SYMPTOM RESPONSE PROFILES FOR PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE INITIATING NEBULIZED ARFORMOTEROL TARTRATE OR PLACEBO

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INTRODUCTION

- Patient-reported symptoms of chronic obstructive pulmonary disease (COPD) provide important supporting information about how patients feel and function, in addition to objective measures of pulmonary function.
- Heterogeneity in health-related quality of life is a common finding in clinical trials[1-5]; therefore, it was not surprising that while examining the distributional characteristics of the St. George's Respiratory Questionnaire (SGRQ), treatment group mean differences in SGRQ scores were negligible.
- Growth mixture modelling (GMM) explores intra-individual variability to provide a more detailed understanding of change over time in patient-reported symptoms and identify subsets of individuals with differential change.
- The Symptoms domain of the SGRQ was selected for this exploratory analysis because of the importance of symptoms to patients, and because active treatments tend to show the greatest improvement in this domain.[6]

OBJECTIVE

- To characterize the symptom response profiles of patients with moderate to severe COPD who initiated treatment with arformoterol or placebo.

METHODS

Study Design

- Data for this analysis came from a multicenter, randomized, placebo-controlled, double-blind, parallel-group, 52-week safety trial.
- Patients with COPD were randomly assigned to twice-daily nebulized arformoterol 15 µg (n = 420) or matched placebo (n = 421).
- Treatment with other COPD medications was permitted, with the exception of other long-acting beta agonists.
- The primary endpoint of the study was time to COPD-related respiratory death or hospitalization for COPD exacerbation.

Primary Inclusion Criteria

- Previously established diagnosis of nonasthmatic COPD
- Forced expiratory volume (liters) in one second (FEV_1) ≤ 50% predicted volume
- FEV_1 > 0.50 liters
- FEV_1/forced vital capacity (FVC) ratio ≤ 70% at screening or randomization
- Aged ≥ 40 years
- Smoking history ≥ 15 pack-years
- Baseline breathlessness severity grade ≥ 2 based on the Modified Medical Research Council (MMRC) Dyspnea Scale Score.

Outcome Measure

- The SGRQ is a validated 50-item patient-reported outcome measure.
- Assessments with the SGRQ were made at randomization and months 3, 6, and 12.
- The SGRQ yields a total score and subscale scores for Symptoms, Activities, and Impacts; the present analyses examined only the SGRQ Symptoms scores.
- SGRQ scores range from 0 to 100, with higher scores indicating worse health status.
- A minimal clinically important response to treatment has been defined as an improvement of 4 points on the SGRQ total score and SGRQ subscale scores.[7]

Statistical Methods

- To determine whether subgroups of differential SGRQ responders existed within the trial populations, GMM was conducted using Mplus (version 7.11).
- Change in SGRQ scores was examined from baseline to month 12 across four assessment time points: randomization, month 3, month 6, and month 12.
- GMMs examine heterogeneity in intercepts and slopes of change within the population by modeling distinct subpopulations; this is accomplished by incorporating a latent categorical variable.[8,9]
  - The best model fit was determined by testing different models specifying different numbers of latent classes (LCs). Both two-class and three-class models were fitted.
  - Model fit was evaluated using empirical and visual examination: Bayesian Information Criteria (BIC), sample-size adjusted BIC, and entropy (accuracy of LC assignment using posterior probabilities).
  - Covariates included age and smoking at baseline, which capture risk factors for COPD.
- Once the best-fitting LC model was determined, differences between subgroups were explored.
  - Bivariate comparisons of demographic and clinical factors and patient-reported outcomes were conducted using one-way analyses of variance and chi-square tests.

RESULTS

Table 1. Patient Characteristics at Baseline

Characteristic	Placebo (n = 421)	Arformoterol 15 µg (n = 420)
Age (years), mean (SD)	63.3 (9.5)	64.2 (9.3)
Female, n (%)	178 (42.3)	183 (43.6)
Race, n (%)		
Black	43 (10.2)	45 (10.7)
White	374 (88.8)	372 (88.6)
Other	4 (1.0)	3 (0.7)
Hispanic ethnicity, n (%)	15 (3.6)	9 (2.1)
Body mass index, mean (SD)	28.6 (6.9)	29.1 (7.3)
COPD exacerbations in last year, mean (SD)	0.8 (1.1)	1.0 (1.4)
Baseline smoking status, n (%)		
Current	218 (51.8)	214 (51.0)
Former	203 (48.2)	206 (49.0)
Pack-years smoked, n (%)		
15 to < 25	41 (9.7)	40 (9.5)
25 to < 30	36 (8.6)	29 (6.9)
30+	344 (81.7)	351 (83.6)
Inhaled or oral steroid use, n (%)	219 (52.0)	218 (51.9)
Oxygen therapy use, n (%)	91 (21.6)	105 (25.0)
MMRC Dyspnea Scale Score, n (%)		
2	101 (24.0)	95 (22.6)
3	224 (53.2)	220 (52.4)
4	96 (22.8)	105 (25.0)
FEV_1, mean (SD)	1.18 (0.49)	1.18 (0.48)
Predicted percentage FEV_1, mean (SD)	39.4 (13.9)	39.7 (13.2)
FEV_1/FVC ratio, mean (SD)	49.4 (14.9)	49.6 (14.4)
Percentage reversibility, mean (SD)	14.6 (15.0)	15.4 (21.5)
GOLD status, n (%)		
B	351 (83.4)	329 (78.3)
D	70 (16.6)	89 (21.2)

