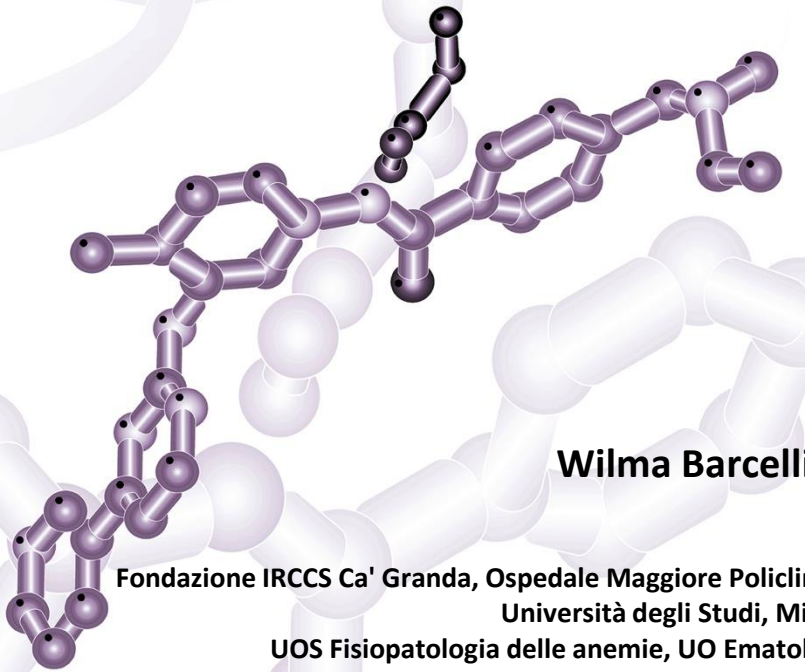
ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI MEDICINA SPECIALISTICA
DIAGNOSTICA E SPERIMENTALE

POLICLINICO DI
SANT'ORSOLA

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna

Ravulizumab



New Drugs in Hematology

President: Pier Luigi Zinzani
Co-President: Michele Cavo

Bologna,
Royal Hotel Carlton
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**Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico,
Università degli Studi, Milano
UOS Fisiopatologia delle anemie, UO Ematologia**

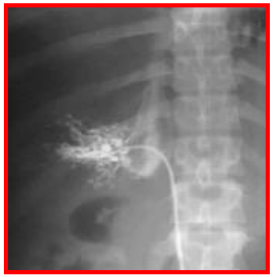
Disclosures of Wilma Barcellini

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Agios					x	x	
Alexion	x				x	x	
Biocryst						x	
Incyte					x	x	
Momenta						x	
Novartis					x	x	
Sanofi					x	x	

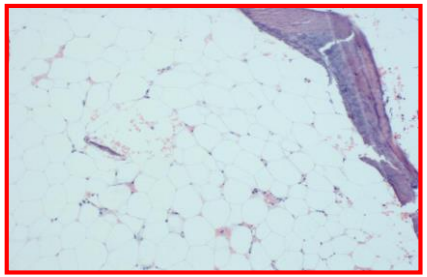
PNH – "the great impersonator"

- **PNH is a rare disease, with an estimated incidence of 1.3 cases/million/year and a prevalence of 15.9 cases/million**
- **PNH is a heterogeneous disease (aspecific symptoms, mild cytopenias up to severe disabling disease), changing over time (possible remission up to clonal evolution)**
- **clinical manifestations determined by the size of the PNH clone and the relationship of PNH with BMF (AA, MDS)**

Intravascular haemolysis – disabling symptoms[1]
- abdominal pain
- dysphagia
- erectile failure
- severe lethargy
- pulmonary hypertension
- renal damage



Thrombosis[2,3]
- liver, cerebral
- occurs in 50% of patients
- in 33% of patients is fatal

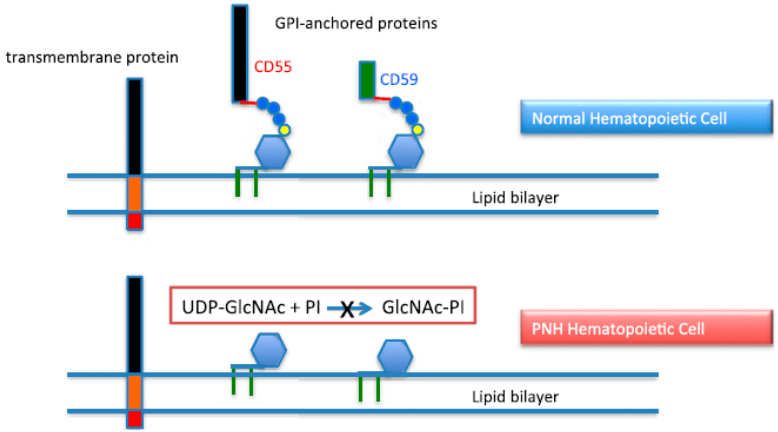


Bone marrow failure
- often precedes PNH[4,5]
- overlap MDS
-clonal evolution

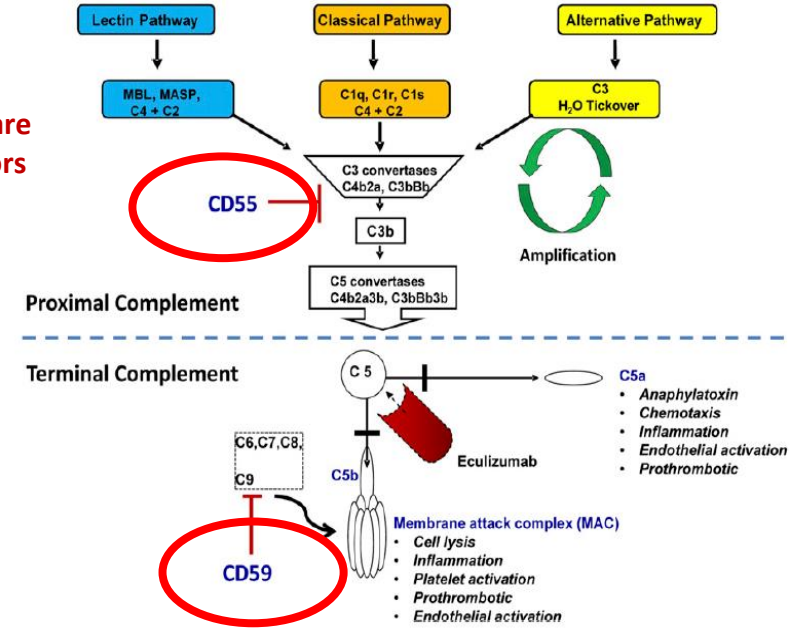
1. Rother et al. JAMA 2005;293:1653-627. 2. Hillmen P, Lewis SM, Bessler M *et al*. N Engl J Med 1995;333:1253-8. 3. Socie G, Mary JY, Gramont A *et al*. Lancet 1996;348:573-7. 4. Wang et al. Blood 2002;100:3897–902. 5. Dunn et al. Ann Int Med 1999;131:401–8. 6. Iwanga et al. Br J Haematol 1998;102:465–74. 7. Luzzato et al. Int J Hematol 2006;84:104-12; Weitz I, et al. *Intern Med J.* 2013;43(3):298-3071

PNH – Pathogenesis /Diagnosis

- **PNH stem cells fail to express GPI-APs because of a somatic mutation of the *PIGA* gene**
- **Among GPI-APs, lack of CD55 and CD59 determines abnormal sensitivity to the lytic action of complement→ intravascular RBC hemolysis, hemoglobinuria.**
- **Easy cytofluorimetric diagnosis (FLAER)**



CD55 and CD 59 are negative regulators of complement activation

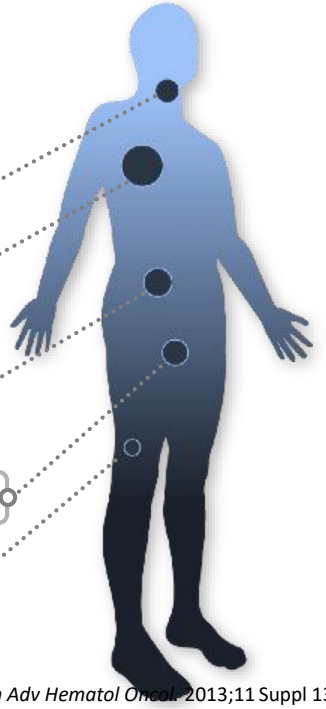


- **Granulocytes provide more accurate representation of PNH clone size**
- **percentages of GPI-negative RBCs may be affected by hemolysis or blood transfusions (underestimation of clone size)**

PNH: clinical features

High disease activity is defined by LDH ≥1.5 x ULN and ≥1 of the following symptoms:

- **Fatigue** 80%
- **Anemia** 88%[4]
- **Dysphagia** 24%
- **Dyspnoea** 64%
- **Abdominal pain** 44%
- **Erectile dysfunction** 38%
- **Hemoglobinuria** 62%



