Psychometric Validation of the QOL-B Respiratory Domain 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 can cause respiratory symptoms such as chronic cough, sputum, hemoptysis, and shortness of breath, as well as a progressive decline in lung function [1-3].
- There is currently no validated PRO instrument to evaluate respiratory symptoms in patients with a new diagnosis (initial or subsequent) of MAC lung disease.

OBJECTIVES

- To evaluate the psychometric properties of the patient-reported QOL-B-RD 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 analyzed were 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 respiratory symptoms:
  - 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 initial 132 subjects randomized (study was still actively enrolling).
    - Treatment was administered for 12 months, followed by 3 months off treatment.
- 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=229 patients [ARISE: n=97, ENCORE: n=132]).
  - Convergent validity was assessed between the QOL-B-RD and the EXACT tool, E-RS scale, SGRQ, and FACIT-Fatigue.
  - Known-groups validity compared QOL-B-RD scores across PGI-S Respiratory severity groups.
  - TRTR was estimated via ICC(A,1) among patients reporting no change in PGI-S Respiratory between screening and baseline.

Table 1. Modern Psychometric Methods: Model Fit Comparisons

	RMSEA (90% CI)	TLI	CFI	Omega	Hierarchical Omega	Omega Ratio	ECV	H-statistic
Initial model evaluation								
2-factor MIRT	0.114 (0.091, 0.139)	0.873	0.912	0.800	-	-	-	-
2-factor Bifactor	0.000 (0.000, 0.059)	1.002	1.000	0.880	0.647	0.735	0.561	0.837
3-factor MIRT	0.142 (0.119, 0.166)	0.804	0.864	0.776	-	-	-	-
3-factor Bifactor	0.108 (0.078, 0.138)	0.888	0.950	0.869	0.731	0.841	0.584	0.828
Item parceling analysis								
Parceled Bifactor Model	0.082 (0.024, 0.141)	0.934	0.984	0.829	0.827	0.997	0.846	0.845

Table 2. Reliability: Internal Consistency Estimates at Baseline

QOL-B-RD Items	McDonald's Omega (95% CI)	Cronbach's Alpha (95% CI)	Item-Total Polyserial Correlation	Cronbach's Alpha If Item Is Dropped
Domain Score	0.80 (0.76, 0.84)	0.79 (0.75, 0.83)		
Item 29			0.83	0.75
Item 30			0.58	0.79
Item 31			0.62	0.78
Item 32			0.57	0.79
Item 33			0.73	0.77
Item 34			0.64	0.78
Item 35			0.70	0.77
Item 36			0.72	0.77
Item 37			0.73	0.77

Table 3. Concurrent Validity at Baseline

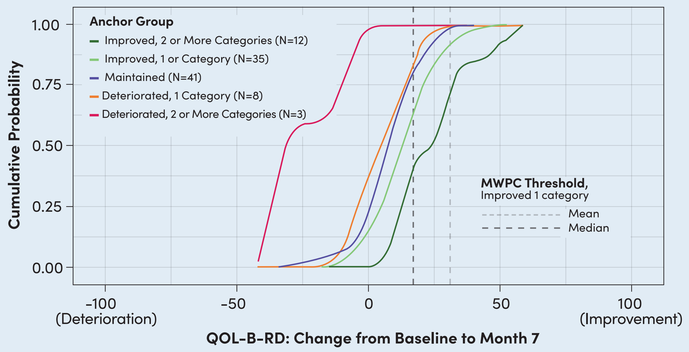
	EXACT	E-RS	FACIT-Fatigue	SGRQ
QOL-B-RD score	-0.70	-0.70	0.49	-0.71

QOL-B-RD and FACIT-Fatigue: Higher score = lower severity, lower score = higher severity.
EXACT, E-RS, and SGRQ: Higher score = higher severity, lower score = lower severity.

