**SUPPLEMENTAL MATERIAL**

# Early Response to Inhaled Bronchodilators and Corticosteroids as a Predictor of 12-Month Response and COPD Exacerbations

*Peter M. Calverley, MD, PhD;[1] Dirkje S. Postma, MD, PhD;[2] Antonio R. Anzueto, MD;[3] Barry J. Make, MD;[4] Göran Eriksson, PhD;[5] Stefan Peterson, PhD;[6] and Christine R. Jenkins, MD, PhD[7]*

## SUPPLEMENTARY RESULTS

### Missing Data

In the 0–2-month analysis, 13.1% and 15.6% of patients had missing data for forced expiratory volume in 1 second ($FEV_1$) and St George's Respiratory Questionnaire (SGRQ) total score, respectively, which were split similarly between drop-out and missing measurements. For both $FEV_1$ and SGRQ total score, the placebo group had the greatest frequency of missing data and the budesonide/formoterol combination therapy group had the lowest frequency of missing data. At 12 months, 17.1% and 20.1% of patients had missing data for $FEV_1$ and SGRQ total score, respectively. Drop-out was the most common reason for missing data.

**SUPPLEMENTARY TABLES**

**Table S1.** Baseline and clinical demographics according to 2-month $FEV_1$ responder status[a] among all patients who received budesonide/formoterol, formoterol, or placebo, and by treatment type, in the two placebo-controlled trials included in the 0–2-month analysis[1,2]

| Characteristics | Budesonide/Formoterol (n = 743) | | | Formoterol (n = 743) | | | Placebo (n = 751) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Responder (n = 300) | Non-responder (n = 376) | Missing (n = 67) | Responder (n = 219) | Non-responder (n = 427) | Missing (n = 97) | Responder (n = 164) | Non-responder (n = 455) | Missing (n = 132) |
| Age, years | 62.0 (9.3) | 63.6 (8.6) | 65.0 (8.4) | 61.0 (9.1) | 63.6 (9.2) | 65.3 (8.9) | 60.7 (9.9) | 63.2 (9.0) | 65.0 (9.2) |
| Male, n (%) | 187 (62.3) | 256 (68.1) | 38 (56.7) | 160 (73.1) | 271 (63.5) | 57 (58.8) | 116 (70.7) | 295 (64.8) | 92 (67.7) |
| BMI, $kg/m^2$ | 26.7 (5.6) | 26.5 (5.6) | 27.6 (6.6) | 27.5 (5.7) | 26.5 (5.5) | 27.3 (6.3) | 27.5 (6.2) | 26.6 (5.8) | 27.8 (6.0) |
| Time since first symptoms, months | 125.9 (85.5) | 126.8 (85.2) | 126.1 (78.2) | 127.7 (92.1) | 128.9 (79.6) | 127.6 (94.3) | 126.7 (84.7) | 127.8 (85.8) | 127.7 (87.6) |
