Poster No. 71
NTM Conference at CSU
Fort Collins, CO
May 27-30, 2025

Validation of the MACrO$_2$ Patient-Reported Outcome (PRO) Measure in Treatment-Refractory MAC Lung Disease (TR-MAC-LD)

Donald M. Bushnell[1], Larissa Stassek[1†], Alex Smith[2‡], Emily Henkle[3], Kevin Winthrop[3], Julie Philley[4], Eric Easom[2], Lynn Connolly[2‡], Jennifer Huber[2‡], Bibiana Castañeda-Ruiz[2‡], Jennifer Long[2‡], Kevin Krause[2‡], Paul Eckburg[2‡]

[1]PPD Evidera Patient Centered Research (Wilmington, NC), [2]AN2 Therapeutics (Menlo Park, CA), [3]OHSU-PSU School of Public Health (Portland, OR), [4]The University of Texas at Tyler (Tyler, TX)

AN2Therapeutics
Menlo Park, CA 94027
www.an2therapeutics.com

INTRODUCTION

OBJECTIVE

The primary aim of this work was to evaluate the item characteristics and performance of the MACrO$_2$ PRO v1.0 in patients with TR-MAC-LD in the process of instrument refinement (item response distribution, potential item reduction or modification, and measurement model) and finalization of the scoring approach. The cumulative evidence on the content and construct validity of the MACrO$_2$ PRO v1.0 (including the quantitative evidence from the present study [EBO-301] and the qualitative evidence from cognitive debriefing and exit interviews) was expected to validate the use of the MACrO$_2$ PRO v1.0 questionnaire to measure a clinical response endpoint and to support labeling claims as a key endpoint in AN2 pivotal studies in patients with TR-MAC-LD.

METHODS

Study Design and Population

- The MACrO$_2$ trial (EBO-301) was a seamless Phase 2/3, randomized, double-blind, placebo-controlled, multicenter, prospective study conducted in the US, Japan, Australia, and South Korea to assess the efficacy, safety, and pharmacokinetics of orally administered epetraborole tablets in adults with TR-MAC-LD
- The following were assessed (Table 1):
  - The MACrO$_2$ PRO v1.0 questionnaire is a patient-reported instrument developed by AN2 for use as an endpoint in clinical trials of patients with TR-MAC-LD (see Poster 73 for information on the development of this PRO). It evaluates 7 individual symptoms: cough with phlegm, mucus, or sputum; dry cough (no phlegm, mucus, or sputum); chest congestion (needing to clear mucus or feeling pressure or tightness in the lungs); coughing up blood; shortness of breath or difficulty taking a deep breath; fatigue or tiredness; and night sweats or unusual sweating. The measure asks patients to rate the severity of each symptom at its worst in the past week, with responses of "absent" (0), "mild" (1), "moderate" (2), "severe" (3), and "extremely severe" (4). The 7 items were summed and transformed to a 0 to 100-point scale with 0 being the optimal score (all symptoms absent) and 100 being the worst score (all symptoms extremely severe).
  - The Quality of Life-Bronchiectasis (QOL-B version 3.1)[1] consists of 37 items divided into 8 domains, including a domain of 9 respiratory symptom items. Each domain score can range from 0 to 100 (higher scores indicate better HRQoL). The recall period is 1 week, and each item uses a 4-point Likert scale.
  - The St. George's Respiratory Questionnaire for COPD (SGRQ-C, version 1)[2] consists of 43 items divided into 3 scored subscales, along with a total score; all scores range from 0 to 100 (lower scores indicate better HRQoL). The recall period and verbal response scales vary between items.
  - The Patient Global Impression of Severity (PGIS) is a global patient rating of the overall severity with responses of "none" (0), "mild" (1), "moderate" (2), "severe" (3), or "very severe" (4). The PGIS was used as the primary means for assessing change between the first two administrations of the MACrO$_2$ PRO v1.0 for test-retest reliability analysis.
  - The Patient Global Impression of Change (PGIC) is a global patient rating of change in MAC-LD symptoms with responses of "much better" (0), "a little better" (1), "no change" (2), "a little worse" (3), or "much worse" (4). The PGIC was used to explore the responder definition.
- Item performance included floor/ceiling effects and item-to-item correlations. Test-retest reliability (intra-class correlation coefficient [ICC]), construct validity (convergent and known-groups validity), responsiveness, and interpretation were evaluated
- All analyses were conducted on pooled, blinded data

