat. Acad. Sci. U S A.* 1978;75(8):3948-3952.

Voydeya®
(danicopana) 50mg · 100mg
Comprimidos revestidos

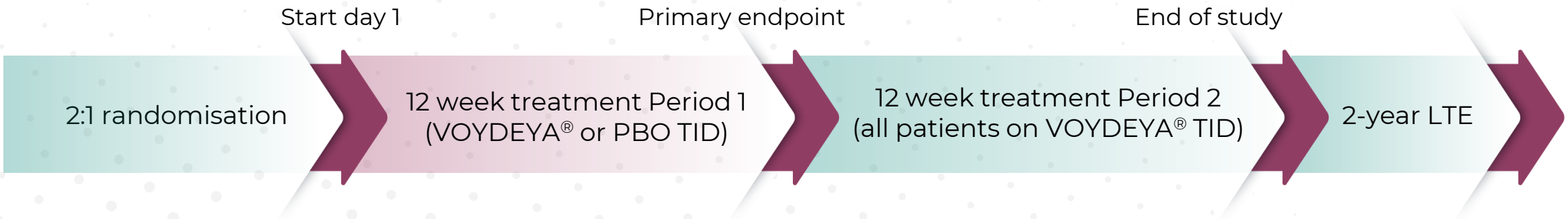
Clinical trials

The Alpha study

AstraZeneca

Phase 3 ALPHA trial: total duration 2 years and 24 weeks[1,2]

VOYDEYA® was studied in a randomised, placebo-controlled, clinical trial[1]



Patient population	Patients ≥18 years with PNH with cs-EVH • Hgb ≤9.5 g/dL • ARC ≥120 x 10^9/L • On SOLIRIS® or ULTOMIRIS® >6 mo
Dosing	VOYDEYA® 150 mg PO TID • Dose escalation to 200 mg PO TID permitted based on clinical response
Efficacy measures	Primary: change from baseline to week 12 in Hgb Key secondary endpoints at week 12 • Proportion of patients with Hgb increase of ≥2 g/dL without transfusion • Proportion of patients with transfusion avoidance • Change from baseline in FACIT-Fatigue score and ARC
Safety	TEAEs and laboratory abnormalities assessed throughout

ARC, absolute reticulocyte count; cs-EVH, clinically significant extravascular hemolysis; FACIT, Functional Assessment of Chronic Illness Therapy; Hgb, hemoglobin; LTE, long-term extension; PBO, placebo; PNH, paroxysmal nocturnal hemoglobinuria; TEAE, treatment emergent adverse event; TID, thrice daily.

1. Lee JW, et al. *Lancet Haematol*. 2023;10:e955–e965; 2. VOYDEYA® Summary of Product Characteristics.

Demographics and baseline labs

Demographics[1]

	VOYDEYA® + ULTOMIRIS® or SOLIRIS® (n = 49)	Placebo + ULTOMIRIS® or SOLIRIS® (n = 24)
Age (years)		
Median (IQR)	57.0 (42.0–67.0)	55.0 (44.5–66.0)
Sex, n (%)		
Male	21 (43%)	9 (38%)
Female	28 (57%)	15 (63%)
Race, n (%)		
White	21 (43%)	10 (42%)
Asian	21 (43%)	9 (38%)
Not reported/unknown	3 (6%)	5 (21%)
American Indian or Alaska native	1 (2%)	0
Black	2 (4%)	0
Other	1 (2%)	0

Disease characteristics[1]

	VOYDEYA® + ULTOMIRIS® or SOLIRIS® (n = 49)	Placebo + ULTOMIRIS® or SOLIRIS® (n = 24)
Haemoglobin (g/dL)		
Mean (SD)	7.61 (0.95)	7.87 (1.03)
ARC (10^9/L)		
Mean (SD)	251.98 (99.96)	229.61 (116.14)
LDH (U/L)		
Mean (SD)	299.25 (105.21)	275.83 (67.65)
FACIT-Fatigue score		
Mean (SD)	34.19 (11.01)	33.61 (10.74)
Transfusion instances*		
Mean (SD)	2.6 (2.1)	2.3 (1.4)
C5 inhibitor, n (%)		
ULTOMIRIS®	32 (65%)	13 (54%)
SOLIRIS®	17 (35%)	11 (46%)

