

# Paroxysmal Nocturnal Hemoglobinuria:

at the crossroads of somatic mutations, clonal expansion and immunity



**Florence, October 3-4, 2024**

**Grand Hotel Baglioni**

**Patient reported outcomes in PNH**

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# Disclosures

- Advisory Board - Novartis, Celgene BMS, Daiichi, Sobi, Alexion
- Speaker Bureau – Celgene BMS, Novartis
- Consultancy – Celgene BMS, Daiichi, Janssen, Alexion



# Patient-Reported Outcomes (PROs)

PROs are indicators for assessing impacts of disease, treatment, and symptoms

PROs include Quality of Life (QoL) + Symptoms obtained directly from patients

QoL is a complex multidomain and variable construct that represents the patient's overall perception of the impact of an illness and its treatment<sup>1,2</sup>

A symptom is any subjective evidence of a disease, health condition or treatment-related effect that can be noticed and recognized only by the patient<sup>3,4</sup>

## PRO measures (PROMs)

Measures (e.g. questionnaire or scale) based on a report that comes directly from the patient about the status of the patient's health condition without interpretation of the patient's response by a clinician or anyone else

1. Bowling A, et al. BMJ. 1996;312:670–674; 2. Gorodokin GI and Novik AA. Annals of Oncology. 2005;16(6):991; 3. Trotti A, et al. J Clin Oncol 2007;25(32):5121–127; 4. Spivak J, et al. The Oncologist 2009; 14 (suppl 1):43–56; 5. Passik SD, et al. J Clin Oncol 1998;16(4):1594–1600; 6. Fallowfield L, et al. Br J Cancer 2001;84(8):1011–1015.



# PRO measures (PROMs) in PNH trials

Author	Year	Number of patients evaluated; form of treatment (SCT/eculizumab/other)	Country of origin	QoL instrument used
Matos-Fernandez [39]	2009	<i>N</i> = 117; SCT (review of SCT in PNH)	Multinational	Surrogate parameters (GvHD, survival)
Brodsky [12]	2008	<i>N</i> = 93; eculizumab (vs placebo)	Multinational	EORTC QLQ-C30, FACIT
Meyers [14]	2007	<i>N</i> = 29; other	Multinational	EORTC QLQ-C30, FACIT plus self-reported symptoms
Hillmen [11]	2006	<i>N</i> = 87; eculizumab (vs placebo)	Multinational	EORTC QLQ-C30, FACIT
Hill [37]	2005	<i>N</i> = 11	UK	EORTC QLQ-C30
Raiola [38]	2000	<i>N</i> = 7; SCT	Italia	Surrogate parameters (Blood counts, GvHD)

1. Hillmen P, et al. N Engl J Med. 2006 Sep 1;355(12):1233-4; 2. Aaronson N, et al. J. Natl. Cancer Inst. 85,365,1993; 3. [http://www.ser.es/wp-content/uploads/2015/03/FACIT-F\\_INDICE.pdf/](http://www.ser.es/wp-content/uploads/2015/03/FACIT-F_INDICE.pdf/)



# EORTC QLQ-C30

- developed to assess PROs of cancer patients, translated into and validated in over 100 languages, and is used in thousands of studies worldwide each year
- 30 items to address 15 HRQoL domains with scores between 0–100
  - Higher score on the Global Health Status/QoL and Functional Scales represent better QoL
  - Higher score on symptom scales represent worse QoL

EORTC QLQ-C30 scales	Number of items	Item range	Item numbers (Version 3)
<b>Global Health Status/QoL</b>	2	1–7	29, 30
<b>Functional scales</b>			
Physical functioning	5	1–4	1–5
Role functioning	2	1–4	6, 7
Emotional functioning	4	1–4	21–24
Cognitive functioning	2	1–4	20, 25
Social functioning	2	1–4	26, 27
<b>Symptom scales</b>			
Fatigue	3	1–4	10, 12, 18
Nausea and vomiting	2	1–4	14, 15
Pain	2	1–4	9, 19
Dyspnea	1	1–4	8
Insomnia	1	1–4	11
Appetite loss	1	1–4	13
Constipation	1	1–4	16
Diarrhea	1	1–4	17
Financial difficulties	1	1–4	28

EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; HRQoL, health related quality of life, QoL, quality of life.

Fayers PM, et al. EORTC. 2001;1–73.



# FACT-F (fatigue)

- A commonly used scale to measure QoL and fatigue of patients with cancer undergoing chemotherapy
- Consists of the 28-item FACT-G questionnaire as a base plus 13 additional items related to fatigue
  - Tiredness, weakness and difficulty conducting everyday activities due to fatigue in the past 7 days.  
Higher scores reflect less fatigue.

## Items of the FACT-F

1. I feel fatigued
2. I feel weak all over
3. I feel listless ("washed out")
4. I feel tired
5. I have trouble starting things because I am tired
6. I have trouble finishing things because I am tired
7. I have energy
8. I am able to do my usual activities
9. I need to sleep during the day
10. I am too tired to eat
11. I need help doing my usual activities
12. I am frustrated by being too tired to do the things I want to do
13. I have to limit my social activity because I am tired

