

# Quality of Life Questionnaire-Bronchiectasis: final psychometric analyses and determination of minimal important difference scores

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## ABSTRACT

**Background** The Quality of Life-Bronchiectasis (QOL-B), a self-administered, patient-reported outcome measure assessing symptoms, functioning and health-related quality of life for patients with non-cystic fibrosis (CF) bronchiectasis, contains 37 items on 8 scales (Respiratory Symptoms, Physical, Role, Emotional and Social Functioning, Vitality, Health Perceptions and Treatment Burden).

**Methods** Psychometric analyses of QOL-B V.3.0 used data from two double-blind, multicentre, randomised, placebo-controlled, phase III trials of aztreonam for inhalation solution (AZLI) in 542 patients with non-CF bronchiectasis and Gram-negative endobronchial infection.

**Results** Excellent internal consistency (Cronbach's  $\alpha \geq 0.70$ ) and 2-week test-retest reliability (intraclass correlation coefficients  $\geq 0.72$ ) were demonstrated for each scale. Convergent validity with 6 min walk test was observed for Physical and Role Functioning scores. No floor or ceiling effects (baseline scores of 0 or 100) were found for the Respiratory Symptoms scale (primary endpoint of trials). Baseline Respiratory Symptoms scores discriminated between patients based on baseline FEV<sub>1</sub>% predicted in only one trial. The minimal important difference score for the Respiratory Symptoms scale was 8.0 points. AZLI did not show efficacy in the two phase III trials. QOL-B responsiveness to treatment was assessed by examining changes from baseline QOL-B scores at study visits at which protocol-defined pulmonary exacerbations were reported. Mean Respiratory Symptoms scores decreased 14.0 and 14.2 points from baseline for placebo-treated and AZLI-treated patients with exacerbations, indicating that worsening respiratory symptoms were reflected in clinically meaningful changes in QOL-B scores.

**Conclusions** Previously established content validity, reliability and responsiveness of the QOL-B are confirmed by this final validation study. The QOL-B is available for use in clinical trials and routine clinical practice.

## INTRODUCTION

Bronchiectasis is a lung disease characterised by chronic cough and sputum production, often accompanied by airway bacterial infection.<sup>1-6</sup> Treatments for non-cystic fibrosis (CF) bronchiectasis are limited and the assessment of new treatments is limited by lack of validated clinical trial endpoints.<sup>7</sup> Unlike CF, large decreases in bacterial density in non-CF bronchiectasis placebo-controlled studies did not lead to improvements in clinical symptoms or FEV<sub>1</sub>,<sup>8</sup>

## Key messages

### What is the key question?

- To compute the psychometric properties of the first disease-specific health-related quality of life measure for non-cystic fibrosis (CF) bronchiectasis.

### What is the bottom line?

- The Quality of Life-Bronchiectasis (QOL-B) has demonstrated excellent psychometric properties in two large-scale clinical trials and minimal important difference values have been calculated for each scale to aid researchers and clinicians in interpreting QOL-B data; the measure is ready for research and clinical use.

### Why read on?

- There is an unmet clinical need for approved therapies in non-CF bronchiectasis; however, these efforts have been hampered by the lack of reliable, disease-specific outcomes.

although improvement on the St George's Respiratory Questionnaire (SGRQ) was observed in exploratory analyses of treatment-adherent patients in a colistin study.<sup>9</sup> Without reliable surrogates for clinical efficacy (e.g., FEV<sub>1</sub>), accurate measures of symptom frequency and severity are needed for bronchiectasis drug development. Furthermore, developing an endpoint assessing functioning of non-CF bronchiectasis patients in their daily lives would complement an exacerbation endpoint.

The Quality of Life-Bronchiectasis (QOL-B), a self-administered patient-reported outcome (PRO) measure, was developed in response to the need for such new measurement tools. It assesses symptoms, functioning and health-related quality of life (HRQoL) for non-CF bronchiectasis patients and includes 37 items on 8 scales (Respiratory Symptoms, Physical, Role, Emotional and Social Functioning, Vitality, Health Perceptions and Treatment Burden).<sup>10 11</sup> Development followed the procedures and analyses recommended by the Food and Drug Administration (FDA) guidance on PROs.<sup>12</sup> Previously reported content validity, cognitive testing and psychometric analyses conducted on interim versions supported QOL-B concepts and items.<sup>10</sup>



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This manuscript presents psychometric analyses of QOL-B Version (V) 3.0 computed using data from two double-blind, multicentre, randomised, placebo-controlled, phase III trials of aztreonam for inhalation solution (AZLI) in patients with non-CF bronchiectasis and Gram-negative endobronchial infection. While these two studies did not demonstrate clinical efficacy,<sup>13</sup> the use of a prespecified protocol-defined criteria for acute bronchiectasis exacerbations facilitated using the QOL-B for quantifying changes in respiratory symptoms during exacerbations. The minimal important difference (MID) scores for each scale were also estimated.

## METHODS

### Study design

QOL-B psychometric analyses presented herein used data from two phase III clinical trials: AIR-BX1 (47 sites; Australia, Canada and the USA; April 2011–March 2013; clinicaltrials.gov: NCT01313624) and AIR-BX2 (65 sites; Australia, Belgium, Canada, France, Germany, Italy, the Netherlands, Spain, UK and the USA; April 2011–July 2013; clinicaltrials.gov: NCT01314716). Both trials had the same design. The trial design, inclusion and exclusion criteria and results are described elsewhere.<sup>13</sup> Briefly, patients received double-blind treatment with AZLI 75 mg or placebo (1:1 randomisation; code generated by Gilead designee; randomisation occurred at baseline using an interactive voice/web response system) administered 3 times daily for 28 days, with each of 2 double-blind treatment courses followed by 28-day off-treatment. Procedures to generate QOL-B translations followed internationally accepted and regulatory guidelines, using formal backward and forward translation methodologies.<sup>12 14 15</sup> Translations and cultural adaptations (e.g., using American English QOL-B in the UK) were tested with patients who were native speakers of the translated/adapted language. A complex, multistep process ensured cultural equivalence and each new translation was piloted in the new language with  $\geq 5$  patients with non-CF bronchiectasis.

Studies were conducted in accordance with principles of the Declaration of Helsinki, International Conference on Harmonisation guidelines and good clinical practice principles. Institutional Review Boards/Ethics Committees approved the study for each site. Patients provided written informed consent prior to study participation.

### Patients

Inclusion/exclusion criteria are described elsewhere.<sup>13</sup> Eligible patients ( $\geq 18$  years of age) had bronchiectasis confirmed by CT chest scan, a positive sputum culture for target Gram-negative organism(s) at screening, chronic sputum production on  $\geq 4$  days/week during prior 4 weeks and FEV<sub>1</sub>  $\geq 20\%$  predicted at screening. Target Gram-negative respiratory pathogens included species of *Achromobacter*, *Burkholderia*, *Citrobacter*, *Enterobacter*, *Escherichia*, *Klebsiella*, *Moraxella*, *Proteus*, *Pseudomonas*, *Serratia* and *Stenotrophomonas*. Patients with CF or with only *Haemophilus influenzae* respiratory infections were excluded.