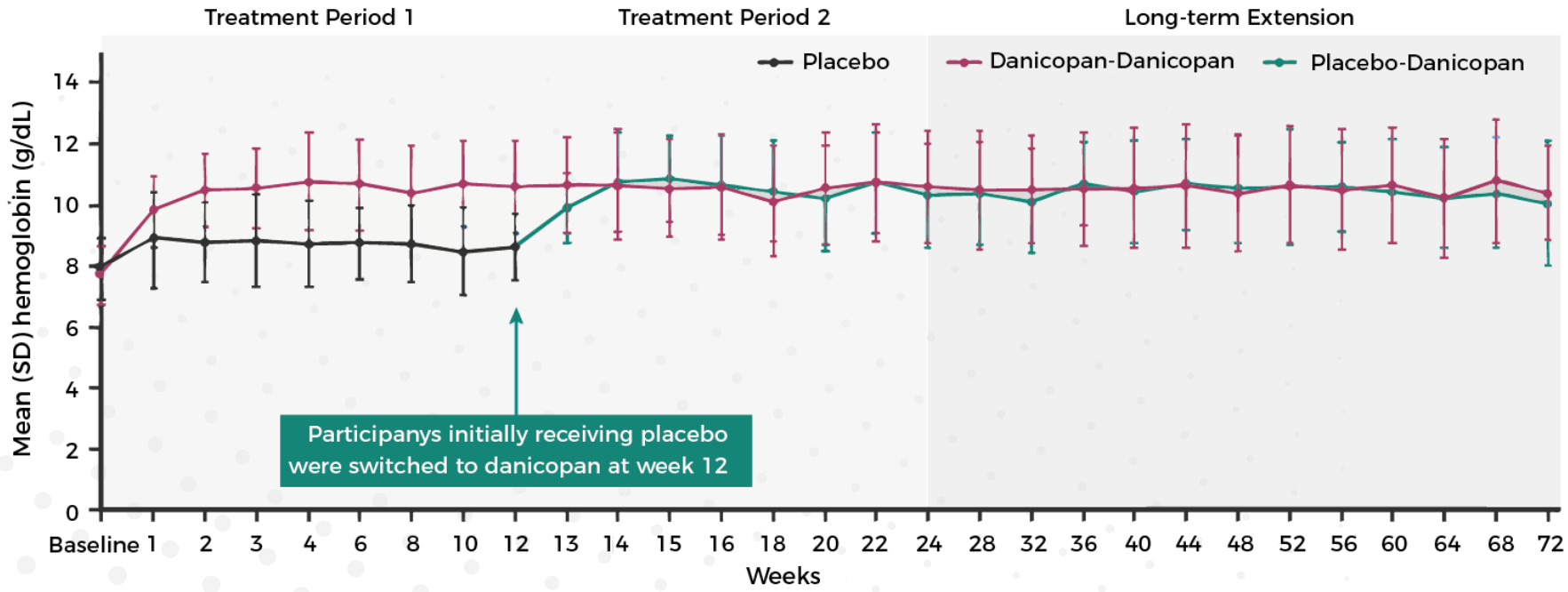
Tables adapted from Lee JW, et al. 2023.[1]

*During the 6 months prior to screening.

ARC, absolute reticulocyte count; C5, complement component 5; FACIT, Functional Assessment of Chronic Illness Therapy; IQR, interquartile range; LDH, lactate dehydrogenase; SD, standard deviation.

1. Lee JW, et al. *Lancet Haematol*. 2023;10:e955–e965; 2. VOYDEYA® Summary of Product Characteristics.

Long term extension: HB response

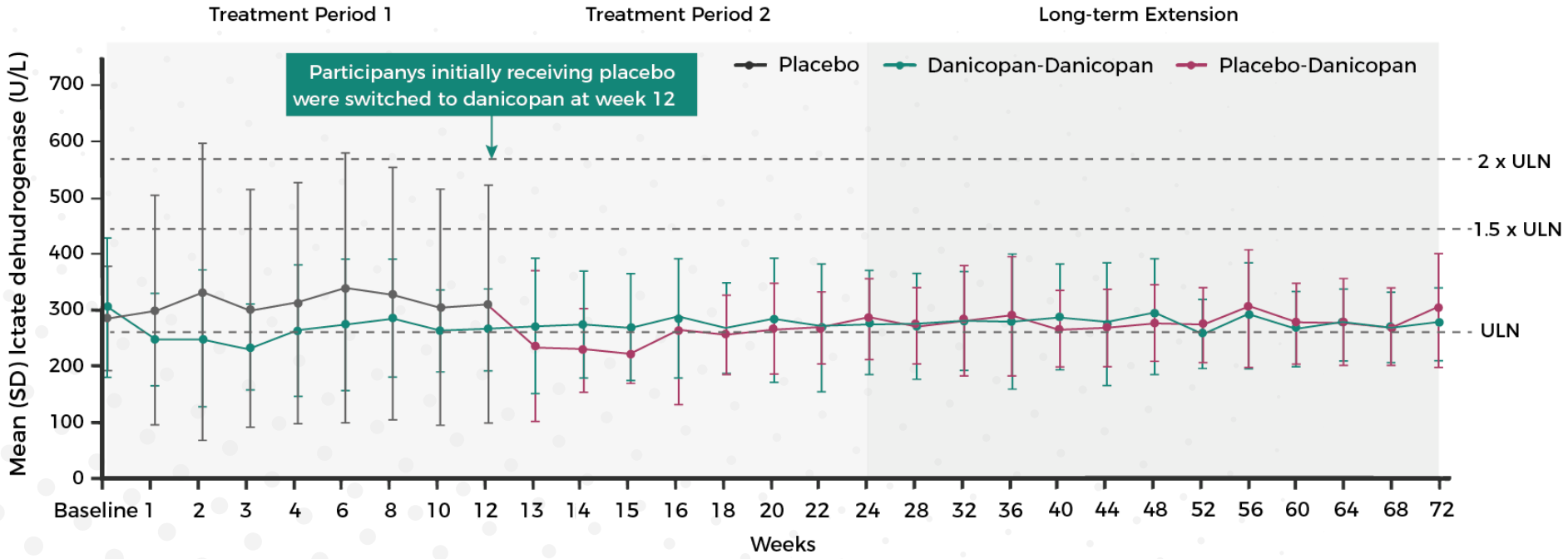


Weeks	BL	1	2	3	4	6	8	10	12	13	14	15	16	18	20	22	24	28	32	36	40	44	48	52	56	60	64	68	72
Danicopan-Danicopan, n	57	50	55	46	52	50	46	38	47	42	45	40	46	40	41	43	47	42	45	38	43	42	40	36	41	35	36	42	38
Placebo-Danicopan, n	29	25	26	24	27	27	24	22	24	24	23	22	26	23	21	21	20	21	21	23	21	20	23	19	21	21	22	21	20