| $FEV_1$ | | | | | | | | | |
| Pre-bronchodilator, % predicted | 35.2 (9.1) | 32.2 (9.7) | 31.1 (10.7) | 35.3 (9.0) | 33.3 (9.8) | 33.6 (11.6) | 35.5 (8.7) | 35.2 (9.3) | 33.8 (10.4) |
| Pre-bronchodilator,[b] L | 1.0 (0.4) | 1.0 (0.4) | 1.0 (0.5) | 1.1 (0.4) | 1.0 (0.4) | 1.0 (0.4) | 1.1 (0.4) | 1.1 (0.4) | 1.0 (0.4) |
| Reversibility, % predicted | 6.7 (5.8) | 4.5 (4.7) | 5.8 (5.1) | 5.7 (5.4) | 5.2 (6.0) | 4.9 (5.7) | 6.6 (8.3) | 5.6 (5.9) | 5.9 (5.9) |
| Post-bronchodilator, % predicted | 41.8 (11.3) | 36.8 (11.2) | 36.9 (12.3) | 41.0 (11.3) | 38.5 (12.2) | 38.3 (14.1) | 42.2 (12.5) | 40.9 (11.4) | 39.5 (12.0) |
| Pre-bronchodilator $FEV_1$/FVC, % | 48.6 (10.4) | 46.0 (10.0) | 47.1 (12.7) | 48.8 (10.2) | 47.0 (10.5) | 46.4 (11.3) | 50.2 (9.1) | 48.0 (10.5) | 46.1 (10.8) |
| Smoking history | | | | | | | | | |
| Median, pack-years | 40.0 | 40.0 | 45.0 | 40.0 | 40.0 | 45.0 | 38.0 | 40.0 | 43.5 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Former smokers, n (%) | 171 (57.0) | 227 (60.4) | 42 (62.7) | 112 (51.1) | 233 (54.6) | 67 (69.1) | 80 (48.8) | 257 (56.5) | 94 (71.2) |
| Current smokers, n (%) | 129 (43.0) | 149 (39.6) | 25 (37.3) | 107 (48.9) | 194 (45.4) | 30 (30.9) | 84 (51.2) | 198 (43.5) | 38 (28.8) |
| SGRQ total score,[b] points (range) | 53.6 (6.7–93.6) | 56.8 (14.0–100.0) | 53.3 (11.9–86.1) | 54.1 (16.4–93.3) | 54.5 (19.8–97.4) | 56.9 (20.6–96.5) | 56.1 (11.7–93.3) | 54.9 (8.8–96.9) | 52.4 (13.6–88.8) |
| Reliever use, No. of inhalations (range) | 3.5 (0.0–21.6) | 3.7 (0.0–21.5) | 3.8 (0.0–19.7) | 3.9 (0.0–27.2) | 3.7 (0.0–18.9) | 4.9 (0.0–32.5) | 3.7 (0.0–12.8) | 3.3 (0.0–28.0) | 3.9 (0.0–22.4) |
| No. of COPD maintenance medications[c], n (%) | | | | | | | | | |
| 0 | 86 (28.7) | 81 (21.5) | 12 (17.9) | 61 (27.9) | 106 (24.8) | 23 (23.7) | 52 (31.7) | 123 (27.0) | 24 (18.2) |
| 1 | 73 (24.3) | 79 (21.0) | 17 (25.4) | 58 (26.5) | 103 (24.1) | 17 (17.5) | 38 (23.2) | 107 (23.5) | 19 (14.4) |
| 2 | 85 (28.3) | 123 (32.7) | 28 (41.8) | 60 (27.4) | 116 (27.2) | 35 (36.1) | 43 (26.2) | 122 (26.8) | 51 (38.6) |
| 3 | 56 (18.7) | 93 (24.7) | 10 (14.9) | 40 (18.3) | 102 (23.9) | 22 (22.7) | 31 (18.9) | 103 (22.6) | 38 (28.8) |

