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# Validation of the Quality of Life-Bronchiectasis (QOL-B) Respiratory Domain Patient-Reported Outcome (PRO) Measure in Treatment-Refractory MAC Lung Disease (TR-MAC-LD)

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## INTRODUCTION

### OBJECTIVE

The primary aim was to evaluate the performance of the Quality of Life Questionnaire – Bronchiectasis (QOL-B version 3.1)[1] respiratory domain (RD) questionnaire and confirm the meaningful score difference (MSD) threshold in patients with TR-MAC-LD. The results of these analyses were expected to validate the use of the QOL-B RD to measure a clinical response endpoint and to support labeling claims as a key endpoint in pivotal AN2 studies in patients with TR-MAC-LD. The main objectives of the analyses were the following:

- Assess item performance using standard classical test theory item reduction methods (including evaluation of missing data, ceiling/floor effects, and item-to-item correlations)
- Examine test-retest reliability (within a 1- to 2-week period)
- Examine construct validity and the planned scoring approach, including MSD
- Inform decisions on the positioning of the QOL-B RD in pivotal AN2 study endpoints

## 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 QOL-B consists of 37 items divided into 8 domains. Each domain score can range from 0 to 100 (with higher scores indicate better HRQoL). The recall period is 1 week, and each item uses a 4-point Likert scale. AN2 focused on analyzing the respiratory domain of the QOL-B (9 items measuring chest congestion, coughing during the day, coughing up mucus, color of sputum, shortness of breath with activity, wheezing, chest pain, shortness of breath when talking, and waking up at night because of cough).
  - 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. The $MACrO_2$ PRO v1.0 evaluates severity (in past week) of 7 individual symptoms. The items are 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 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 QOL-B RD 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; MAC = *Mycobacterium avium* complex; 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 item responses at Study Day 1 ranged from 2.29 (Item 31: cough up mucus [SD 0.930]) to 3.40 (Item 35: chest pain [SD 0.587]); missing data were very minimal (data not shown)
- The QOL-B RD had good test-retest reliability (ICC=0.83) (data not shown)
- As expected, the correlations between QOL-B RD score and the other key PROs were moderate to strong; correlations increased in strength over time (Table 3)
- Significant improvements were seen with $MACrO_2$ PRO Items 1 and 5 (p<0.001), PGIS (p<0.0001), QOL-B Items 1 and 15 (p<0.001), and SGRQ-C Item 14 (p<0.0001), demonstrating strong known-groups validity (Table 4)
- Patients who had improved PGIS scores at Month 6 had least squares (LS) mean of 10.97 vs. those with no change in PGIS (LS mean 2.59) (p<0.001) (Figure 1)
- Meaningful score difference for improvement ranged between 9 and 13, with a single estimate (mean of all values) of 11.1 (Figure 2)

**Table 3.** Convergent Validity of the QOL-B RD (Key Results)

| Measures | Day 1 (Randomization/Baseline) | | | Month 3 (Day 85 ± 7 Days) | | | Month 6 (Day 169 ± 7 Days) | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | r[a] | p-value | N | r[a] | p-value | N | r[a] | p-value |
| **PGIS** | 80 | -0.71 | <.001 | 74 | -0.80 | <.001 | 68 | -0.81 | <.001 |
| **$MACrO_2$ PRO[b]** | | | | | | | | | |
| Item 1 | 80 | -0.55 | <.001 | 75 | -0.70 | <.001 | 69 | -0.71 | <.001 |
| Item 2 | 80 | -0.45 | <.001 | 75 | -0.58 | <.001 | 69 | -0.53 | <.001 |
| Item 3 | 80 | -0.43 | <.001 | 75 | -0.73 | <.001 | 69 | -0.72 | <.001 |
| Item 5 | 80 | -0.64 | <.001 | 75 | -0.74 | <.001 | 69 | -0.77 | <.001 |
| **SGRQ-C** | | | | | | | | | |
| Symptoms | 80 | -0.70 | <.001 | 74 | -0.80 | <.001 | 69 | -0.81 | <.001 |
| Activity | 80 | -0.71 | <.001 | 74 | -0.73 | <.001 | 68 | -0.83 | <.001 |
| Impacts | 80 | -0.82 | <.001 | 74 | -0.79 | <.001 | 68 | -0.80 | <.001 |
| Total Score | 80 | -0.84 | <.001 | 74 | -0.83 | <.001 | 68 | -0.86 | <.001 |

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

[a] Spearman's rank correlation coefficient

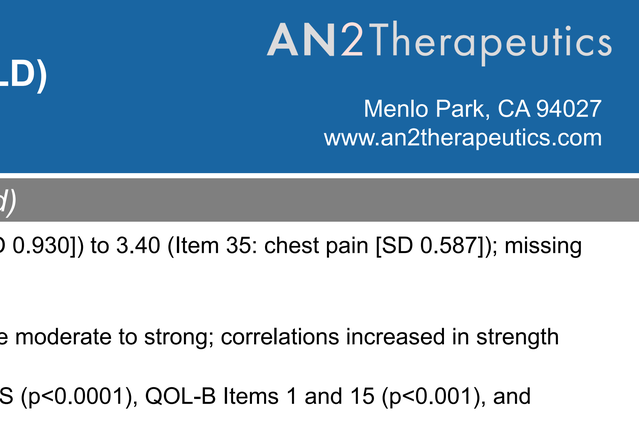
[b] $MACrO_2$ PRO v1.0, Item 1: Cough with phlegm, mucus, or sputum; Item 2: Dry cough (no phlegm, mucus, or sputum); Item 3: Chest congestion (needing to clear mucus or feeling pressure or tightness in the lungs); Item 5: Shortness of breath or difficulty taking a deep breath