Table 1. Schedule of PRO Administration for Psychometric Analyses in Study EBO-301

Month	Screening	Treatment Period								
		Randomization	1	2	3	3+1W	4	5	6	6+1W
Study Day/ Visit Window	D-14 to D-7	D1	D29 ± 7d	D57 ± 7d	D85 ± 7d	1W (+1d) after M3	D113 ± 7d	D141 ± 7d	D169 ± 7d	1W (+1d) after M6
MACrO$_2$ PRO	X	X	Weekly and at Monthly Visits							
QOL-B, SGRQ-C	X	X	X	X	X		X	X	X	
PGIS	X	X	X	X	X	X	X	X	X	X
PGIC			X	X	X		X	X	X	

Note: This table has been edited for this poster presentation, the EBO-301 trial protocol should be referenced for the full schedule of assessments.
D = Day; M = Month; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PRO = patient-reported outcome; QOL-B = Quality of Life Questionnaire – Bronchiectasis; SGRQ-C = St. George's Respiratory Questionnaire for COPD (chronic obstructive pulmonary disease); W = Week.

RESULTS

- Mean age was 64.7 years (±10.0), 71.3% female, 63.8% Asian, with 86.3% having bronchiectasis (Table 2)

Table 2. Sample Characteristics at Day 1 (Randomization/Baseline; N=80)

Patient characteristics	
Female sex, n (%)	57 (71.3)
Mean age, y (SD)	64.7 (10.0)
Race, n (%)	
Asian	51 (63.8)
White	28 (35.0)
Time since first diagnosis of TR Disease, y (SD)	4.4 (4.2)
Underlying lung disease, n (%) (not mutually exclusive)	
None reported	8 (10.0)
Bronchiectasis	69 (86.3)
Chronic obstructive pulmonary disease	14 (17.5)

TR = treatment refractory, y = year.

RESULTS *(continued)*

- Mean responses at Study Day 1 ranged from 0.30 (Item 4: coughing up blood [SD 0.74]) to 2.06 (Item 6: fatigue or tiredness [SD 1.02]) (Table 3)
- The MACrO$_2$ PRO had good test-retest reliability (ICC=0.77) (data not shown)
- As expected, correlations between the MACrO$_2$ PRO v1.0 score and the other key PROs were moderate to strong; correlations increased in strength over time (Table 4)
- Significant improvements were seen with PGIS ($p<0.0001$, Figure 1) and PGIC ($p<0.01$, Figure 2). Patients with improved PGIS scores at Month 6 had a least squares mean of -16.54 versus those with no change (-5.45)
- Meaningful score difference for improvement ranged between -7.5 and -14.0 with a single estimate (mean of all values) of -11.3 (Figure 3)

Table 3. Summary Statistics of the MACrO$_2$ PRO v1.0 at Day 1 (Randomization/Baseline)

Item Score [a]	N	Mean (SD)	Median	Range (Min, Max)	n (%) at Floor [b]	n (%) at Ceiling [c]	n (%) Missing
1.Cough with phlegm, mucus, or sputum	80	1.99 (0.80)	2	4 (0, 4)	3 (3.8)	1 (1.3)	0 (0)
2.Dry cough (no phlegm, mucus, or sputum)	80	1.83 (0.79)	2	3 (0, 3)	3 (3.8)	0 (0)	0 (0)
3.Chest congestion (needing to clear mucus or feeling pressure or tightness in the lungs)	80	1.45 (0.93)	2	3 (0, 3)	16 (20.0)	0 (0)	0 (0)
4.Coughing up blood	80	0.30 (0.74)	0	3 (0, 3)	66 (82.5)	0 (0)	0 (0)
5.Shortness of breath or difficulty taking a deep breath	80	1.71 (0.93)	2	4 (0, 4)	9 (11.3)	2 (2.5)	0 (0)
6.Fatigue or tiredness	80	2.06 (1.02)	2	4 (0, 4)	3 (3.8)	7 (8.8)	0 (0)
7.Night sweats or unusual sweating	80	0.98 (0.95)	1	3 (0, 3)	31 (38.8)	0 (0)	0 (0)
Total Scaled Score	80	36.83 (13.67)	34	71 (11, 82)	0 (0.0)	0 (0)	0 (0)