GOLD = Global Initiative for Chronic Obstructive Lung Disease; SD = standard deviation.

- Figure 1 displays the trajectories from baseline to month 12 of the SGRQ Symptoms scores of 200 randomly selected patients receiving arformoterol and placebo.
  - Visual examination suggests considerable variability in the trajectories.
  - Specifically analyzing the variability using GMMs may reveal subsets of individuals (i.e., LCs) with a differential response than that represented by the overall mean.
- GMM successfully identified two LCs of differential responders within each treatment arm (Figure 2).

Figure 1. Variability in Individual Growth Curves (N = 200)

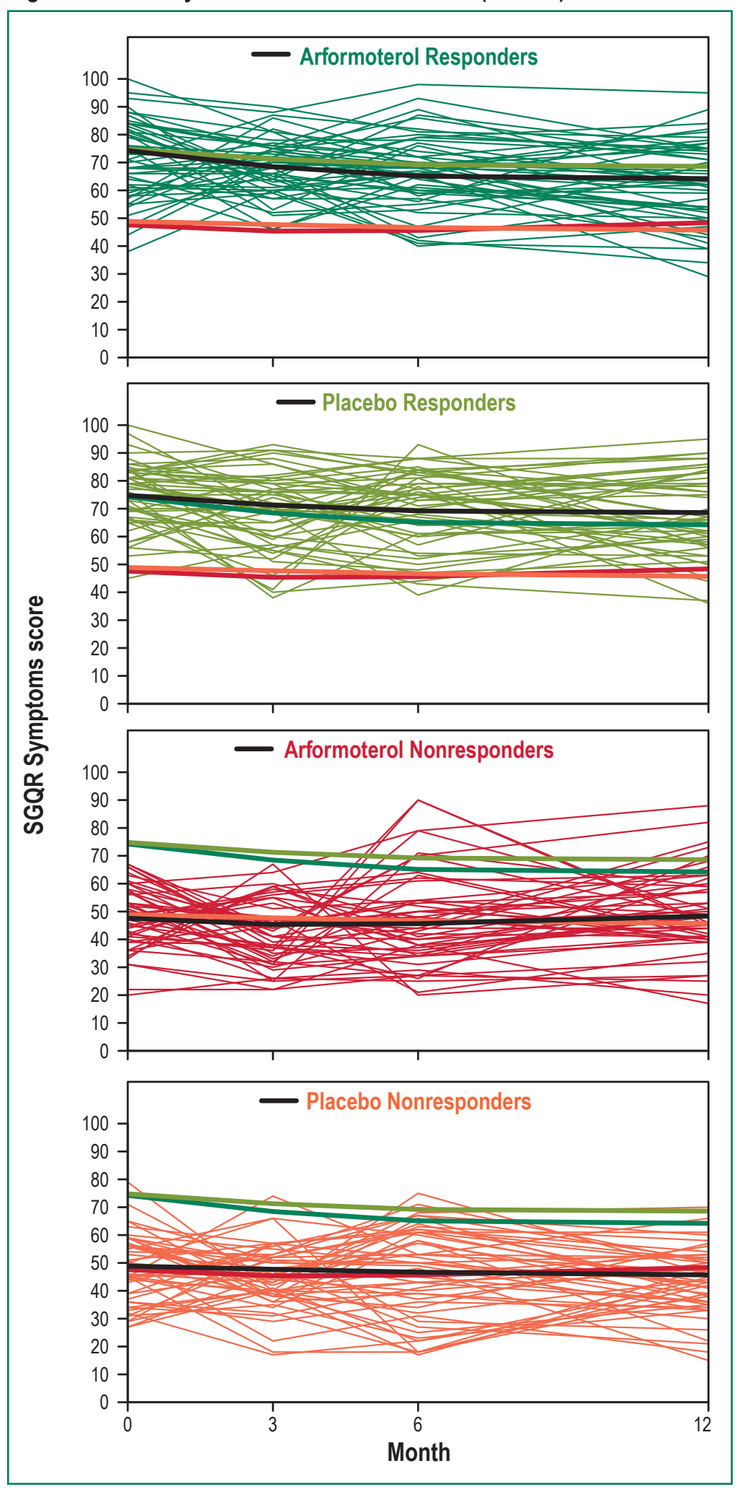
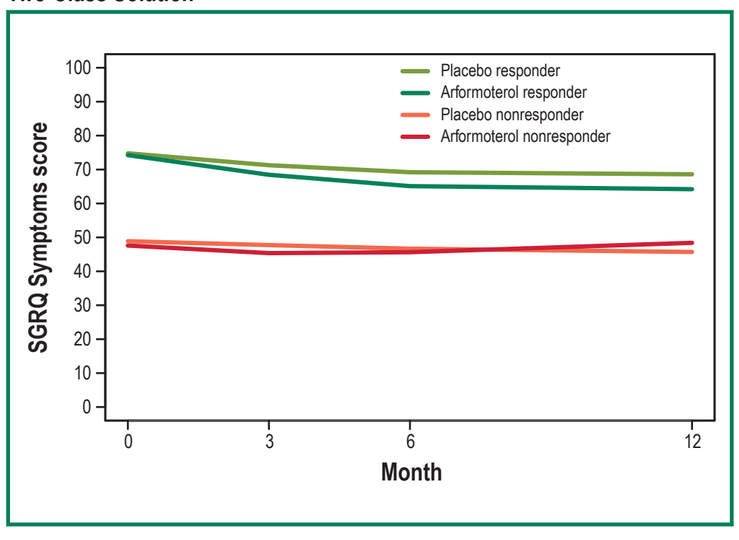