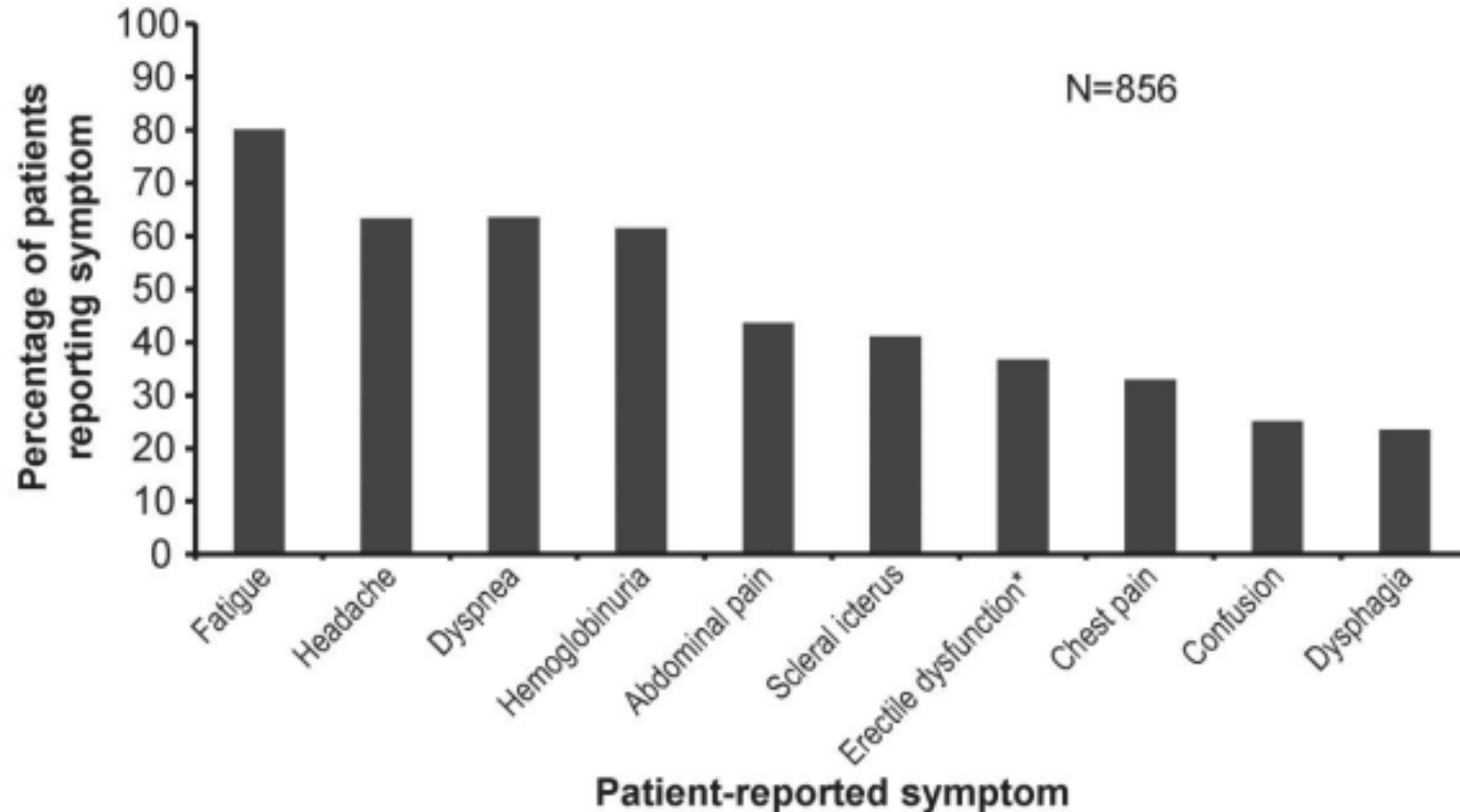
FACT-F, functional assessment of chronic illness therapy-fatigue.

Yellen SB, et al. J Pain Symptom Manage. 1997;13(2):63–74.



# Symptoms in untreated PNH patients

International PNH registry



Schrezenmeier H, et al. Haematologica 2014

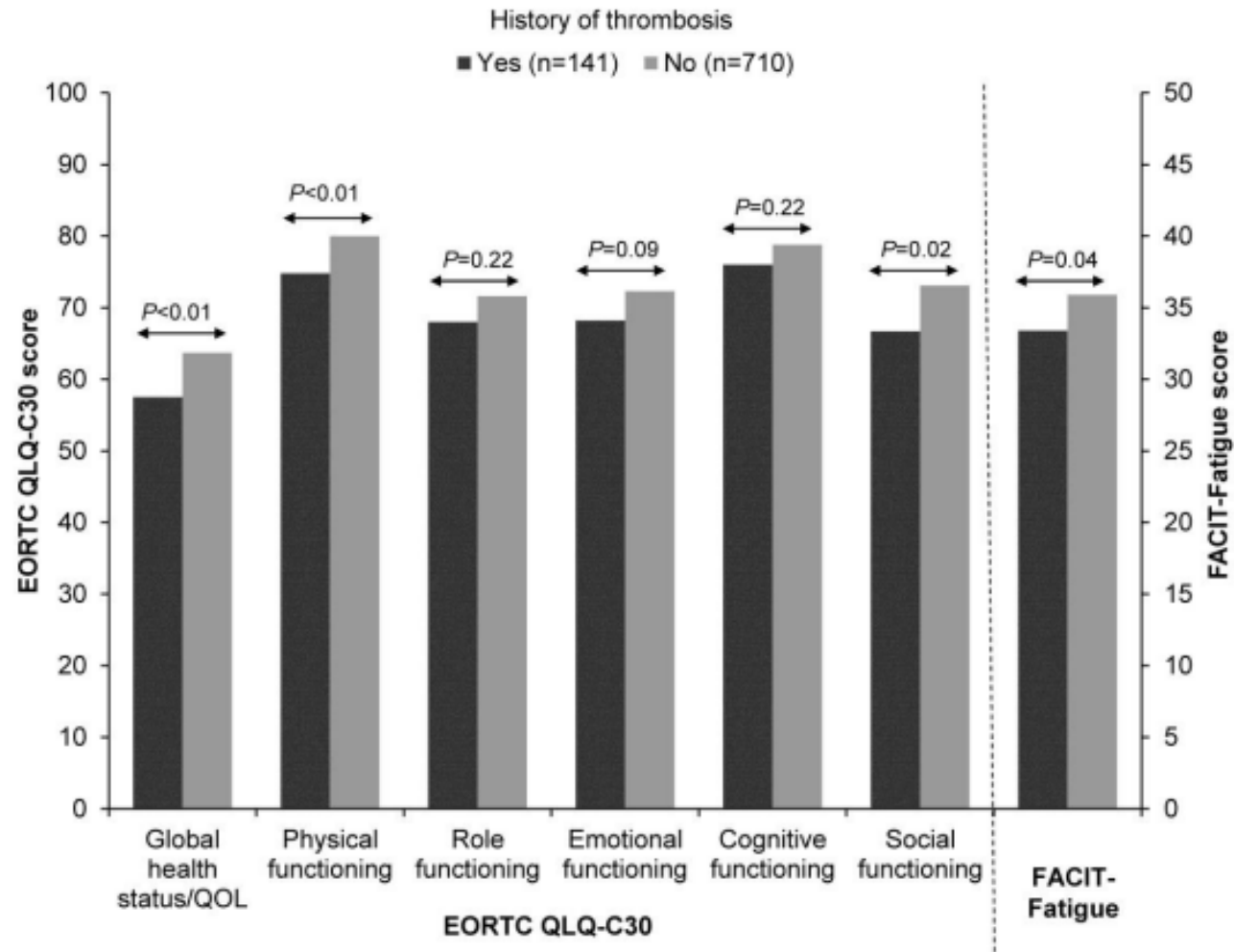
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# FACIT scores according to history of thrombosis

