ORIGINAL RESEARCH ARTICLE

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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

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Supplementary Material

This supplementary material contains the tables and figures referred to in the full version of this article, which can be found at http://drugs.adisonline.com.

ONLINE SUPPLEMENT TABLES

Table SI. AEs Considered by the investigator to be related to study medication reported by ≥3 patients

Variable	BUD/FM pMDI 320/9 μg bid (n = 494)	BUD/FM pMDI 160/9 μg bid (n = 494)	FM DPI 9 μg bid (n = 495)	Placebo (n = 481)
Mean exposure (days), SD	305 (115)	299 (118)	289 (127)	270 (139)
AE, n (%)				
≥1 AE	63 (12.8)	51 (10.3)	42 (8.5)	30 (6.2)
Oral candidiasis	22 (4.5)	13 (2.6)	0	6 (1.2)
COPD	5 (1.0)	12 (2.4)	12 (2.4)	10 (2.1)
Dysphonia	13 (2.6)	5 (1.0)	1 (0.2)	0
Muscle spasms	5 (1.0)	4 (0.8)	1 (0.2)	2 (0.4)
Dyspnoea	1 (0.2)	3 (0.6)	3 (0.6)	3 (0.6)
Ventricular extrasystoles	3 (0.6)	3 (0.6)	1 (0.2)	0
Bronchitis	3 (0.6)	1 (0.2)	2 (0.4)	0
Cough	2 (0.4)	1 (0.2)	2 (0.4)	0
Insomnia	0	2 (0.4)	0	3 (0.6)
Pharyngolaryngeal pain	1 (0.2)	1 (0.2)	2 (0.4)	1 (0.2)
Atrial fibrillation	1 (0.2)	1 (0.2)	2 (0.4)	0
Cataract	0	2 (0.4)	0	1 (0.2)
Dizziness	0	2 (0.4)	1 (0.2)	0
Headache	1 (0.2)	1 (0.2)	0	1 (0.2)
Laryngitis	2 (0.4)	1 (0.2)	0	0
Lower respiratory tract infection	0	0	2 (0.4)	1 (0.2)
Tremor	3 (0.6)	0	0	0
Ventricular tachycardia	2 (0.4)	1 (0.2)	0	0

AE = adverse event; **bid** = twice daily; **BUD** = budesonide; **COPD** = chronic obstructive pulmonary disease; **DPI** = dry powder inhaler; **FM** = formoterol; **pMDI** = pressurized metered-dose inhaler.

Table SII. Pneumonia-related AEs and AEs potentially related to lung infections

Variable	BUD/FM pMDI 320/9 μg bid (n = 494)	BUD/FM pMDI 160/9 μg bid (n = 494)	FM DPI 9 μg bid (n = 495)	Placebo (n = 481)
Mean exposure (days), SD	305 (115)	299 (118)	289 (127)	270 (139)
Pneumonia-related (total), n (%)	20 (4.0)	17 (3.4)	17 (3.4)	24 (5.0)
Pneumonia	15 (3.0)	15 (3.0)	17 (3.4)	23 (4.8)
Bronchopneumonia	2 (0.4)	1 (0.2)	0	1 (0.2)
Lobar pneumonia	2 (0.4)	0	0	0
Pneumonia staphylococcal	1 (0.2)	1 (0.2)	0	0
Potential lung infections other than pneumonia (total), n (%)	40 (8.1)	34 (6.9)	35 (7.1)	30 (6.2)
Bronchitis	24 (4.9)	22 (4.5)	24 (4.8)	18 (3.7)
Lower respiratory tract infection (viral)	6 (1.2)	7 (1.4)	5 (1.0)	3 (0.6)
Lower respiratory tract infection (bacterial)	7 (1.4)	1 (0.2)	3 (0.6)	5 (1.0)
Bronchitis (bacterial)	1 (0.2)	1 (0.2)	3 (0.6)	2 (0.4)
Obstructive chronic bronchitis with acute exacerbation	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Bronchitis (chronic)	1 (0.2)	0	1 (0.2)	1 (0.2)
Lower respiratory tract infection	1 (0.2)	1 (0.2)	1 (0.2)	0
Sinobronchitis	0	1 (0.2)	0	1 (0.2)
Tracheobronchitis	0	2 (0.4)	0	0

AE = adverse event; **bid** = twice daily; **BUD** = budesonide; **DPI** = dry powder inhaler; **FM** = formoterol; **pMDI** = pressurized metered-dose inhaler; **SD** = standard deviation.