### Study measures

Three measures of clinical response were specified in the protocol and used to measure discriminant and/or convergent validity, including FEV<sub>1</sub>, the 6 min Walk Test (6MWT)<sup>16</sup> and the Euro Quality of Life-5 Dimensions (EQ-5D).<sup>17</sup>

Spirometry was performed at each visit, after administration of a short acting inhaled bronchodilator.

The 6MWT, measuring distance walked in 6 min, was administered at every visit. No MID has been reported for non-CF bronchiectasis. In patients with COPD, a change of 54–80 m is

perceived as a small improvement/worsening in walking ability<sup>18</sup>; another study suggests that a change of 10% from baseline is clinically important.<sup>19</sup>

The EQ-5D, a standardised self-reported measure of global health status, was administered at the beginning and at the end of each treatment course. Results for the EQ-5D visual analogue scale (VAS) are presented. General health states were assessed by responses on a vertical scale from 0 (worst imaginable) to 100 (best imaginable). No MID has been reported for non-CF bronchiectasis.

QOL-B V3.0 was administered at every study visit; V3.0 differs only very slightly from the final V3.1 (an example was provided and a ‘not applicable’ category was added to 1 item on the V3.1 Social Functioning scale).<sup>10 20</sup> Each of the 37 items is scored from 1 to 4, and each of the 8 scale scores is standardised on a 0–100 point scale, with higher scores representing fewer symptoms or better functioning and HRQoL. A total score is not calculated. Scales contain between 3 and 9 items, thus changing 1 answer category will correspond to a change of 1.1 to 3.7 points.

The Global Rating of Change Questionnaire (GRCQ) V2.2 (15 point Likert-like scale) and V3.0 (7 point scale) were administered at day 14, immediately after the QOL-B. Each GRCQ item corresponded to 1 of the 8 QOL-B scales and patients responded to each GRCQ item using a VAS. Changes from baseline at day 14 were evaluated from –7 (a very great deal worse) to +7 (a very great deal better) for items on GRCQ V2.2 and from –3 (a great deal worse) to +3 (a great deal better) for GRCQ V3.0 (the Respiratory Symptoms GRCQ V2.2 and V3.0 are provided in online supplementary figure S1). Zero indicated no change. A switch from the 15-point to the 7-point GRCQ scoring system was made following a suggestion from a regulatory agency while these two trials were ongoing. Scores are presented based on GRCQ V3.0. GRCQ V2.2 scores (–7 to 7) were converted to the V3.0 scale (–3 to 3) by multiplying by 3/7.

Protocol-defined exacerbations were defined as acute worsening of respiratory disease meeting  $\geq 3$  major criteria (increased sputum production, sputum discolouration, dyspnoea and cough) or 2 major criteria and  $\geq 2$  minor criteria (fever  $>38^{\circ}\text{C}$  at a clinic visit, increased malaise or fatigue, FEV<sub>1</sub> [L] or FVC decreased  $>10\%$  from baseline and new/increased haemoptysis).<sup>13</sup>

### Analyses

Statistical analyses were performed with SAS V9.2 (SAS Institute, Cary, North Carolina, USA). Internal consistency was measured using Cronbach’s  $\alpha$ .<sup>21</sup> Test score reproducibility over 14 days (i.e., test–retest reliability) was calculated with intraclass correlation coefficients (ICCs).<sup>22</sup> Spearman’s correlations were calculated. The protocols specified that AIR-BX1 and AIR-BX2 study results were to be analysed separately; pooled data were used for some exploratory analyses. MIDs were calculated for each scale.<sup>23–25</sup> For patients in the minimal change GRCQ category ( $>0.5$ – $1.5$  improvement or worsening from baseline on the 3-point scale), their mean change from baseline QOL-B scores at day 14 was the anchor-based MID. Two distribution-based MIDs were calculated: 1/2 SD of the change from baseline QOL-B scores at day 14 and 1 SE of measurement (SEM) for baseline scores ( $\text{SEM}=\text{SD}\sqrt{(1-\alpha)}$ ). The 6 MIDs (3 methods across 2 studies) were averaged and rounded to the nearest integer to generate a final MID for each scale.

## RESULTS

In AIR-BX1, 266 patients were randomised and treated (AZLI:  $n=134$ ; placebo:  $n=132$ ). In AIR-BX2, 274 patients were randomised and 272 were treated (AZLI: 135; placebo: 137). Demographic and baseline characteristics were comparable for

both treatment arms, except for a significant difference ( $p=0.017$ ) in the distribution of patients within FEV<sub>1</sub>% predicted categories in AIR-BX1, with 38.8% of AZLI-arm patients having baseline FEV<sub>1</sub> <50% predicted compared with 25.0% of placebo-arm patients (table 1). Additional baseline characteristics are described elsewhere.<sup>13</sup>

### Floor and ceiling effects

Floor and ceiling effects were assessed by examining baseline QOL-B scores, to determine whether patients had room to both improve and worsen on each scale (table 2). Floor effects were not observed. One patient (0.4%) in each study had a Respiratory Symptoms score of 0 and ≤5.1% of patients on each study had scores of 0 on any of the other scales. Ceiling effects (baseline scores of 100) were not observed for the Respiratory Symptoms scale. Ceiling effects were observed on the Emotional Functioning (24.1% and 22.3% of patients on AIR-BX1 and AIR-BX2, respectively), and on the Treatment Burden scale (13.4% and 11.3% of patients).

### Internal consistency

Internal consistency of QOL-B scales was assessed with Cronbach's  $\alpha$  (table 3). Values were ≥0.70 for each scale, showing good reliability (i.e., items on each scale correlated with each other, forming a unitary construct).<sup>21</sup>

### Discriminant validity

Mean baseline QOL-B scores were compared for patients differing by other health status indicators (table 4). The QOL-B Physical Functioning scale discriminated between patients on the basis of FEV<sub>1</sub>% predicted; in both studies, mean baseline Physical Functioning scores were approximately 20–30 points larger for patients with baseline FEV<sub>1</sub> ≥80% predicted compared with <50% predicted. Discrimination was less robust for Respiratory Symptoms, Vitality, Role Functioning and Health Perception scales; mean scores at baseline were approximately 10 points larger for patients with baseline FEV<sub>1</sub> ≥80% predicted compared with <50% predicted only in AIR-BX2. Statistically significant discrimination on the basis of median

