

ONLINE SUPPLEMENT MATERIAL

FVC OUTCOMES (LLN DEFINITION)

Changes from baseline in predose FVC were worse for FAO+ versus FAO- patients receiving placebo in both studies (Figure E2). In patients with mild to moderate asthma (study I), slight improvements from baseline in predose FVC were observed in both FAO+ and FAO- patients (using the LLN definition) who were assigned to placebo and received short-acting β -agonist (SABA) only during both the run-in and randomized treatment periods.

TABLE E1. – LLN Reference Equations^a

Race	Sex	LLN
Caucasians	Male	$78.388 - 0.2066 \times \text{age}$
	Female	$81.015 - 0.2125 \times \text{age}$
African Americans	Male	$78.822 - 0.1828 \times \text{age}$
	Female	$80.978 - 0.2039 \times \text{age}$
Mexican Americans	Male	$80.925 - 0.2186 \times \text{age}$
	Female	$83.044 - 0.2248 \times \text{age}$

LLN = lower limit of normal.

^aHankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general US population. *Am Rev Respir Crit Care Med* 1999; 159:179–187.

TABLE E2. – Overlap Between FAO Definitions

	FEV ₁ /FVC Criterion	<LLN (<i>n</i> = 116)	≥LLN (<i>n</i> = 371)
Mild to moderate	<0.70 (<i>n</i> = 76)	70	6
	≥0.70 (<i>n</i> = 411)	46	365
Moderate to severe	<0.70 (<i>n</i> = 184)	170	14
	≥0.70 (<i>n</i> = 375)	56	319

FAO = fixed airflow obstruction; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; LLN = lower limit of normal.

TABLE E3. – Study I (Mild-to-Moderate Asthma): Treatment Outcomes Based on FAO Category Using <0.70 Definition

Outcome	Adjusted Mean Change From Baseline							
	BUD/FM pMDI 160/9 µg		BUD pMDI 160 µg		FM DPI 9 µg		Placebo	
	FAO+ (n = 17) ^a	FAO- (n = 112) ^a	FAO+ (n = 20) ^a	FAO- (n = 107) ^a	FAO+ (n = 16) ^a	FAO- (n = 105) ^a	FAO+ (n = 24) ^a	FAO- (n = 107) ^a
FEV ₁ (L)	0.391	0.319	0.22	0.216	0.005	0.198	0.087	0.024
FVC (L)	0.346	0.204	0.201	0.159	-0.0043	0.145	0.814	0.044
Withdrawals due to asthma events ^b (%)	0	8.9	20	3.7	25	20	41.7	31.8
Asthma control days (%)	18.2	22.1	18.5	21.1	11.1	12.1	7.4	6.4
Rescue medication use (inh/d)	-2.22	-1.71	-1.10	-1.38	-1.06	-1.38	0.81	-0.36
Awakening-free nights (%)	19.8	22.0	17.3	21.3	15.2	19.2	8.5	14.0

BUD = budesonide; DPI = dry powder inhaler; FAO = fixed airflow obstruction; FEV₁ = forced expiratory volume in 1 second; FM = formoterol; FVC = forced vital capacity; pMDI = pressurized metered-dose inhaler.

^aPatient numbers varied slightly across variables.

^bBased on predefined criteria (Table 1).

TABLE E4. – Study II (Moderate-to-Severe Asthma): Treatment Outcomes Based on FAO Category Using <0.70 Definition

Outcome	Adjusted Mean Change From Baseline							
	BUD/FM pMDI 320/9 µg		BUD pMDI 320 µg		FM DPI 9 µg		Placebo	
	FAO+ (n = 47) ^a	FAO- (n = 77) ^a	FAO+ (n = 32) ^a	FAO- (n = 77) ^a	FAO+ (n = 38) ^a	FAO- (n = 85) ^a	FAO+ (n = 39) ^a	FAO- (n = 86) ^a
FEV ₁ (L)	0.191	0.176	0.011	0.096	-0.159	-0.033	-0.181	-0.177
FVC (L)	0.172	0.142	-0.020	0.058	-0.142	-0.016	-0.193	-0.142
Withdrawals due to asthma events ^b (%)	4.3	14.3	21.9	19.5	47.4	30.6	51.3	48.8
Asthma control days (%)	17.0	18.6	2.6	8.2	3.7	5.8	1.6	0
Rescue medication use (inh/d)	-1.20	-1.07	-.017	-0.54	-0.31	-0.75	0.62	0.74
Awakening-free nights (%)	14.5	11.7	16.7	14.7	12.7	11.5	9.5	5.3

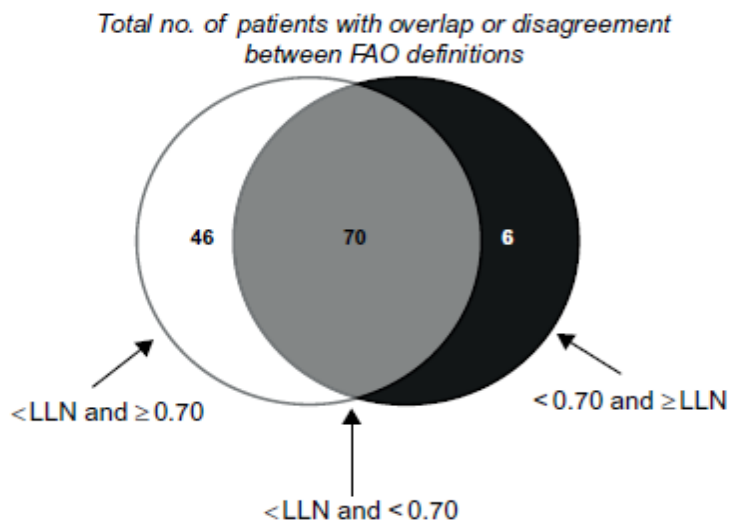
BUD = budesonide; DPI = dry powder inhaler; FAO = fixed airflow obstruction; FEV₁ = forced expiratory volume in 1 second; FM = formoterol; FVC, forced vital capacity; pMDI = pressurized metered-dose inhaler.