Change in Hb across 72 weeks of treatment. Summary of actual Hb values, irrespective of transfusions, over 72 weeks of treatment with Voydeya® as an add-on therapy. Mean (SD) values of Hb (g/dL) for treatment groups are plotted across each time point, and corresponding n values are shown in the table below. BL, baseline

Kulasekararaj A et al. Blood. 2025 Feb 20;145(8):811-822.

Long term extension: LDH response



Weeks	BL	1	2	3	4	6	8	10	12	13	14	15	16	18	20	22	24	28	32	36	40	44	48	52	56	60	64	68	72
Danicopan-Danicopan, n	56	51	57	54	56	54	54	51	52	53	53	51	54	54	49	54	52	51	49	51	53	51	48	44	48	45	47	47	46
Placebo-Danicopan, n	28	28	29	27	25	28	25	26	25	26	25	25	27	26	27	27	26	26	25	23	23	24	24	24	24	23	24	23	22

Change in LDH across 72 weeks of treatment. Summary of actual values of LDH over 72 weeks of treatment with Voydeya® as an add-on therapy. Mean (SD) values of LDH (U/L) for treatment groups are plotted across each time point, and corresponding n value are shown in the table below. BL, baseline.

Kulasekararaj A et al. Blood. 2025 Feb 20;145(8):811-822.

Phase 3 ALPHA trial: safety data

VOYDEYA®, in combination with Soliris® and Ultomiris®, was associated with a generally acceptable adverse event profile[1]

	VOYDEYA® plus ULTOMIRIS® or SOLIRIS® (N=49)	Placebo plus ULTOMIRIS® or SOLIRIS® (N=24)
Any TEAE*	35 (71%) [106]	15 (63%) [65]
Any SAE	2 (4%) [2]	1 (4%) [2]
Abdominal pain	0	1 (4%) [1]
Anaemia	0	1 (4%) [1]
Cholecystitis	1 (2%) [1]	0
COVID-19	1 (2%) [1]	0
Any TEAEs by relationship		
Related	9 (18%) [22]	7 (29%) [12]
Not related	30 (61%) [84]	15 (63%) [53]
SAEs by relationship		
Related	0	0
Not related	2 (4%) [2]	1 (4%) [2]
Grade 3 TEAEs	7 (14%) [9]	3 (13%) [3]
AEs of special interest		
Meningococcal infections	0	0
Liver enzyme elevations†	6 (12%) [9]	2 (8%) [3]
AEs leading to withdrawal of study drug‡	2 (4%) [3]	1 (4%) [1]
Death	0	0

Data are n (%) [number of events]. Grade was not collected for serious adverse events, adverse events of special interest, or adverse events leading to discontinuation.
*Two participants had haemolysis in the VOYDEYA® group, based on investigator discretion. Both were non-serious and resolved without dose changes or red blood cell transfusions. One participant had haemolysis (LDH value 1.2 × ULN), as well as grade 1 skin abrasion and abrasion wound over the right palm thenar eminence. The other participant had haemolysis (LDH value 1.2 × ULN), as well as grade 3 increased concentrations of ALT and grade 1 increased concentrations of AST. †None of the liver enzyme elevations were serious. ‡One participant in the VOYDEYA® group had an adverse event that started during treatment period 1 related to study drug that led to treatment withdrawal during treatment period 2, and the participant discontinued treatment according to protocol-specified liver enzyme elevation discontinuation criteria. One participant in the VOYDEYA® group had two adverse events of grade 3 AST increase related to study drug; the participant recovered after drug withdrawal. One participant in the placebo group had one adverse event of grade 2 AST increase related to the study drug.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.
1. Lee JW, et al. *Lancet Haematol*. 2023;10:e955–e965.

VOYDEYA®, in combination with Soliris® and Ultomiris®, was associated with a generally acceptable adverse event profile[1]

Phase 3 ALPHA trial: safety data (continued)

	VOYDEYA® plus ULTOMIRIS® or SOLIRIS® (n=49)			Placebo plus ULTOMIRIS® or SOLIRIS® (n=49)		
	Grade 1–2	Grade 3	Grade 4–5	Grade 1–2	Grade 3	Grade 4–5
Anaemia	0	0	0	2 (8%)	1 (4%)	0
Asthenia	0	0	0	3 (13%)	1 (4%)	0
Cholecystitis	0	1 (2%)	0	0	0	0
Contusion	1 (2%)	0	0	3 (13%)	0	0
COVID-19	1 (2%)	1 (2%)	0	0	0	0
Diarrhoea	4 (8%)	0	0	3 (13%)	0	0
Headache	5 (10%)	0	0	1 (4%)	0	0
Increased ALT	0	2 (4%)	0	0	0	0
Increased AST	1 (2%)	1 (2%)	0	2 (8%)	0	0
Increased BP	0	1 (2%)	0	0	0	0
Insomnia	0	0	0	3 (13%)	0	0
Leukopenia*	0	1 (2%)	0	0	0	0
Neutropenia*	0	2 (4%)	0	0	0	0
Thrombocytopenia	0	0	0	0	1 (4%)	0