Thrombosis accounts for
40% to 67%
of the mortality from the disease

Renal failure is the cause of death in
8% to 18%
of PNH patients

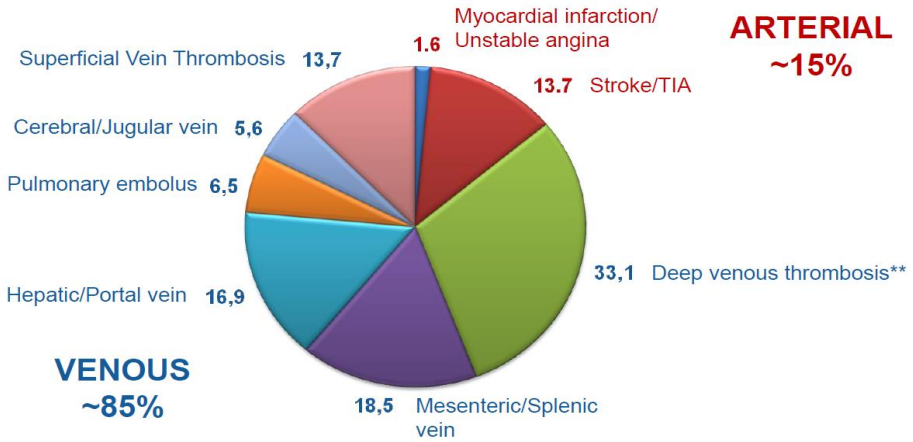
47%
suffer from **pulmonar hypertension**[5]

Scherezenmeier H, et al. *Haematologica*. 2014;99(5):922-929. Sharma VR. *Clin Adv Hematol Oncol*. 2013;11 Suppl 13(9):2-8. Roth A et al. Eur J Haematol. 2018 Jul;101(1):3-11.. Hill A, Rother RP, et al. *Br J Haematol.* 2010;149(3):414-425

Thrombotic risk increases with PNH clone size

Typical and atypical sites of thrombosis

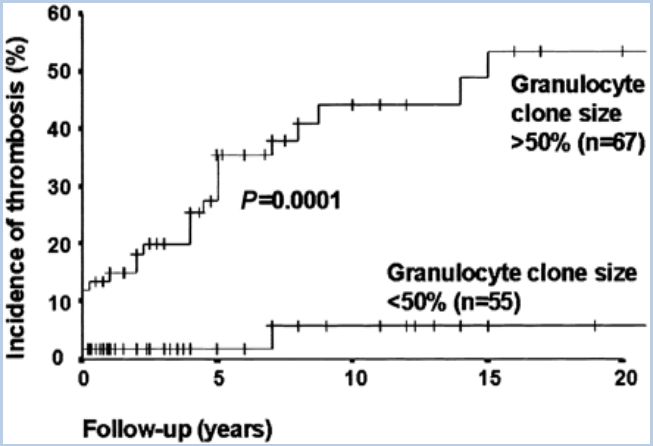
Analysis of 124 events in 63 patients



**18,5% at lower limbs, and 14,5% at other sites (inferior vena cava, pelvic veins, urethral veins, axillary veins, subclavian veins, brachiocephalic veins).

Hillmen P *et al. Blood* 2007;110:4123–4128.

The 10-year cumulative incidence rate of thrombosis (primary prophylaxis patients excluded)



44% if granulocyte clone size larger than 50%
5.8% if clone size smaller than 50% ($P < 0.01$)

Hillmen P et al. Blood 2007;110(12):4123-8 ; Rother RP et al. JAMA 2005;293:1653-62; Brodsky RA. Blood Rev 2008;22:65-74; Hillmen P et al. NEJM 1995;333:1253-8; Hill A et al. Blood 2006;108:979; Audebert et al. J Neurol 2005; 2521379–86; Hall et al. Blood 2003;102:3587–91. Brodsky R et al. *Blood.* 2010;116:4237

Thromboembolism (TE) is a serious and life-threatening complication in PNH

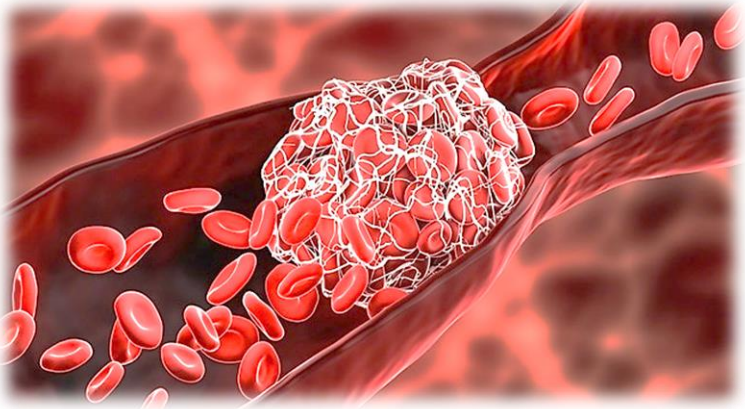
" We can safely say that PNH is the most vicious acquired thrombophilic state known in medicine[2]"

29% to 44% of patients have suffered from at least on TE event in the course of the disease[1]

An initial thrombotic event increases the relative risk of death **5 to 10 fold**[1]

TE accounts for **40%-67%** of deaths and is **the leading** cause of mortality in PNH[1]

1



The relative risk of venous TE in PNH patients is about **62-fold** greater than in the general population[3]

TE events have been observed in patients with PNH **despite the use of anticoagulants**[1]

1. Hillmen P, et al. *Blood*. 2007;110(12):4123-4128. **2.** Luzzatto L, et al. *Br J Haematol*. 2011;153(6):709-720. **3.** McKeage K. *Drugs*. 2011;71(17):2327-2345.

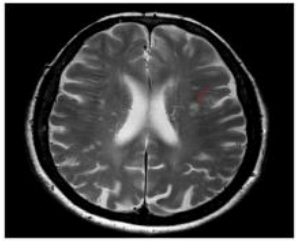
MRI detects undiagnosed vascular complications in PNH

- **In neurologically asymptomatic PNH patients, brain MRI ischemic lesions were more frequent and severe, compared with age and sex-matched controls**
  - **Increased frequency of periventricular WM vascular degeneration (32% versus 5.2%, p = 0.04)**
  - **More severe lesions (ARWMC scale score >4) (26% versus 2.6%, p = 0.05)**
  - **Higher overall ARWMC scale score (3.5 ± 1.07 versus 2.0 ± 0.8, mean ± SD, p < 0.0001).**
  - **Presence of vascular abnormalities suspected for prior partial venous thrombosis observed in PNH cases only.**
- **Whole body MRI was able to detect silent bone and renal infarctions, and a clinically non-critical arterial occlusion in both patients on eculizumab and treatment-naïve**

A

Patient N.	White Matter Changes (ARWMC scale)			
	Leukoaraiosis	Deep WM alterations	Periventricular WM alterations	Venous system abnormalities
1	0	0	0	yes
2	1	4	0	no
6	0	4	0	yes
7	0	2	1	no
10	1	5	1	no
11	1	4	1	yes
12	1	4	0	no
14	1	0	1	no
16	0	0	0	yes
18	1	2	1	no
19	1	3	1	no

B



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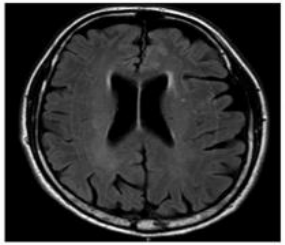

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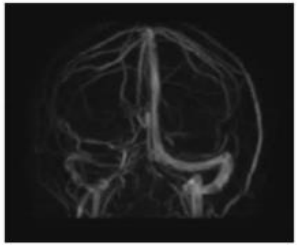
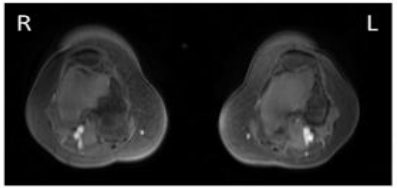
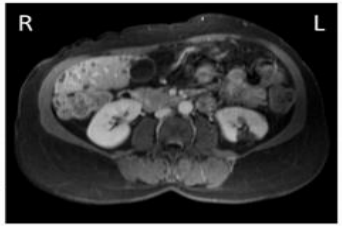






MRI may be useful at diagnosis and during the course of the disease to detect previously undiagnosed vascular complications, affecting treatment indications and regimens.