Figure 2. Growth Curves of SGRQ Symptoms Scores for the Two-Class Solution



- According to the BIC, adjusted BIC, and entropy indices, the two-class solution provided a better fit than the three-class solution. BIC and adjusted BIC were lower for the two-class solution than the three-class solution, and entropy was higher (BIC: 20959.8 vs. 20972.8; adjusted BIC: 20880.4 vs. 20871.2; entropy: 0.80 vs. 0.76).
- The two LCs are referred to as responders and nonresponders.
- There were a number of differences between LC responders and nonresponders at baseline. Table 2 shows that LC responders were significantly worse on many of the COPD outcomes at baseline.

Table 2. Descriptive Statistics for Baseline Characteristics by SGRQ Symptoms LC Responder Status

Characteristic	Responder LC n[a] = 563-571	Nonresponder LC n[a] = 247-259	*P* Value
FEV_1, mean (SD)	115.7 (48.90)	123.1 (47.37)	0.0419
Exacerbations, mean (SD)	0.96 (1.29)	0.69 (1.09)	0.0018
SGRQ,[b] mean (SD)			
Total	59.81 (14.30)	40.57 (12.99)	< 0.0001
Symptoms	75.43 (11.86)	45.97 (11.19)	< 0.0001
Impacts	46.13 (18.35)	27.43 (15.21)	< 0.0001
Activities	74.54 (16.23)	59.56 (18.60)	< 0.0001
Clinical COPD Questionnaire,[c] mean (SD)	3.29 (1.09)	2.05 (0.93)	< 0.0001
MMRC Dyspnea Scale Score,[d] mean (SD)	3.13 (0.68)	2.75 (0.63)	< 0.0001
Age, mean (SD)	63.02 (9.4)	63.09 (9.4)	0.0033
Current smoker, n (%)	317 (55.52)	114 (44.02)	0.0021
GOLD status, n (%)			
B	450 (79.0)	223 (86.4)	0.0106
D	120 (21.0)	35 (13.6)	

[a] Sample sizes vary across characteristics due to missing data.
[b] SGRQ: 0 = best, 100 = worst.
[c] Clinical COPD Questionnaire: 0 = best, 6 = worst.
[d] MMRC Dyspnea Scale Score: 0 = best (breathless with strenuous exercise), 4 = worst (too breathless to leave the house)

Note: Patients had to have an MMRC Dyspnea Scale Score ≥ 2 to participate in the study. LCs are based on GMM analysis of the SGRQ Symptoms scores.