Table adapted from Lee JW, et al. 2023.[1]

Data are n (%). Grade 1–2 events occurring in ≥10% of patients and all grade 3–5 events are shown. Presented adverse event terms included grade 1 or 2 events reported in ≥10% of participants in either treatment group and all events of grade 3 or above.
*1 participant in the VOYDEYA® group had both leukopenia and neutropenia.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; C5, complement component 5; ULN, upper limit of normal.

1. Lee JW, et al. *Lancet Haematol*. 2023;10:e955–e965.

Patients with symptomatic anaemia on C5 inhibition due to extravascular haemolysis[1-3]

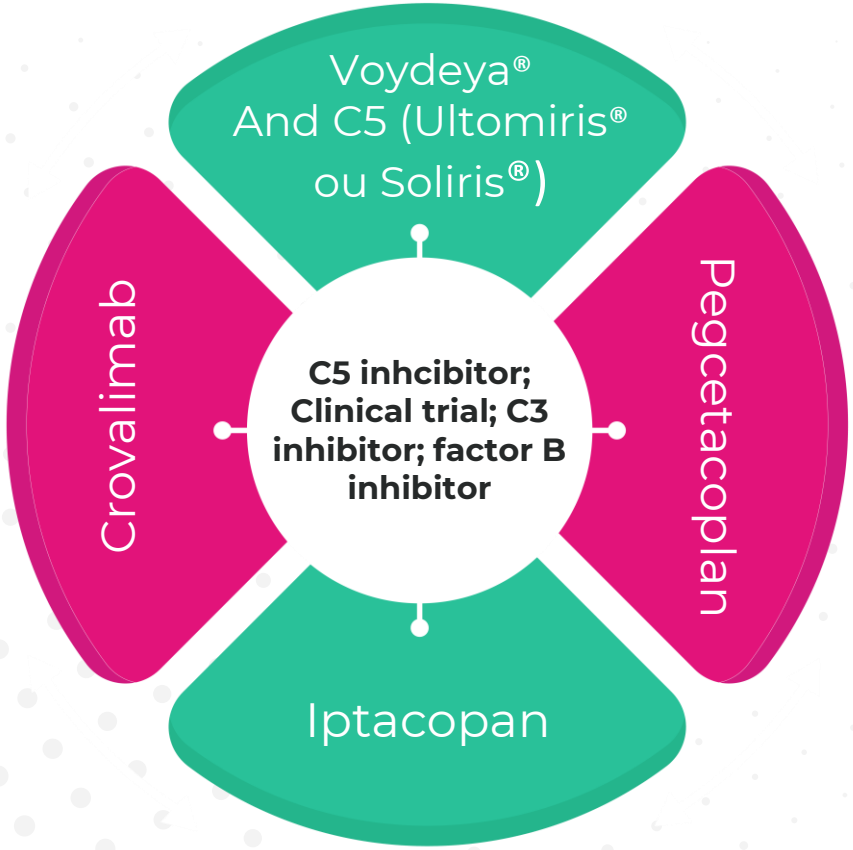
Treatment	Method of administration	Advantages
Pegcetacoplan C3 inhibitor	Sc self-administered twice a week infusion	Non-oral (if GI issues) Not daily
Voydeya® (danicopana) 50mg · 100mg Comprimidos revestidos + ULTOMIRIS® (ravulizumabe) Solução para Diluição para Infusão ou SOLIRIS® (eculizumabe) (add on oral factor D therapy)	TDS oral treatment added to C5 inhibitor	Remain with C5 inhibitor ´backbone´ incase of breakthrough/missed tablets
Iptacopan Factor B Inhibitor	Oral twice a day	Monotherapy oral

1. Bula do produto Voydeya® (danicopana). AstraZeneca Brasil LTDA; 2. Bula do produto Empaveli® (pegcetacoplan). Apellis; 3. Bula do produto Fabhalta® (iptacopan). Novartis

Treatment decisions for patients with symptomatic anemia due to EVH in 2025:

Clinician decisions

- Current PNH disease control
- Method of administration
- Symptoms of EVH
- Thrombotic history
- Anticipated compliance
- Family planning
- Longevity of data
- Availability of treatment



Patient decisions

- Current PNH symptoms
- Method of administration
- Quality of life
- Lifestyle factors
- Anticipated compliance
- Family planning
- Longevity of data