**Table 1** Demographic and baseline characteristics

	AIR-BX1			AIR-BX2		
	AZLI (N=134)	Placebo (N=132)	p Value*	AZLI (N=136)	Placebo (N=138)	p Value*
Age, years; mean (SD)	64.2 (12.9)	64.9 (12.1)	0.65	63.3 (14.2)	62.7 (13.3)	0.75
Age, years; range	23–83	20–88		22–85	18–87	
FEV <sub>1</sub> % predicted, mean (SD)	60.4 (22.6)	64.5 (18.7)	0.11	63.8 (19.5)	63.4 (21.6)	0.88
Range	18.1–109.4	20.6–114.1		22.7–115.5	19.5–115.3	
<50% predicted, n (%)	52 (38.8)	33 (25.0)	0.017	37 (27.2)	42 (30.4)	0.32
≥50 to <80% predicted, n (%)	49 (36.6)	70 (53.0)		72 (52.9)	61 (44.2)	
≥80% predicted, n (%)	33 (24.6)	29 (22.0)		27 (19.9)	35 (25.4)	
BMI, mean (SD)	25.0 (5.1)	24.7 (4.9)	0.66	23.9 (5.0)	24.7 (6.0)	0.25
Female, n (%)	84 (62.7)	97 (73.5)	0.07	89 (65.4)	101 (73.2)	0.19
Target Gram-negative pathogen at baseline,† n (%)	131 (97.8)	129 (97.7)	1.0	135 (100)‡	136 (99.3)‡	0.62
6MWT, metres; mean (SD)	421 (119.3)	426 (118.5)	0.74	423 (127.5)	428 (120.8)	0.75
EQ-5D visual analogue score at baseline,§ mean (SD)	66.1 (18.1)	69.9 (16.5)	0.08	65.7 (16.0)	68.0 (14.9)	0.23
QOL-B V.3.0 Scales: scores at baseline; mean (SD), range						
		Points for change of 1 answer category for 1 item¶				
Respiratory Symptoms	55.0 (19.3) 3.7–96.3	55.5 (19.3) 0–96.3	0.82	56.2 (18.0) 7.4–95.8	57.4 (18.1) 0–96.3	0.60
Physical Functioning	51.6 (30.5) 0–100	55.7 (29.7) 0–100	0.27	49.7 (30.1) 0–100	47.9 (28.8) 0–100	0.61
Vitality	50.4 (20.6) 0–100	49.5 (21.4) 0–100	0.72	50.6 (23.0) 0–100	49.3 (19.3) 0–100	0.60
Role Functioning	62.9 (25.0) 0–100	64.7 (24.4) 13.3–100	0.53	61.3 (26.6) 0–100	63.3 (26.5) 0–100	0.51
Health Perceptions	44.6 (20.6) 0–100	47.3 (22.1) 0–91.7	0.30	43.9 (20.1) 0–91.7	42.9 (20.5) 0–91.7	0.67
Emotional Functioning	78.3 (20.4) 8.3–100	78.4 (20.1) 25.0–100	0.98	77.5 (22.4) 0–100	76.9 (19.2) 8.3–100	0.80
Social Functioning	54.8 (26.0) 0–100	51.3 (27.2) 0–100	0.28	55.3 (27.2) 0–100	54.6 (27.4) 0–100	0.83
Treatment Burden**	65.6 (24.0) 0–100	66.8 (24.7) 0–100	0.70	63.2 (23.8) 0–100	66.7 (23.7) 0–100	0.25

\*Arms compared with t test for continuous and Fisher's exact test for categorical variables.

†Target Gram-negative respiratory pathogens at baseline (day –14 or day 1) included: *Achromobacter*, *Burkholderia*, *Citrobacter*, *Enterobacter*, *Escherichia*, *Klebsiella*, *Moraxella*, *Proteus*, *Pseudomonas*, *Serratia* or *Stenotrophomonas* sp.

‡Data available for 135 (AZLI) and 137 (placebo) patients.

§Data available for AIR-BX1: 131 (AZLI), 131 (placebo); AIR-BX2: 133(AZLI), 134 (placebo).

¶After standardising scores on a 100-point scale; assuming there were no missing responses on the scale.

\*\*Data available for AIR-BX1: 127 (AZLI), 120 (placebo); AIR-BX2: 121 (AZLI), 126 (placebo); patients who were not currently receiving treatment for bronchiectasis were instructed to skip this scale.

6MWT, 6 min walk test; AZLI, aztreonam for inhalation solution; BMI, body mass index; EQ-5D, Euro Quality of Life-5 Dimensions; QOL-B, Quality of Life-Bronchiectasis.

**Table 2** Floor and ceiling effects: QOL-B scores at baseline

QOL-B V.3.0 scale	AIR-BX1 (N=266)		AIR-BX2 (N=274)	
	Floor effects* (score=0) n (%)	Ceiling effects* (score=100) n (%)	Floor effects* (score=0) n (%)	Ceiling effects* (score=100) n (%)
Respiratory Symptoms	1 (0.4)	0 (0)	1 (0.4)	0 (0)
Physical Functioning	8 (3.0)	21 (7.9)	12 (4.4)	16 (5.8)
Vitality	8 (3.0)	5 (1.9)	7 (2.6)	4 (1.5)
Role Functioning	1 (0.4)	21 (7.9)	4 (1.5)	20 (7.3)
Health Perceptions	3 (1.1)	1 (0.4)	4 (1.5)	0 (0)
Emotional Functioning	0 (0)	64 (24.1)	1 (0.4)	61 (22.3)
Social Functioning	10 (3.8)	11 (4.1)	14 (5.1)	9 (3.3)
Treatment Burden†	2 (0.8)	33 (13.4)	3 (1.2)	28 (11.3)

\*QOL-B responses at baseline (day 0) were used for the analyses included in this table.

†Patients who were not receiving treatment for bronchiectasis were instructed to skip the Treatment Burden scale; analyses presented in this table used responses from 247 patients in AIR-BX1 and 247 patients in AIR-BX2 and percentages were calculated using these numbers as denominators.

QOL-B, Quality of Life-Bronchiectasis.

baseline 6MWT results was observed in both studies for Physical Functioning, Vitality, Role Functioning and Health Perception scores, and only in AIR-BX2 for Respiratory Symptoms and Emotional Functioning scores. Some of the statistically significant differences observed for 6MWT categories ( $p < 0.05$ ) were smaller than the MID values for these scales (see table 7) and thus were not considered clinically meaningful.

### Convergent validity

Correlations between baseline QOL-B scores and other health status indicators are summarised (table 5). Moderate correlations were observed for baseline QOL-B Physical Functioning scores (AIR-BX2 only) and baseline FEV<sub>1</sub>% predicted, with weak or no correlations observed for other baseline QOL-B scores and FEV<sub>1</sub>% predicted. Moderate correlations were observed for Physical Functioning and Role Functioning scores and 6MWT results, with weak or no correlations observed for other scales. Moderate to strong correlations were observed between baseline QOL-B scores and most baseline EQ-5D VAS scores.

### Test-retest reliability

QOL-B test-retest reliability was assessed by ICC values (table 6). Values were  $\geq 0.70$  for each scale, indicating good score reproducibility over the 14-day interval.<sup>22</sup>

**Table 3** Internal consistency of QOL-B scales

QOL-B V.3.0 scale	AIR-BX1 (N=266)		AIR-BX2 (N=274)	
	n*	Cronbach's $\alpha$	n*	Cronbach's $\alpha$
Respiratory Symptoms	246	0.84	254	0.79
Physical Functioning	260	0.92	267	0.91
Vitality	264	0.77	271	0.70
Role Functioning	253	0.83	255	0.86
Health Perceptions	260	0.79	265	0.75
Emotional Functioning	262	0.84	269	0.82
Social Functioning	253	0.78	259	0.76
Treatment Burden†	233	0.79	232	0.77

\*QOL-B responses at baseline (day 0) were used for the analyses presented in this table.

†Patients who were not receiving treatment for bronchiectasis were instructed to skip the Treatment Burden scale.

QOL-B, Quality of Life-Bronchiectasis.