Data are given as mean (SD), unless otherwise stated. BMI = body mass index; COPD = chronic obstructive pulmonary disease; $FEV_1$ = forced expiratory volume in 1 second; FVC = forced vital capacity; ICS = inhaled corticosteroid; LA = long-acting bronchodilator; SD = standard deviation; SGRQ = St George's Respiratory Questionnaire.

[a] $FEV_1$ response was defined as an improvement in $FEV_1$ of ≥100 mL.

[b] Measured at randomization.

[c] The number of COPD maintenance medications is defined as follows: 0 = no maintenance treatment with LA or ICS (short-acting bronchodilators only); 1 = one LA or ICS; 2 = two LA or ICS; 3 = three LA or ICS.

**Table S2.** Baseline and clinical demographics according to 2-month SGRQ responder status[a] among all patients who received budesonide/formoterol, formoterol, or placebo, and by treatment type, in the two placebo-controlled trials included in the 0–2-month analysis[1,2]

| Characteristics | Budesonide/Formoterol (n = 743) | | | Formoterol (n = 743) | | | Placebo (n = 751) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Responder (n = 324) | Non-responder (n = 331) | Missing (n = 88) | Responder (n = 263) | Non-responder (n = 366) | Missing (n = 114) | Responder (n = 243) | Non-responder (n = 352) | Missing (n = 156) |
| Age, years | 62.7 (9.2) | 63.0 (8.7) | 65.1 (8.7) | 61.7 (9.1) | 63.5 (9.2) | 64.8 (9.2) | 62.0 (9.7) | 62.7 (9.0) | 64.8 (9.2) |
| Male, n (%) | 208 (64.2) | 221 (66.8) | 52 (59.1) | 172 (65.4) | 248 (67.8) | 68 (59.6) | 159 (65.4) | 236 (67.1) | 108 (69.2) |
| BMI, kg/m$^2$ | 26.4 (5.4) | 26.7 (5.8) | 27.1 (6.2) | 26.4 (5.2) | 27.0 (5.9) | 27.3 (6.2) | 26.9 (5.6) | 26.8 (6.1) | 27.7 (6.1) |
| Time since first symptoms, months | 124.3 (84.6) | 128.4 (86.6) | 126.1 (77.6) | 130.9 (87.6) | 127.6 (81.9) | 125.0 (91.2) | 132.8 (94.9) | 125.0 (79.1) | 125.2 (85.5) |
| $FEV_1$ | | | | | | | | | |
| Pre-bronchodilator, % predicted | 33.7 (9.9) | 33.4 (9.2) | 31.7 (10.4) | 35.3 (9.4) | 33.1 (9.6) | 33.8 (11.4) | 35.8 (9.4) | 35.0 (9.1) | 33.8 (10.0) |
| Pre-bronchodilator,[b] L | 1.0 (0.4) | 1.0 (0.4) | 1.0 (0.5) | 1.1 (0.4) | 1.0 (0.4) | 1.0 (0.4) | 1.1 (0.4) | 1.1 (0.4) | 1.0 (0.4) |
| Reversibility, % predicted | 6.0 (5.7) | 5.1 (5.0) | 5.3 (4.9) | 5.4 (5.9) | 5.4 (5.7) | 5.0 (5.6) | 6.0 (6.9) | 5.9 (6.5) | 5.9 (5.8) |
| Post-bronchodilator, % predicted | 39.6 (11.9) | 38.5 (11.2) | 37.0 (11.713) | 40.6 (11.9) | 38.5 (12.0) | 38.6 (13.7) | 41.8 (12.1) | 40.9 (11.6) | 39.6 (11.6) |
| Pre-bronchodilator $FEV_1$/FVC, % | 47.5 (10.8) | 46.7 (9.5) | 47.3 (12.3) | 48.4 (10.6) | 47.1 (10.2) | 46.4 (11.5) | 49.3 (10.0) | 48.1 (10.3) | 46.4 (10.6) |
| Smoking history | | | | | | | | | |
| Median, pack-years | 40.0 | 40.0 | 45.0 | 40.0 | 40.0 | 45.0 | 40.0 | 40.0 | 40.0 |
| Former smokers, n (%) | 195 (60.2) | 191 (57.7) | 54 (61.4) | 133 (50.6) | 202 (55.2) | 77 (67.5) | 128 (52.7) | 196 (55.7) | 107 (68.6) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Current smokers, n (%) | 129 (39.8) | 140 (42.3) | 34 (38.6) | 130 (49.4) | 164 (44.8) | 37 (32.5) | 115 (47.3) | 156 (44.3) | 49 (31.4) |
| SGRQ total score,[b] points (range) | 58.3 (19.5–100.0) | 52.5 (6.7–93.9) | 53.7 (11.9–92.7) | 56.2 (16.4–97.4) | 52.7 (17.2–93.3) | 57.4 (20.6–96.5) | 59.3 (16.9–96.9) | 52.2 (8.8–93.3) | 53.4 (13.6–88.8) |
| Reliever use, No. of inhalations (range) | 3.8 (0.0–21.6) | 3.6 (0.0–21.5) | 3.4 (0.0–19.7) | 3.8 (0.0–27.2) | 3.7 (0.0–20.0) | 4.6 (0.0–32.5) | 3.6 (0.0–16.2) | 3.3 (0.0–28.0) | 3.9 (0.0–22.4) |
| No. of COPD maintenance medications[c], n (%) | | | | | | | | | |
| 0 | 86 (26.5) | 74 (22.4) | 19 (21.6) | 78 (29.7) | 85 (23.2) | 27 (23.7) | 78 (32.1) | 90 (25.6) | 20 (12.8) |
| 1 | 82 (25.3) | 66 (19.9) | 21 (23.9) | 73 (27.8) | 86 (23.5) | 19 (16.7) | 65 (26.8) | 75 (21.3) | 15 (9.6) |
| 2 | 94 (29.0) | 108 (32.6) | 34 (38.6) | 67 (25.5) | 104 (28.4) | 40 (35.1) | 63 (25.9) | 94 (26.7) | 38 (24.4) |
| 3 | 62 (19.1) | 83 (25.1) | 14 (15.9) | 45 (17.1) | 91 (24.9) | 28 (24.6) | 37 (15.2) | 93 (26.4) | 27 (17.3) |

Data are given as mean (SD), unless otherwise stated. BMI = body mass index; COPD = chronic obstructive pulmonary disease; $FEV_1$ = forced expiratory volume in 1 second; FVC = forced vital capacity; ICS, inhaled corticosteroid; LA = long-acting bronchodilator; SD = standard deviation; SGRQ = St George's Respiratory Questionnaire.