Author Slide – Dr. Morag Griffin

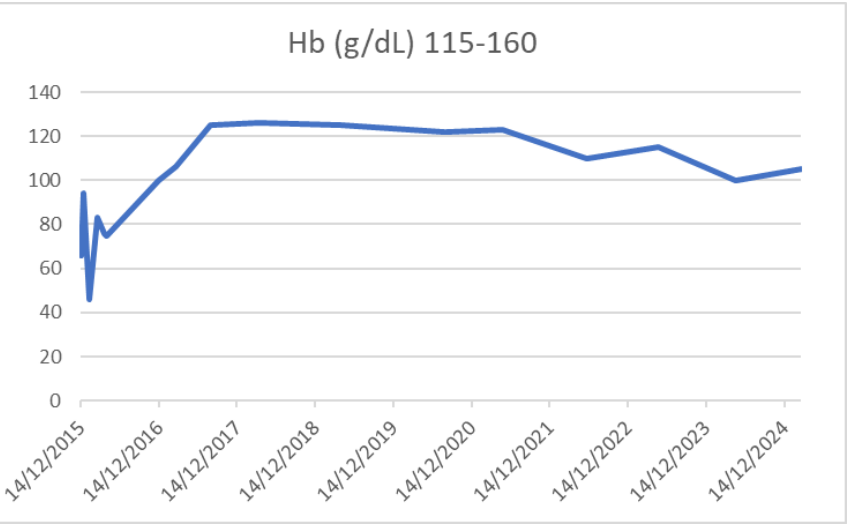
What about our patient?

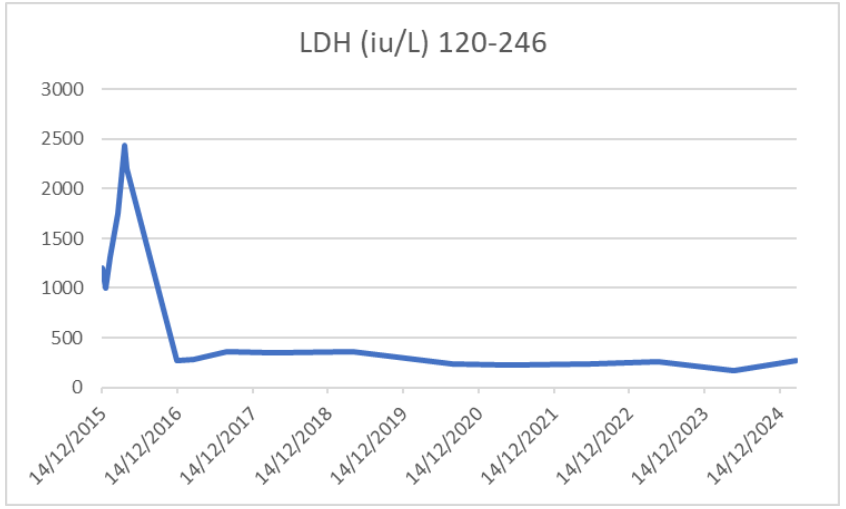
26-year-old man

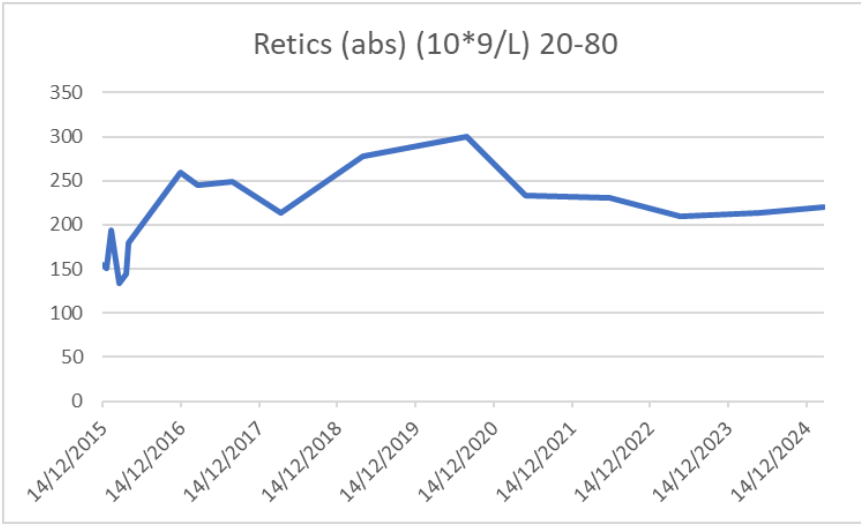
- 5 hospital admissions on arrival to UK
- Hb 66g/l, WCC 3 x10*9/l, plt 126 x10*9/l, retics 145; LDH 1747 IU/L (ULN 250IU/L)
- Ferritin 23ug/l – commenced replacement

- Referred to haematology for transfusions…
- Hb 83g/l; retics 144z10*9/l; LDH 1747 IU/l (ULN 250)
- Diagnosed with PNH
- Vaccinated

- Much improved
- Keen to switch to ravulizumab
- Transitioned well, no issues







Author Slide – Dr. Morag Griffin

Dosing of Voydeya®

- **Standard dose:** 150mg TDS
- Option for dose escalation to 200mg TDS if patients have not normalised Hb after minimum 4 weeks – in practice this would be after 3 months