International PNH registry



Schrezenmeier H, et al. Haematologica 2014

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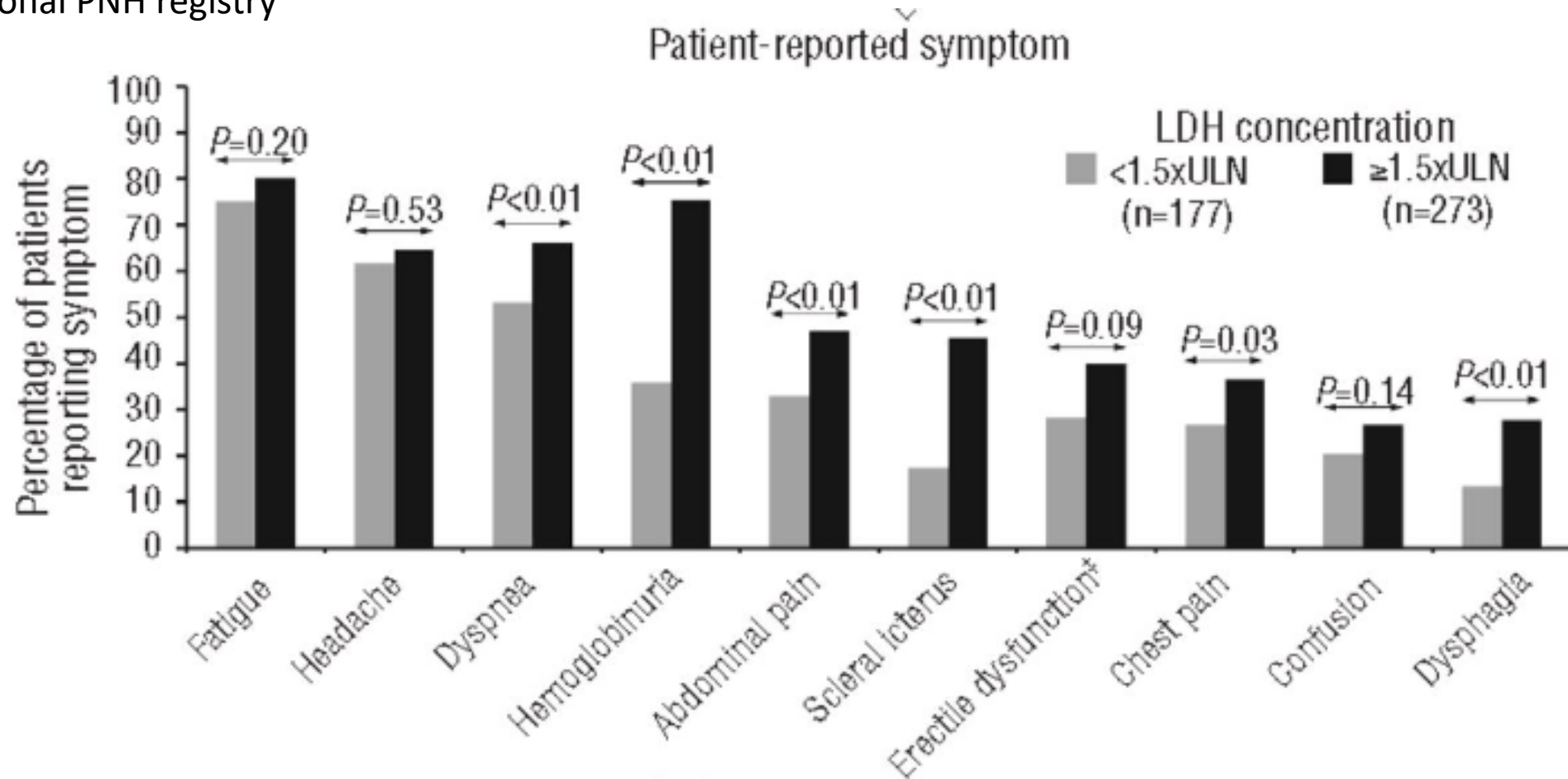
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# Symptoms by LDH concentration

International PNH registry



Schrezenmeier H, et al. Haematologica 2014



# QLQ-AA/PNH: Disease-specific measure

- 54 items covering themes with a recall period of 2 weeks.
- Impact on QoL, experience with PNH, and symptomsLa misura valuta alcuni sintomi ma il focus degli item è sull'impatto sulla qualità della vita e sull'esperienza sanitaria
- Undergoing further evaluation

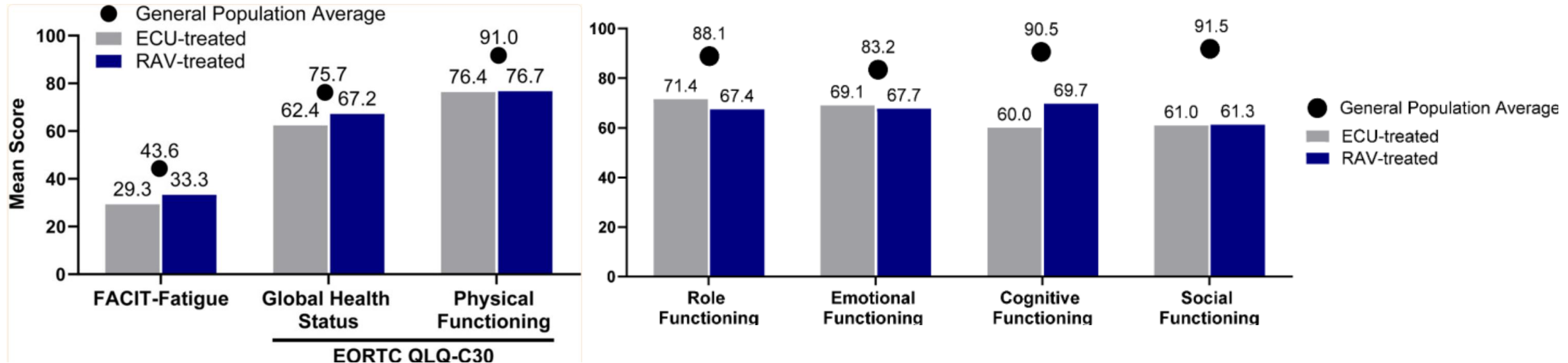
Kaiser K, et al. Patient Prefer Adherence. 2020 Apr 5;14:705-715  
Niedeggen C, et al. Ann Hematol. 2019; 98(7): 1547–1559.

