PCR196

Psychometric Validation of the PROMIS Fatigue-Short Form 7a in Adults with Newly Diagnosed or Recurrent *Mycobacterium avium* Complex (MAC) Lung Disease: The ARISE and ENCORE Studies

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WHAT WAS KNOWN

- MAC is the leading cause of NTM lung disease, which may be associated with a progressive decline in lung function and significant symptom burden, including fatigue [1-3].
- There is currently no validated PRO instrument to evaluate fatigue symptoms in patients with a new diagnosis (initial or subsequent) of MAC lung disease.

OBJECTIVES

- To evaluate the psychometric properties of the patient-reported PROMIS-F SF-7a in adults with a new diagnosis (initial or subsequent) of MAC lung disease who had not initiated antibiotics for their current MAC infection.

METHODS

- Data were analyzed from two double-blind, randomized, active-control trials with identical eligibility criteria that assessed the impact of once-daily ALIS treatment on symptoms of MAC lung disease, including fatigue:
  - ARISE (NCT04677543): Baseline and longitudinal data blinded to treatment allocation.
    - Treatment was administered for 6 months, followed by 1 month off treatment (end of study assessment: month 7).
  - ENCORE (NCT04677569): Baseline data blinded to treatment allocation from the initial 132 subjects randomized (study was still actively enrolling).
    - Treatment was administered for 12 months, followed by 3 months off treatment.
- Untransformed PROMIS-F SF-7a scores were analyzed.
- Modern psychometric methods were employed to test item properties and empirically justify the final scoring algorithm (see **Supplemental Material**).
- Classical measurement properties evaluated included reliability (internal consistency, TRTR), convergent and known-groups validity, and anchor-based MWPC.
- Modern psychometric methods, internal consistency (omega, Cronbach's alpha), convergent validity (Pearson correlations), and known-groups validity were analyzed at baseline (N=230 patients [ARISE: n=98, ENCORE: n=132]).

Figure 1. MWPC: PGI-S Anchor Scale Response Options

PATIENT GLOBAL IMPRESSION OF SEVERITY (PGI-S)
(VERSION 2.0, 04FEB2021)

Instructions: The following questions ask about the severity of your lung condition over the past week.

Please choose only 1 answer for each question.

FATIGUE

2. How severe was your fatigue **over the past week**?

☐ Not at all ☐ Mildly ☐ Moderately ☐ Very ☐ Extremely

Table 1. Modern Psychometric Methods: Unidimensional IRT Model Fit

RMSEA (90% CI)	TLI	CFI	Omega
0.073 (0.038, 0.108)	0.980	0.986	0.917

Table 2. Reliability: Internal Consistency Estimates at Baseline

PROMIS-F SF-7a Items	McDonald's Omega (95% CI)	Cronbach's Alpha (95% CI)	Item-Total Polyserial Correlation	Cronbach's Alpha If Item Is Dropped
Score	0.87 (0.84, 0.89)	0.86 (0.83, 0.89)		
Item 1			0.87	0.83
Item 2			0.84	0.84
Item 3			0.89	0.83
Item 4			0.89	0.83
Item 5			0.85	0.84
Item 6			0.81	0.85
Item 7			0.46	0.90

Table 3. Concurrent Validity at Baseline

	EXACT	E-RS	FACIT-Fatigue	SGRQ
PROMIS-F SF-7a score	0.56	0.52	-0.80	0.66

PROMIS F-SF 7a: Higher score = worse fatigue, lower score = less fatigue.
EXACT, E-RS, and SGRQ: Higher score = higher severity, lower score = lower severity.
FACIT-Fatigue: Higher score = lower severity, lower score = higher severity.

Table 4. Known-Groups Validity at Baseline

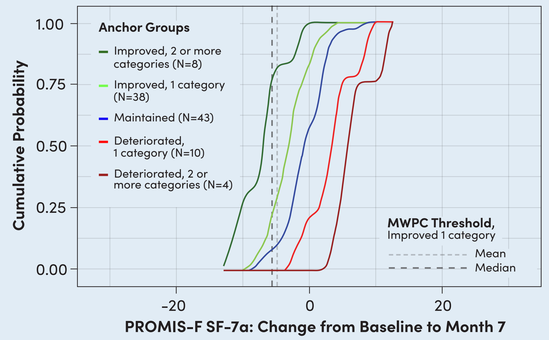
PGI-S Fatigue Group	N	LS Means Estimate (95% CI)	LS Means Contrast	*p*-value	Semi-Partial Omega Squared (95% CI)
Not at all (Reference)	21	11.81 (10.33, 13.29)			
Mildly	88	15.67 (14.95, 16.40)	-3.86	<0.001	0.08 (0.03, 0.16)
Moderately	83	20.64 (19.90, 21.38)	-8.83	<0.001	0.32 (0.23, 0.41)
Very	34	24.41 (23.25, 25.58)	-12.60	<0.001	0.43 (0.34, 0.51)
Extremely	4	25.75 (22.35, 29.15)	-13.94	<0.001	0.19 (0.11, 0.28)

Table 5. MWPC: Anchor-based Mean and Median Change from Baseline in PROMIS-F SF-7a Score at End of Study (N=99 ARISE Patients) [a]

Anchor Group	Anchor Group Thresholds: Mean (95% CI)	Anchor Group Thresholds: Median (95% CI)	N (%)
Improved, 2+ categories	-8.50 (-12.89, -4.11)	-8.00 (-14.00, -7.00)	6 (6.06)
Improved, 1 category	-3.69 (-4.77, -2.61)	-4.00 (-6.00, -3.00)	39 (39.39)
Maintained	-0.50 (-1.63, 0.63)	-1.00 (-2.00, 2.00)	40 (40.40)
Deteriorated, 1 category	3.40 (0.51, 6.29)	3.00 (-1.00, 5.00)	10 (10.10)
Deteriorated, 2+ categories	7.50 (NA)[b]	6.00 (NA)[b]	4 (4.04)

[a] End of study: 1 month off treatment (month 7). [b] Sample size did not permit calculation of CIs.