### MID values

Changes from baseline QOL-B scores at day 14 were categorised by GRCQ responses. QOL-B scores were grouped for patients whose GRCQ scores indicated 'no change' or 'minimal,' 'moderate' or 'large change' from baseline to day 14. Each change from baseline category included improving and worsening scores. Data for the Respiratory Symptoms scale are presented (see online supplementary table S1). Mean change on the QOL-B scale for patients in the 'minimal change' GRCQ category was the anchor-based MID; values for the Respiratory Symptoms scale were 6.7 (AIR-BX1) and 11.4 (AIR-BX2) points (table 7). MIDs derived from 1/2 SD of baseline scores were 8.0 (AIR-BX1) and 7.7 (AIR-BX2) points for the Respiratory Symptoms scale and values derived from the SEM of baseline scores were 7.7 (AIR-BX1) and 8.2 (AIR-BX2) points. Averaging these 6 MID estimates generated a final MID of 8.0 points for the Respiratory Symptoms scale.

### Responsivity to treatment or change in health status

Clinically significant changes from baseline QOL-B Respiratory Symptoms scores were not observed after 14 days of AZLI or placebo treatment, because none of the mean changes exceeded the 8.0 point MID (see online supplementary table S2). Changes in FEV<sub>1</sub> and 6MWT were also comparable between arms, as were changes on other QOL-B scales. In contrast, larger decreases from baseline sputum bacterial density after treatment were observed for the AZLI arm compared with placebo.

Because AZLI did not show clinically significant efficacy in the two phase III trials, an exploratory analysis was performed using change from baseline QOL-B Respiratory Symptoms scores for patients with a protocol-defined exacerbation reported at a study visit at which the QOL-B was also administered. These exacerbations occurred 6 days to approximately 4 months after baseline. Mean (SD) change from baseline QOL-B Respiratory Symptoms score was -14.2 (16.5) points for the 30 AZLI-treated patients with a protocol-defined exacerbation recorded at a study visit for which QOL-B scores were available (range: -50.5 to +18.5 points; figure 1A). Mean (SD) change from baseline was -14.0 (16.7) points for the corresponding 30 placebo-treated patients (range: -66.7 to +11.1 points; figure 1B). These mean values both exceeded the -8.0-point MID and were thus considered to represent clinically relevant worsening of respiratory symptoms in these study populations.

**Table 4** Discrimination of QOL-B scores by other indices of health status

QOL-B scale	AIR-BX1				AIR-BX2			
	Mean (SD) QOL-B scores at baseline for patients with baseline FEV <sub>1</sub>							p Value*
	<50% predicted (N=85)	≥50 to <80% predicted (N=119)	≥80% predicted (N=62)	<50% predicted (N=79)	≥50 to <80% predicted (N=133)	≥80% predicted (N=62)		
Respiratory Symptoms	53.4 (18.7)	54.8 (19.3)	58.5 (19.9)	0.27	51.7 (17.5)	57.6 (18.3)	61.6 (16.7)	0.004
Physical Functioning	44.9 (30.6)	54.1 (28.6)	64.8 (28.9)	< 0.001	35.5 (25.0)	49.6 (29.0)	63.8 (28.0)	<0.001
Vitality	51.2 (19.7)	49.0 (21.9)	50.1 (21.0)	0.77	47.0 (20.1)	49.1 (21.5)	55.5 (21.1)	0.050
Role Functioning	63.7 (25.1)	62.8 (23.7)	65.8 (26.2)	0.74	54.5 (26.8)	64.4 (25.5)	67.9 (26.3)	0.005
Health Perceptions	44.7 (20.8)	45.5 (21.1)	48.6 (22.6)	0.52	40.4 (18.8)	42.5 (21.4)	49.1 (18.7)	0.030
Emotional Functioning	79.0 (21.0)	78.5 (19.9)	77.3 (20.1)	0.88	76.2 (21.1)	77.2 (21.4)	78.4 (19.5)	0.82
Social Functioning	57.1 (25.4)	50.5 (26.6)	52.4 (28.0)	0.22	53.3 (28.1)	55.1 (27.9)	56.6 (25.0)	0.77
Treatment Burden†	65.0 (24.6)	68.5 (24.4)	63.1 (23.6)	0.36	62.6 (23.5)	67.2 (23.3)	63.0 (24.9)	0.34

QOL-B scale	AIR-BX1			AIR-BX2		
	Mean (SD) QOL-B scores at baseline for patients with baseline 6MWT:					
	Below median‡ (N=128)	Above median‡ (N=138)	p Value*	Below median‡ (N=138)	Above median‡ (N=136)	p Value*
Respiratory Symptoms	53.6 (19.7)	56.7 (18.8)	0.20	52.8 (18.7)	60.7 (16.5)	<0.001§
Physical Functioning	42.0 (29.7)	64.5 (26.2)	<0.001	37.5 (26.4)	59.9 (28.0)	<0.001
Vitality	46.1 (20.5)	53.5 (20.9)	0.004§	44.9 (19.2)	55.0 (21.9)	<0.001
Role Functioning	57.9 (25.0)	69.2 (23.2)	< 0.001	54.8 (26.4)	69.7 (24.5)	<0.001
Health Perceptions	42.1 (20.7)	49.6 (21.3)	0.004§	40.2 (19.6)	46.5 (20.5)	0.009§
Emotional Functioning	77.5 (20.5)	79.2 (20.0)	0.49	74.3 (21.5)	80.0 (19.9)	0.024§
Social Functioning	52.1 (27.7)	53.9 (25.7)	0.58	53.8 (28.1)	56.0 (26.5)	0.52
Treatment Burden¶	64.5 (24.3)	67.8 (24.3)	0.29	65.2 (24.7)	64.7 (22.9)	0.87

\*p Value is from an ANOVA model with the FEV<sub>1</sub>% predicted or 6MWT category as a fixed effect. Note: patients were not randomised by these categories at baseline.

†Patients who were not receiving treatment for bronchiectasis were instructed to skip the Treatment Burden scale; data available for 82, 112 and 53 patients in AIR-BX1 and 73, 122 and 52 patients in AIR-BX2.

‡Median 6MWT was 427 metres (range 61–761) for AIR-BX1 and 436 metres (range 18–704) for AIR-BX2.

§The difference between responses below and above the median baseline 6MWT was statistically significant (p<0.05) but was less than the MID for that scale (table 7) and thus was not considered clinically significant.

¶Patients who were not receiving treatment for bronchiectasis were instructed to skip the Treatment Burden scale; data available for 126 and 121 patients in AIR-BX1 and 125 and 122 patients in AIR-BX2.

6MWT, 6 min walk test; MID, minimal important difference; QOL-B, Quality of Life-Bronchiectasis; ANOVA, analysis of variance.