Egfr: estimated glomerular filtration rate

Voydeya® (danicopana). Bula do produto. AstraZeneca Brasil LTDA

Practical considerations

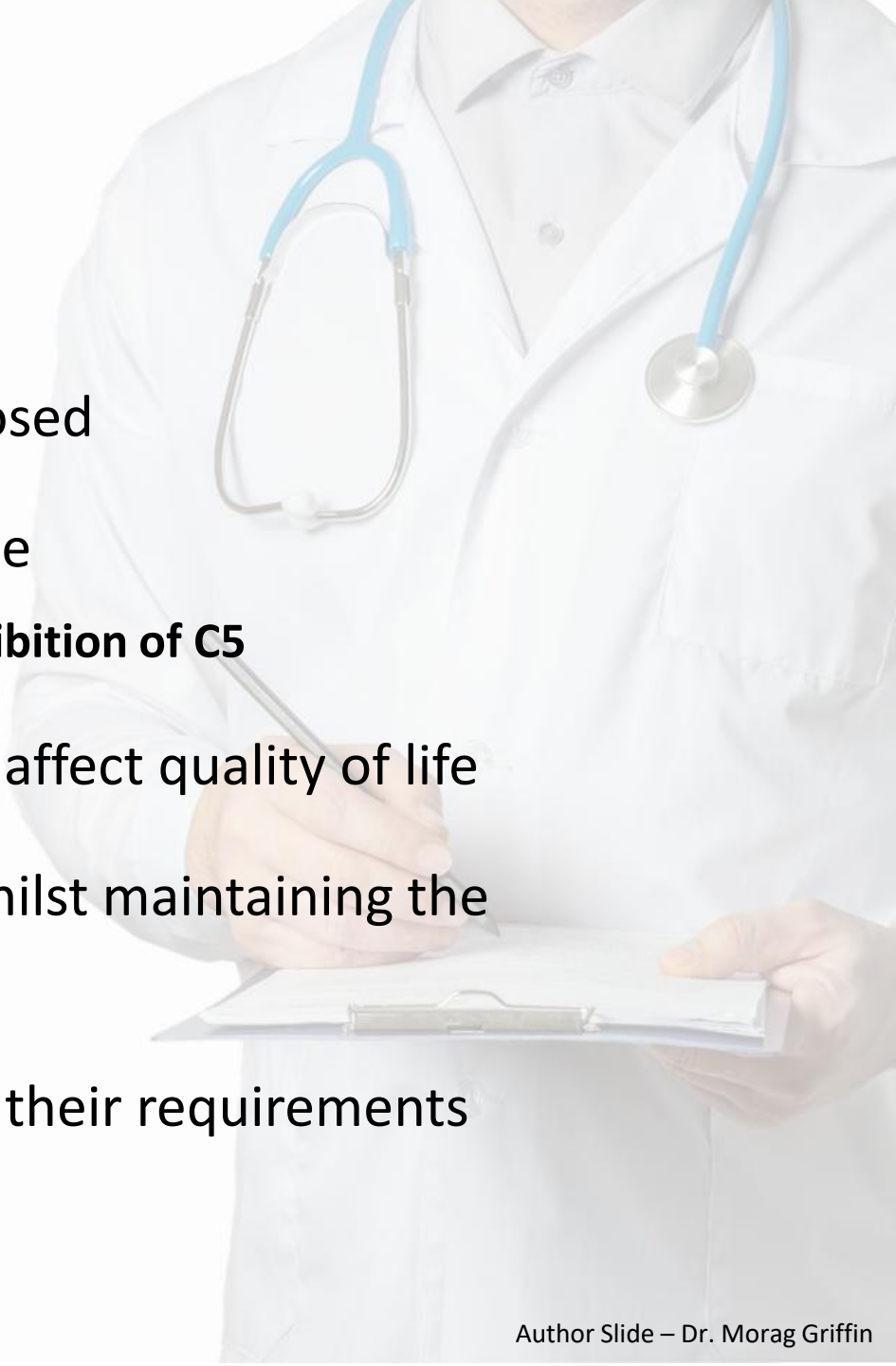
From UK PNH team

- Treatment commenced in hospital
- Haemophilus (not applicable for Brazil's label) and pneumococcal vaccination; check status of meningiccocal vaccination
- Monitoring of liver function – initially every 4 weeks
- Some drug interactions eg statins may need adjusting
- **Monitoring:**
  - As per standard PNH follow-up
  - Bloods: FBC, reticulocytes, renal and liver function, PNH clone, DAT, Fasting cholesterol
  - Check compliance
- Patient education

Author Slide – Dr. Morag Griffin

Conclusion

- PNH remains a rare but treatable condition once diagnosed
- C5 inhibition has transformed PNH into a chronic disease
  - **Ultomiris® provides immediate, complete, and sustained inhibition of C5**
- Extravascular haemolysis is not life-threatening but can affect quality of life
- Voydeya® is an effective add on therapy to treat EVH whilst maintaining the 'backbone' of C5 inhibition
- In 2025: We have many options to treat patients to suit their requirements and needs



