Psychometric Validation of PROMIS-Fatigue-MS-8a Questionnaire in Relapsing Multiple Sclerosis Participants Enrolled in a Phase 2 Trial of Frexalimab

PCR66

Patrick Vermersch[1], Gavin Giovannoni[2], Benoit Arnould[3], Natalia Hakimi-Hawken[4], Lita Araujo[5], Stephane Saubadu[6], Philippe Truffinet[6], Samuel Gourlain[7], Jerome Msihid[8]

[1]Univ-Lille, Inserm U1172, CHU Lille, FHU Precise, Lille, France; [2]Queen Mary University of London, London, UK; [3]Sanofi, Lyon, France; [4]Sanofi, Amsterdam, The Netherlands; [5]Sanofi, Cambridge, MA, USA; [6]Sanofi, Chilly-Mazarin, France; [7]Aixial, Sevres, France; [8]Sanofi, Gentilly, France

BACKGROUND

- Fatigue is one of the most prominent debilitating symptoms of multiple sclerosis (MS) that impacts all aspects of the patient's quality of life.[1]
- The Critical Path Working Group has generated evidence to support the qualification of the Patient-Reported Outcomes Measurement Information System Short Form-Fatigue-Multiple Sclerosis 8a (PROMIS-Fatigue-MS-8a) questionnaire with the United States Food and Drug Administration to assess fatigue in clinical trials.[2]
- Currently, there are limited psychometric studies performed on PROMIS-Fatigue-MS-8a questionnaire.
- Frexalimab demonstrated efficacy and safety with high-dose treatment in a phase 2 trial (NCT04879628).[3,4]

OBJECTIVE

- To validate the psychometric properties of the PROMIS-Fatigue-MS-8a questionnaire in participants with relapsing multiple sclerosis (RMS) enrolled in a phase 2 frexalimab trial.

METHODS

- PROMIS-Fatigue-MS-8a is an 8-item, patient-reported questionnaire using a 5-point Likert scale from 1 (never/not at all) to 5 (almost always/very much) with a recall period of last 7 days.
  - A total raw score is derived by summing up the scores for each item (range: 8–40) and then converted to a T-score metric (range: 34.1–80.9); Higher scores indicate more fatigue.
- Psychometric properties of PROMIS-Fatigue-MS-8a were assessed using patient-reported outcome data from the 12-week, double-blind, randomised, placebo-controlled part of a frexalimab phase 2 trial in adult participants with RMS (NCT04879628).
  - Key inclusion criteria of this trial:
    - Participants aged 18 to 55 years.
    - Diagnosed with RMS (relapsing-remitting MS or secondary progressive MS with relapses) according to the revised 2017 McDonald criteria.[5]
      - At least 1 documented relapse within the previous year, or ≥2 documented relapses within the previous 2 years or ≥1 active gadolinium-enhancing brain lesion on a magnetic resonance imaging scan in the past 6 months and prior to screening.
    - Expanded Disability Status Scale score 0 to 5.5 at screening.
- Internal consistency, test-retest reliability, convergent validity, construct validity and sensitivity to change were assessed by means of Cronbach's alpha coefficient, intraclass correlation coefficient (ICC), Spearman or polyserial correlation coefficients, analysis of variance (ANOVA) and analysis of covariance (ANCOVA), respectively.
- Analyses were performed using baseline and Week 12 data from pooled treatment arms.

RESULTS

Study population

- Pooled data from 129 patients with RMS were included in the psychometric analysis: mean (standard deviation [SD]) age 36.6 (9.4) years, 65.9% female, and mean (SD) time since symptom onset 7.7 (7.2) years.
- The mean (SD) baseline T-score of PROMIS-Fatigue-MS-8a was 52.7 (10.7).

Psychometric properties

Item-to-item correlations

- Item-to-item correlations were acceptable (i.e. between 0.4 and 0.9) for most of the items, at both visits.

Internal consistency

- Excellent internal consistency for PROMIS-Fatigue-MS-8a was found at baseline (Cronbach's α = 0.96, 95% confidence interval [CI]: 0.95, 0.97) and Week 12 (Cronbach's α = 0.96 [0.95, 0.97]).