## DISCUSSION

Results of psychometric analyses of QOL-B V.3.0 data from 542 patients in two placebo-controlled AZLI trials support psychometric analyses reported for a preliminary version of the QOL-B (V.2.0), which included data from 89 patients in an open-label AZLI study.<sup>10</sup> For QOL-B V.3.0, adequate internal consistency and test–retest reliability were demonstrated for all 8 scales. For the Respiratory Symptom scale, the primary endpoint of the two phase III trials, floor and ceiling effects were not observed. Analyses of discriminant validity on the basis of baseline FEV<sub>1</sub>% predicted values indicated that mean baseline Respiratory Symptoms scores were approximately 10 points larger (indicating fewer symptoms) for AIR-BX2 patients with baseline FEV<sub>1</sub> ≥80% predicted compared with <50% predicted, but no statistically significant discrimination was observed in AIR-BX1. As was observed in the previous validation study of QOL-B V.2.0,<sup>10</sup> the Physical Functioning scale discriminated well between levels of disease severity based on lung function measurements, with a statistically significant

≥20-point spread for patients differing by baseline lung function. This discriminant validity, both the ~10-point spread in Respiratory Symptoms scores for AIR-BX2 and the ≥20-point spread in Physical Functioning scores for both studies, is larger than the corresponding MID values (8 and 10 points, respectively) and thus are also considered clinically meaningful. However, the lack of consistent significant discrimination for QOL-B Respiratory Symptoms scores and FEV<sub>1</sub>% predicted agrees with results from prior studies, in which FEV<sub>1</sub> was not strongly associated with decreases in airway bacteria after treatment or with better health status.<sup>8 26 27</sup>

In the absence of demonstrable efficacy in the two phase III trials, responsiveness to treatment was assessed for the QOL-B Respiratory Symptoms scale by examining mean changes from baseline for patients with a protocol-defined pulmonary exacerbation at a study visit at which the QOL-B had been administered. Mean scores decreased 14.2 and 14.0 points from baseline for AZLI-treated and placebo-treated patients with exacerbations, respectively, indicating that the patients'

**Table 5** Convergent validity: correlation between baseline QOL-B scores and other measures of health status

QOL-B scale	Correlations of baseline scores on QOL-B scales with other measures of health status					
	FEV <sub>1</sub> % predicted		6MWT		EQ-5D VAS	
	AIR-BX1 (N=266)	AIR-BX2 (N=274)	AIR-BX1 (N=266)	AIR-BX2 (N=274)	AIR-BX1 (N=266)	AIR-BX2 (N=274)
Respiratory Symptoms	0.118 (n=266) p=0.054	0.185 (n=274) p=0.002	0.170 (n=266) p=0.005	0.268 (n=274) p<0.001	0.512 (n=262) p<0.001	0.519 (n=267) p<0.001
Physical Functioning	0.273 (n=266) p<0.001	0.364 (n=274) p<0.001	0.526 (n=266) p<0.001	0.472 (n=274) p<0.001	0.568 (n=262) p<0.001	0.633 (n=267) p<0.001
Vitality	0.011 (n=266) p=0.86	0.115 (n=274) p=0.06	0.294 (n=266) p<0.001	0.267 (n=274) p<0.001	0.546 (n=262) p<0.001	0.631 (n=267) p<0.001
Role Functioning	0.075 (n=266) p=0.22	0.218 (n=274) p<0.001	0.364 (n=266) p<0.001	0.347 (n=274) p<0.001	0.621 (n=262) p<0.001	0.663 (n=267) p<0.001
Health Perceptions	0.090 (n=266) p=0.14	0.145 (n=274) p=0.016	0.279 (n=266) p<0.001	0.195 (n=274) p=0.001	0.662 (n=262) p<0.001	0.640 (n=267) p<0.001
Emotional Functioning	-0.019 (n=266) p=0.75	0.050 (n=274) p=0.41	0.128 (n=266) p=0.036	0.153 (n=274) p=0.011	0.294 (n=262) p<0.001	0.432 (n=267) p<0.001
Social Functioning	-0.062 (n=266) p=0.31	0.033 (n=274) p=0.59	0.107 (n=266) p=0.08	0.097 (n=274) p=0.11	0.376 (n=262) p<0.001	0.378 (n=267) p<0.001
Treatment Burden*	0.004 (n=247) p=0.95	0.061 (n=247) p=0.34	0.154 (n=247) p=0.016	-0.011 (n=247) p=0.86	0.463 (n=244) p<0.001	0.331 (n=241) p<0.001

Spearman's correlation coefficients are presented.

\*Patients who were not receiving treatment for bronchiectasis were instructed to skip the Treatment Burden scale; analyses presented in this table used responses from 247 patients in AIR-BX1 and 247 patients in AIR-BX2.

6MWT, 6 min walk test; EQ-5D, Euro Quality of Life-5 Dimensions; QOL-B, Quality of Life-Bronchiectasis; VAS, visual analogue scale.

worsening respiratory symptoms were reflected in changes in mean QOL-B Respiratory Symptoms scores.

For each scale, MID estimates from two distribution-based methods and one anchor-based method (using the GRCQ as an

anchor) were averaged to determine the final MID. The anchor-based MID estimates showed more variation between studies than was observed for the distribution-based estimates, and some anchor-based estimates also differed substantially from the

**Table 6** Test-retest reliability: intraclass correlation coefficients between screening (day 14) and baseline (day 0) for QOL-B scores

QOL-B V.3.0 scale	AIR-BX1 (N=266)		AIR-BX2 (N=274)	
	n*	Intraclass correlation coefficient	n*	Intraclass correlation coefficient
Respiratory Symptoms	266	0.85	268	0.82
Physical Functioning	266	0.84	273	0.86
Vitality	266	0.72	273	0.76
Role Functioning	265	0.87	270	0.86
Health Perceptions	266	0.79	272	0.74
Emotional Functioning	266	0.79	273	0.80
Social Functioning	266	0.77	270	0.84
Treatment Burden†	222	0.78	220	0.74

\*Intraclass correlation coefficients were determined from screening and baseline measurements, both of which occurred before AZLI/placebo treatments. Analyses included patients for whom the specified QOL-B scale measurements were available at both screening and baseline.

†Patients who were not receiving treatment for bronchiectasis were instructed to skip the Treatment Burden scale.  
QOL-B, Quality of Life-Bronchiectasis.

**Table 7** MID Estimates for the QOL-B scales

QOL-B V.3.0 scale and method of estimating MID	AIR-BX1		AIR-BX2		Final MID*
	MID	n	MID	n	
Respiratory Symptoms					8.0
Anchor-based†	6.7	56	11.4	77	
1/2 SD‡	8.0	266	7.7	274	
SEM§	7.7	266	8.2	274	
Physical Functioning					10.0
Anchor-based†	8.7	61	11.3	53	
1/2 SD‡	10.1	266	9.9	274	
SEM§	8.4	266	8.6	274	
Vitality					10.0
Anchor-based†	11.9	49	8.9	51	
1/2 SD‡	9.5	266	9.4	274	
SEM§	10.0	266	11.6	274	
Role Functioning					8.0
Anchor-based†	11.8	49	0.0	34	
1/2 SD‡	8.6	266	8.2	274	
SEM§	10.0	266	10.1	274	
Health Perceptions					8.0
Anchor-based†	7.6	50	3.6	58	
1/2 SD‡	8.2	266	7.9	274	
SEM§	9.8	266	10.1	274	
Emotional Functioning					7.0
Anchor-based†	5.1	44	4.6	40	
1/2 SD‡	7.1	266	6.8	274	
SEM§	8.2	266	8.8	274	
Social Functioning					9.0
Anchor-based†	10.3	37	2.0	33	
1/2 SD‡	7.8	266	7.3	274	
SEM§	12.6	266	13.3	274	
Treatment Burden					9.0
Anchor-based†	6.9	37	5.9	45	
1/2 SD‡	9.8	247	10.0	232	
SEM§	11.3	247	11.6	232	

\*Final MIDs were the average of the 6 MID values obtained for each scale, rounded to the nearest integer.

