Acceptance Code: PCR248

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Meaningful Within-Patient Change Threshold Range for the FACIT-Fatigue in Paroxysmal Nocturnal Haemoglobinuria (PNH)

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Key Findings and Conclusions

- The Patient Global Impression of Severity (PGIS) was confirmed as an appropriate anchor to calculate meaningful within-patient change (MWPC) thresholds for the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue) in PNH
- The PGIS category of improvement by 1 level of severity provided a range for the FACIT-Fatigue MWPC of 7.5- to 9.5-point change from baseline
- Patient interviews provided additional context on the magnitude of changes from baseline on the FACIT-Fatigue that patients viewed as meaningful and further support the proposed range
- A change in the range of 7.5 to 9.5 points on the FACIT-Fatigue reprsents a useful starting point for classifying fatigue as meaningfully improved, thereby identifying a MWPC range for the FACIT-Fatigue in patients with PNH
- These results do not speak to the minimally important change, a value that is likely to be lower for many individuals

This study is sponsored by Novartis Pharmaceuticals Corporation.

Poster presented at The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Europe 2023, held in Copenhagen, Denmark on 12-15 November 2023

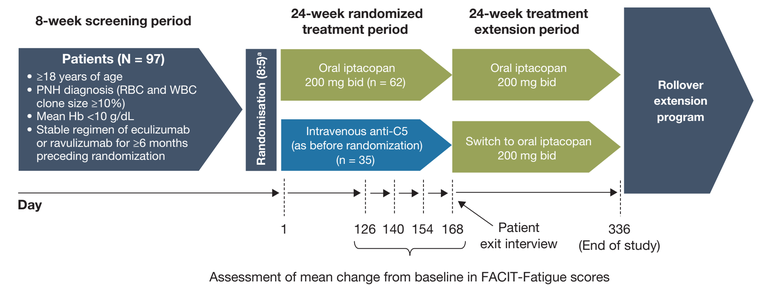
Introduction

- PNH is a rare, chronic haematologic disorder characterized by intravascular haemolysis, thrombophilia, and bone marrow failure[1,2]
- Fatigue is the most prevailing symptom of PNH and was measured in this study using the FACIT-Fatigue[3,4]
- The FACIT-Fatigue is a 13-item questionnaire assessing self-reported tiredness, weakness, and difficulties with daily life activities. It was originally developed to measure fatigue in patients with cancer and has support for its content validity and reliability in PNH. A higher FACIT-Fatigue score represents less fatigue[4]
- MWPC thresholds are important for demonstrating the magnitude of change that reflects meaningful improvement in patient disease experience with treatment[5]; however, rigorously determined MWPC thresholds for the FACIT-Fatigue with patient-centred anchors are lacking in PNH
- We describe the derivation of patient-centred, evidence-based MWPC thresholds for the FACIT-Fatigue in PNH using anchor-based methods

Methods

- This analysis used data from APPLY-PNH (NCT04558918), a 24-week randomized, open-label, multicentre, phase 3 study of iptacopan in adult patients with PNH and residual anaemia (mean haemoglobin <10 g/dL) despite anti-C5 treatment[6]
- FACIT-Fatigue changes from baseline to days 126, 140, 154, and 168 during the active-controlled treatment period were measured as a secondary end point (**Figure 1**)
- The PGIS assesses the overall severity of fatigue, and PGIS responses were collected on the same days as FACIT-Fatigue responses. In this study, the PGIS was used as an anchor to determine the MWPC threshold from baseline in FACIT-Fatigue score
- PGIS change categories were calculated as differences with respect to baseline levels; an increase in symptom severity indicated worsening fatigue, a difference of zero indicated unchanged fatigue, and a decrease in symptom severity indicated improvement in fatigue. The magnitude of the change was also considered
- PGIS change categories “Worse 1” and “Worse 2” are labels for 1 and 2 steps in the worsening direction. “Improve 1”, “Improve 2”, and “Improve 3” are labels for 1, 2, and 3 steps change in the improvement direction. These labels were used to summarize the changes in the FACIT-Fatigue and to obtain the MWPC thresholds
- Polyserial correlations between PGIS change categories and FACIT-Fatigue change from baseline were calculated to determine the degree of association between the change in FACIT-Fatigue and the change in PGIS anchor score[7]
- Patient exit interview data were used to obtain the patient perspective on meaningfulness of changes in fatigue and the level of change on the PGIS that was deemed meaningful to support the MWPC threshold determination

Figure 1. APPLY-PNH Study Design



bid, twice daily; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy – Fatigue; Hb, haemoglobin; PNH, paroxysmal nocturnal haemoglobinuria; RBC, red blood cell; WBC, white blood cell.
[a] Stratified by prior anti-C5 treatment and RBC transfusions in the preceding 6 months (yes/no).