Barcellini W, Sci Rep 2018; Alashkar F. Sci Rep 2018

PNH – Disease classification (IPIG)

Table 2. Classification of PNH

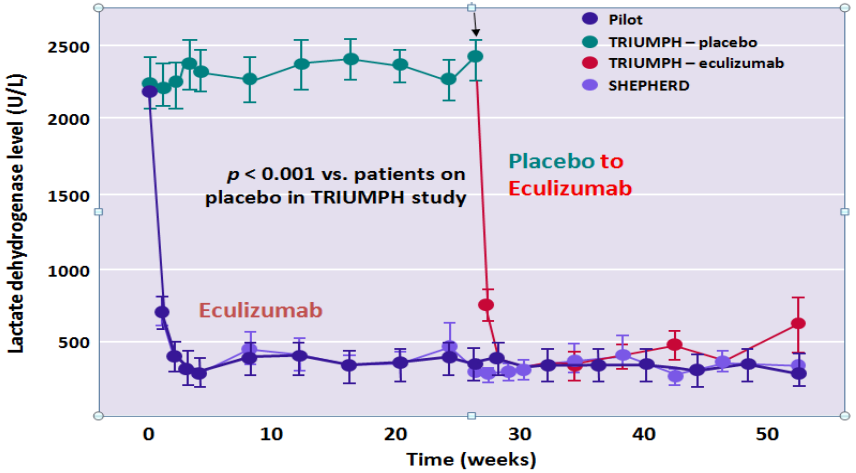
Category	Rate of intravascular hemolysis*	Bone marrow	Flow cytometry	Benefit from eculizumab
Classic	Florid (markedly abnormal LDH often with episodic macroscopic hemoglobinuria)	Cellular marrow from erythroid hyperplasia and normal or near-normal morphology†	Large population (>50%) of GPI-AP–deficient PMNs‡	Yes
PNH in the setting of another bone marrow failure syndrome§	Mild (often with minimal abnormalities of biochemical markers of hemolysis)	Evidence of a concomitant bone marrow failure syndrome§	Although variable, the percentage of GPI-AP–deficient PMNs is usually relatively small (<50%)	Typically no, but some patients have relatively large clones and clinically significant hemolysis and may benefit from treatment
Subclinical	No clinical or biochemical evidence of intravascular hemolysis	Evidence of a concomitant bone marrow failure syndrome§	Small (<10%) population of GPI-AP–deficient PMNs detected by high-resolution flow cytometry	No

Based on recommendations of the International PNH Interest Group.[3]
*Based on macroscopic hemoglobinuria, serum LDH concentration, and reticulocyte count.
†Karyotypic abnormalities are uncommon.
‡Analysis of PMNs is more informative than analysis of RBCs because of selective destruction GPI-AP–deficient RBCs.
§Aplastic anemia or low-risk myelodysplastic syndrome.

Therapy of PNH

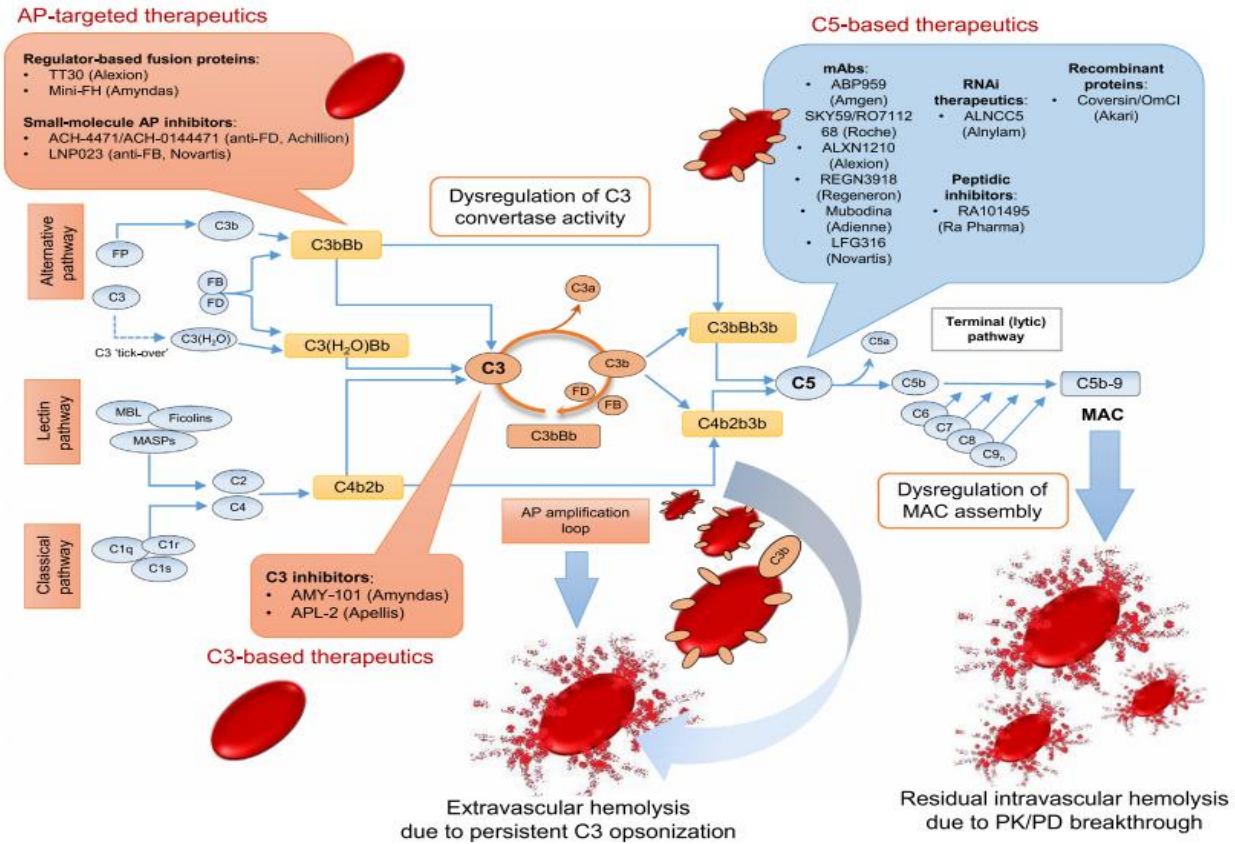
- **Supportive care including**: folic acid, recurrent transfusions, iron replacement
- **Primary prophylaxis with warfarin** (clone size >50%, before eculizumab or where the drug is unavailable)
- **Allogeneic bone marrow transplant:** the only possible curative approach, however with important transplant-related mortality and morbidity, mainly for SAA-PNH

- **Eculizumab** (anti-C5 Ab): improvement of anemia, fatigue, transfusion need, and 85% reduction in thrombosis
- ***Indications:***
  - Symptomatic PNH patients: e.g. transfusion-dependent due to the hemolysis (not due to a potential cytopenia)
  - Thromboembolic events
  - PNH-associated renal insufficiency
  - Abdominal pain crises
  - Other severe PNH-related symptomes/complications
  - Long-term risk situations for VTE (e.g. immobilisation)
  - Pregnancy
- ***Treatment:*** Eculizumab 900 mg every 14±2 days
- ***Dose modifications:*** Eculizumab 1200 mg every 14±2 days or shortening of the interval to 12 days in case of breakthrough haemolysis
- ***Vaccination:*** Tetravalent conjugate vaccine (A,C, W135, Y(***Menveo***®)) at therapy start**;** B-vaccine (***Bexsero***®) during ongoing therapy (0-1),
- ***Be aware:*** Ongoing risk of meningococcal infections, risk of haemolysis/ thromboses due to surgery, infection etc.



Hall et al. Blood 2003; Parker et al. Blood 2005; Hillmen et al. N Eng J Med 2006; Hillmen et al. Blood 2007

New drugs for PNH

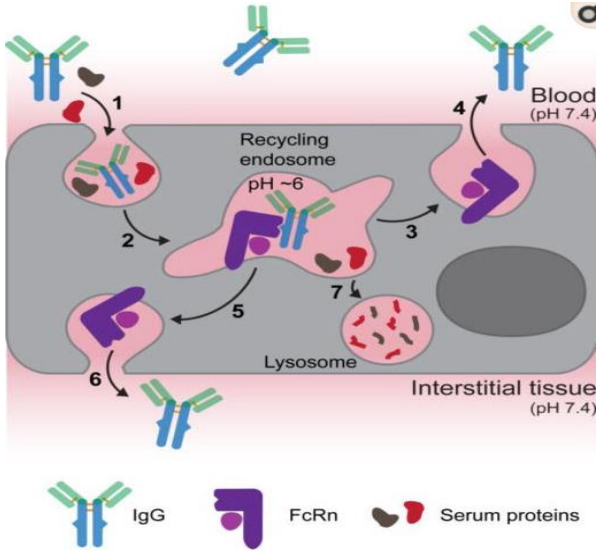


Mastellos DC, Reis ES, Yancopoulou D, Risitano AM, Lambris JD.Semin Hematol. 2018

Ravulizumab

Modification of eculizumab for increased half-life

- Histidine substitution at two positions within the first and second heavy chain complementarity-determining regions of eculizumab generates a novel mAb
- This extends its PK and PD in the presence of human C5 in a mouse model
- Additional modifications were made to the Fc region from eculizumab to further increase the half-life by increasing its affinity for FcRn



- The neonatal Fc Receptor (Fc-Rn) was firstly described about 50 years ago, and is responsible for the salvage of IgG from catabolism
- FcRn is structurally homologous to the MHC Class I heterodimeric receptor family, and is expressed by several cells including macrophages, monocytes, B cells, and dendritic cells·
- Ab recycling by FcRn engineering protect Ab from degradation
- Conversely, blocking Fc-Rn may increase IgG clearance (including pathogenic autoantibodies), resulting in reduced IgG

Ravulizumab has a half-life ~4x longer than eculizumab. Administration every 8 weeks!

Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study

Jong Wook Lee,[1] Flore Sicre de Fontbrune,[2] Lily Wong Lee Lee,[3] Viviani Pessoa,[4] Sandra Gualandro,[5] Wolfgang Füreder,[6] Vadim Ptushkin,[7] Scott T. Rottinghaus,[8] Lori Volles,[8] Lori Shafner,[8] Rasha Aguzzi,[8] Rajendra Pradhan,[8] Hubert Schrezenmeier,[9,10] and Anita Hill[11]

[1]Department of Hematology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [2]Hematology Transplant Unit, Hôpital Saint-Louis, Paris, France; [3]Hematology Unit, Queen Elizabeth Hospital, Kota Kinabalu, Sabah, Malaysia; [4]Hematology, Hemorio, Rio de Janeiro, Brazil; [5]Department of Haematology, University of São Paulo Medical School, São Paulo, Brazil; [6]Division of Hematology & Hemostaseology, Department of Internal Medicine I, Medical University of Vienna, Vienna, Austria; [7]Outpatient Department for Hematology, Oncology and Chemotherapy, S. P. Botkin Hospital, Moscow, Russia; [8]Alexion Pharmaceuticals, Inc, Boston, MA; [9]Institute of Transfusion Medicine, University of Ulm, Ulm, Germany; [10]Institute for Clinical Transfusion Medicine and Immunogenetics, German Red Cross Blood Transfusion Service Baden-Württemberg-Hessen and University Hospital Ulm, Ulm, Germany; and [11]Department of Haematology, Leeds Teaching Hospitals, Leeds, United Kingdom

Blood 2019; 133: 530–539.

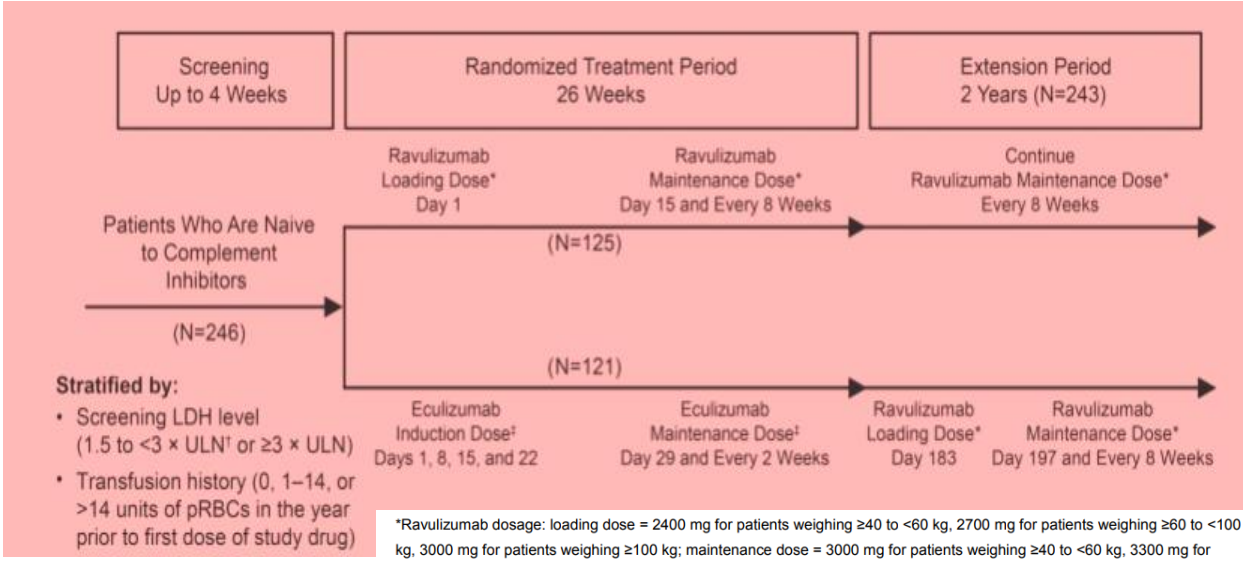
Phase 3, multicenter, randomized, open-label, active-controlled study

Key inclusion criteria:

- ≥18 years of age
- PNH clone size of at least 5%
- LDH level ≥1.5× ULN
- Within 3 months of screening, ≥1 of the following PNH-related signs or symptom
  - fatigue
  - hemoglobinuria
  - abdominal pain
  - anemia (ie, hemoglobin level <10 g/dL)
  - history of MAVEs (including thrombosis)
  - dysphagia
  - erectile dysfunction
  - history of packed red blood cell transfusion because of PNH

Key exclusion criteria:

- current or previous exposure to a complement inhibitor
- weight <40 kg
- history of bone marrow transplantation
- history of meningococcal infection;
- platelet count <30 × 10^9/L
- absolute neutrophil count <0.5 × 10^9/L



*Ravulizumab dosage: loading dose = 2400 mg for patients weighing ≥40 to <60 kg, 2700 mg for patients weighing ≥60 to <100 kg, 3000 mg for patients weighing ≥100 kg; maintenance dose = 3000 mg for patients weighing ≥40 to <60 kg, 3300 mg for patients weighing ≥60 to <100 kg, 3600 mg for patients weighing ≥100 kg. †The ULN for LDH is 246 U/L. LDH indicates lactate dehydrogenase, pRBCs packed red blood cells, and ULN upper limit of normal. ‡Eculizumab dosage: induction dose = 600 mg; maintenance dose = 900 mg.

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Blood 2019; 133: 530–539.

- **The objective of the study was to assess the noninferiority of ravulizumab vs eculizumab in adult PNH patients naive to complement inhibitor therapy**
- **The coprimary end points** were:
  - **transfusion avoidance**, defined as the proportion of patients who remain transfusion-free and do not require a transfusion per protocol-specified guidelines (transfusion administered if Hb ≤9 g/dL with anemia-related signs or symptoms or a Hb≤7 g/dL regardless of the presence of clinical signs or symptoms)
  - **hemolysis as measured by LDH normalization**
- Key secondary end points included percentage change from baseline to day 183 in LDH, quality of life, the proportion of patients with breakthrough hemolysis, proportion of patients with stabilized hemoglobin, change in free C5 concentrations, etc
- **Adverse events (AEs)** were documented and immunogenicity, reflected by development of antidrug antibodies, was also monitored. A safety review committee performed safety monitoring, and an independent data monitoring committee was in place to monitor **meningococcal infections**

Results (1)

No noteworthy differences between treatment groups in demographics or baseline clinical characteristics

In particular:

- sex/age/race
- LDH (ratio to ULN or absolute value)
- previous transfusions
- PNH clone
- age at PNH diagnosis
- years from diagnosis to enrolment
- History of MAVE

Characteristic	Ravulizumab (N = 125)	Eculizumab (N = 121)
Sex, n (%)		
Male	65 (52.0)	69 (57.0)
Female	60 (48.0)	52 (43.0)
Age at first infusion of study drug, mean (SD), y	44.8 (15.2)	46.2 (16.2)
Race, n (%)		
Asian	72 (57.6)	57 (47.1)
Japanese	19 (15.2)	15 (12.4)
White	43 (34.4)	51 (42.1)
Black or African American	2 (1.6)	4 (3.3)
American Indian or Alaska Native	1 (0.8)	1 (0.8)
Other	4 (3.2)	4 (3.3)
Not reported	3 (2.4)	4 (3.3)
Weight, mean (SD), kg	68.2 (15.6)	69.2 (14.9)
Height, mean (SD), cm	166.3 (9.0)	166.2 (10.7)
LDH ratio, n (%)		
1.5 to <3× ULN*	18 (14.4)	16 (13.2)
≥3× ULN	107 (85.6)	105 (86.8)
Packed RBC units received within 1 y before study entry, randomization strata, n (%)		
0 U	23 (18.4)	21 (17.4)
1-14 U	79 (63.2)	78 (64.5)
>14 U	23 (18.4)	22 (18.2)
Age at PNH diagnosis, mean (SD), y	37.9 (14.9)†	39.6 (16.7)‡
Number of years from PNH diagnosis to consent, median (minimum, maximum), y	3.8 (0, 41)†	3.9 (0, 34)‡
LDH, mean (SD), U/L	1633.5 (778.8)	1578.3 (727.1)
PNH clone size, mean (SD), %		
Type II RBCs	12.4 (20.5)‖	13.7 (17.7)¶
Type III RBCs	26.3 (17.2)‖	25.2 (16.9)¶
Total RBCs	38.4 (23.7)	38.7 (23.2)
Granulocytes	84.2 (21.0)	85.3 (19.0)
Monocytes	86.9 (18.1)	89.2 (15.2)
History of major adverse vascular events, n (%)	17 (13.6)	25 (20.7)