†Anchor-based MID=mean change from baseline QOL-B score at day 14 for patients with minimal change on the corresponding GRCQ (>0.5 to 1.5 improvement or worsening of scores on -3 to 3 scale).

‡1/2 SD of mean change from baseline QOL-B score at day 14.

§SEM for baseline scores; SEM=SD $\sqrt{(1-\alpha)}$ , with SD of mean baseline score and  $\alpha$ =Cronbach's  $\alpha$ .

GRCQ, Global Rating of Change Questionnaire; MID, minimal important difference; QOL-B, Quality of Life-Bronchiectasis; SEM, SE of measurement.

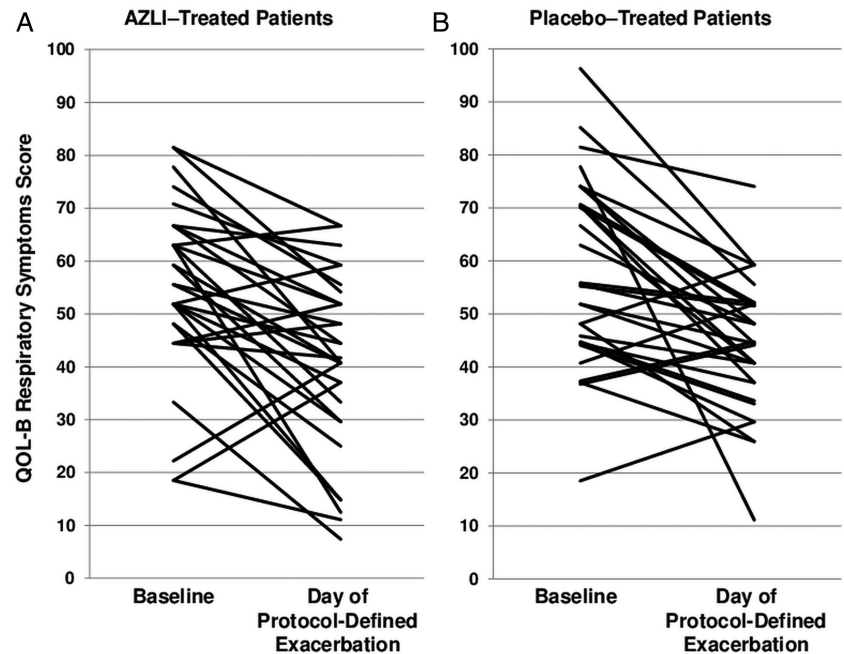
distribution-based estimates. These findings illustrate the complexity of determining MIDs using an anchor-based method and suggest that the final MIDs for scales with large differences (e.g., Role or Social Functioning) should be used with caution.

Each QOL-B item had 4 possible answer categories; e.g., the item 'Have you been coughing during the day' could be answered by selecting 'a lot,' 'a moderate amount,' 'a little' or 'not at all.' A change of one answer category for any of the nine items on the Respiratory Symptoms scale corresponded to 3.7 points; e.g., changing from 'a lot' to a 'moderate amount' of coughing during the day increased the Respiratory Symptoms score by 3.7 points. Thus, meeting the 8.0-point MID required an average overall improvement or worsening of 2.2 answer categories. The MID for the Physical Functioning scale was 10.0 points. Because a change of 1 answer category for any of 5 items on this scale corresponded to 6.7 points, meeting the Physical Functioning scale MID required an average overall improvement or worsening of 1.5 answer categories. For a group of patients to meet the MID for the other 6 scales required an average overall improvement or worsening of from 0.8 to 1.2 answer categories.

Limitations of other PRO or HRQoL measures that have been used in this patient population include minimal coverage of respiratory symptoms (Leicester Cough Questionnaire<sup>28</sup>; Chronic Respiratory Questionnaire<sup>29</sup> (CRQ)), lengthy or variable recall intervals (SGRQ<sup>30</sup>) and substantial response burden (some SGRQ and CRQ forms). The QOL-B is the first PRO for non-CF bronchiectasis developed according to the FDA guidance.<sup>12</sup>

Some minor limitations to the QOL-B emerged from these analyses. In this study population, approximately one quarter of the patients had baseline scores of 100 on the Emotional Functioning scale, indicating that it would not be well suited to monitor improvements from baseline in a comparable study population. The discrepancies in MID values obtained by the different methods for some of the scales also suggest that MIDs should be reassessed in each population of patients in which this measure is used; this conclusion is in line with literature recommendations for using MID values.<sup>31</sup> The lack of improvement on the QOL-B Respiratory Symptoms scale after treatment with AZLI is not considered a limitation of the measure, but more likely reflects the lack of clinical benefit of this treatment in this

**Figure 1** Change from baseline Quality of Life-Bronchiectasis (QOL-B) Respiratory Symptoms scores on the day of a protocol-defined exacerbation. A, AZLI-treated patients (n=30). B, Placebo-treated patients (n=30). Analysis included patients with QOL-B scores at baseline and at a study visit at which treatment was initiated with intravenous, inhaled, intramuscular or oral antibiotics for a protocol-defined exacerbation.



patient population.<sup>13</sup> The analysis showing responsiveness of the measure to protocol-defined exacerbations was exploratory in nature; it included only 60 of the 154 patients who had such exacerbations and did not take into account other changes in health status or QOL-B scores that may have occurred between baseline and the day of the exacerbation.

In conclusion, the QOL-B is a disease-specific questionnaire that measures symptoms, functioning and HRQoL relevant to patients with non-CF bronchiectasis. Content validity, reliability and responsiveness have been established in a series of cognitive testing and interview studies and have been confirmed by the results of this final validation study. The QOL-B measure has been translated into more than 38 languages and is freely available<sup>20</sup> for use in clinical trials and routine clinical practice.

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formerly an employee of Gilead Sciences and remains a stockholder. TGO: is an employee and stockholder of Gilead Sciences. AFB: received research funding from Gilead Sciences.