**Table 4**. QOL-B RD Score by Known-groups at Day 1 (N=80)

| Anchor | QOL-B RD Score at Day 1 | | Overall *F* Test | |
|---|---|---|---|---|
| | N | Mean (SD) | Test Value | p-value |
| **QOL-B Item 1 (impact on vigorous activity)** | | | 6.51 | <0.0001 |
| 1 (A lot of difficulty) | 19 | 46.2 (18.12) | | |
| 2 (Moderate difficulty) | 25 | 58.7 (16.45) | | |
| 3 (A little difficulty) | 24 | 67.1 (17.21) | | |
| 4 (No difficulty) | 12 | 77.5 (10.62) | | |
| **QOL-B Item 15 (global health)** | | | 11.01 | <0.0001 |
| 1 (Excellent) | 0 | NE | | |
| 2 (Good) | 16 | 77.4 (8.72) | | |
| 3 (Fair) | 35 | 64.9 (16.52) | | |
| 4 (Poor) | 29 | 47.4 (17.18) | | |
| **$MACrO_2$ PRO Item 1 (cough with phlegm, mucus, or sputum)** | | | 5.70 | <0.0001 |
| 0 (Absent) | 3 | 84.0 (5.66) | | |
| 1 (Mild) | 16 | 71.2 (13.58) | | |
| 2 (Moderate) | 41 | 63.7 (17.58) | | |
| 3 (Severe) | 19 | 44.4 (15.95) | | |
| 4 (Extremely Severe) | 1 | 40.7 (NA) | | |
| **$MACrO_2$ PRO Item 5 (shortness of breath)** | | | 9.02 | <0.0001 |
| 0 (Absent) | 9 | 81.1 (6.53) | | |
| 1 (Mild) | 20 | 74.0 (10.84) | | |
| 2 (Moderate) | 38 | 55.4 (16.12) | | |
| 3 (Severe) | 11 | 45.5 (21.15) | | |
| 4 (Extremely Severe) | 2 | 35.2 (7.86) | | |
| **PGIS** | | | 14.31 | <0.0001 |
| 0 (None) | 4 | 80.2 (9.36) | | |
| 1 (Mild) | 14 | 77.4 (10.92) | | |
| 2 (Moderate) | 40 | 65.0 (13.96) | | |
| 3 (Severe) | 21 | 39.9 (14.10) | | |
| 4 (Very Severe) | 1 | 44.4 (NA) | | |
| **SGRQ-C Item 14 (how chest trouble affects)** | | | 7.66 | <0.0001 |
| A (It does not stop me doing anything I would like to do) | 14 | 71.5 (18.74) | | |
| B (It stops me doing one or two things I would like to do) | 46 | 66.0 (14.04) | | |
| C (It stops me doing most of the things I would like to do) | 18 | 43.4 (17.91) | | |
| D (It stops me doing everything I would like to do) | 2 | 33.3 (15.71) | | |

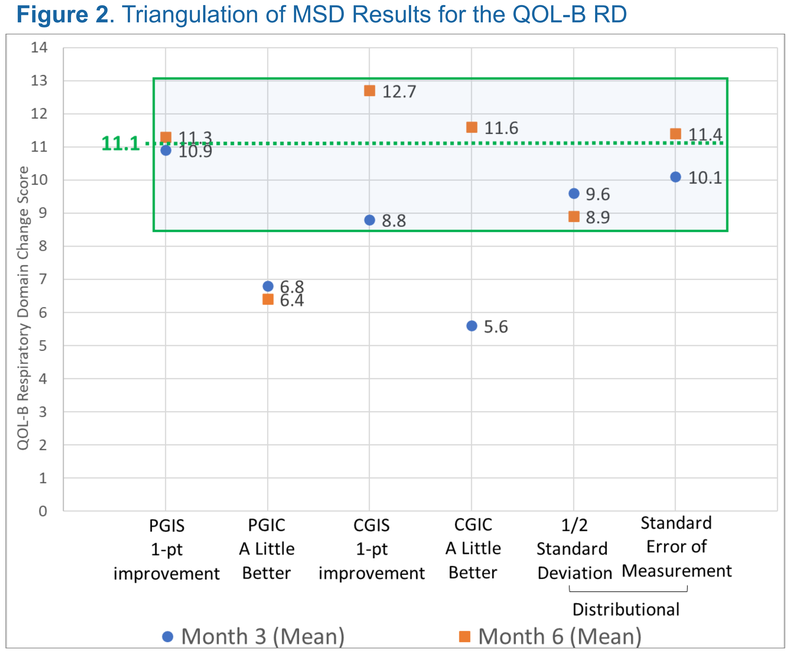
PGIS = Patient Global Impression of Severity; PRO = patient-reported outcome; QOL-B RD = Quality of Life Questionnaire – Bronchiectasis Respiratory Domain; SGRQ-C = St. George's Respiratory Questionnaire for COPD (chronic obstructive pulmonary disease).

**Figure 1**. Change in QOL-B RD Score by Change in PGIS Score




PGIS = Patient Global Impression of Severity; QOL-B RD = Quality of Life Questionnaire – Bronchiectasis Respiratory Domain

**Figure 2**. Triangulation of MSD Results for the QOL-B RD




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; QOL-B RD = Quality of Life Questionnaire – Bronchiectasis Respiratory Domain; .

## CONCLUSIONS

The results indicate that the QOL-B RD performed well within the target population. The measure is reliable and valid. The triangulated meaningful change analyses suggested MSD (improvement) of 11.1 (range: 9–13). The QOL-B RD would be an appropriate endpoint to use in clinical trials of patients with TR-MAC-LD.

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**CONFLICTS OF INTEREST:**
DMB and LS are paid consultants to the pharmaceutical industry, including AN2 Therapeutics.

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