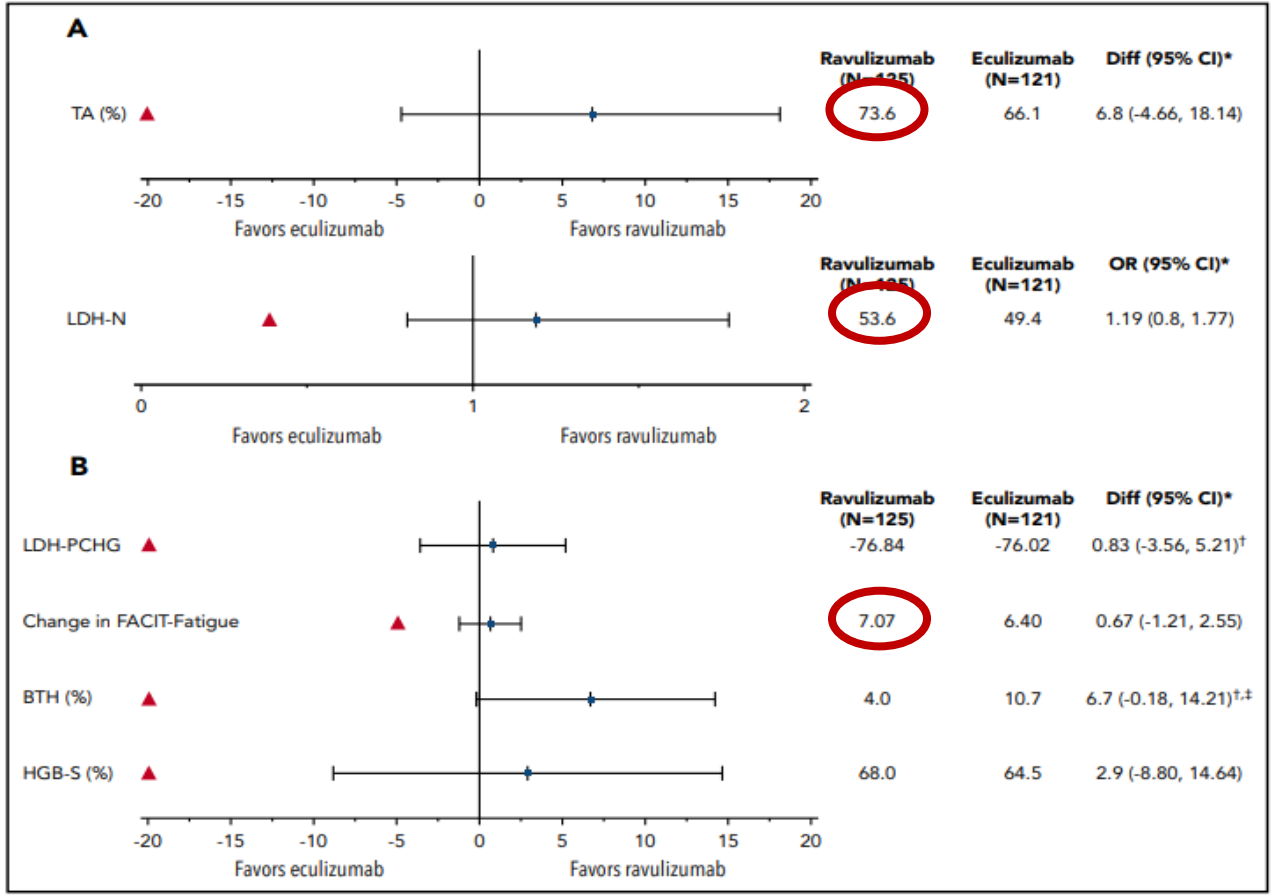
Results (2)

Ravulizumab met the objective of **noninferiority** compared with eculizumab on **both coprimary end points**

- **transfusion avoidance (TA)** and
- **LDH normalization (LDH-N)**

Point estimates for coprimary end points **favored ravulizumab**

In particular:
- LDH-PCHG (percent change)
- Change in FACIT-Fatigue
- Breakthrough hemolysis (BTH)
- Hemoglobin stabilization (HGB-S)

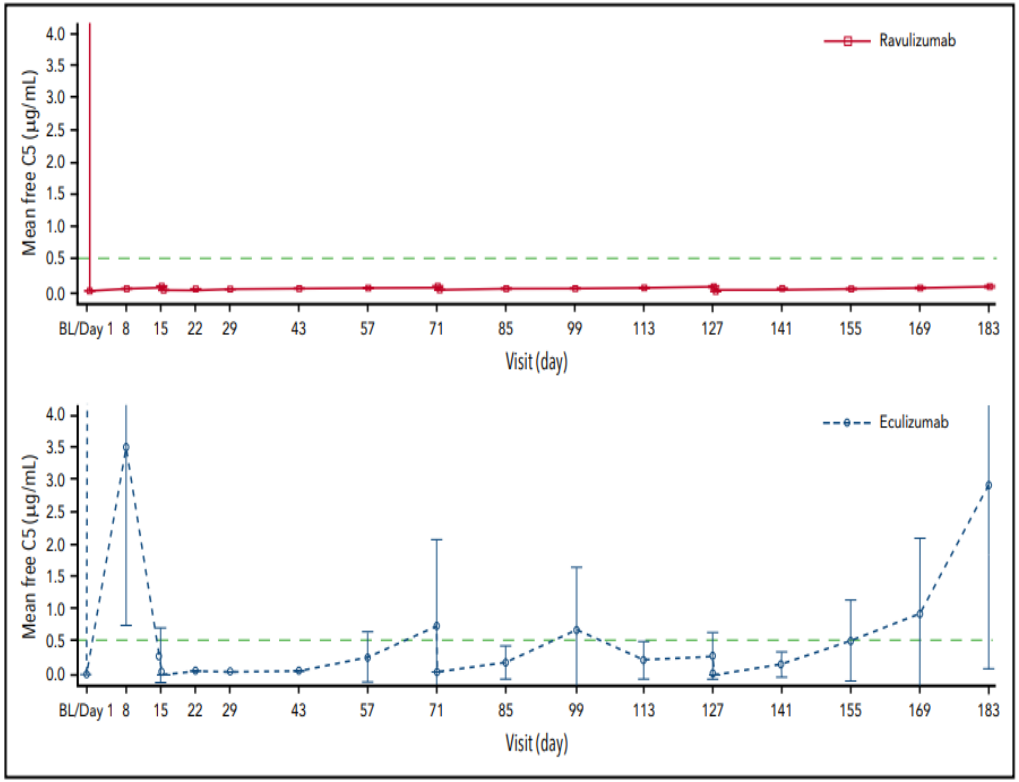


Red triangle indicates the noninferiority margin

Results (3)

Ravulizumab achieved complete terminal complement inhibition (defined as serum free C5 <0.5 µg/mL) by the end of the first infusion, which was sustained throughout the 183-day treatment period in all patients

This threshold was not consistently met in patients receiving eculizumab



Safety

The most frequently reported AE was headache (36.0% and 33.1% in ravulizumab and eculizumab)
SAEs obseved in 11 ravulizumab and 9 eculizumab
No cases of meningococcal, *Aspergillus* infections, or sepsis

Immunogenicity was low with 1 treatment-emergent antidrug antibody–positive sample in each treatment arm. Antibody titers were low (≤1) and not neutralizing, with no apparent effects on pharmacokinetics/pharmacodynamics or safety

Phase 3, open-label, non-inferiority, randomised, active-controlled, multicentre study

Key inclusion criteria:

- **treatment of ≥6 months at labeled dose before study entry with stable disease**
- LDH level ≤1.5× ULN
- ≥18 years of age
- PNH clone size of at least 5%
- Vaccination against *Neisseria meningitidis* <3 years before study entry

Key exclusion criteria:

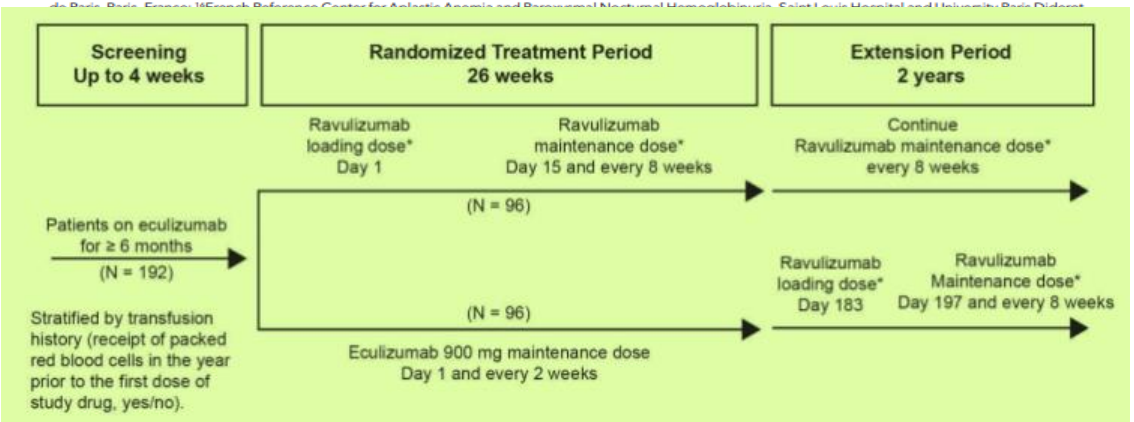
- LDH value >2× the ULN in the 6 months before day 1
- major adverse vascular event within 6 months before day 1
- weight <40 kg
- history of bone marrow transplantation
- history of meningococcal infection
- platelet count <30 × 10^9/L
- absolute neutrophil count <0.5 × 10^9/L

Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor–experienced adult patients with PNH: the 302 study

Blood (2019) 133 (6): 540–549.