**Patient consent** Obtained.

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#### REFERENCES

- O'Donnell AE. Bronchiectasis. *Chest* 2008;134:815–23.
- Bilton D. Update on non-cystic fibrosis bronchiectasis. *Curr Opin Pulm Med* 2008;14:595–9.
- Tsang KW, Bilton D. Clinical challenges in managing bronchiectasis. *Respirology* 2009;14:637–50.
- McShane PJ, Naureckas ET, Tino G, *et al.* Non-cystic fibrosis bronchiectasis. *Am J Respir Crit Care Med* 2013;188:647–56.
- Sidhu MK, Mandal P, Hill AT. Bronchiectasis: an update on current pharmacotherapy and future perspectives. *Expert Opin Pharmacother* 2014;15:505–25.
- Barker AF. Bronchiectasis. *N Engl J Med* 2002;346:1383–93.
- Smith MP, Hill AT. Evaluating success of therapy for bronchiectasis: what end points to use? *Clin Chest Med* 2012;33:329–49.
- Barker AF, Couch L, Fiel SB, *et al.* Tobramycin solution for inhalation reduces sputum *Pseudomonas aeruginosa* density in bronchiectasis. *Am J Respir Crit Care Med* 2000;162:481–5.
- Haworth C, Foweraker J, Wilkinson P, *et al.* Inhaled colistin in patients with bronchiectasis and chronic *Pseudomonas aeruginosa* infection. *Am J Respir Crit Care Med* 2014;189:975–82.
- Quittner AL, Marciel KK, Salathe MA, *et al.* A preliminary Quality of Life Questionnaire-Bronchiectasis: A patient-reported outcome measure for bronchiectasis. *Chest* 2014;146:437–48.
- Olveira C, Olveira G, Espildora F, *et al.* Validation of a quality of life questionnaire for bronchiectasis: psychometric analyses of the Spanish QOL-B-V3.0. *Qual Life Res* 2014;23:1279–92.
- US Food and Drug Administration. Guidance for industry. Patient-reported outcome measures: use in medical product development to support labeling claims. 2009. <http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf>
- Barker AF, O'Donnell AE, Flume PA, *et al.* Aztreonam for Inhalation Solution (AZLI) in patients with non-CF bronchiectasis: the results from two randomized double-blind placebo-controlled Phase 3 trials. *Lancet Respir Med* 2014;2:738–49.
- Wild D, Grove A, Martin M, *et al.* Principles of good practice for the translation and cultural adaptation process for Patient-Reported Outcomes (PRO) measures: report of the ISPOR task force for translation and cultural adaptation. *Value Health* 2005;8:94–104.
- Acquadro C, Jambon B, Ellis D, *et al.* Language and translation issues. In: Spilker B, ed. *Quality of life and pharmacoeconomics in clinical trials*. 2nd edn. Philadelphia: Lippincott-Raven Publishers, 1996:575–85.



- 16 American Thoracic Society. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002;166:111–17.
- 17 Euro Quality of Life-5 Dimensions (EQ-5D). <http://www.euroqol.org/about-eq-5d.html>
- 18 Wise RA, Brown CD. Minimal clinically important differences in the six-minute walk test and the incremental shuttle walking test. *COPD* 2005;2:125–9.
- 19 Puhan MA, Mador MJ, Held U, *et al.* Interpretation of treatment changes in 6-minute walk distance in patients with COPD. *Eur Respir J* 2008;32: 637–43.
- 20 Quittner AL, Marciel KK, Barker AF. Quality of Life-Bronchiectasis. The measure is available without charge at: [http://www.psy.miami.edu/qol\\_b/](http://www.psy.miami.edu/qol_b/)
- 21 Ware J, Brook R, Williams K, *et al.* Conceptualization and measurement of health for adults in the health insurance study. Model of Health and Methodology. Rand Corporation. 1980;R-1987/1-HEW. <http://www.rand.org/pubs/reports/2006/R1987.1.pdf>
- 22 Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;33:159–74.
- 23 Guyatt GH, Osoba D, Wu AW, *et al.* Methods to explain the clinical significance of health status measures. *Mayo Clin Proc* 2002;77:371–83.
- 24 Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials* 1989;10:407–15.
- 25 Wyrwich KW, Tierney WM, Wolinsky FD. Further evidence supporting an SEM-based criterion for identifying meaningful intra-individual changes in health-related quality of life. *J Clin Epidemiol* 1999;52:861–73.
- 26 Bilton D, Henig N, Morrissey B, *et al.* Addition of inhaled tobramycin to ciprofloxacin for acute exacerbations of *Pseudomonas aeruginosa* infection in adult bronchiectasis. *Chest* 2006;130:1503–10.
- 27 Lee AL, Button BM, Ellis S, *et al.* Clinical determinants of the 6-Minute Walk Test in bronchiectasis. *Respir Med* 2009;103:780–5.
- 28 Birring SS, Prudon B, Carr AJ, *et al.* Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). *Thorax* 2003;58:339–43.
- 29 Guyatt GH, Berman LB, Townsend M, *et al.* A measure of quality of life for clinical trials in chronic lung disease. *Thorax* 1987;42:773–8.
- 30 Jones PW, Quirk FH, Baveystock CM, *et al.* A self-complete measure of health status for chronic airflow limitation: the Saint George's Respiratory Questionnaire. *Am Rev of Respir Dis* 1992;145:1321–7.
- 31 Revicki D, Hays RD, Cella D, *et al.* Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. *J Clin Epidemiol* 2008;61:102–9.

Online Table 1. Change in QOL-B Respiratory Symptoms Scores from Baseline to Day 14 for Patients in Different GRCQ Absolute Change Categories

Mean (SD) change from baseline QOL-B Respiratory Symptom score at Day 14						
<b>AIR-BX1</b>						
GRCQ Categories*	AZLI (N = 124)		Placebo (N = 125)		All Patients (N = 249)	
	Mean (SD)	n (%)	Mean (SD)	n (%)	Mean (SD)	n (%)
No Change	0.5 (11.6)	53 (42.7)	3.6 (10.3)	78 (62.4)	2.4 (10.9)	131 (52.6)
Minimal Change	5.0 (15.0)	29 (23.4)	8.6 (12.6)	27 (21.6)	6.7 (13.9)	56 (22.5)
Moderate Change	17.0 (22.9)	36 (29.0)	8.7 (15.2)	18 (14.4)	14.1 (20.8)	54 (21.7)
Large Change	32.7 (11.3)	6 (4.8)	17.1 (-)	2 (1.6)	30.5 (11.9)	8 (3.2)
<b>AIR-BX2</b>						
GRCQ Categories*	AZLI (N = 124)		Placebo (N= 127)		All Patients (N = 251)	
	Mean (SD)	n (%)	Mean (SD)	n (%)	Mean (SD)	n (%)
No Change	1.1 (14.3)	47 (37.9)	2.4 (11.4)	74 (58.3)	1.9 (12.6)	121 (48.2)
Minimal Change	14.1 (13.1)	44 (35.5)	7.8 (13.6)	34 (26.8)	11.4 (13.5)	78 (31.1)
Moderate Change	11.1 (13.9)	22 (17.7)	11.0 (16.5)	15 (11.8)	11.1 (14.8)	37 (14.7)
Large Change	16.5 (18.1)	11 (8.9)	27.8 (18.3)	4 (3.1)	19.5 (18.2)	15 (6.0)

\* GRCQ Respiratory Domain categories: no change in symptoms ( $\leq 0.5$ ), minimal change ( $> 0.5$  to  $1.5$ ); moderate change ( $> 1.5$  to  $2.5$ ), and large change ( $> 2.5$  to  $3.0$ ). GRCQ categories were based on the absolute value of GRCQ scores; the categories measured the magnitude of change in respiratory symptoms and included both improving symptoms (positive scores) and worsening symptoms (negative scores). The “N” for each column is the overall number of patients with GRCQ data; note that QOL-B Respiratory Symptoms scores were missing for 3 AZLI-treated patients (no change: 1; moderate change: 2) and 1 placebo-treated patient (large change) in AIR-BX1 and 2 AZLI treated (minimal and moderate change) patients in AIR-BX2. GRCQ = Global Rating of Change Questionnaire; QOL-B = Quality of Life-Bronchiectasis; SD = standard deviation