Table SIII. Discontinuations due to adverse events

Variable	BUD/FM pMDI 320/9 μg bid (n = 494)	BUD/FM pMDI 160/9 μg bid (n = 494)	FM DPI 9 μg bid (n = 495)	Placebo (n = 481)
Mean exposure (days), SD	305 (115)	299 (118)	289 (127)	270 (139)
DAE, n (%)				
Patients with any DAE	56 (11.3)	61 (12.3)	61 (12.3)	60 (12.5)
COPD	20 (4.0)	30 (6.1)	36 (7.3)	29 (6.0)
Dyspnoea	4 (0.8)	4 (0.8)	3 (0.6)	7 (1.5)
Pneumonia	1 (0.2)	0	1 (0.2)	6 (1.2)
Bronchitis	1 (0.2)	1 (0.2)	2 (0.4)	3 (0.6)
Oral candidiasis	2 (0.4)	3 (0.6)	0	0
Ventricular extrasystoles	1 (0.2)	3 (0.6)	1 (0.2)	0
Bacterial upper respiratory tract infection	1 (0.2)	1 (0.2)	0	2 (0.4)
Cough	0	1 (0.2)	1 (0.2)	1 (0.2)
Viral lower respiratory tract infection	1 (0.2)	1 (0.2)	1 (0.2)	0
Muscle spasms	3 (0.6)	0	0	0
Myocardial infarction	0	3 (0.6)	0	0
Ventricular tachycardia	2 (0.4)	1 (0.2)	0	0

bid = twice daily; **BUD** = budesonide; **COPD** = chronic obstructive pulmonary disease; **DAE** = discontinuation due to adverse event; **DPI** = dry powder inhaler; **FM** = formoterol; **pMDI** = pressurized metered-dose inhaler; **SD** = standard deviation.

Table SIV. Incidence of non-fatal SAEs reported by ≥3 patients

Variable	BUD/FM pMDI 320/9 μg bid (n = 494)	BUD/FM pMDI 160/9 μg bid (n = 494)	FM DPI 9 μg bid (n = 495)	Placebo (n = 481)
Mean exposure (days), SD	305 (115)	299 (118)	289 (127)	270 (139)
SAE, n (%)				
Patients with any SAE	77 (15.6)	67 (13.6)	88 (17.8)	58 (12.1)
COPD	35 (7.1)	33 (6.7)	39 (7.9)	27 (5.6)
Pneumonia	5 (1.0)	5 (1.0)	8 (1.6)	12 (2.5)
Atrial fibrillation	1 (0.2)	5 (1.0)	3 (0.6)	0
Angina pectoris	1 (0.2)	0	3 (0.6)	1 (0.2)
Bronchitis	0	3 (0.6)	2 (0.4)	0
Coronary artery disease	1 (0.2)	1 (0.2)	2 (0.4)	1 (0.2)
Acute myocardial infarction	1 (0.2)	1 (0.2)	2 (0.4)	0
Cardiac failure	1 (0.2)	0	2 (0.4)	1 (0.2)
Cholelithiasis	0	0	2 (0.4)	2 (0.4)
Myocardial infarction	0	3 (0.6)	0	1 (0.2)
Abdominal hernia	1 (0.2)	1 (0.2)	1 (0.2)	0
Aortic aneurysm	0	1 (0.2)	2 (0.4)	0

Bladder cancer	1 (0.2)	0	2 (0.4)	0
Cardiac failure congestive	1 (0.2)	2 (0.4)	0	0
Cor pulmonale	1 (0.2)	0	1 (0.2)	1 (0.2)
Non-cardiac chest pain	1 (0.2)	0	2 (0.4)	0
Pulmonary embolism	1 (0.2)	1 (0.2)	0	1 (0.2)
Respiratory failure	0	1 (0.2)	1 (0.2)	1 (0.2)

bid = twice daily; **BUD** = budesonide; **COPD** = chronic obstructive pulmonary disease; **DPI** = dry powder inhaler; **FM** = formoterol; **pMDI** = pressurized metered-dose inhaler; **SAE** = serious adverse event; **SD** = standard deviation.