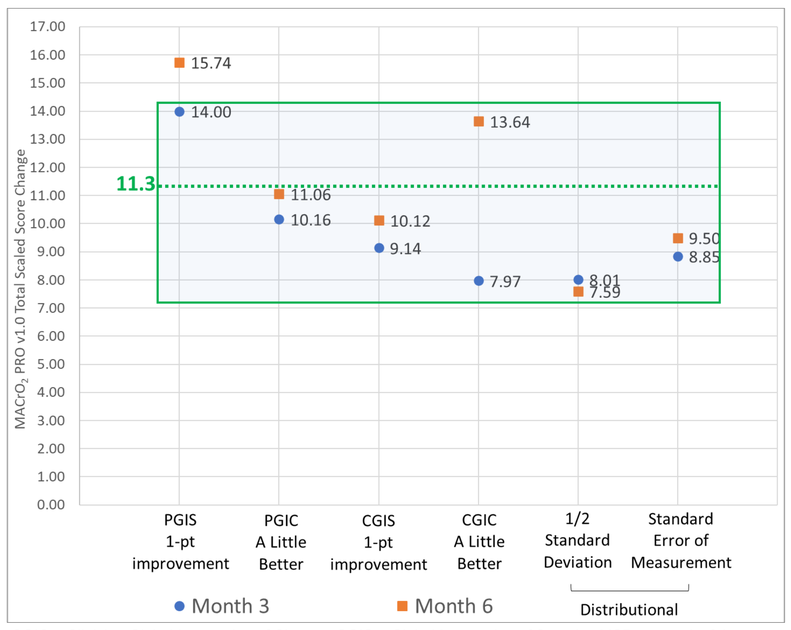
Max = maximum; Min = minimum; PRO = patient-reported outcome.
[a] Response scale for MACrO$_2$ PRO v1.0 items: "absent" (0), "mild" (1), "moderate" (2), "severe" (3), and "extremely severe" (4).
[b] Responses at the floor: lowest possible score "absent" (0).
[c] Responses at the ceiling: highest possible score "extremely severe" (4).

Table 4. Convergent Validity of the MACrO$_2$ PRO v1.0 (Key Results)

	Day 1 (Randomization/ Baseline)			Month 3 (Day 85 ± 7 Days)			Month 6 (Day 169 ± 7 Days)		
Measures	N	r [a]	p-value	N	r [a]	p-value	N	r [a]	p-value
PGIS	80	0.553	<.001	74	0.801	<.001	68	0.807	<.001
QOL-B									
Respiratory Symptoms	80	-0.729	<.001	75	-0.857	<.001	69	-0.847	<.001
Physical	80	-0.556	<.001	75	-0.721	<.001	69	-0.695	<.001
Role	80	-0.593	<.001	75	-0.732	<.001	69	-0.704	<.001
Vitality	80	-0.569	<.001	75	-0.543	<.001	69	-0.533	<.001
Health Perceptions	80	-0.530	<.001	75	-0.624	<.001	69	-0.555	<.001
SGRQ-C									
Symptoms	80	0.503	<.001	74	0.765	<.001	69	0.715	<.001
Activity	80	0.547	<.001	74	0.710	<.001	68	0.709	<.001
Impacts	80	0.694	<.001	74	0.767	<.001	68	0.809	<.001
Total Score	80	0.671	<.001	74	0.802	<.001	68	0.808	<.001