Results

Baseline demographics and disease characteristics

- Of the 97 patients randomised in APPLY-PNH, 95 patients had baseline and postbaseline FACIT-Fatigue measurements and were included in the patient-reported outcome (PRO)–evaluable set
- The patient interview set (n = 17) is a subset of the PRO-evaluable set and does not include patients who discontinued study treatment
- The baseline demographic and disease characteristics for the patient interview subset and PRO-evaluable set are shown in **Table 1**

Table 1. Baseline Demographic and Disease Characteristics

	PRO-evaluable set n = 95	Patient interview subset n = 17
Mean age (SD), years	51.4 (16.8)	46.8 (14.0)
Female, n (%)	65 (68.4)	12 (70.6)
Mean time since diagnosis (SD), years	12.4 (10.26)	12.0 (10.86)
Mean PNH monocyte clone size (SD) [range], %	95.1 (7.34) [62.3-100.0]	96.3 (4.17) [84.3-99.9]
Mean PNH granulocyte clone size (SD) [range], %	74.9 (20.36) [0.7-98.8]	70.6 (27.56) [0.7-92.5]
Prior anti-C5 therapy, n (%)		
Eculizumab	62 (65.3)	11 (64.7)
Ravulizumab	33 (34.7)	6 (35.3)
Received RBC transfusions,[a] n (%)	55 (57.9)	10 (58.8)
Mean baseline Hb (SD) [range], g/dL	8.9 (0.78) [6.2-9.9]	9.3 (0.45) [8.3-9.9]
Mean baseline ARC (SD) [range], × 10^9/L	193.3 (82.79) [51-563]	220.9 (70.76) [95-374]
Mean FACIT-Fatigue score (SD) [range]	33.4 (10.52) [10.0-52.0]	32.7 (10.69) [11.0-50.0]
Total No. of Symptoms,[b] n (%)		
0	33 (35.1)	5 (29.4)
1	30 (31.9)	6 (35.3)
+1	31 (33.0)	6 (35.3)

ARC, absolute reticulocyte count; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy – Fatigue; Hb, haemoglobin; PNH, paroxysmal nocturnal haemoglobinuria; PRO, patient-reported outcome; RBC, red blood cell.
[a] In the 6 months prior to randomisation; [b] The total number of symptoms was measured at baseline by an investigator assessed presence of PNH signs and symptoms scale used in medical practice; [c] One patient had missing data in the PRO-evaluable set for PNH symptoms at baseline.

Correlation between FACIT-Fatigue change scores and PGIS change categories

- The smallest polyserial correlation between PGIS change categories and FACIT-Fatigue change scores was observed on day 7 as 0.42, with a range of 0.58 to 0.78 after Day 7 (**Table 2**)
- The magnitude of polyserial correlations indicated a strong association between the PGIS anchor and the FACIT-Fatigue change score

Table 2. Polyserial Correlations Between PGIS Change Categories and FACIT-Fatigue Change From Baseline Scores[a]

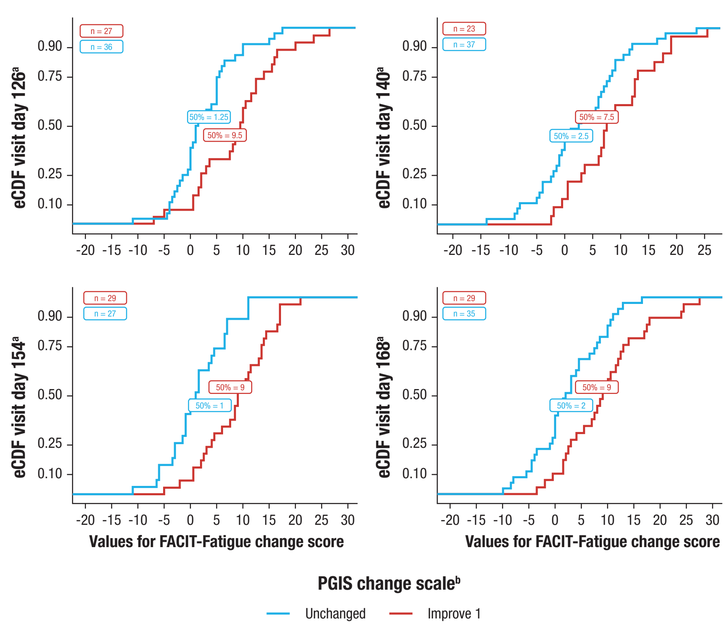
Statistic	Day 7	Day 14	Day 42	Day 84	Day 126	Day 140	Day 154	Day 168
n	87	85	93	86	87	86	84	90
Correlation (SE)	0.42 (0.098)	0.63 (0.067)	0.77 (0.045)	0.70 (0.058)	0.65 (0.063)	0.58 (0.073)	0.78 (0.045)	0.66 (0.061)

FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy – Fatigue; PGIS, Patient Global Impression of Severity.
[a] For calculations of polyserial correlation, categories “Worsened by 2” with “Worsened by 1” and “Improved by 2” with “Improved by 3” were merged.