Test-retest reliability

- An ICC [95% CI] of 0.79 [0.67, 0.87] and 0.82 [0.70, 0.90] was reported in stable patients defined as per Patient Global Impression of Severity-Fatigue (PGIS-Fatigue) and Patient Global Impression of Change-Fatigue (PGIC-Fatigue) scores, respectively, between baseline and Week 12 demonstrating adequate (ICC threshold ≥0.70) test-retest reliability.

Construct validity

- PROMIS-Fatigue-MS-8a had good convergent validity **(Table 1)**.
  - Very high correlations (r >0.70) between the T-score and the physical and psychological domains of Multiple Sclerosis Impact Scale-29 version 2 and PGIS-Fatigue were observed at baseline and Week 12.

Table 1: Convergent validity of PROMIS-Fatigue-MS-8a at baseline and Week 12

	Correlation with PROMIS-Fatigue-MS-8a T-score	
Scores	**Baseline (*N* = 128)**	**Week 12 (*N* = 128)**
MSIS-29v2 physical impact score[a]	0.81	0.82
MSIS-29v2 psychological impact score[b]	0.76	0.83
PGIS-Fatigue score[b]	0.80	0.78

[a]Spearman correlation; [b]Polyserial correlation.
MSIS-29v2, Multiple Sclerosis Impact Scale-29 version 2; *N*, number of participants; PGIS-Fatigue, Patient Global Impression of Severity-Fatigue; PROMIS-Fatigue-MS-8a, Patient-Reported Outcomes Measurement Information System Short Form-Fatigue-Multiple Sclerosis 8a.

- PROMIS-Fatigue-MS-8a was able to distinguish between patients with different fatigue severity levels (all P <0.001) **(Table 2)**.
  - Groups defined by PGIS-Fatigue scores showed large effect sizes (>0.8) at baseline and Week 12 **(Table 2)**.

Table 2: Construct validity of PROMIS-Fatigue-MS-8a at baseline and Week 12

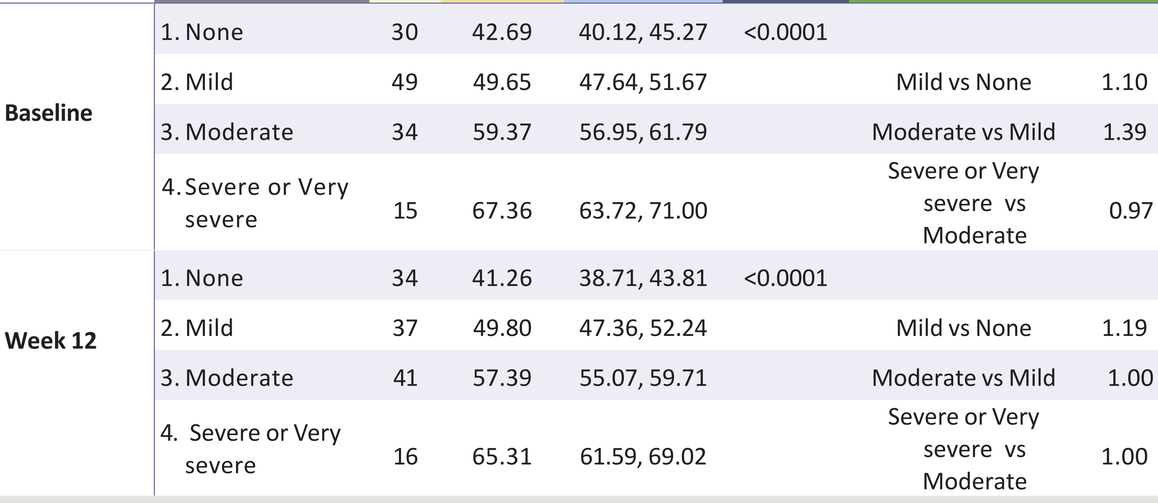
Timepoint	PGIS-Fatigue score	*N*	LS means	95% CI	*P*-value	Effect size	
Baseline	1. None	30	42.69	40.12, 45.27	<0.0001		
	2. Mild	49	49.65	47.64, 51.67		Mild vs None	1.10
	3. Moderate	34	59.37	56.95, 61.79		Moderate vs Mild	1.39
	4. Severe or Very severe	15	67.36	63.72, 71.00		Severe or Very severe vs Moderate	0.97
Week 12	1. None	34	41.26	38.71, 43.81	<0.0001		
	2. Mild	37	49.80	47.36, 52.24		Mild vs None	1.19
	3. Moderate	41	57.39	55.07, 59.71		Moderate vs Mild	1.00
	4. Severe or Very severe	16	65.31	61.59, 69.02		Severe or Very severe vs Moderate	1.00