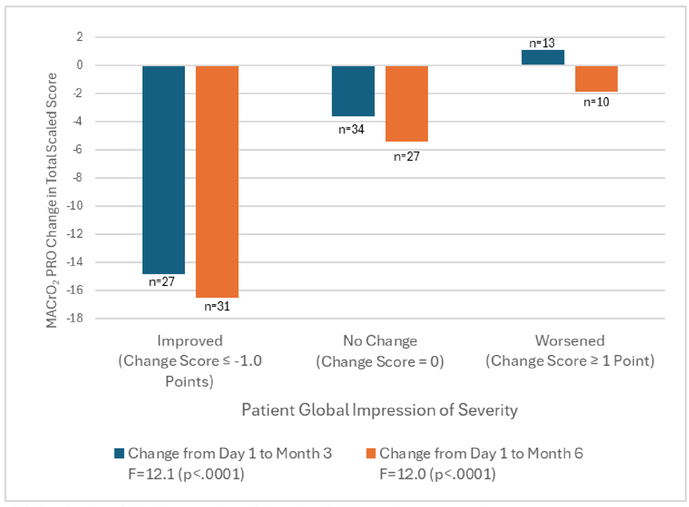
PGIS = Patient Global Impression of Severity; PRO = patient-reported outcome; QOL-B = Quality of Life Questionnaire – Bronchiectasis; SGRQ-C = St. George's Respiratory Questionnaire for COPD (chronic obstructive pulmonary disease).

Figure 3. Triangulation of MSD Results for the Scaled MACrO$_2$ PRO v1.0



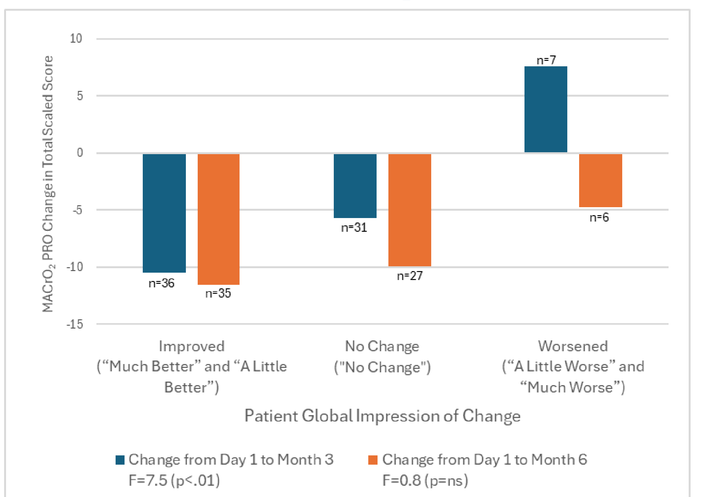
CGIC = Clinician Global Impression of Change; CGIS = Global Impression of Severity; MSD = meaningful score difference; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PRO = patient-reported outcome.

Figure 1. Responsiveness of MACrO$_2$ PRO v1.0 by PGIS



PGIS = Patient Global Impression of Severity; PRO = patient-reported outcome.

Figure 2. Responsiveness of MACrO$_2$ PRO v1.0 by PGIC



PGIC = Patient Global Impression of Change; PRO = patient-reported outcome.

CONCLUSIONS

The results overall indicate that the MACrO$_2$ PRO v1.0 performed well within the target population. The novel measure is reliable and valid. The suggested meaningful score difference (improvement) was -11.3 (range -7.5 to -14). The MACrO$_2$ PRO is a promising tool for assessing symptom response in TR-MAC-LD.

† Main/presenting author
‡ Author contributions made while affiliated with AN2 Therapeutics, but author may no longer be affiliated with the organization

CONFLICTS OF INTEREST:
DMB and LS are paid consultants to the pharmaceutical industry, including AN2 Therapeutics.
ACKNOWLEDGEMENTS:
This study was funded by AN2 Therapeutics (Menlo Park, CA). We acknowledge Marissa Stefan of PPD Evidera Patient Centered Research for her help in managing this project.

REFERENCES:

1. Quittner AL, Marciel KK, Salathe MA, et al. A preliminary quality of life questionnaire-bronchiectasis: a patient-reported outcome measure for bronchiectasis. Chest. 2014;146(2):437-448. doi:10.1378/chest.13-1891
2. Meguro M, Barley EA, Spencer S, Jones PW. Development and validation of an improved, COPD-specific version of the St. George Respiratory Questionnaire. Chest. 2007;132(2):456-463. doi:10.1378/chest.06-0702