Fatigue Severity Thresholds in Cold Agglutinin Disease: Post-Hoc Analyses on the FACIT-Fatigue Scale from Two Phase 3 Trials

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INTRODUCTION

- Cold agglutinin disease (CAD) is a rare autoimmune haemolytic anemia characterized by haemolysis mediated by classic complement pathway activation.
- Fatigue is the most common symptom of CAD and significantly impacts all aspects of a patient's daily life.
- Fatigue was assessed as a key secondary endpoint using the 13-item Functional Assessment of Chronic Illness Therapy-Fatigue scale (FACIT-Fatigue) in the two Phase 3 trials for sutimlimab in patients with CAD: CARDINAL (NCT03347396) and CADENZA (NCT03347422).
- However, evidence on the fatigue severity thresholds in CAD as measured by the FACIT-Fatigue total score is not established.

AIMS

- To establish the FACIT-Fatigue severity thresholds in patients with CAD.
- To assess fatigue improvement in the CARDINAL and CADENZA trials using these severity thresholds.

METHODS

Study design

- This analysis used the pooled treatment groups and visit data of patients from Part A (26 Week [W] sutimlimab treatment period) and Part B (open-label extension, all patients who received sutimlimab) of the CARDINAL and CADENZA trials.
  - CARDINAL was an open-label, single-arm, phase 3 study in patients with CAD with a recent history of transfusion.
  - CADENZA was a randomized, double-blind, placebo-controlled, phase 3 study in patients with CAD without a recent history of transfusion.

Statistical methodology

- The 13-item FACIT-Fatigue scale assesses self-reported fatigue and its impact on daily activities (over the past W) and function on a 5-point Likert scale. The total scores ranged from 0 to 52 and higher scores indicated less fatigue.
- The severity thresholds of FACIT-Fatigue total score were estimated via anchor-based methods, using descriptive statistics and receiver operating characteristic (ROC) curves.
- The anchors used in this analysis were:
  - Patient global impression of fatigue severity (PGIS): none, mild, moderate, severe or very severe.
  - Short Form 12-item (SF-12) health survey v2 item 1-General Health: excellent or very good, good, fair, poor.
- Polyserial correlation with FACIT-Fatigue total score was used to assess the adequacy of anchors.
- Descriptive statistics of FACIT-Fatigue total score at each level of both anchors were provided, and the value of the first quartile was used as the cut-off value for each anchor category.
- A ROC curve was used to classify a patient's anchor level based on FACIT-Fatigue total score, and Youden's index was used to determine the optimal cut-off value. The area under the ROC curve (AUROC) was used to evaluate model discrimination.

Application of severity thresholds to CARDINAL and CADENZA

- The FACIT-Fatigue severity thresholds derived from ROC curve method using PGIS anchor were used for assessing fatigue improvement over time, by treatment group for CADENZA.

RESULTS

- A total of 719 observations with PGIS data and 791 observations with SF-12 item 1 data were extracted from the pooled data of CARDINAL (N=24 patients) and CADENZA (N=42 patients) trials.

- The correlation between FACIT-Fatigue total score and PGIS was −0.86 (very strong), while the correlation between FACIT-Fatigue total score and SF-12 item 1 was −0.73 (strong).
  - PGIS was the preferred anchor as it focused on fatigue and has shown stronger correlation results.

Descriptive statistics

- When PGIS was used as an anchor, FACIT-Fatigue total scores ranged from 49 to 52 for none, 39 to 48 for mild, 28 to 38 for moderate and 0 to 27 for severe or very severe categories (**Figure 1A**).
- When SF-12 item 1 was used as an anchor, FACIT-Fatigue total scores ranged from 47 to 52 for excellent or very good, 38 to 46 for good, 24 to 37 for fair and 0 to 23 for poor categories (**Figure 1B**).