Online Table 2. Efficacy and Microbiological Measures: Change from Baseline to Day 14 of Treatment with AZLI/Placebo

	AIR-BX1				AIR-BX2				
	AZLI (N=134)		Placebo (N=132)		AZLI (N=136)		Placebo (N=138)		
Mean (SD) change from baseline at Day 14									
QOL-B scales	Points for change of 1 answer category for 1 item*	n	n	n	n	n	n	n	n
Respiratory Symptom	3.7	5.6 (19.1)	129	4.6 (12.2)	129	7.6 (16.3)	131	3.8 (14.3)	134
Physical Functioning	6.7	-1.9 (24.3)	131	0.7 (15.2)	129	-1.4 (21.7)	133	1.2 (17.9)	133
Vitality	11.1	0.5 (21.3)	132	1.6 (16.5)	129	-0.6 (20.6)	133	1.7 (16.7)	132
Role Functioning	6.7	-1.5 (20.1)	131	2.2 (13.4)	129	-2.0 (17.6)	130	-0.7 (15.0)	133
Health Perceptions	8.3	0.5 (18.4)	131	-0.7 (14.3)	129	0.8 (16.0)	132	1.8 (15.7)	134
Emotional Functioning	8.3	0.1 (14.9)	132	0.0 (13.5)	129	1.4 (13.9)	133	3.1 (13.4)	132
Social Functioning	8.3	1.2 (17.4)	131	1.7 (13.8)	129	0.4 (15.2)	130	2.1 (13.9)	134
Treatment Burden	11.1	-2.3 (18.4)	123	-4.6 (20.7)	111	-4.4 (18.1)	114	-7.1 (21.7)	118
FEV <sub>1</sub> % predicted, % change		-1.0 (12.7)	127	-1.1 (8.0)	130	-1.9 (11.9)	131	0.2 (9.9)	134
Log <sub>10</sub> CFU/g of sputum for target gram-negative pathogens <sup>†</sup>		-2.6 (2.8)	97	-0.2 (1.8)	102	-2.7 (2.8)	101	-0.2 (1.9)	104
6MWT, meters		-3 (43.9)	125	6 (40.2)	127	4 (61.5)	128	3 (41.6)	131
EQ-5D visual analog scale, points <sup>‡</sup>		3.1 (18.2)	125	0.1 (14.9)	128	2.0 (14.8)	128	-0.7 (15.0)	126

\* After standardizing scores on a 100-point scale; assuming responses were provided for all items on the scale (ie, no missing responses).

† Target gram-negative organisms included: *Achromobacter*, *Burkholderia*, *Citrobacter*, *Enterobacter*, *Escherichia*, *Klebsiella*, *Moraxella*, *Proteus*, *Pseudomonas*, *Serratia*, and *Stenotrophomonas* species. CFUs were imputed as 0 for patients with no pathogens present.

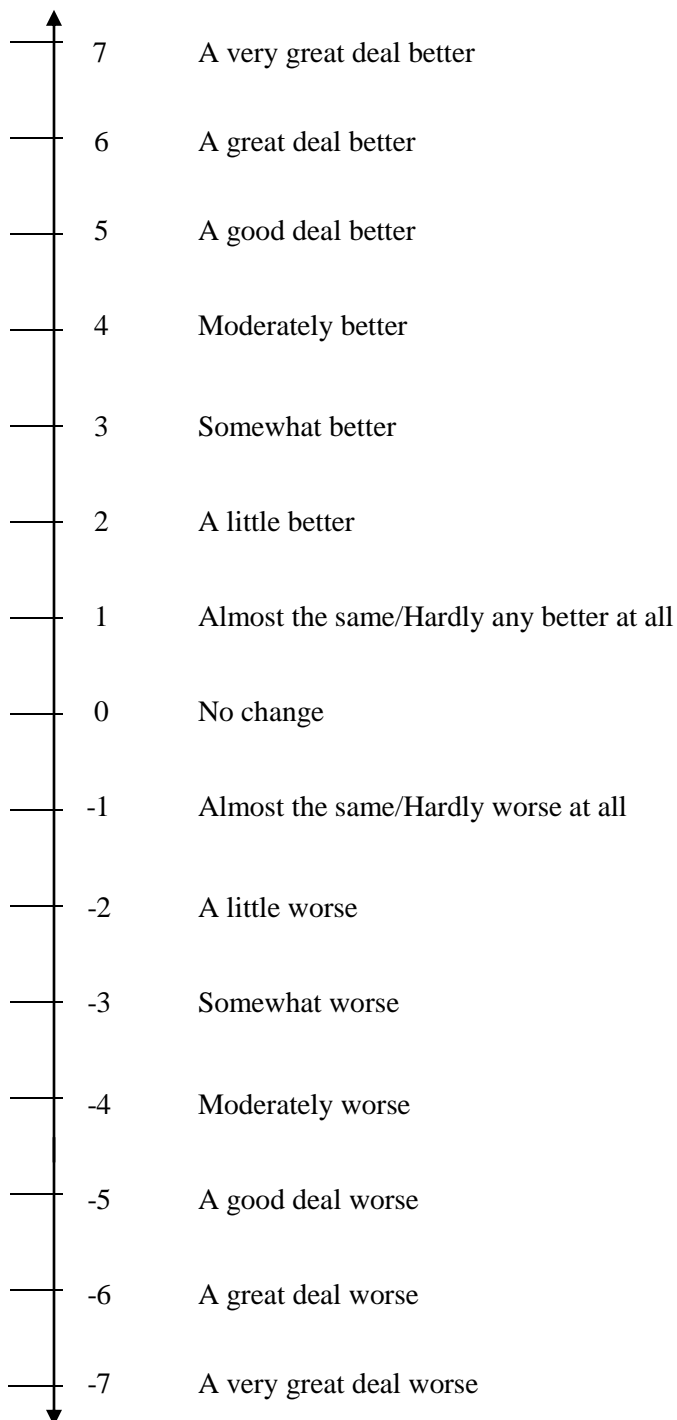
‡ EQ-5D VAS (possible range 0 to 100 points) was not administered at Day 14; these are data from Day 28, at the end of Course 1.

6MWT = 6-minute walk test; CFU = colony forming units; EQ-5D = Euro Quality of Life-5 Dimensions; FEV<sub>1</sub> = forced expiratory volume in 1 second QOL-B = Quality of Life-Bronchiectasis; SD = standard deviation

Online Figure 1. Respiratory Symptoms GRCQ (Global Rating of Change Questionnaire) Version 2.2 (A) and Version 3.0 (B).

A. GRCQ V2.2 for Respiratory Symptoms

In the last 2 weeks, have there been any changes in your RESPIRATORY symptoms (e.g., coughing, mucus production, wheezing) related to your bronchiectasis?



B. GRCQ V3.0 for Respiratory Symptoms

In the last 2 weeks, have there been any changes in your **respiratory symptoms** (e.g., coughing, mucus production, wheezing) related to your bronchiectasis?

My respiratory symptoms are...