# QoL of patients receiving C5 inhibitors in USA

PNH Burden of illness survey study:

122 American patients living with PNH, at the time of the survey

mean age 46.8 (SD 15.7) years (ECU n=32; RAV n=82)



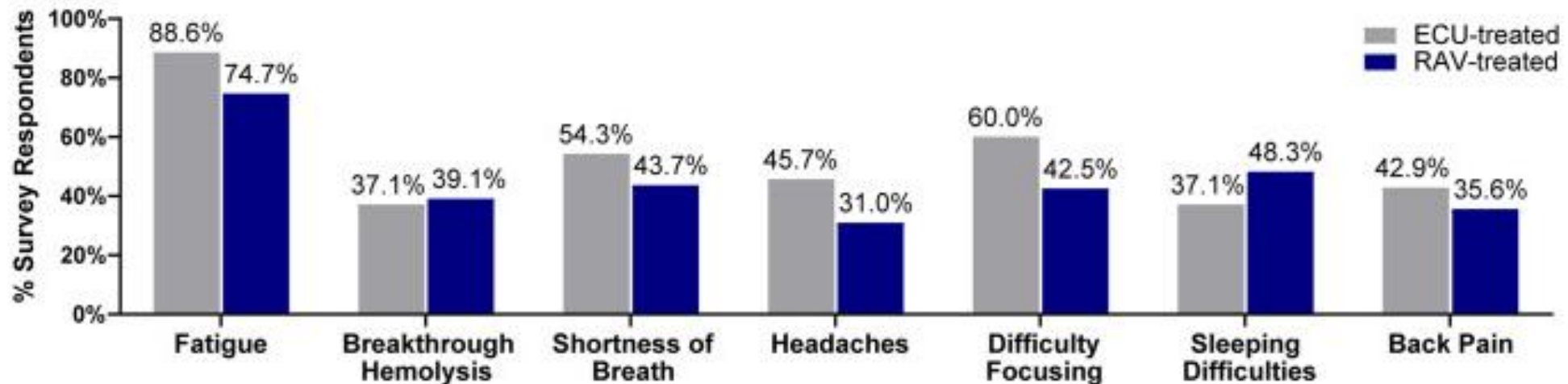
Dingli D, et al. Ann Hematol. 2022; 101(2): 251–263.



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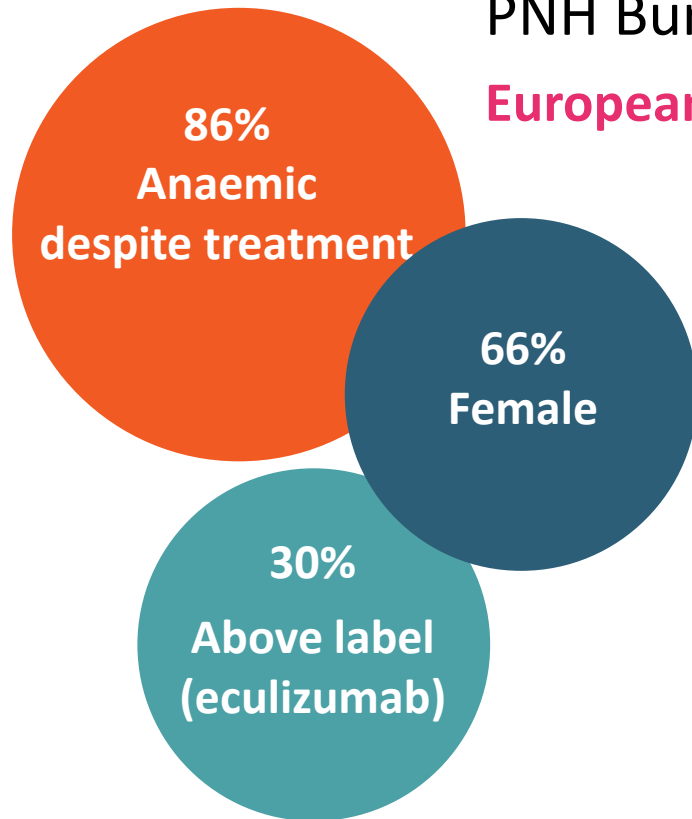
Dingli D, et al. Ann Hematol. 2022; 101(2): 251–263.



# PROS of patients receiving C5 inhibitors in France, Germany and UK

PNH Burden of illness survey study:

European patients living with PNH, at the time of the survey<sup>1,2</sup>



71 patients (mean age 43 years) completed the survey (ECU n=49; RAV n=22)

- Patients were mostly female (66%; n=47)
- Despite patients (99%; n=70) had been treated with C5i for at least 3 months, most (86%; n=54) were still anemic (Hb  $\leq$ 12.0 g/dL)
  - Thirty-six patients had Hb levels  $<$ 10.5
- Almost a third (30%; n=14) of the eculizumab group was prescribed above-label doses<sup>1,2</sup>