Author Slide – Dr. Morag Griffin

Soliris® (eculizumabe) solução para diluição para infusão. **CONTRAINDICAÇÕES: Hipersensibilidade ao eculizumabe, às proteínas murinas ou a qualquer um dos excipientes da fórmula. A terapêutica com Soliris® (eculizumabe) não deve ser iniciada em pacientes: com infecção por Neisseria meningitidis não resolvida; que não estejam vacinados contra Neisseria meningitidis (a menos que recebam tratamento profilático com antibióticos apropriados até 2 semanas após a vacinação).** Cuidados e Advertências: Soliris® aumenta a suscetibilidade dos pacientes a infecção meningocócica (Neisseria meningitidis), todos os pacientes devem ser vacinados pelo menos 2 semanas antes de receber Soliris® (eculizumabe), a menos que o risco de atrasar a terapia ultrapasse os riscos de desenvolver uma infecção meningocócica. Os pacientes que sejam tratados com Soliris® em menos de 2 semanas após receberem a vacina meningocócica devem receber tratamento com antibióticos profiláticos apropriados até 2 semanas após a vacinação. Gravidez: Não existem estudos adequados e bem controlados de mulheres grávidas tratadas com eculizumabe. Dados limitados ao número de gravidezes expostas ao eculizumabe (menos de 300 resultados de gravidez) indicam que não há aumento do risco de formação fetal ou toxicidade fetal-neonatal. Entretanto, devido a falta de estudos bem controlados, a incerteza permanece. Assim sendo, a análise do risco-benefício individual é recomendada antes do início e durante o tratamento com eculizumabe em mulheres grávidas. Caso tal tratamento seja necessário durante a gravidez, recomenda-se um monitoramento materno e fetal de acordo com as diretrizes locais. **INTERAÇÕES MEDICAMENTOSAS: Não foram realizados estudos de interação medicamentosa.** A troca de plasma, plasmaférese e a infusão de plasma fresco congelado, demonstraram reduzir os níveis séricos de Soliris®. Uma dosagem suplementar de Soliris® é necessária nesses casos. Consulte a bula para orientação. O uso concomitante de Soliris® com bloqueadores dos receptores Fc neonatais (FcRn) pode diminuir as exposições sistêmicas e reduzir a eficácia de Soliris®. Monitore de perto a eficácia reduzida de Soliris®. O tratamento crônico intravenoso com imunoglobulina humana (IVIg) pode interferir com o mecanismo de reciclagem dos receptores monoclonais endossomal neonato Fc (FcRn), tal como o eculizumabe, dessa forma diminuindo assim as concentrações séricas de eculizumabe. Os estudos de interação medicamentosa não foram realizados com eculizumabe em pacientes tratados com IVIg. **REAÇÕES ADVERSAS**: A reação adversa mais frequente foi cefaleia (principalmente na fase inicial), e a reação adversa mais grave foi a infecção meningocócica. **Reg. MS – 1.1618.0304.001-1 (SOL_001).**

Para mais informações consulte a bula do medicamento:

SOLIRIS®
(eculizumabe)

Ultomiris® (ravulizumabe) solução para diluição para infusão. Indicações: Ultomiris® (ravulizumabe) é indicado para o tratamento de pacientes adultos e pediátricos com um peso corporal de 10 kg ou acima com hemoglobinúria paroxística noturna (HPN) em pacientes com hemólise com sintoma(s) clínico(s) indicativo(s) de alta atividade da doença e em pacientes clinicamente estáveis após terem sido tratados com eculizumabe por no mínimo os últimos 6 meses. Ultomiris® (ravulizumabe) é indicado no tratamento de pacientes com um peso corporal de 10 kg ou acima com síndrome hemolítico-urêmica atípica (SHUa) não tratados anteriormente com inibidor do complemento ou que receberam eculizumabe por no mínimo 3 meses e possuem evidência de resposta a eculizumabe. Ultomiris® (ravulizumabe) é indicado no tratamento de pacientes adultos com Miastenia Gravis generalizada (MGg) positivo para anticorpo anti-receptor de acetilcolina (AChR). Ultomiris® (ravulizumabe) é indicado no tratamento de pacientes adultos com doença do espectro da neuromielite óptica (NMOSD) positivos para anticorpos anti-aquaporina-4 (AQP4+). **Contraindicações: Hipersensibilidade ao ravulizumabe ou a qualquer um dos excipientes da fórmula. A terapêutica com Ultomiris® não deve ser iniciada em pacientes: com infecção por Neisseria meningitidis não resolvida e em pacientes que não estão atualmente vacinados contra Neisseria meningitidis, a menos que recebam tratamento profilático com antibióticos apropriados até 2 semanas após a vacinação.** Cuidados e advertências: Infecção Meningocócica Grave: Ultomiris® aumenta a susceptibilidade dos pacientes à infecção/sepse meningocócica (Neisseria meningitidis). Todos pacientes devem ser vacinados contra infecções meningocócicas pelo menos duas semanas antes de iniciar o tratamento com Ultomiris® (ravulizumabe) a não ser que o risco de atrasar o início do tratamento supere o risco de desenvolver infecção meningocócica. Pacientes que iniciam o tratamento com Ultomiris® (ravulizumabe) menos de 2 semanas depois de ter recebido a vacina meningocócica devem receber tratamento profilático com antibióticos apropriados até 2 semanas depois da vacinação. Imunização: A vacinação pode ativar o complemento. Outras infecções sistêmicas: A terapia com Ultomiris® deve ser administrada com cautela em pacientes com infecções sistêmicas ativas. Atenção: Este medicamento contém açúcar, portanto, deve ser usado com cautela em portadores de diabetes. Gravidez: Categoria C: Este medicamento não deve ser utilizado por mulheres grávidas sem orientação médica. Não há dados clínicos disponíveis sobre exposição na gravidez. O ravulizumabe pode possivelmente causar a inibição do complemento terminal na circulação fetal**. Interações Medicamentosas: Não foram realizados estudos de interação medicamentosa. A utilização concomitante de Ultomiris® com bloqueadores do receptor Fc neonatal (FcRn) pode diminuir as concentrações sistêmicas e reduzir a eficácia de Ultomiris®. Monitore atentamente qualquer redução na eficácia de Ultomiris®.** Reações adversas: Em todos os estudos clínicos, as reações adversas mais graves de Ultomiris® foram infecções/sepse meningocócica. As reações medicamentosas adversas mais comuns (≥ 10%) em todos os ensaios clínicos foram cefaléia, nasofaringite, infecção do trato respiratório superior, diarréia, febre, náuseas, artralgia, fadiga, dorsalgia, dor abdominal e tontura. **Reg. MS – 1.1618.0301 (ULT_001). BR-35029**