Austin G. Kulasekararaj,[1] Anita Hill,[2] Scott T. Rottinghaus,[3] Saskia Langemeijer,[4] Richard Wells,[5] F. Ataulfo Gonzalez-Fernandez,[6] Anna Gaya,[7] Jong Wook Lee,[8] Emilio Ojeda Gutierrez,[9] Caroline I. Piatek,[10] Jeff Szer,[11] Antonio Risitano,[12] Shinji Nakao,[13] Eric Bachman,[3] Lori Shafner,[3] Andrew I. Damokosh,[3] Stephan Ortiz,[3] Alexander Röth,[14] and Regis Peffault de Latour[15-17]

[1]Department of Haematological Medicine, King's College Hospital, National Institute of Health Research/Wellcome King's Clinical Research Facility, London, United Kingdom; [2]Department of Haematology, Leeds Teaching Hospitals, Leeds, United Kingdom; [3]Alexion Pharmaceuticals, Inc., Boston, MA; [4]Radboudumc, Nijmegen, The Netherlands; [5]Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [6]Hospital Clinico Universitario San Carlos, Department of Hematology, The Clínic Institute of Haematological and Oncological Diseases, Madrid, Spain; [7]Hospital Clínic de Barcelona, Barcelona, Spain; [8]Department of Hematology, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea; [9]Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain; [10]Jane Anne Nohl Division of Hematology, Keck School of Medicine of USC, Los Angeles, CA; [11]Clinical Haematology, Royal Melbourne Hospital, Melbourne, VIC, Australia; [12]Hematology, Department of Clinical Medicine and Surgery, Federico II University, Naples, Italy; [13]Haematology/Respiratory Medicine, Faculty of Medicine, Institute of Medical Pharmaceutical and Health Sciences, Kanazawa University, Kanazawa, Ishikawa, Japan; [14]Department of Hematology, West German Cancer Center, University Hospital Essen, Essen, Germany; [15]Bone Marrow Transplantation Unit, Saint Louis Hospital, Assistance Publique–Hôpitaux de Paris, Paris, France; [16]French Reference Center for Aplastic Anemia and Paroxysmal Nocturnal Hemoglobinuria, Saint Louis Hospital and University Paris Diderot



Body weight, kg	*Ravulizumab loading dose, mg (Day 1)	*Ravulizumab maintenance dose, mg (Day 15 and q8w thereafter)
≥40 to <60	2400	3000
≥60 to <100	2700	3300
≥100	3000	3600

Phase 3, open-label, non-inferiority, randomised, active-controlled, multicentre study

Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor–experienced adult patients with PNH: the 302 study

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- **The primary efficacy end point was hemolysis, as measured by percentage change in LDH levels from baseline to day 183**
- Key secondary efficacy end points were:
  - proportion of patients with **breakthrough hemolysis**
  - change from baseline in **quality of life**
  - **transfusion** avoidance
  - proportion of patients with **stabilized hemoglobin**
  - change in **clinical manifestations of PNH**
  - proportion of patients experiencing major **adverse vascular events**
  - change in free **C5 concentration** over time

Safety

Adverse events were recorded by type, incidence, and severity. Antidrug antibodies were also assessed

Results (1)

Patient demographics and baseline clinical characteristics were well balanced between treatment groups. In particular no differences in:

- Sex/age/race/weight/height
- LDH, haptoglobin
- Hemoglobin at enrolment
- Transfusions received 1 year before study
- PNH clone
- Years on eculizumab before enrolment
- Age at PNH diagnosis
- History of MAVE
- History of aplastic anemia

Characteristic	Ravulizumab (n = 97)	Eculizumab (n = 98)
Sex, no. (%)		
Male	50 (51.5)	48 (49.0)
Female	47 (48.5)	50 (51.0)
Age at first infusion of study drug, mean (SD), y	46.6 (14.4)	48.8 (14.0)
Race, no. (%)		
White	50 (51.5)	61 (62.2)
Asian	23 (23.7)	19 (19.4)
Japanese	5 (5.2)	7 (7.1)
African American	5 (5.2)	3 (3.1)
Other/multiple	3 (3.1)	1 (1.0)
Not reported/unknown	16 (16.5)	14 (14.3)
Weight, mean (SD), kg	72.4 (16.8)	73.4 (14.6)
Height, mean (SD), cm	168.3 (10.1)	168.8 (9.9)
Years on eculizumab before first study infusion	6.0 (3.5)	5.6 (3.5)
Patients with packed red blood cells/whole blood transfusions received within 1 y before first dose, no. (%)	13 (13.4)	12 (12.2)
Age at PNH diagnosis, mean (SD), y	34.1 (14.4)	36.8 (14.1)
Time from PNH diagnosis to consent, mean (SD), y	12.4 (8.4)	11.9 (9.4)
LDH, mean (SD),* U/L	228.0 (48.7)	235.2 (49.7)
PNH clone size, mean (SD), %		
Type II red blood cells	14.9 (19.6)	16.3 (23.6)
Type III red blood cells†	44.6 (30.5)	43.5 (29.7)
Total red blood cells	60.6 (32.5)	59.5 (31.4)
Granulocyte	82.6 (23.6)	84.0 (21.4)
Monocyte	85.6 (20.5)	86.1 (19.7)
Hemoglobin, g/L, mean (SD)‡	110.8 (18.4)	109.1 (18.4)
Haptoglobin, g/L, mean (SD)§	0.283 (0.235)	0.255 (0.174)
History of major adverse vascular events, no. (%)	28 (28.9)	22 (22.4)
History of aplastic anemia, no. (%)	34 (35.1)	39 (39.8)

Results (2)

Ravulizumab achieved noninferiority compared with eculizumab for:

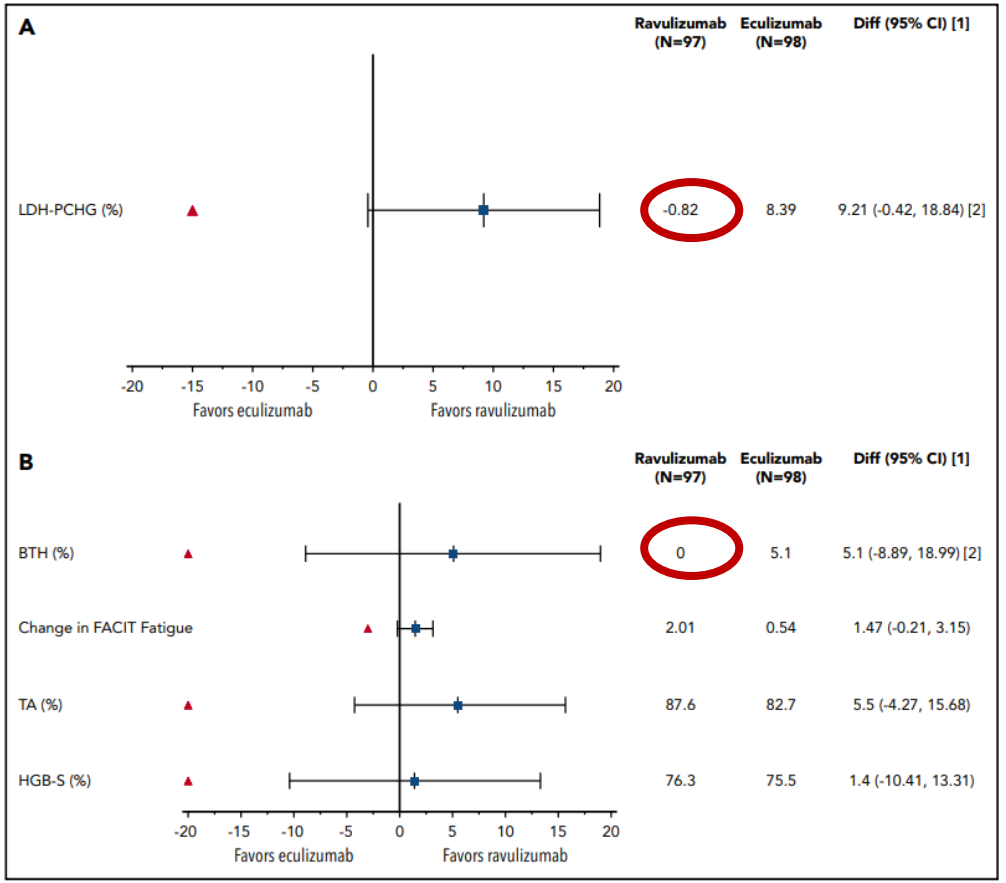
- **LDH-PCHG (percent change)**

  patients taking ravulizumab continued to maintain normal LDH levels. In patients who continued to be treated with eculizumab, levels increased modestly