Figure 1. Distribution of FACIT-Fatigue total score by anchors: (A) PGIS and (B) SF-12 item 1


(A) PGIS

(B) SF-12 item 1
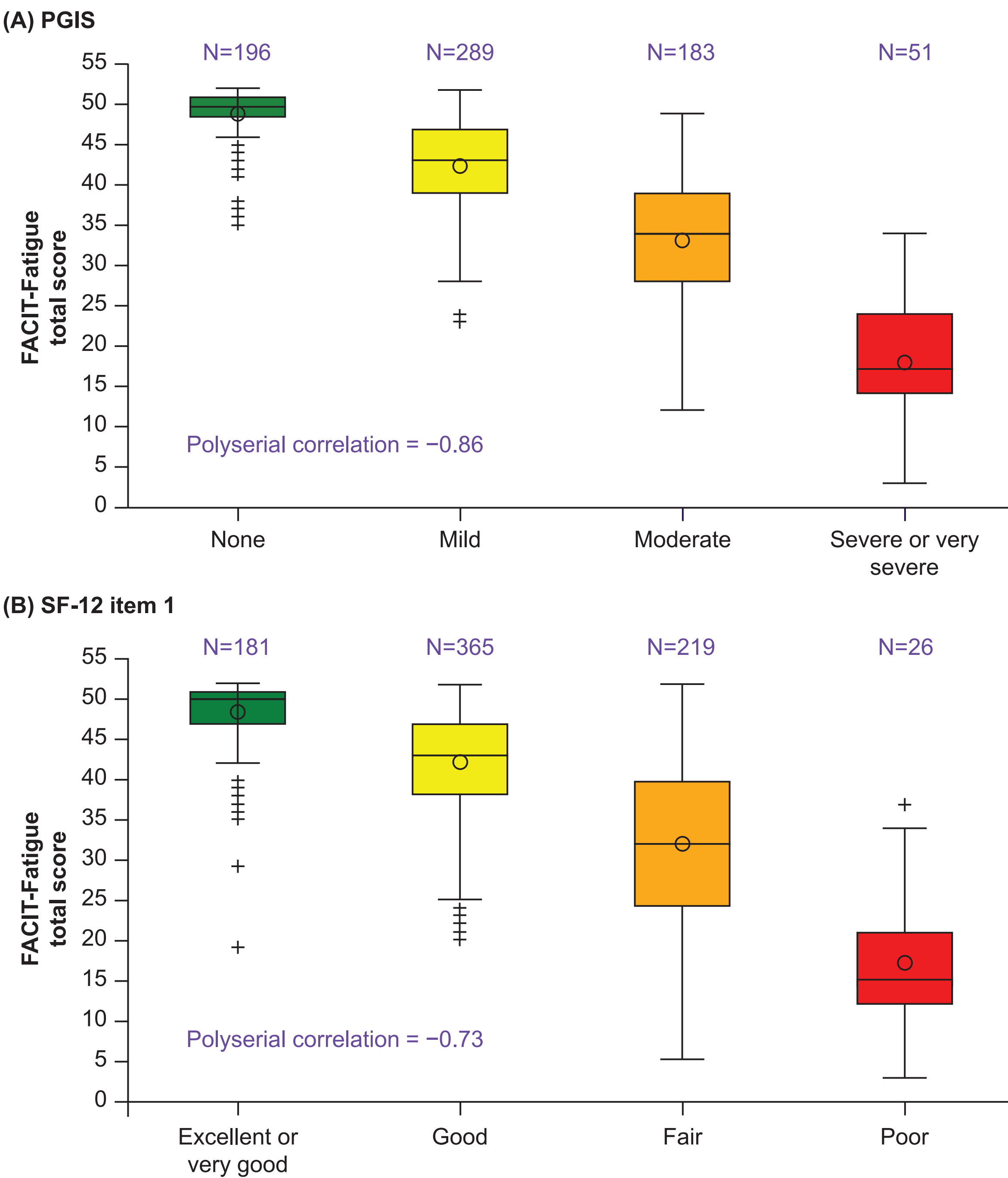
Box = interquartile range (IQR=Q3-Q1); circle inside box = mean; line inside box = median; whiskers = maximum and minimum observations inside [Q1-1.5(IQR), Q3+1.5(IQR)]; plus beyond whiskers = outliers.
FACIT, Functional Assessment of Chronic Illness Therapy; IQR, interquartile range; PGIS, Patient Global Impression of (fatigue) Severity; Q1, first quartile; Q3, third quartile; SF, Short Form.

ROC curve analyses

- The AUROC ranged from 0.86 to 0.98, indicating moderately to highly accurate model discrimination.
- When PGIS was used as an anchor, at max Youden's index of 0.57, the optimal cut-off point to discriminate no severity vs mild to very severe categories was 48 points.