Effect sizes were defined as – small: r <0.5; moderate: 0.5 ≤ r ≤ 0.8 and high: r >0.8. P-value of the anchor level effect, based on ANOVA model.
ANOVA, analysis of variance; CI, confidence interval; LS, least square; *N*, number of participants; PGIS-Fatigue, Patient Global Impression of Severity-Fatigue; PROMIS-Fatigue-MS-8a, Patient-Reported Outcomes Measurement Information System Short Form-Fatigue-Multiple Sclerosis 8a.

Sensitivity to change

- Sensitivity to change was demonstrated at Week 12 by statistically significant differences in T-scores between groups defined by change in PGIS-Fatigue (P = 0.0006) and by PGIC-Fatigue (P <0.0001) **(Figure 1)**.
- Large effect sizes (>0.8) between consecutive group mean changes were observed for overall fatigue symptom 'much better' versus 'a little better' in PGIC-Fatigue **(Figure 1)**.

Figure 1: Sensitivity to change of PROMIS-Fatigue-MS-8a using mean change from baseline to Week 12 by PGIS-Fatigue and PGIC-Fatigue groups



Effect sizes were defined as – small: r <0.5; moderate: 0.5 ≤ r ≤ 0.8 and high: r >0.8. P-value of the anchor subgroup effect, based on an ANCOVA model controlling for baseline score.
ANCOVA, analysis of covariance; CI, confidence interval; LS, least square; *N*, number of participants; PGIC-Fatigue, Patient Global Impression of Change-Fatigue; PGIS-Fatigue, Patient Global Impression of Severity-Fatigue; PROMIS-Fatigue-MS-8a, Patient-Reported Outcomes Measurement Information System Short Form-Fatigue-Multiple Sclerosis 8a.

CONCLUSION

This study demonstrated that PROMIS-Fatigue-MS-8a is reliable, valid and responsive to change, suggesting it as a fit-for-purpose instrument to evaluate fatigue in adults with RMS.

Disclosures

Patrick Vermersch: Received honoraria and consulting fees from Biogen, Sanofi, Novartis, Teva, Merck, Roche, Imcyse, AB Science and BMS-Celgene and research support from Novartis, Sanofi and Roche.

Gavin Giovannoni: Received compensation over the last 5 years for serving as a consultant or speaker for or received research support from AbbVie, Aslan, Atara Bio, Biogen, BMS-Celgene, GlaxoSmithKline, GW Pharma, Janssens/J&J, Japanese Tobacco, Jazz Pharmaceuticals, LifNano, Merck & Co, Merck KGaA/EMD Serono, Moderna, Novartis, Sanofi, Roche/Genentech and Teva.

Jerome Msihid, Natalia Hakimi-Hawken, Benoit Arnould, Lita Araujo, Stephane Saubadu and **Philippe Truffinet:** Employees of Sanofi and may hold stocks or stock options in the company.

Samuel Gourlain: Employee of Aixial. Aixial was contracted by Sanofi to perform this study.

Poster presented at ISPOR Europe, November 12–15, 2023; Copenhagen, Denmark

Funding

This study was funded by Sanofi.

Acknowledgements

Medical writing and editorial assistance were provided by Sanjeev Kallapari and Chiranjit Ghosh, PhD of Sanofi.

References

1. Janardhan V, *et al*. *J Neurol Sci*. 2002;205(1):51–58.
2. Critical Path Institute. The patient reported outcome consortium. https://c-path.org/programs/proc/. Accessed 20 October 2023.
3. Vermersch P, et al. Frexalimab, a CD40L Inhibitor, in Relapsing Multiple Sclerosis: Results from a Randomized Controlled Phase 2 Trial. Presented at: CMSC 2023; May 31–Jun 03, 2023; Aurora, CO, USA.
4. Vermersch P, et al. Phase 2 efficacy and safety of frexalimab: Six-month results of a novel CD40L inhibitor in relapsing multiple sclerosis. Presented at: ECTRIMS 2023; Oct 11–13, 2023; Milan, Italy.
5. Thompson AJ, *et al*. *Lancet Neurol*. 2018; 17(2):162–173.