Hb, haemoglobin; PNH, paroxysmal nocturnal haemoglobinuria

Panse et al. Eur J Haematol 2022

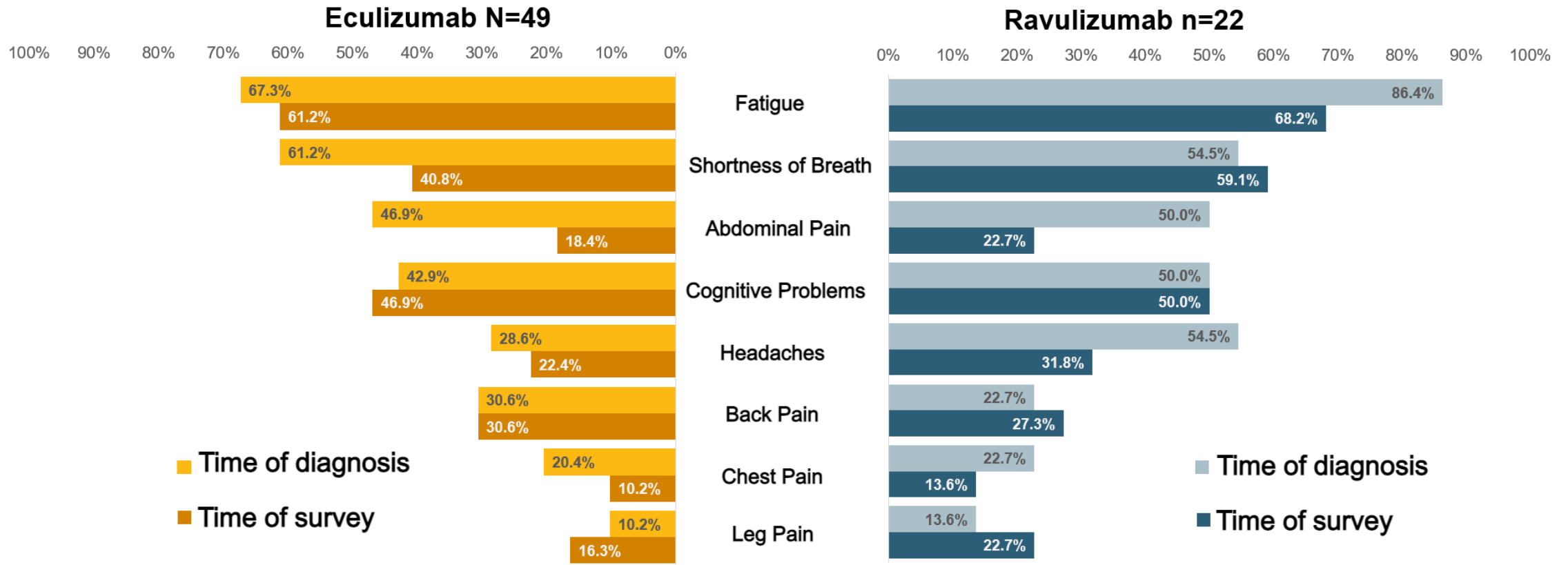
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# Symptoms by treatment

## PNH symptoms (recall from last 7 days)



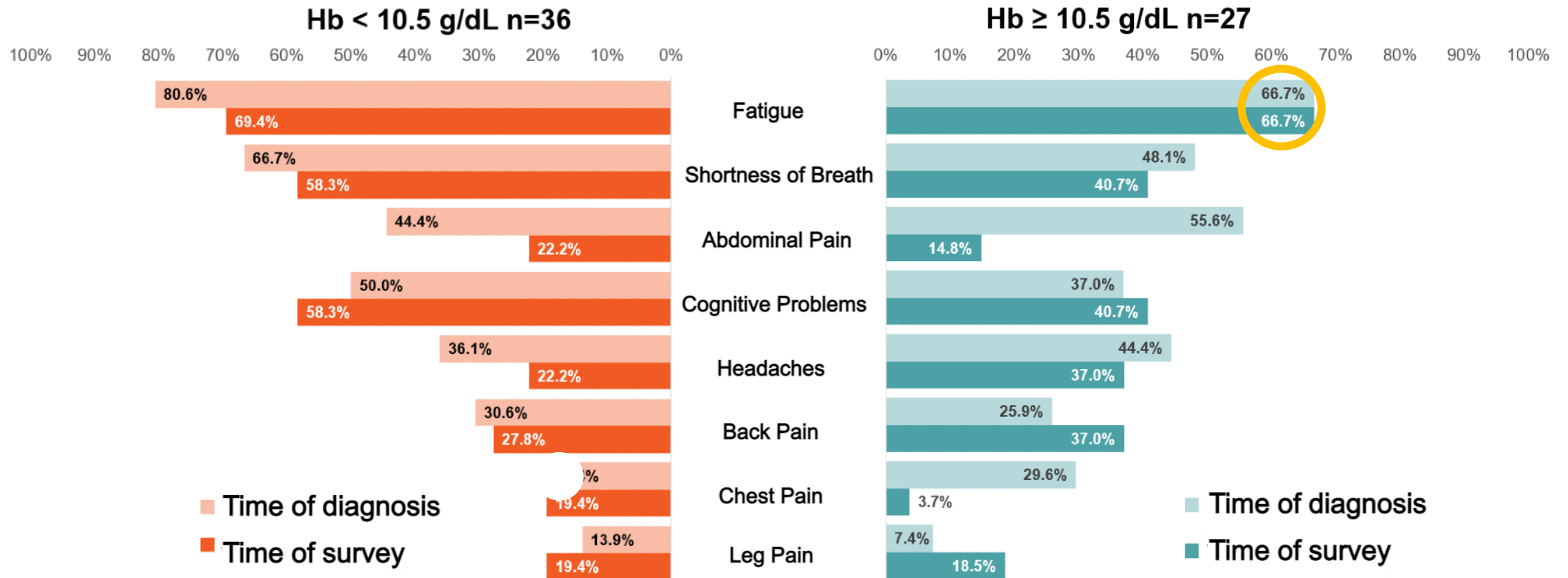
Cognitive problems incl. memory lost, confusion, brain fog problems concentrating and difficult focusing on tasks

Panse et al. Eur J Haematol 2022



# Symptoms by severity of anemia

Patients suffer from fatigue and other PNH related symptoms irrespective of Hb levels and despite C5i treatment