- **Breakthrough hemolysis (BTH)**

  No patients treated with ravulizumab experienced breakthrough hemolysis vs 5 patients treated with eculizumab

- **Change in FACIT-Fatigue**
- **transfusion avoidance (TA)**
- **Hemoglobin stabilization (HGB-S)**
- **LDH normalization (LDH-N)**

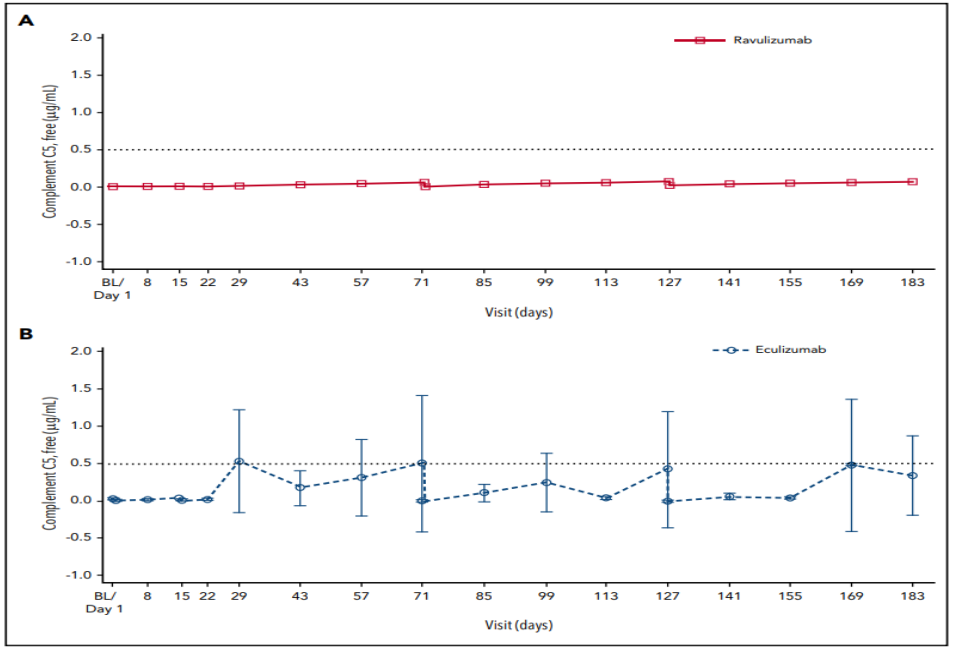


Red triangle indicates the noninferiority margin

Results (3)

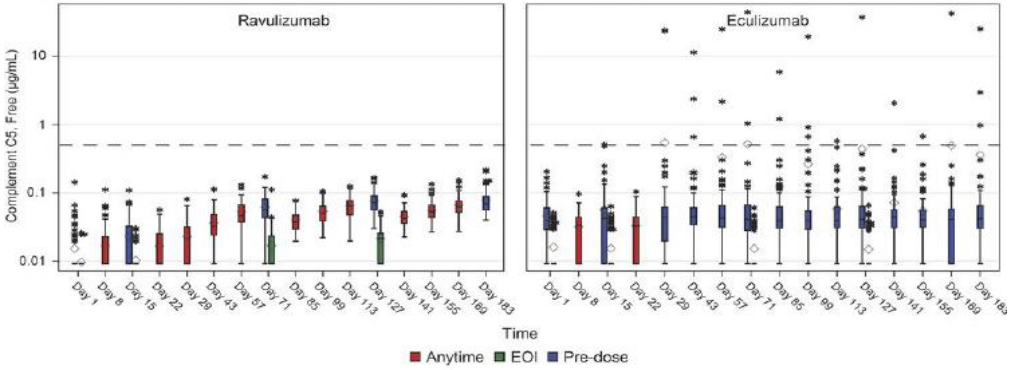
Mean serum free C5 concentrations were suppressed to <0.5 µg/mL by the end of the first infusion and at all subsequent visits for all patients receiving ravulizumab

This threshold was not consistently met in the eculizumab group



Safety

The most frequently reported AE was headache (26.8% and 17.3% in ravulizumab and eculizumab)
SAEs obseved in 4 ravulizumab and 8 eculizumab
No cases of meningococcal infections observed.
No treatment-emergent antidrug antibodies in patients treated with ravulizumab

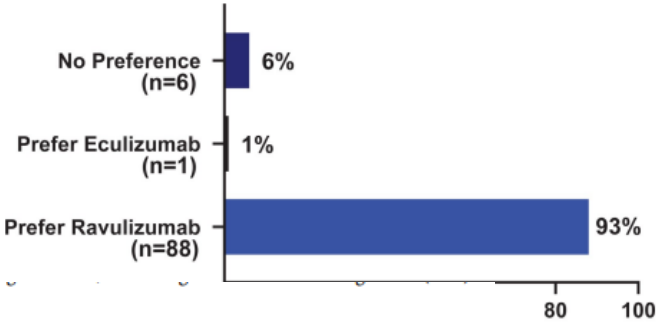


PLoS One, 2020

RESEARCH ARTICLE

Patient preferences and quality of life implications of ravulizumab (every 8 weeks) and eculizumab (every 2 weeks) for the treatment of paroxysmal nocturnal hemoglobinuria

John Devin Peipert[1], Austin G. Kulasekararaj[2], Anna Gaya[3], Saskia M. C. Langemeijer[4], Susan Yount[1], F. Ataulfo Gonzalez-Fernandez[5], Emilio Ojeda Gutierrez[6], Christa Martens[1], Amy Sparling[1], Kimberly A. Webster[1], David Cella[1], Ioannis Tomazos[7], Masayo Ogawa[7], Caroline I. Piatek[8], Richard Wells[9], Flore Sicre de Fontbrune[10], Alexander Röth[11], Lindsay Mitchell[12], Anita Hill[13]*, Karen Kaiser[1]*



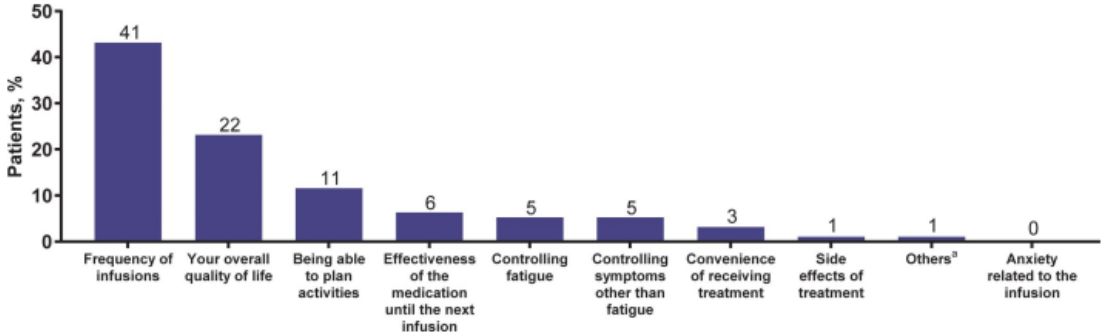


Fig 3. Patients' most important factor for deciding medication preference (N = 95). The number of patients selecting each preference is at top of bar. [a]Participants selecting "Other" were prompted to provide details.