Para mais informações consulte a bula do medicamento:

ULTOMIRIS®
(ravulizumabe)
Solução para Diluição para Infusão

Voydeya® (danicopana) comprimidos revestidos. Indicações: Voydeya® (danicopana) é indicado como um tratamento adicional a Ultomiris® (ravulizumabe) ou Soliris® (eculizumabe) para o tratamento de sinais ou sintomas de hemólise extravascular em pacientes adultos com hemoglobinúria paroxística noturna (HPN) que apresentam anemia hemolítica residual. **Contraindicações: Pacientes com hipersensibilidade à danicopana ou a qualquer dos excipientes listados na composição. A terapia com Voydeya® não deve ser iniciada em pacientes com infecção por Neisseria meningite disnão resolvida e pacientes com histórico de vacinação desconhecido ou que não estão atualizados com suas vacinas meningocócicas. Os pacientes que iniciarão o tratamento com Voydeya® menos de 2 semanas após receberem uma vacina meningocócica devem receber o tratamento com antibióticos profiláticos adequados até 2 semanas a pós a vacinação.** Cuidados e Advertências: Infecções Meningocócicas Graves – Os pacientes devem estar atualizados com suas vacinas meningocócicas antes de receber a primeira dose de Voydeya®. Os pacientes que iniciam o tratamento com Voydeya® menos de 2 semanas após receberem a vacina meningocócica devem receber tratamento com antibióticos profiláticos apropriados até 2 semanas após a vacinação. Todos os pacientes tratados com Voydeya® devem ser monitorados quanto a sinais precoces de infecção e sepse meningocócica, avaliados imediatamente caso haja suspeita de infecção e tratados com antibióticos apropriados. Exames Laboratoriais - Foram observadas elevações de alanina aminotransferase em estudos clínicos. Recomenda-se a realização de testes de enzimas hepáticas antes do início do tratamento. Após o início do tratamento, recomenda-se monitoramento laboratorial bioquímico de rotina de acordo com o tratamento de HPN. Considerar interrupção ou descontinuação do tratamento caso as elevações sejam clinicamente significativas ou se os pacientes se tornarem sintomáticos. Não foram realizados estudos em pacientes com comprometimento hepático severo. Uso em populações específicas – Mulheres férteis deverão utilizar métodos contraceptivos eficazes durante tratamento com Voydeya® e até 3 dias após a descontinuação. Gravidez: Categoria C. Não há dados disponíveis sobre o uso de Voydeya® em gestantes. É preferível evitar o uso durante a gestação. Não há dados sobre a presença de Voydeya® no leite humano, efeito no lactente, na produção de leite e na fertilidade. Voydeya® contém sódio e lactose monoidratada. Pacientes com problemas hereditários raros de intolerância à galactose, deficiência total de lactase ou má-absorção de glicose-galactose não devem utilizar este medicamento. **Interações Medicamentosas: Efeitos de outros medicamentos com danicopana - Dados não clínicos disponíveis mostraram que a via de depuração predominante para danicopana não depende do metabolismo no citocromo P450 (CYP). Efeitos da danicopana sobre outros medicamentos - Danicopana não é um inibidor de CYP1A2, CYP2C8 e CYP2D6. Substratos da glicoproteína-P (gp-P) - A coadministração de doses orais únicas de fexofenadina e tacrolimus, substratos da gp-P com a danicopana administrada até o estado estacionário resultou em aumentos da concentração sérica máxima (Cmax) e da área sob a curva de concentração plasmáticatempo (AUC)0-inf dos substratos da gp-P, sugerindo que danicopana é uma inibidora da gp-P e pode ser necessária cautela na administração concomitante de medicamentos que são conhecidos por serem substratos da gp-P. Substratos de substrato da proteína de resistência ao câncer de mama (BCRP) - A coadministração de uma dose oral única de rosuvastatina, um substrato de BCRP, com danicopana administrada até o estado estacionário, resultou num aumento da Cmáx e da AUC0-inf da rosuvastatina, sugerindo que danicopana é uma inibidora de BCRP e pode ser necessária precaução na administração concomitante de fármacos que sejam conhecidos como substratos da BCRP.** Reações adversas: As reações adversas à droga mais comuns (≥ 10%) em todos os estudos clínicos foram aumento de enzima hepática e cefaleia. Não foram observadas reações adversas graves à droga em pacientes com HPN em estudos clínicos. Reg. MS – 1.1618.0306. (VOY_01).

Voydeya®
(danicopana) 50mg · 100mg
Comprimidos revestidos

Para mais informações consulte a bula do medicamento:

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