Empirical distribution curves (eCDFs) of FACIT-Fatigue change scores by PGIS change categories

- In the PGIS change categories with the largest sample size (unchanged and improved by 1), the distributions were separate and parallel, indicating that the PGIS performs adequately as an anchor and can separate improvement from unchanged (**Figure 2**)

Figure 2. eCDFs of FACIT-Fatigue Change Scores by PGIS Severity Change Categories in the PRO-Evaluable Set



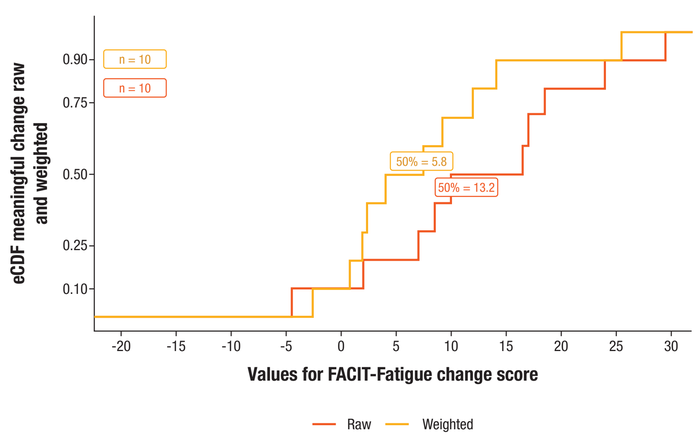
eCDF, empirical distribution curve; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy – Fatigue; PGIS, Patient Global Impression of Severity; PRO, patient-reported outcome.
[a] Sample size and median values for the 50% quantile are highlighted by boxes; [b] Improve 1 is the label for a 1 step change in the improvement direction for the PGIS change category.

- The PGIS change reflecting a 1 category improvement in severity was chosen as the primary anchor due to its larger sample size among the improvement categories (**Figure 2**) and being indicated by 40% (6 of 15) of participants in the patient interviews as a meaningful change
- Using a 1-level change in severity category of PGIS and median FACIT-Fatigue change from baseline values, the MWPC threshold for FACIT-Fatigue change scores at days 126, 140, 154, and 168 was 7.5 to 9.5 points (**Figure 2**)

Derivation of meaningful FACIT-Fatigue changes, using patient interview as a supporting anchor

- The distribution of FACIT-Fatigue change from baseline scores of participants in the patient interview is shifted towards large improvements compared to non-participants or the overall study population. Similarly, PGIS change categories for improvement predominate. The reference visit for the patient interview is Day 168 (**Supplemental Figure 1**)
- The patient interview was semi-structured and used to obtain the patient perspective about any change in fatigue symptoms or impact after receiving treatment, and the meaningfulness of this change. The actual interview transcripts were reviewed and common ‘concepts’ were extracted
- FACIT-Fatigue change from baseline score on Day 168 for patients who reported meaningful improvement in ≥50% of the total ‘concepts’ were evaluated (**Figure 3**)
- The FACIT-Fatigue scores of participants in the interview were transported to the overall population calculating weights based on the probability of participation in the interview as an adjustment for selection bias. **Figure 3** shows raw and weighted scores
- The medians of the raw (13.2) and weighted scores (5.8) in **Figure 3** can be interpreted as bounds for the FACIT-Fatigue MWPC threshold from the patient interview. These values encompass the range of values that emerged from the PGIS anchor (7.5-9.5 points) and further support the MWPC threshold derived from the PGIS

Figure 3. eCDF for Patients Who Expressed Meaningful Improvement in ≥50% of ‘Concepts’[a,b]



eCDF, empirical distribution curve; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy – Fatigue.
[a] Sample size and median value for the 50% quantile are highlighted by boxes; [b] n-values represent the number of patients from the patient interview subset who reported meaningful improvement (10/17).

Acknowledgments

We thank the patients and health care professionals who participated in this study, which was sponsored by Novartis Pharmaceuticals Corporation. We thank Erika Tomei, PhD, from Clinical Thinking, who provided medical writing support funded by Novartis Pharmaceuticals Corporation in accordance with the Good Publication Practice (GPP 2022) guidelines.

Disclosures

GB is an employee of Novartis Pharma AG. **SV** is an employee of Novartis Pharmaceuticals Corporation and holds shares and/or stock options in the company. DC is the President of FACIT.org and has received research support and consulting fees from Alexion, AstraZeneca Rare Disease.

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Funding Source

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