Table 4. Known-Groups Validity at Baseline

PGI-S Respiratory Group	N	LSM Estimate (95% CI)	LSM Contrast	*p*-value	Semi-Partial Omega Squared (95% CI)
Not at all (Reference)	24	80.42 (75.75, 85.09)			
Mildly	100	71.18 (68.90, 73.45)	9.24	<0.01	0.13 (0.06, 0.21)
Moderately	70	59.56 (56.82, 62.29)	20.86	<0.001	0.36 (0.27, 0.45)
Very	33	40.61 (36.63, 44.60)	39.81	<0.001	0.45 (0.36, 0.53)
Extremely	2	62.96 (46.78, 79.14)	17.46	0.25	0.20 (0.12, 0.29)

Figure 2. MWPC: eCDF of QOL-B-RD Change Score from Baseline to End of Study by Anchor Group (N=99 ARISE Patients)[a]



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

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

	Anchor Group Thresholds		
Anchor Group	**Mean (95% CI)**	**Median (95% CI)**	**N (%)**
Improved, 2+ categories	24.40 (13.70, 35.09)	25.93 (11.11, 29.63)	12 (12.12)
Improved, 1 category	14.77 (10.00, 19.55)	14.81 (8.82, 18.52)	35 (35.35)
Maintained	6.49 (2.57, 10.41)	3.70 (0.00, 11.11)	41 (41.41)
Deteriorated, 1 category	4.63 (-4.09, 13.35)	3.70 (-7.41, 14.81)	8 (8.08)
Deteriorated, 2+ categories	-28.40 (NA)[b]	-37.04 (NA)[b]	3 (3.03)

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

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.

BREATHING

2. How severe were your breathing symptoms (e.g., congestion, cough, mucus, wheezing, shortness of breath, etc.) **over the past week**?

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

- 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 the corresponding PGI-S Respiratory 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 Respiratory was used to define the meaningful improvement anchor group, from which improvement thresholds were estimated.

RESULTS

- Overall, 229 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 9 items and a unidimensional unit-weighted score for the QOL-B-RD (**Table 1**).
- The QOL-B-RD demonstrated strong internal consistency (Cronbach's alpha: 0.79; **Table 2**) and acceptable TRTR (ICC[A,1]: 0.69).
- Convergent validity was supported (**Table 3**), with the highest correlations observed between the QOL-B-RD and validators that measure respiratory symptoms (i.e., EXACT, E-RS, SGRQ), as expected.
- Known-groups validity was demonstrated across PGI-S Respiratory groups (**Table 4**).
  - Patients who responded 'not at all' at baseline had significantly higher QOL-B-RD scores (indicating fewer respiratory symptoms) at baseline compared with those who selected 'mildly' to 'very'; a sequentially ordered lower mean QOL-B-RD score was observed at each increased severity level.
  - Patients who responded 'extremely' had a lower mean score (indicating more respiratory symptoms) than those who selected 'not at all' or 'mildly', but higher scores than those responding 'moderately' or 'very'; however, only 2 subjects responded 'extremely', so these results should therefore be interpreted with caution.
- MWPC analyses supported a 14.81-point median change from baseline (95% CI: 8.82, 18.52 points) as a proposed threshold of clinically meaningful within-patient improvement for the QOL-B-RD (9-items) (**Table 5**).
  - The eCDF curves showed clear and consistent separation between the improved and maintained anchor groups across all QOL-B-RD score changes, including the 14.81 MWPC threshold (**Figure 2**).

WHAT THIS STUDY ADDS

- The findings demonstrate the QOL-B-RD has adequate reliability, validity, and responsiveness for assessing respiratory 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; ECV, explained common variance; E-RS, EXACT Respiratory Symptoms; EXACT, Exacerbations of Chronic Pulmonary Disease Tool; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy Fatigue Scale; ICC, intraclass correlation coefficient; LSM, least squares means; MAC, Mycobacterium avium complex; MIRT, multidimensional item response theory; MWPC, meaningful within-patient change; NA, not applicable; NTM, nontuberculous mycobacteria; PGI-S, Patient Global Impression of Severity; PRO, patientreported outcome; QOL-B-RD, Quality of Life-Bronchiectasis-Respiratory Domain; 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 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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