Panse et al. Eur J Haematol 2022

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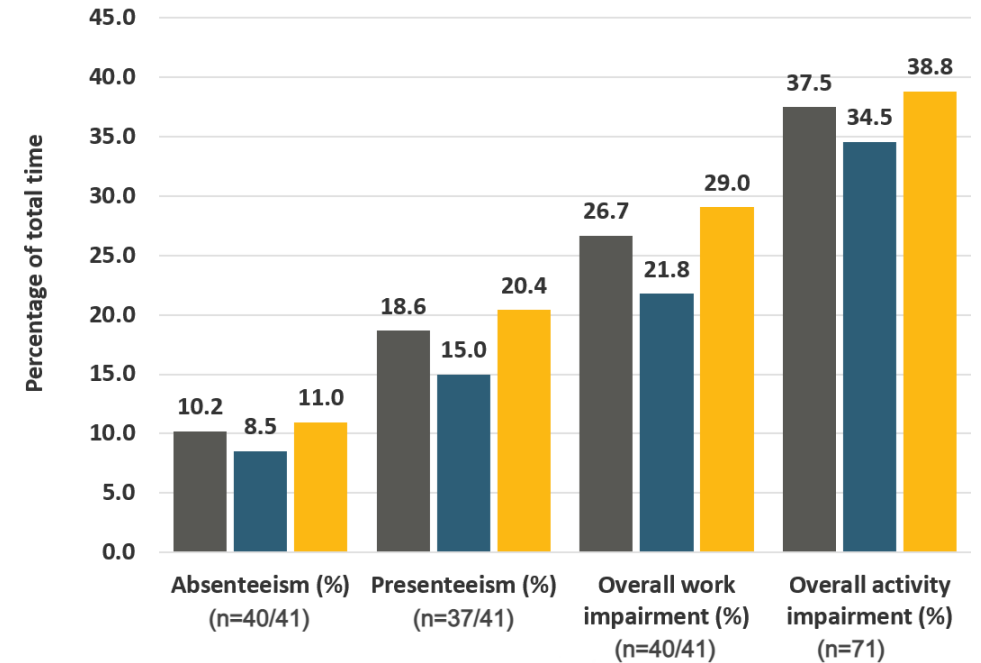
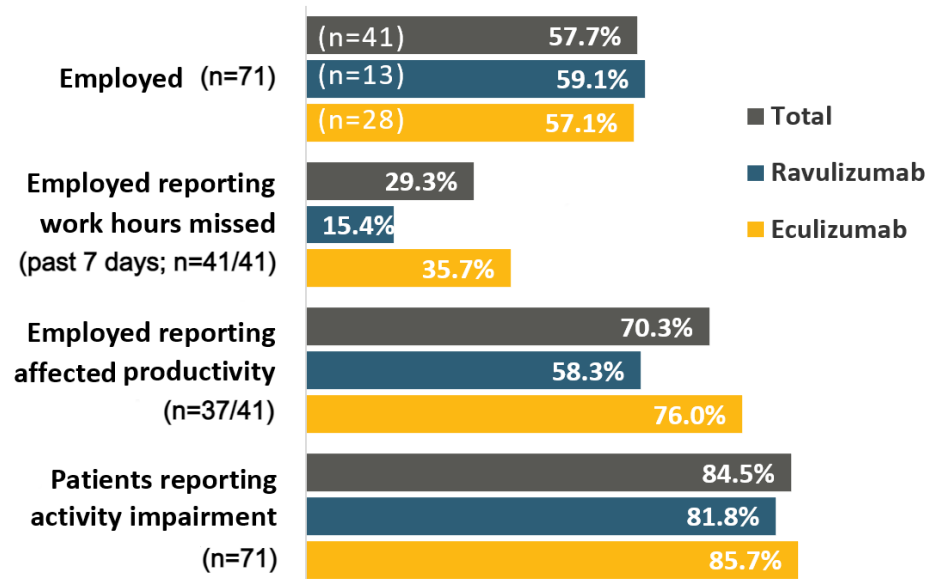
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# Impact on activity and productivity

Patients reported PNH affected them at work and throughout the day<sup>1</sup>

## Employment and Work Productivity



- The majority (58%) of this primarily working-age population (mean age 43 years) was employed; 70% had work affected (27% of the working time)
- 85% reported overall activity impairment for a mean 37.5% of working hours in the past 7 days

Panse et al. Eur J Haematol 2022





# Minimal Clinically Important Difference (MCID)

- The smallest difference in the measure (score) that patients perceive as important, either in terms of benefit or harm, and which would lead a care provider to consider changing the patient's management.
- Specific to domain scores within a given tool
- It is different from a p-value (“significant difference”)
  - In fact, a statistically significant change may be described without that difference reaching minimal importance (patients’ perception of change”)



# PROs in clinical trials

Drug	Study Name	Number of Participants	Main Message
Eculizumab	Triumph	87 (43 eculizumab)	FACIT-F score significantly increased from baseline in eculizumab arm
	Shepherd	97	Both FACIT-F score and EORTC-QLQ-C30 improved from baseline to week 52
	Japanese experience	54	Both FACIT-F score and EORTC-QLQ-C30 meaningfully increased
Ravulizumab	301	246 (125 ravulizumab, 121 eculizumab)	Improvement in FACIT-F score and EORTC-QLQ-C30 similar in the ravulizumab and eculizumab group
	302	195 (97 ravulizumab, 98 eculizumab)	Change in FACIT-F score from the baseline significantly higher in the ravulizumab group; change in EORTC-QLQ-C30 similar in both groups
	302 extension	191 (96 ravulizumab, 95 eculizumab to ravulizumab)	Mean FACIT-F score remained stable through study period; mean EORTC-QLQ-C30 was similar in both groups
	302s	95	Ravulizumab preferred over eculizumab by a significant proportion of patients

Drug	Study Name	Number of Participants	Main Message
Pegcetacoplan	Pegasus	80 (41 pegcetacoplan, 39 eculizumab)	FACIT-F score increased from baseline in pegcetacoplan arm
Crovalimab	Composer	29	Both FACIT-F score and EORTC-QLQ-C30 improved from baseline
Danicopan	<a href="#">NCT03053102</a>	10	Significant increase of mean FACIT-Fatigue score from baseline at days 28 and day 84
	<a href="#">NCT03472885</a>	12	Mean FACIT-Fatigue score increased by 11 points at week 24
Iptacopan	<a href="#">NCT03439839</a>	10	The FACIT-F score improved significantly in most patients

EORTC, European Organisation for Research and Treatment of Cancer-QLQ-C30 score; FACIT-F, the Functional assessment of chronic illness-Fatigue.