Figure 2. MWPC: eCDF of PROMIS-F SF-7a Change from Baseline to End of Study by Anchor Group (N=99 ARISE Patients)[a]



[a] End of study: 1 month off treatment (month 7).

- Convergent validity was assessed between the PROMIS-F SF-7a and the EXACT tool, E-RS scale, SGRQ, and FACIT-Fatigue.
- Known-groups validity compared PROMIS-F SF-7a scores across PGI-S Fatigue groups.
- TRTR was estimated via ICC(A,1) among patients reporting no change in PGI-S Fatigue between screening and baseline.
- Anchor-based MWPC thresholds were estimated between baseline and end of study (month 7) and supplemented with eCDF curves (N=99 ARISE patients).
  - Anchor scale and response options are shown in **Figure 1**.
  - MWPC was characterized via point estimates obtained from the median change score associated with corresponding PGI-S Fatigue change groups (i.e., improved 2+ categories, improved 1 category, maintained, deteriorated 1 category, deteriorated 2+ categories).
  - Improvement of 1 category on the PGI-S Fatigue was used to define the meaningful improvement anchor group, from which improvement thresholds were estimated.

RESULTS

- Overall, 230 patients were included in the psychometric analysis; 68% were ≥ 65 years old, 81% were female, and 73% were White (**Supplemental Table**).
- Modern psychometric methods supported the relevance of all items and a unidimensional unit-weighted sum score for the PROMIS-F SF-7a (**Table 1; Supplemental Figure**).
- The PROMIS-F SF-7a demonstrated strong internal consistency (Cronbach's alpha: 0.86, **Table 2**) and TRTR (ICC[A,1]: 0.76).
- Convergent validity was supported (**Table 3**).
  - The moderate-to-strong positive correlation (0.66) between the PROMIS-F SF-7a and SGRQ suggests that increasing fatigue levels correspond to diminished respiratory HRQOL.
- Known-groups validity was demonstrated across PGI-S Fatigue groups (**Table 4**).
  - Patients who responded 'not at all' on the PGI-S-Fatigue had significantly lower PROMIS-F SF-7a scores at baseline compared with those who selected any of the other responses ($p<0.001$); a sequentially ordered higher mean PROMIS F-SF-7a score was observed at each increased severity level, as expected.
- MWPC analyses supported a -4.00-point median change from baseline (95% CI: -3.00, -6.00 points) as a proposed threshold of clinically meaningful within-patient improvement for the PROMIS-F SF-7a (**Table 5**).
  - The eCDF curves showed clear and consistent separation between the improved and maintained anchor groups across all PROMIS F-SF 7a score changes including the -4.00 threshold (**Figure 2**).

WHAT THIS STUDY ADDS

- The findings demonstrate the PROMIS-F SF-7a has adequate reliability, validity, and responsiveness for assessing fatigue symptoms in adults with a new diagnosis (initial or subsequent) of MAC lung disease.

ABBREVIATIONS:
ALIS, amikacin liposome inhalation suspension; CI, confidence interval; CFI, comparative fit index; eCDF, empirical cumulative distribution function; E-RS, EXACT Respiratory Symptoms; EXACT, Exacerbations of Chronic Pulmonary Disease Tool; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy Fatigue Scale; HRQOL, health-related quality of life; ICC, intraclass correlation coefficient; IRT, item response theory; LSM, least squares means; MAC, *Mycobacterium avium* complex; MWPC, meaningful within-patient change; NA, not applicable; NTM, nontuberculous mycobacteria; PGI-S, Patient Global Impression of Severity; PRO, patient-reported outcome; PROMIS-F SF-7a, Patient-Reported Outcomes Measurement Information System Fatigue Short Form 7a; RMSEA, root mean squared error of approximation; SGRQ, St. George Respiratory Questionnaire; TLI, Tucker-Lewis index; TRTR, test retest reliability.

AUTHOR DISCLOSURES:
Kevin C. Mange, Mariam Hassan, Marie-Laure Nevoret, Dayton W. Yuen, and Monika Ciesielska are employees and shareholders of Insmed Incorporated. Daniel Serrano, Bryant Barnes, Shauna McManus, and Lauren Podger were employees of OPEN Health Group at the time of study, which was funded by Insmed Incorporated. Charles L. Daley reports grant support, advisory board fees, and consulting fees from Insmed Incorporated. Dr. Daley also reports grant support from AN2 Therapeutics, Bugworks, Paratek Pharmaceuticals, Juvabis; advisory board work with AN2 Therapeutics, AstraZeneca, Cepheid, Hyfe, MannKind, Matinas Biopharma, NobHill, Spero Therapeutics, Zambon; consulting with Genentech, Pfizer; data monitoring committee work with Otsuka Pharmaceutical, Eli Lilly and Company, Bill and Melinda Gates Foundation.

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