- Similar cut-off points were obtained with different levels of PGIS and SF-12 item 1 anchors.
- The severity thresholds of FACIT-Fatigue total score obtained from the PGIS anchor with ROC curves ranged from 48 to 52 for none, 40 to 47 for mild, 29 to 39 for moderate and 0 to 28 for severe or very severe categories. Similar severity thresholds were obtained when SF-12 item 1 was used as an anchor (**Figure 2**).

Figure 2. FACIT-Fatigue severity thresholds using descriptive and ROC curve methods with PGIS and SF-12 item 1 as anchors
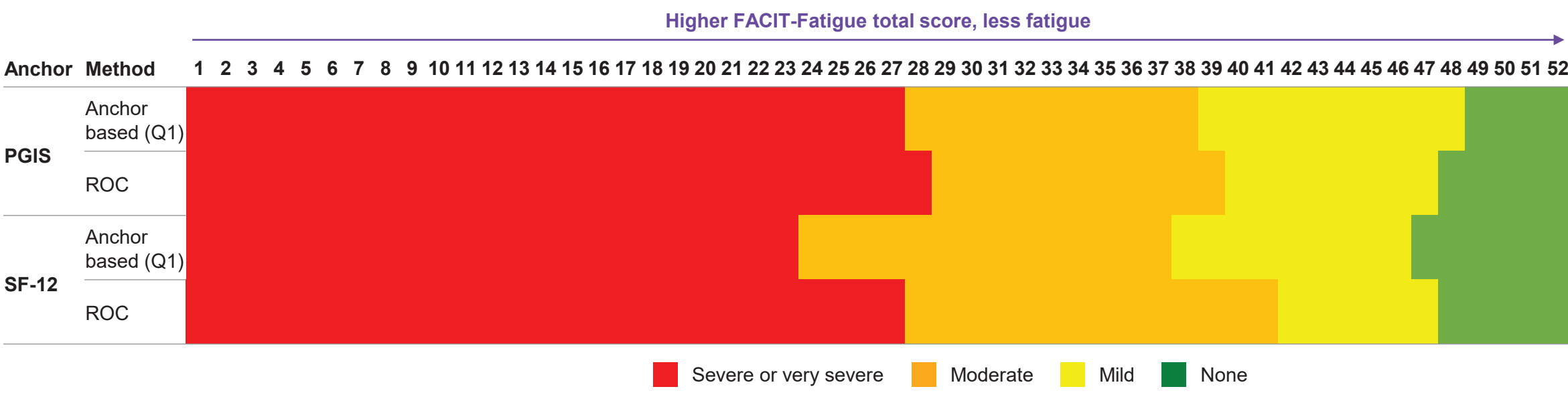
FACIT, Functional Assessment of Chronic Illness Therapy; PGIS, Patient Global Impression of (fatigue) Severity; Q1, first quartile; ROC, receiver operating characteristic; SF, Short Form.

Application of severity thresholds to CARDINAL and CADENZA

- In patients who received sutimlimab throughout the CARDINAL trial, the proportion of patients (n [%]) in severe or very severe category decreased one week after treatment initiation and was sustained throughout the trial (baseline: 9 [40.9%]; W1: 4 [17.4%]; W26: 2 [11.1%]; W39: 3 [15.8%]; W87: 2 [10.5%]) (**Figure 3**).
- This treatment effect was consistent in patients who received sutimlimab throughout the CADENZA trial (baseline: 9 [40.9%]; W1: 4 [18.2%]; W26: 1 [5.3%]; W39: 1 [5.6%]; W87: 1 [7.7%]) (**Figure 4A**).
- In the CADENZA trial, for patients who received placebo (first 26 W), followed by sutimlimab, the proportion (n [%]) of patients in severe or very severe category remained similar to that at baseline for the first 26 W and decreased after receiving sutimlimab (baseline: 7 [35.0%], W1: 8 [42.1%]; W26: 7 [36.8%], W39: 2 [11.1%], W87: 2 [13.3%]) (**Figure 4B**).
- Importantly, in patients who received sutimlimab in the CARDINAL and CADENZA trials, the proportion of patients in none to mild fatigue category also increased one week after treatment initiation and sustained throughout the trial.