- The responder LC (67.7% of the sample) showed numerical improvements in the average SGRQ Symptoms scores from baseline to month 12.
  - High baseline SGRQ Symptoms scores indicated that responders were more severe at baseline.
  - The average change from baseline to month 12 was –8.8 points.
- The nonresponder LC (32.3% of the sample) showed little change in the average SGRQ Symptoms scores from baseline to month 12.
  - Lower baseline SGRQ Symptoms scores indicated that nonresponders were less severe at baseline.
  - The average change from baseline to month 12 was –1.6 points.
- Table 3 shows the post hoc comparisons between the responder LC and nonresponder LC subgroups.

Table 3. Change in COPD Outcomes From Baseline to Month 12 by SGRQ Symptoms LC Responder Status

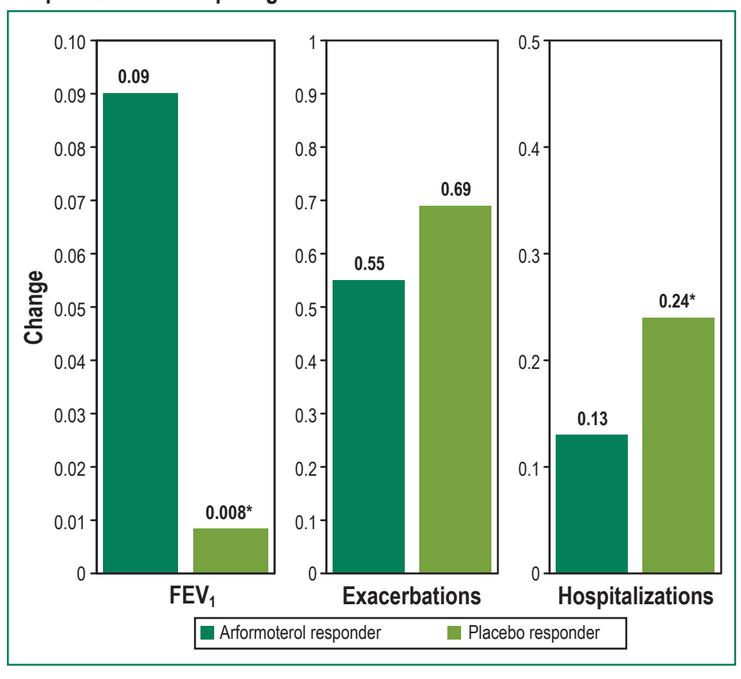
Characteristic	Responder LC n[a] = 306-571	Nonresponder LC n[a] = 129-259	*P* Value
FEV_1, mean (SD)	5.05 (32.79)	2.67 (33.14)	0.4766
Exacerbations, mean (SD)	0.62 (1.10)	0.45 (0.98)	0.0262
Hospitalizations, mean (SD)	0.19 (0.56)	0.10 (0.38)	0.0152
SGRQ,[b] mean (SD)			
Total	–4.81 (12.10)	–1.37 (11.88)	0.0067
Symptoms	–8.82 (15.89)	–1.55 (14.45)	< 0.0001
Impacts	–3.98 (14.63)	–0.87 (13.35)	0.0306
Activities	–4.02 (14.36)	–1.50 (16.99)	0.1240
Clinical COPD Questionnaire,[c] mean (SD)	–0.19 (1.03)	–0.05 (0.94)	0.1748
MMRC Dyspnea Scale Score,[d] mean (SD)	–0.23 (0.93)	–0.41 (1.03)	0.0672

[a] Sample sizes vary across outcomes due to missing data.
[b] SGRQ: 0 = best, 100 = worst; negative change indicates improvement.
[c] Clinical COPD Questionnaire: 0 = best, 6 = worst ; negative change indicates improvement.
[d] MMRC Dyspnea Scale Score: 0 = best (breathless with strenuous exercise), 4 = worst (too breathless to leave the house); negative change indicates improvement.

Note: Patients had to have an MMRC Dyspnea Scale Score ≥ 2 to participate in the study. LCs are based on GMM analysis of the SGRQ Symptoms scores.

- Among the responder LC, those treated with arformoterol versus placebo had the following outcomes (Figure 3):
  - Comparable improvements in symptoms (–10.3 vs. –7.2, $P > 0.05$)
  - Similar number of exacerbations (0.55 vs. 0.69, $P > 0.05$),
  - Significantly greater improvements in FEV_1 (0.09 vs. 0.008, $P = 0.03$)
  - Significantly fewer hospitalizations (0.13 vs. 0.24, $P = 0.02$).

Figure 3. Bar Plot of Responder LC Means for FEV_1, Exacerbations, and Hospitalizations Comparing Arformoterol With Placebo



CONCLUSIONS

- In this analysis, symptom response profiles were best explained by two LCs.
- Among the responder LC, arformoterol appeared to improve lung function and reduce hospitalizations.
- Arformoterol may be particularly effective among patients who are unable to quit smoking and have more severe symptoms.

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