[a] SGRQ response was defined as a reduction (ie, an improvement) in the SGRQ total score of ≥4 points.

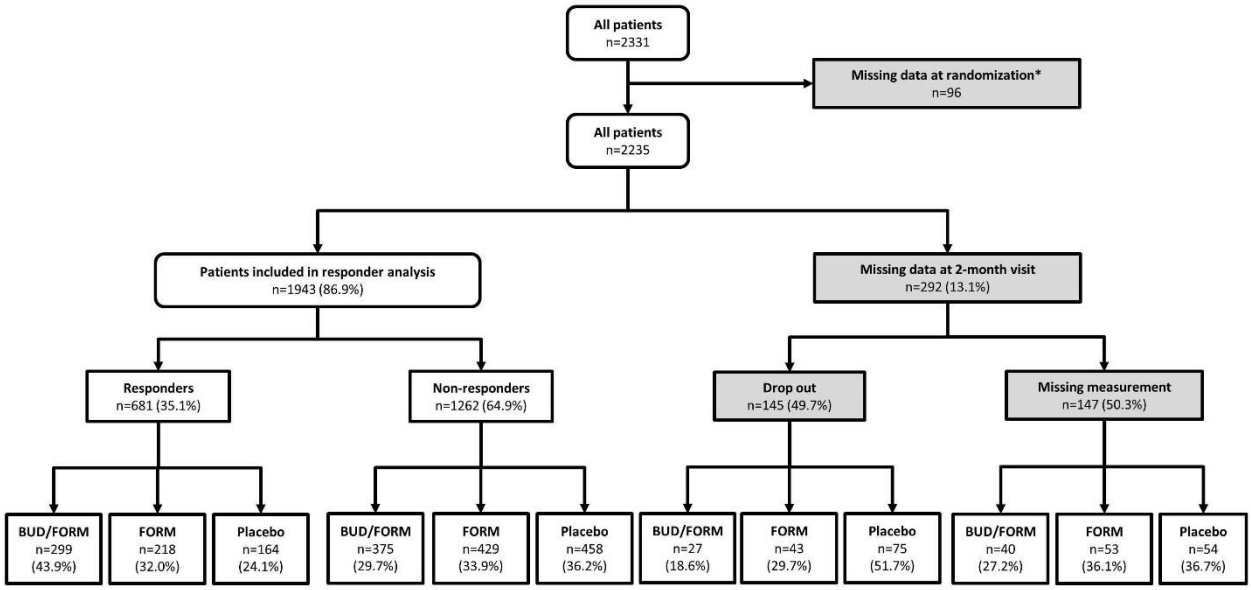
[b] Measured at randomization.

[c] The number of COPD maintenance medications is defined as follows: 0 = no maintenance treatment with LA or ICS (short-acting bronchodilators only); 1 = one LA or ICS; 2 = two LA or ICS; 3 = three LA or ICS.

**SUPPLEMENTARY FIGURE LEGENDS**

**Figure S1.** Proportion of patients who received treatment with budesonide/formoterol or formoterol who were classified as responders or non-responders, or who had missing data for $FEV_1$, at **(A)** 2 months[1,2] and **(B)** 12 months.[2,3] Responders are defined as patients with an improvement in $FEV_1$ of ≥100 mL from baseline. *Missing $FEV_1$. BUD = budesonide; $FEV_1$ = forced expiratory volume in 1 second; FORM = formoterol.