Figure 3. Proportion of sutimlimab-treated patients by FACIT-Fatigue severity thresholds in the CARDINAL trial

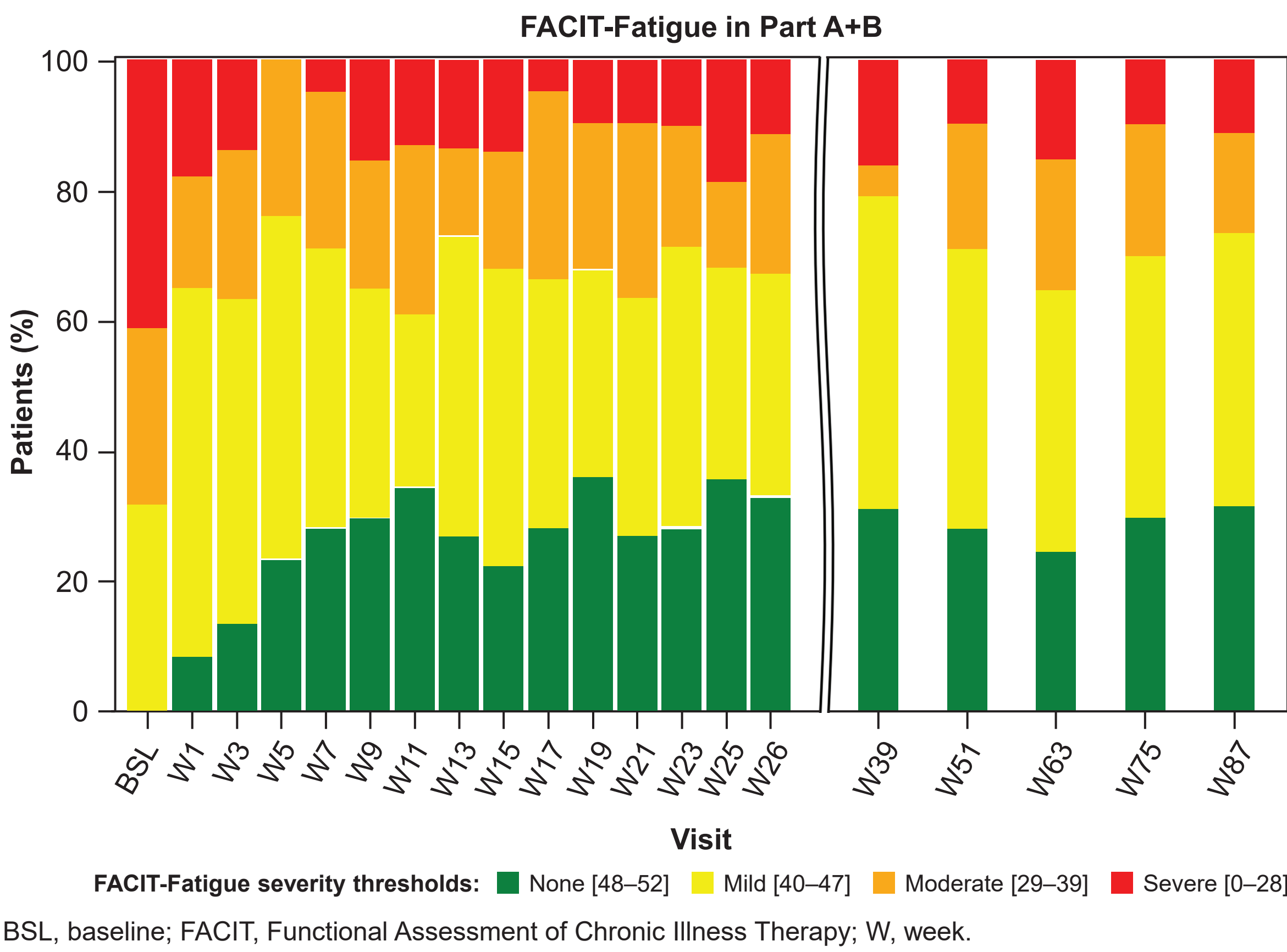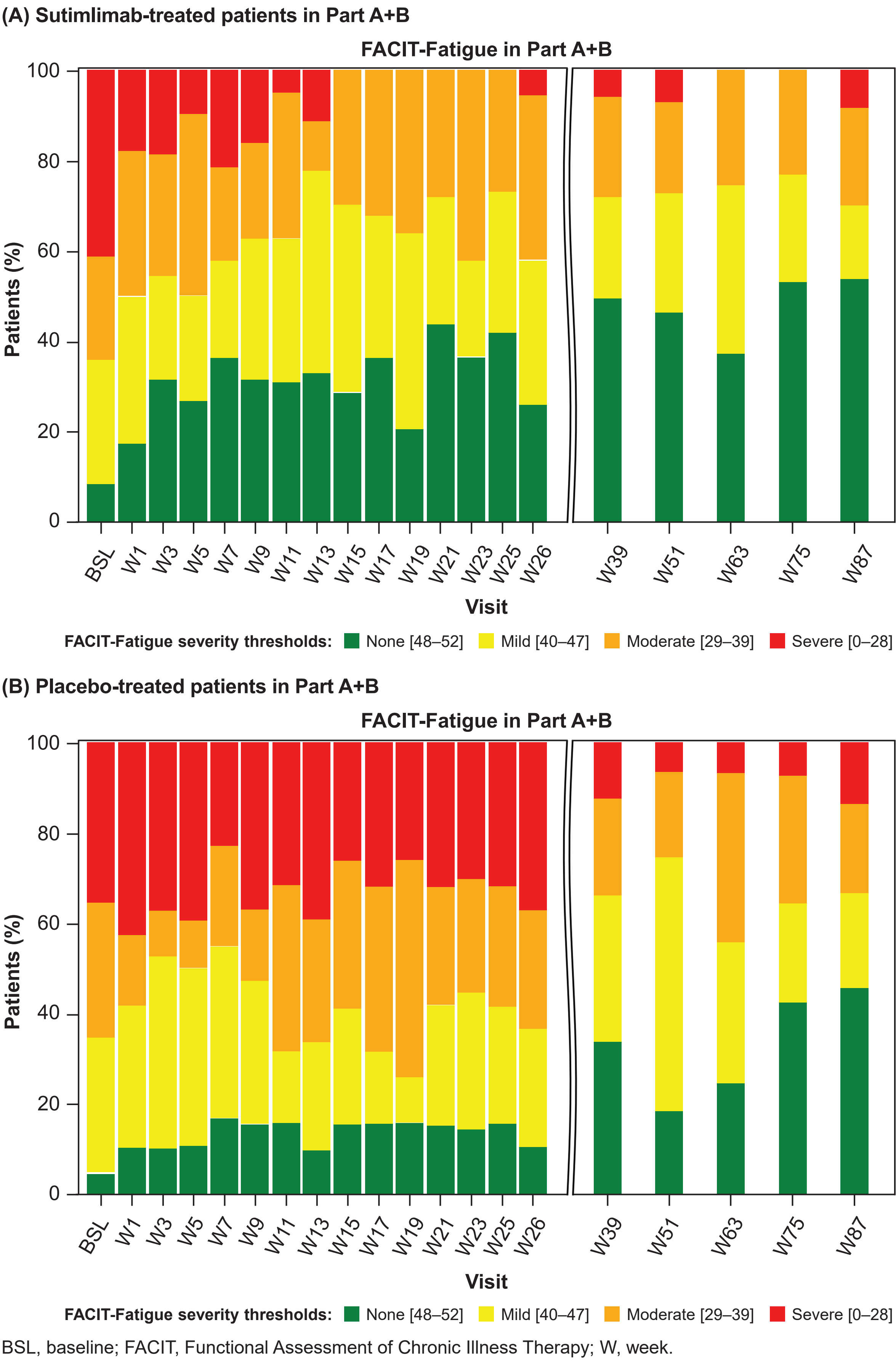BSL, baseline; FACIT, Functional Assessment of Chronic Illness Therapy; W, week.

Figure 4. Proportion of patients by FACIT-Fatigue severity thresholds in the CADENZA trial – (A) sutimlimab-treated patients in Part A+B and (B) placebo-treated patients in Part A+B

(A) Sutimlimab-treated patients in Part A+B

(B) Placebo-treated patients in Part A+B

BSL, baseline; FACIT, Functional Assessment of Chronic Illness Therapy; W, week.

CONCLUSIONS

- The various methods used in this study resulted in similar severity thresholds for FACIT-Fatigue in CAD.
- The severity thresholds obtained from the ROC curve method using PGIS anchor were applied to the CARDINAL and CADENZA trials.
- The application of these thresholds to the two Phase 3 trials showed that sutimlimab treatment led to a rapid and sustainable improvement in fatigue severity (increase in the proportion of patients in none to mild fatigue category and decrease in severe or very severe category) in patients with CAD.

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