Table SV. Geometric means 24-hour urinary cortisol (nmol/24 hours) at 6 months and end of treatment

	BUD/FM pMDI 320/9 μg bid	BUD/FM pMDI 160/9 μg bid	FM DPI 9 μg bid	Placebo
6 Months				
No. of patients	48	44	38	45
Baseline	48.68	43.74	47.72	36.58
Mean	33.54*	41.62	50.55	45.75
End of treatment				
No. of patients	48	47	38	45
Baseline	48.68	43.73	47.72	36.58
Mean	34.32†	40.84	53.20	46.11

* $p < 0.05$ vs placebo, † $p < 0.05$ vs FM.

bid = twice daily; **BUD** = budesonide; **DPI** = dry powder inhaler; **FM** = formoterol; **pMDI** = pressurized metered-dose inhaler.

Table SVI. Number (%) of patients with outlier assessments during treatment for QTc

Assessment	BUD/FM pMDI 320/9 μg bid	BUD/FM pMDI 160/9 μg bid	FM DPI 9 μg bid	Placebo
Bazett's				
QTc interval ≥450 msec*	72 (14.8)	83 (17.0)	59 (12.2)	66 (14.0)
QTc interval ≥500 msec	4 (0.8)	5 (1.0)	5 (1.0)	6 (1.3)
QTc change ≥60 msec	8 (1.6)	12 (2.5)	7 (1.4)	7 (1.5)
Fridericia's				
QTc interval ≥450 msec*	29 (6.0)	27 (5.5)	36 (7.4)	27 (5.7)
QTc interval ≥500 msec	1 (0.2)	2 (0.4)	2 (0.4)	4 (0.8)
QTc change ≥60 msec	5 (1.0)	6 (1.2)	5 (1.0)	6 (1.3)

*For patients with baseline <450 msec.

bid = twice daily; **BUD** = budesonide; **DPI** = dry powder inhaler; **FM** = formoterol; **pMDI** = pressurized metered-dose inhaler.

Table SVII. Total lumbar spine and total hip BMD (g/cm^2): mean (SD) changes from baseline to end of treatment

Variable	BUD/FM pMDI 320/9 μg bid	BUD/FM pMDI 160/9 μg bid	FM DPI 9 μg bid	Placebo
Total lumbar spine BMD				
Baseline				
No. of patients	87	86	81	66
Mean (SD)	1.01 (0.19)	0.99 (0.20)	0.96 (0.16)	0.97 (0.18)
Change from baseline				
No. of patients	83	83	79	66
Mean (SD)	–0.01 (0.04) * † ‡	0.01 (0.04)	0.00 (0.04)	0.01 (0.04)
Total hip BMD				
Baseline				
No. of patients	86	86	80	66
Mean (SD)	0.87 (0.15)	0.86 (0.18)	0.85 (0.16)	0.87 (0.15)
Change from baseline				
No. of patients	84	82	76	65
Mean (SD)	–0.01 (0.02)†	0.00 (0.02)	0.00 (0.02)	–0.01 (0.02)

* $p < 0.05$ vs placebo, † $p < 0.05$ vs FM, ‡$p < 0.01$ vs BUD/FM 160/9 μg.

bid = twice daily; **BMD** = bone mineral density; **BUD** = budesonide; **DPI** = dry powder inhaler; **FM** = formoterol; **pMDI** = pressurized metered-dose inhaler; **SD** = standard deviation.

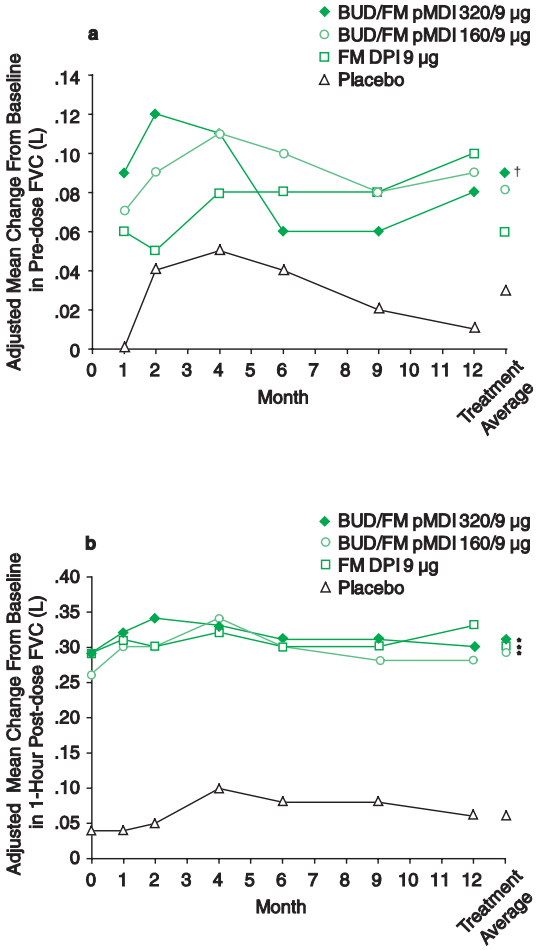
Table SVIII. Intraocular pressure and lenticular opacity: mean (SD) changes from baseline to end of treatment