(A)


All patients
n=2331
Missing data at randomization*
n=96
All patients
n=2235
Patients included in responder analysis
n=1943 (86.9%)
Missing data at 2-month visit
n=292 (13.1%)
Responders
n=681 (35.1%)
Non-responders
n=1262 (64.9%)
Drop out
n=145 (49.7%)
Missing measurement
n=147 (50.3%)
BUD/FORM
n=299
(43.9%)
FORM
n=218
(32.0%)
Placebo
n=164
(24.1%)
BUD/FORM
n=375
(29.7%)
FORM
n=429
(33.9%)
Placebo
n=458
(36.2%)
BUD/FORM
n=27
(18.6%)
FORM
n=43
(29.7%)
Placebo
n=75
(51.7%)
BUD/FORM
n=40
(27.2%)
FORM
n=53
(36.1%)
Placebo
n=54
(36.7%)

(B)

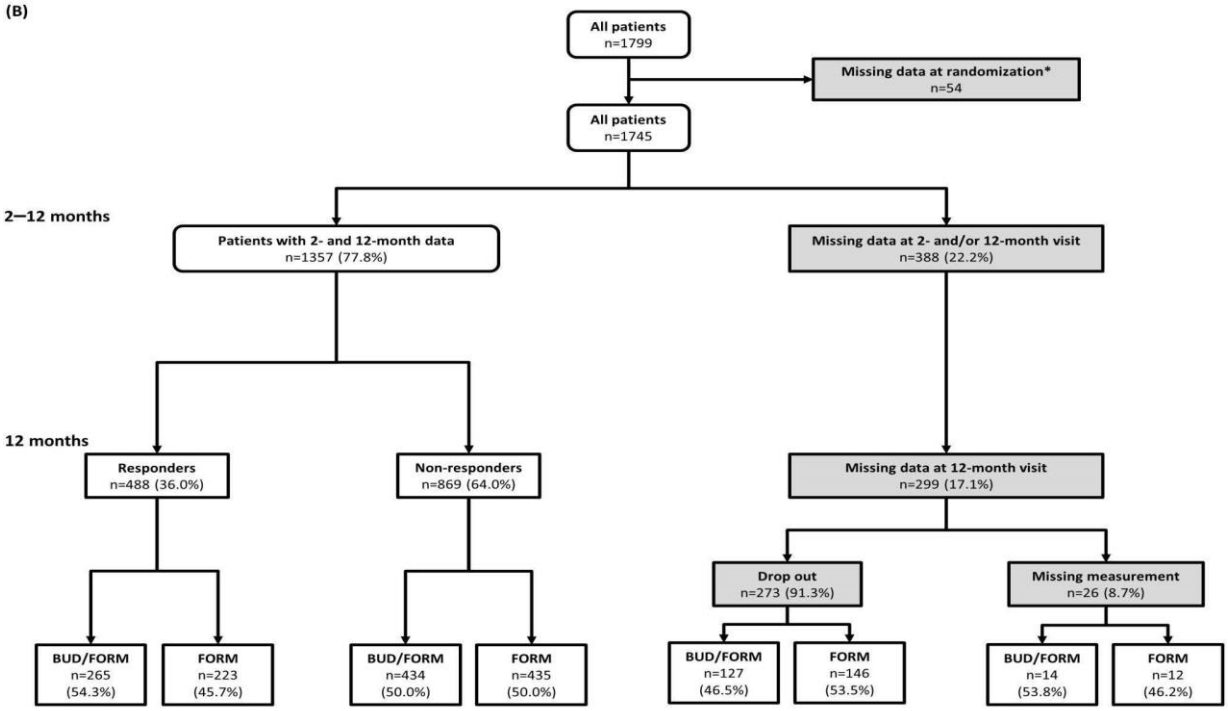
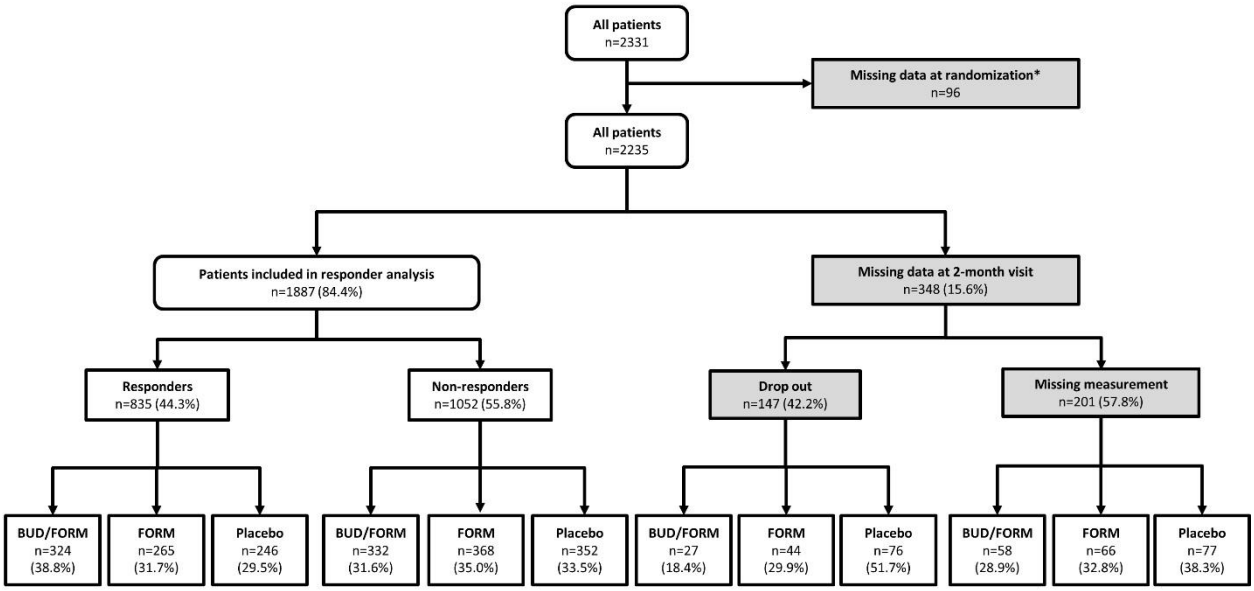
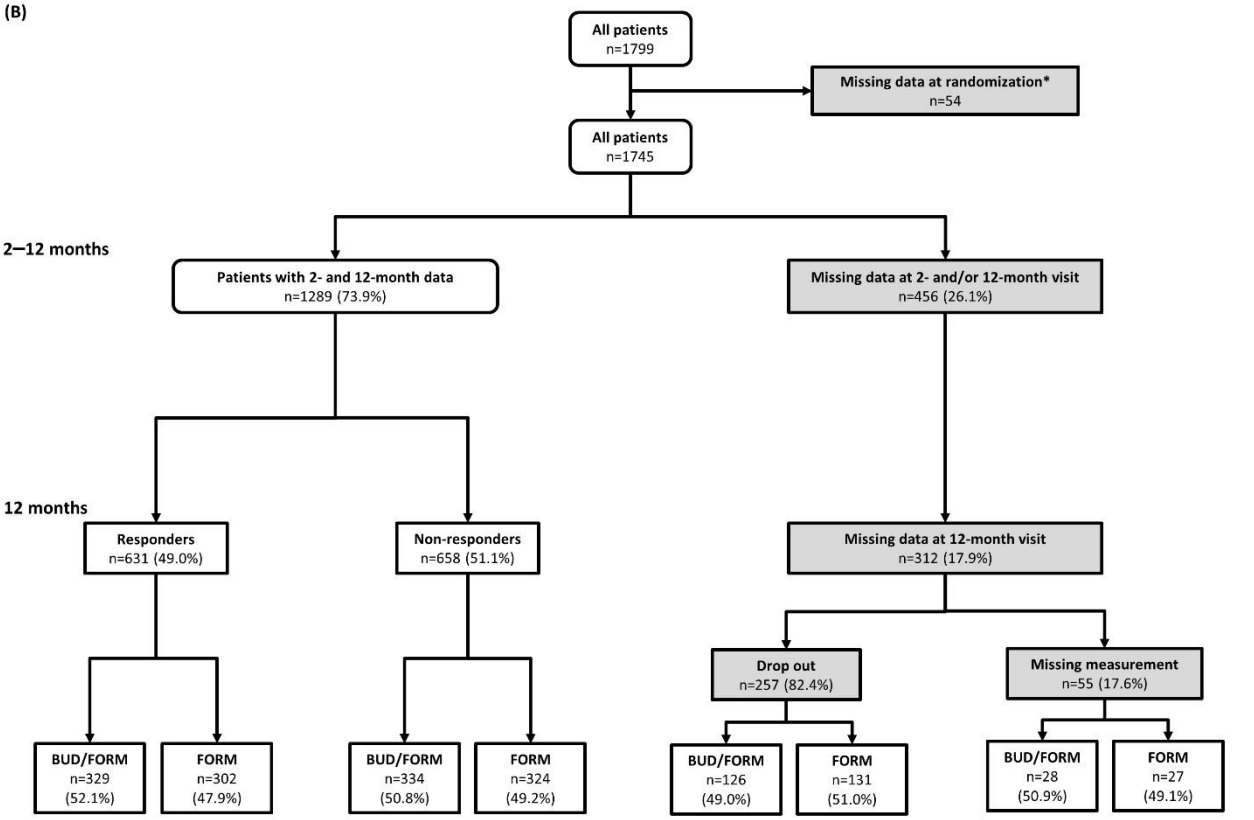