Fattizzo B, et al J Blood Med. 2022 Jun 17;13:327-335.

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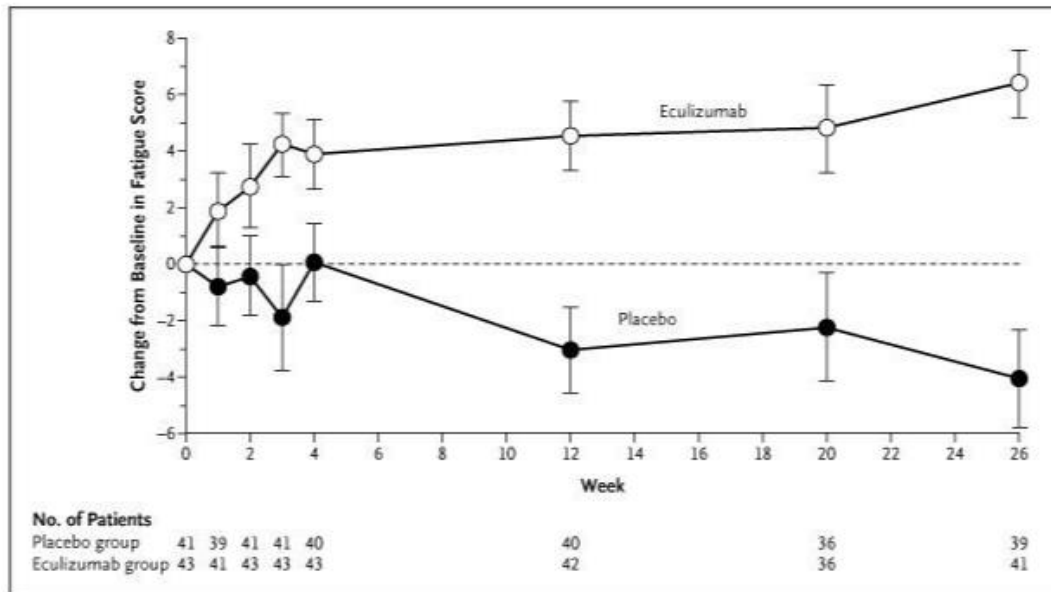
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# Eculizumab in PNH: PROs

- A double-blind, randomized, placebo-controlled, multicenter, phase 3 trial
- 87 patients randomized to receive placebo or eculizumab

## FACIT-fatigue



## EORTC QLQ-C30

Scale	Mean Change in Score from Baseline to Week 26 <sup>†</sup>		Absolute Difference	P Value <sup>‡</sup>
	Placebo Group	Eculizumab Group		
Global health status scale	-8.5	10.9	19.4	<0.001
Functioning scales				
Role	-6.9	17.9	24.8	<0.001
Social	2.0	16.7	14.7	0.003
Cognitive	-6.1	7.9	14.0	0.002
Physical	-3.5	9.4	12.9	<0.001
Emotional	-3.7	7.5	11.2	0.008
Symptom scales				
Fatigue	10.0	-16.9	26.9	<0.001
Pain	5.3	-12.3	17.6	0.002
Nausea and vomiting	2.8	-0.4	3.2	0.06
Single-item measures				
Dyspnea	8.9	-7.9	16.8	<0.001
Loss of appetite	3.3	-10.3	13.6	<0.001
Insomnia	4.9	-7.9	12.8	0.01
Financial difficulties	0.0	-10.3	10.3	0.19
Constipation	0.0	-6.3	6.3	0.20
Diarrhea	5.7	4.8	0.9	0.15

\* The quality of life was assessed with the EORTC QLQ-C30 instrument.

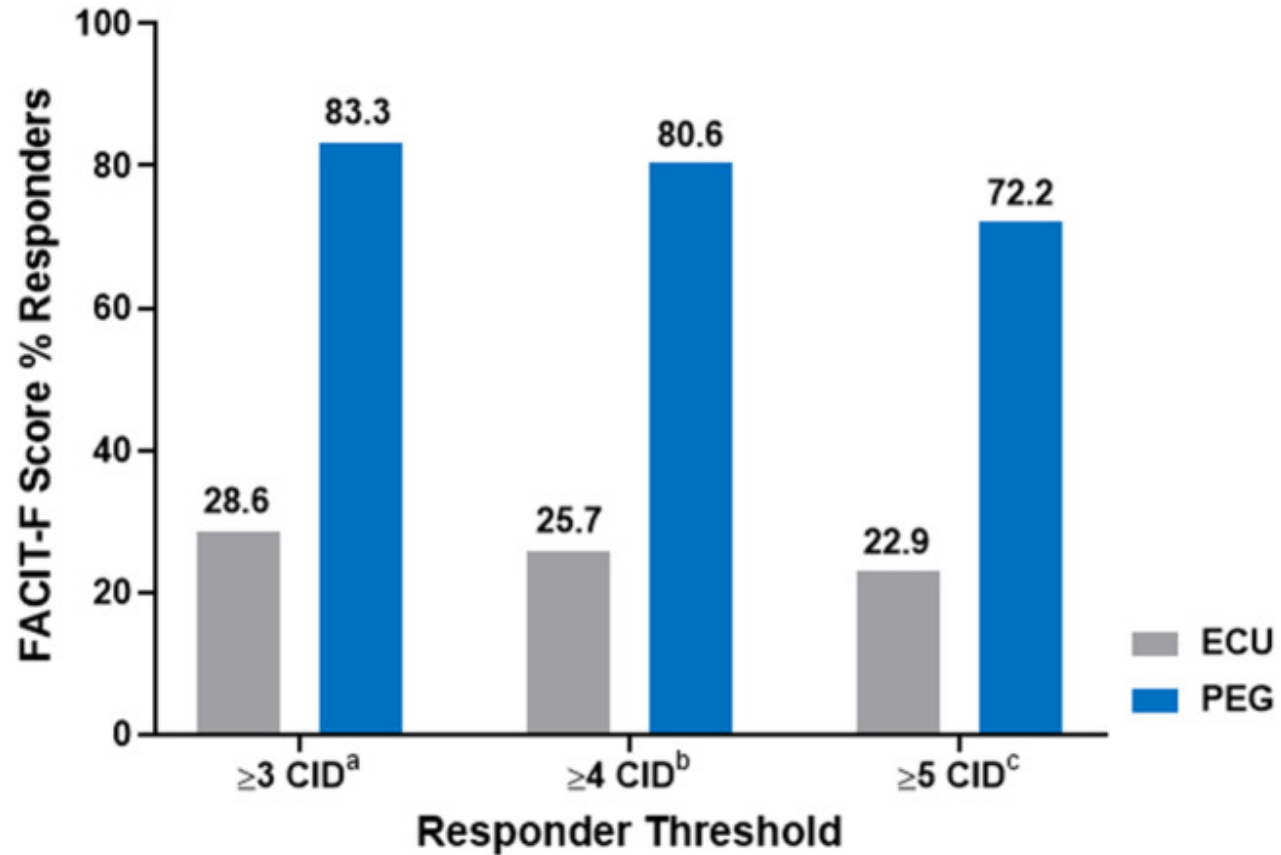
<sup>†</sup> A positive value for a score on the scales for global health status and functioning indicates improvement, whereas a negative value for a score on the symptom scales and for a score on the single-item measures indicates improvement.