One-year outcomes from a phase 3 randomized trial of ravulizumab in adults with paroxysmal nocturnal hemoglobinuria who received prior eculizumab

Austin G. Kulasekararaj[1] | Anita Hill[2] | Saskia Langemeijer[3] | Richard Wells[4] | F. Ataúlfo González Fernández[5] | Anna Gaya[6] | Emilio Ojeda Gutierrez[7] | Caroline I. Piatek[8] | Lindsay Mitchell[9] | Kensuke Usuki[10] | Alberto Bosi[11] | Robert A. Brodsky[12] | Masayo Ogawa[13] | Ji Yu[13] | Stephan Ortiz[13] | Alexander Röth[14] | Jong Wook Lee[15] | Régis Peffault de Latour[16,17,18]

Eur J Haematol. 2021

- Extension period in which patients continued ravulizumab (n = 96) or switched from eculizumab to ravulizumab (n = 95).
- **Hb stabilization, LDH, QoL, and proportions of patients avoiding transfusion remained stable in both groups**
- All patients lmaintained **serum free C5 evels < 0.5 µg/mL**.
- Adverse events were generally similar between groups, and rates were lower in the extension period.
- 4 patients (ravulizumab-ravulizumab, n = 3; eculizumab-ravulizumab, n = 1) experienced breakthrough hemolysis, but none associated with serum free C5 ≥ 0.5 µg/mL.

No evidence for hypogammaglobulinemia in patients with paroxysmal nocturnal hemoglobinuria (PNH) chronically treated with ravulizumab

Ferras Alashkar[1], Scott Rottinghaus[2], Colin Vance[3], Dörte Herich-Terhürne[1], Ulrich Dührsen[1], Roland Assert[4], Alexander Röth[1]*

1 Department of Hematology, West German Cancer Center, University Hospital Essen, Essen, Germany, **2** Alexion Pharmaceuticals, Inc, Boston, MA, United States of America, **3** Rheinisch-Westfälisches Institut für Wirtschaftsforschung, Essen, Germany, **4** Department of Clinical Chemistry, University Hospital Essen, Essen, Germany

PLoS One. 2020

- Ravulizumab has increased affinity for the neonatal Fc receptor (FcRn), competing with endogenous IgG. Saturation of the FcRn pathway by ravulizumab may result in enhanced endogenous IgG clearance.
- IgG and subclasses dosed longitudinally in 12 ravulizumab-treated for a median of 21 months
- **No treatment-associated hypogammaglobulinemia**

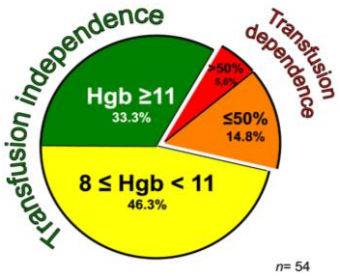
Ravulizumab: conclusions

In naïve PNH patients ravulizumab every 8 weeks demonstrated **non-inferiority** to eculizumab across all primary and secondary efficacy endpoints including **transfusion avoidance, normalization of LDH levels, stabilization of hemoglobin levels and incidence of breakthrough hemolysis**

In eculizumab-experienced PNH patients ravulizumab is non-inferior to eculizumab across all efficacy endpoints being the **normalization of LDH levels** the primary endpoint. **Breakthrough hemolysis, transfusion avoidance, and hemoglobin stabilization** endpoints were met as well

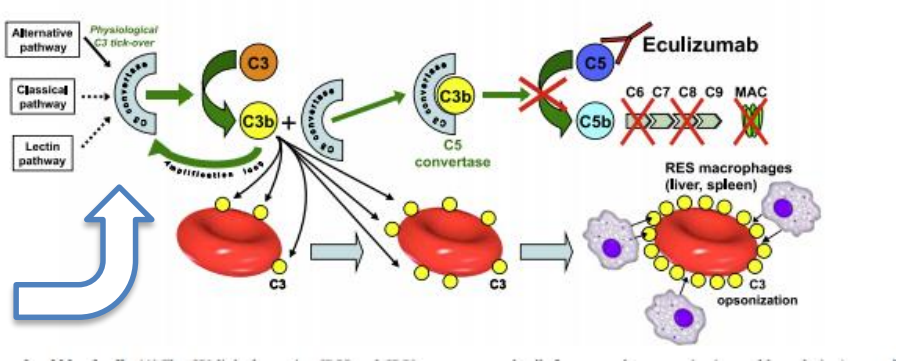
Free C5 levels <0.5 μg/mL correlated with maximal intravascular hemolysis control and complete terminal complement inhibition. **Ravulizumab provided immediate, complete, and sustained inhibition of C5 over the entire 8-week dose interval in both groups, unlike eculizumab**

Patients with PNH may be **safely and effectively switched from labeled-dose eculizumab every 2 weeks to ravulizumab every 8 weeks**



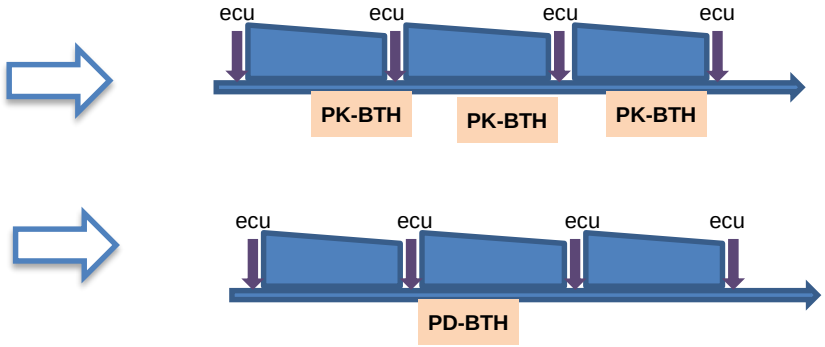
Unmeet needs for PNH patients on eculizumab: residual anemia

- **Underlying bone marrow failure**
- **genetic variants of complement-related genes**
- **C3-mediated extravascular hemolysis, 25-50% of patients: no reliable treatment option, steroids discouraged, splenectomy anecdotically reported effective, upstream inhibition of complement ?**



- **pharmacokinetic [PK] breakthrough hemolysis, occurring 1–2 days before the next dosing of eculizumab (15%-20%) of patients**
- **pharmacodynamic [PD] breakthrough due to hemolytic paroxysms in concomitance with massive complement activation (infections, surgery, etc)**

Ravulizumab better than eculizumab



Luzzatto L, F1000Res. 2016; Notaro R, Sica M. Semin Hematol. 2018; Risitano A. AJH 2018. Mastellos DC, Sem. Hematol 2018.

New drugs targeting the complement cascade…

More than 10 years ago… eculizumab iv every 2 weeks

Since 2-3 years several clinical trials

Ravulizumab, iv every 8 weeks, targeting C5, approved AIFA

Ravulizumab, sc weekly, targeting C5

Pegcetacoplan, sc twice weekly, targeting C3, approved FDA

Crovalimab, sc every 4 weeks, targeting C5

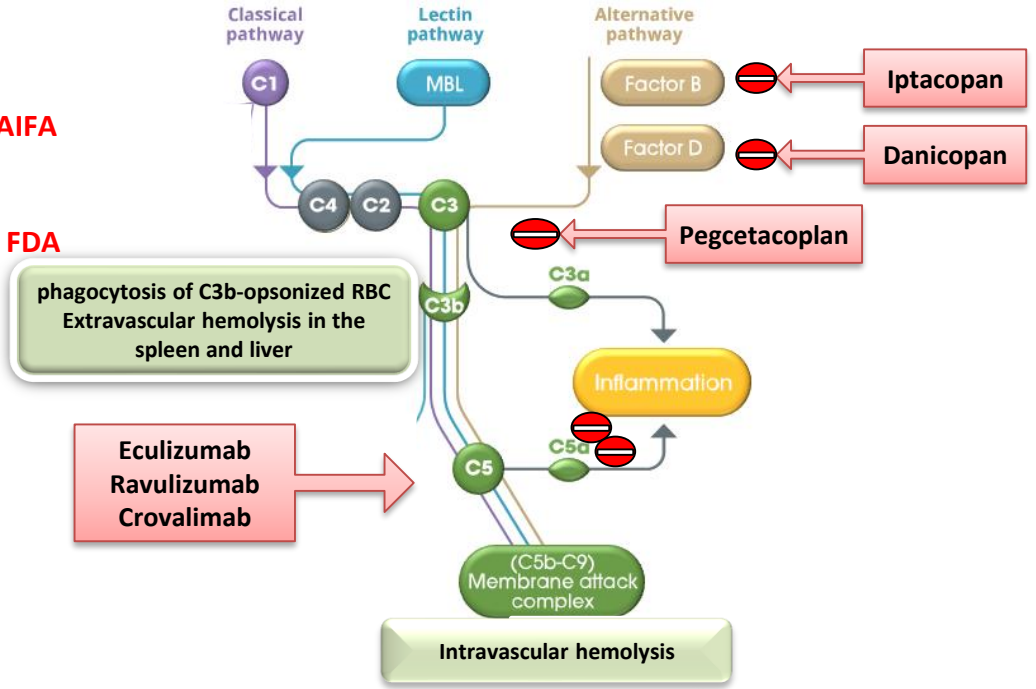
Danicopan, oral thrice daily, targeting factor D

Iptacopan, oral twice daily, targeting factor B

And more coming….

Danicopan, oral twice daily, targeting factor D

BCX9930, oral twice daily, targeting factor D



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