All patients
n=1799
Missing data at randomization*
n=54
All patients
n=1745
2—12 months
Patients with 2- and 12-month data
n=1357 (77.8%)
Missing data at 2- and/or 12-month visit
n=388 (22.2%)
12 months
Responders
n=488 (36.0%)
Non-responders
n=869 (64.0%)
Missing data at 12-month visit
n=299 (17.1%)
Drop out
n=273 (91.3%)
Missing measurement
n=26 (8.7%)
BUD/FORM
n=265
(54.3%)
FORM
n=223
(45.7%)
BUD/FORM
n=434
(50.0%)
FORM
n=435
(50.0%)
BUD/FORM
n=127
(46.5%)
FORM
n=146
(53.5%)
BUD/FORM
n=14
(53.8%)
FORM
n=12
(46.2%)

**Figure S2.** Proportion of patients who received treatment with budesonide/formoterol or formoterol who were classified as responders or non-responders, or who had missing data for SGRQ total score, at **(A)** 2 months[1,2] and **(B)** 12 months.[2,3] Responders are defined as patients with an improvement in the SGRQ total score of ≥4 points from baseline. *Missing SGRQ total score. BUD = budesonide; FORM = formoterol; SGRQ = St George's Respiratory Questionnaire.

(A)


All patients
n=2331
Missing data at randomization*
n=96
All patients
n=2235
Patients included in responder analysis
n=1887 (84.4%)
Missing data at 2-month visit
n=348 (15.6%)
Responders
n=835 (44.3%)
Non-responders
n=1052 (55.8%)
Drop out
n=147 (42.2%)
Missing measurement
n=201 (57.8%)
BUD/FORM
n=324
(38.8%)
FORM
n=265
(31.7%)
Placebo
n=246
(29.5%)
BUD/FORM
n=332
(31.6%)
FORM
n=368
(35.0%)
Placebo
n=352
(33.5%)
BUD/FORM
n=27
(18.4%)
FORM
n=44
(29.9%)
Placebo
n=76
(51.7%)
BUD/FORM
n=58
(28.9%)
FORM
n=66
(32.8%)
Placebo
n=77
(38.3%)

(B)


All patients
n=1799
Missing data at randomization*
n=54
All patients
n=1745
2–12 months
Patients with 2- and 12-month data
n=1289 (73.9%)
Missing data at 2- and/or 12-month visit
n=456 (26.1%)
12 months
Responders
n=631 (49.0%)
Non-responders
n=658 (51.1%)
Missing data at 12-month visit
n=312 (17.9%)
Drop out
n=257 (82.4%)
Missing measurement
n=55 (17.6%)
BUD/FORM
n=329
(52.1%)
FORM
n=302
(47.9%)
BUD/FORM
n=334
(50.8%)
FORM
n=324
(49.2%)
BUD/FORM
n=126
(49.0%)
FORM
n=131
(51.0%)
BUD/FORM
n=28
(50.9%)
FORM
n=27
(49.1%)

SUPPLEMENTARY REFERENCES


**1.** Tashkin DP, Rennard SI, Martin P, et al. Efficacy and safety of budesonide and formoterol in one pressurized metered-dose inhaler in patients with moderate to very severe chronic obstructive pulmonary disease: results of a 6-month randomized clinical trial. *Drugs.* 2008;68(14):1975–2000.

**2.** Rennard SI, Tashkin DP, McElhattan J, et al. Efficacy and tolerability of budesonide/formoterol in one hydrofluoroalkane pressurized metered-dose inhaler in patients with chronic obstructive pulmonary disease: results from a 1-year randomized controlled clinical trial. *Drugs.* 2009;69(5):549–565.

**3.** Sharafkhaneh A, Southard JG, Goldman M, Uryniak T, Martin UJ. Effect of budesonide/formoterol pMDI on COPD exacerbations: a double-blind, randomized study. *Respir Med.* 2012;106(2):257–268.