Variable	BUD/FM pMDI 320/9 μg bid	BUD/FM pMDI 160/9 μg bid	FM DPI 9 μg bid	Placebo
Intraocular pressure (mmHg)				
No. of patients	122	105	118	116
Baseline	15.5 (3.3)	15.3 (2.8)	15.4 (2.8)	15.8 (3.3)
Change from baseline	0.6 (4.0)	0.9 (3.2)	0.7 (3.0)	0.6 (3.1)
Lenticular opacity score (posterior subcapsular)				
No. of patients	119	98	116	112
Baseline	0.4 (0.7)	0.5 (0.9)	0.5 (0.8)	0.5 (0.8)
Change from baseline	0.2 (0.5)*	0.1 (0.2)	0.1 (0.4)	0.1 (0.5)

*p = 0.022 vs BUD/FM 160/9 μg.

bid = twice daily; **BUD** = budesonide; **DPI** = dry powder inhaler; **FM** = formoterol; **pMDI** = pressurized metered-dose inhaler; **SD** = standard deviation.

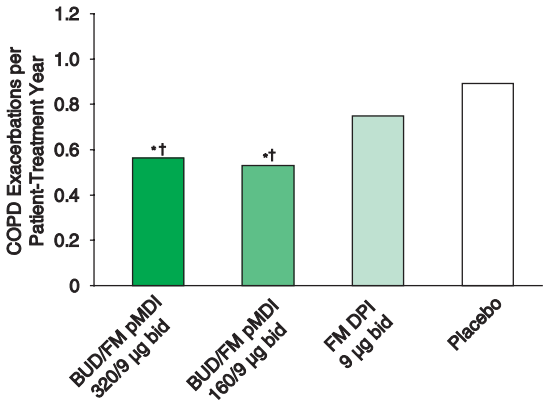
Figure S1



Least squares mean change from baseline by study visit over the randomized treatment period in A) pre-dose FVC and B) 1-hour post-dose FVC.

FVC = forced vital capacity; **BUD** = budesonide; **FM** = formoterol. † $p < 0.05$ vs placebo, * $p \leq 0.001$ vs placebo.

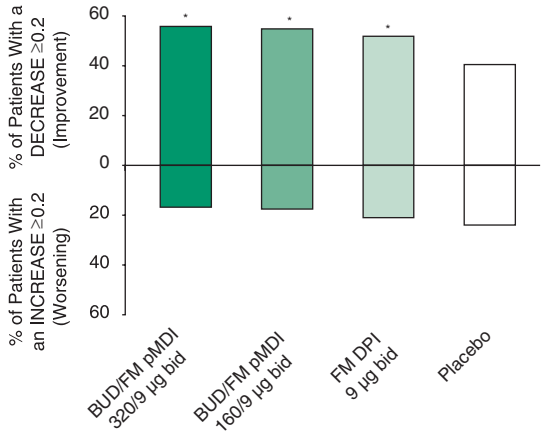
Figure S2



COPD exacerbations as the total rate per patient-treatment year.

COPD = chronic obstructive pulmonary disease; **BUD** = budesonide; **FM** = formoterol; **pMDI** = pressurized metered-dose inhaler; **bid** = twice daily; **DPI** = dry powder inhaler. $^{*}p < 0.01$ vs formoterol, † $p < 0.001$ vs placebo.

Figure S3



Percentage of patients with categorical changes of ≥0.2 from baseline for dyspnoea over the randomized treatment period.

BUD = budesonide; **FM** = formoterol; **pMDI** = pressurized metered-dose inhaler; **bid** = twice daily; **DPI** = dry powder inhaler. $^{*}p < 0.001$ vs placebo.