<sup>‡</sup> P values are from a mixed model, with baseline scores as the covariate, treatment and time as fixed effects, and the patient identifier as a random effect.

Hillmen P, et al. N Engl J Med. 2006 Sep 1;355(12):1233-4



# Pegasus trial: Pegcetacoplan vs Eculizumab fatigue - Clinical Important Difference (CID)



N= 10 30 9 29 8 26

Mean Hb (g/dl):

<sup>a</sup>For ≥3 CID; ECU = -0.20 and PEG = 3.1; <sup>b</sup>For ≥4 CID; ECU = -0.22 and PEG = 3.13; <sup>c</sup>For ≥5 CID; ECU = -0.07 and PEG = 3.19.

Cella D, et al. Ann Hematol. 2022; 101(9): 1905–1914.



# Pegasus trial: Pegcetacoplan vs Eculizumab PROs

	PEG (N=41)		ECU (N=39)	
	Baseline <sup>a</sup>	CFB at Wk 16 <sup>b</sup>	Baseline <sup>a</sup>	CFB at Wk 16 <sup>b</sup>
<b>Global Health Status/QoL</b>	56.30 (20.39)	<b>15.44</b> (3.05)	56.53 (20.24)	-3.83 (3.13)
<b>Functional scales</b>				
Physical functioning	71.38 (20.23)	<b>16.20</b> (2.34)	72.11 (20.14)	0.53 (2.44)
Role functioning	63.82 (29.56)	<b>16.15</b> (4.11)	59.65 (33.92)	-6.93 (4.25)
Emotional functioning	72.36 (25.38)	6.26 (3.39)	69.59 (22.67)	-2.65 (3.49)
Cognitive functioning	76.02 (24.45)	5.37 (3.21)	75.23 (25.95)	-8.87 (3.34)
Social functioning	69.51 (28.84)	<b>13.18</b> (3.40)	64.86 (32.82)	-0.16 (3.54)

CFB = Change from Baseline

Cella D, et al. Ann Hematol. 2022; 101(9): 1905–1914.



# Pegasus trial: Pegcetacoplan vs Eculizumab PROs

	PEG (N=41)		ECU (N=39)	
	Baseline <sup>a</sup>	CFB at Wk 16 <sup>b</sup>	Baseline <sup>a</sup>	CFB at Wk 16 <sup>b</sup>
<b>Symptom scales</b>				
Fatigue	49.59 (29.09)	-22.34 (3.31)	50.29 (24.74)	-0.47 (3.41)
Nausea and vomiting	3.66 (8.75)	-0.10 (2.40)	5.26 (11.69)	6.13 (2.39)
Pain	19.51 (26.85)	1.31 (4.11)	15.79 (25.10)	9.48 (4.19)
Dyspnea	33.33 (27.90)	-21.26 (3.61)	43.86 (32.05)	-3.86 (3.70)
Insomnia	32.52 (34.55)	-9.63 (3.61)	29.82 (29.80)	-5.53 (3.72)
Appetite loss	12.20 (17.88)	-4.68 (2.98)	13.16 (23.94)	2.06 (3.05)
Constipation	11.38 (20.56)	3.38 (2.81)	10.81 (22.30)	-5.60 (2.87)
Diarrhea	11.38 (23.11)	-0.33 (3.45)	11.71 (21.11)	8.27 (3.57)
Financial difficulties	18.70 (26.93)	-8.99 (3.62)	24.32 (37.39)	0.89 (3.84)

Cella D, et al. Ann Hematol. 2022; 101(9): 1905–1914.



# Pegasus trial: PRO correlations

	Hemoglobin (r)	Reticulocyte count (r)	Indirect bilirubin (r)
FACIT-F			
Total score	0.47****	-0.37**	-0.25*
EORTC QLQ-C30			
Global Health Status/QoL	0.44****	-0.31**	-0.13
Function scale			
Physical function	0.45****	-0.28*	-0.26*
Symptom scale			
Fatigue	-0.39***	0.28*	0.18
Single item			
Dyspnea	-0.49****	0.38**	0.26*

Correlations - \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ , \*\*\*\* $p < 0.0001$

Cella D, et al. Ann Hematol. 2022; 101(9): 1905–1914.



# Final conclusions

- Patients with PNH suffer a poorer QoL than the general population, with fatigue and symptoms persisting from diagnosis
- The lifelong nature of PNH and the occurrence of breakthrough hemolysis and thrombotic and infectious complications still burden the clinical course and affect individual health perception
- Given the variety of novel compounds and the potential to differently improve residual anemia in PNH, patients' perspective and efficacy on PROs will become more and more crucial in individualized treatment selection
- Recent studies with novel drugs clearly showed improvement in QoL in PNH patients beyond the benefit reached with eculizumab