^aPatient numbers varied slightly across variables.

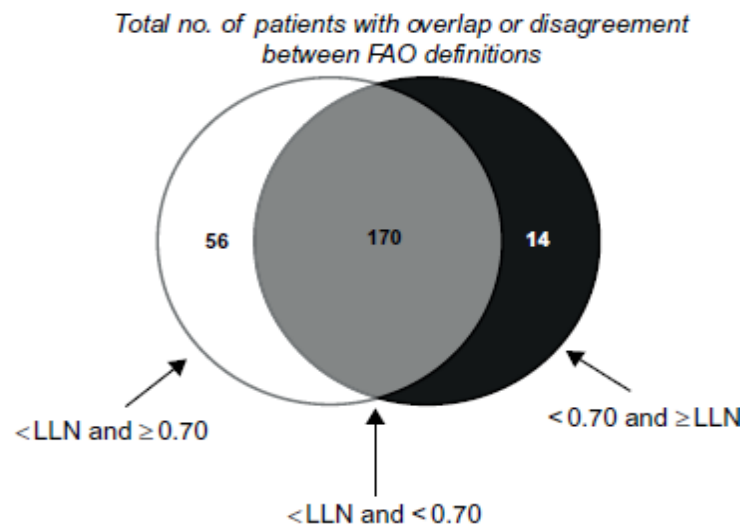
^bBased on predefined criteria (Table 1).

FIGURE E1. Overlap in FAO definitions and influence of age between FAO definitions in study I (mild-to-moderate asthma) (**A**) and study II (moderate-to-severe asthma) (**B**). FAO = fixed airflow obstruction; LLN = lower limit of normal.

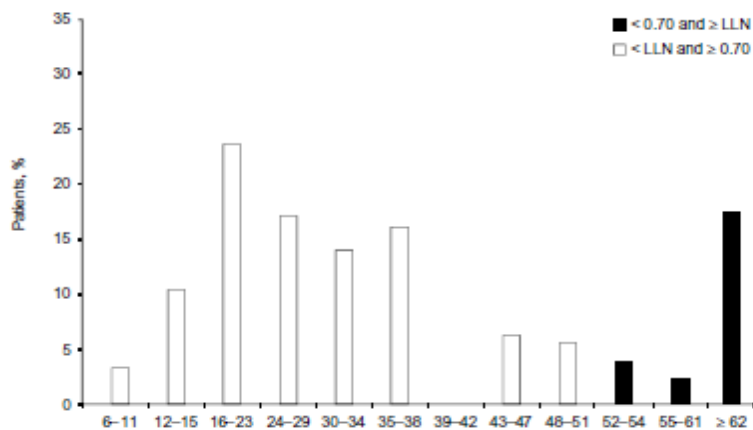
A



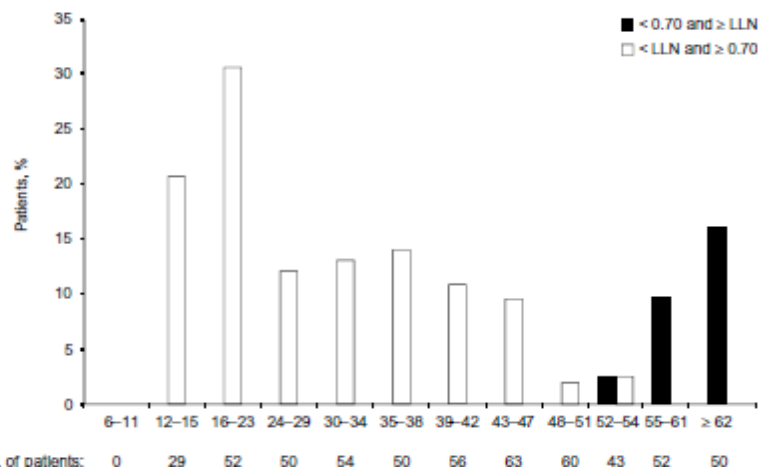
B



Influence of age on disagreement between FAO definitions



Influence of age on disagreement between FAO definitions



Total no. of patients:

Total no. of patients:

FIGURE E2. — Adjusted mean changes from baseline in predose FVC by FAO category (LLN definition) in study I (mild to moderate asthma) and study II (moderate to severe asthma). Note: run-in treatment was placebo for study I and lower dose budesonide for study II (see methods section for run-in and treatment details). BUD/FM = budesonide/formoterol; FAO = fixed airflow obstruction; FVC = forced vital capacity; LLN = lower limit of normal; PBO = placebo.

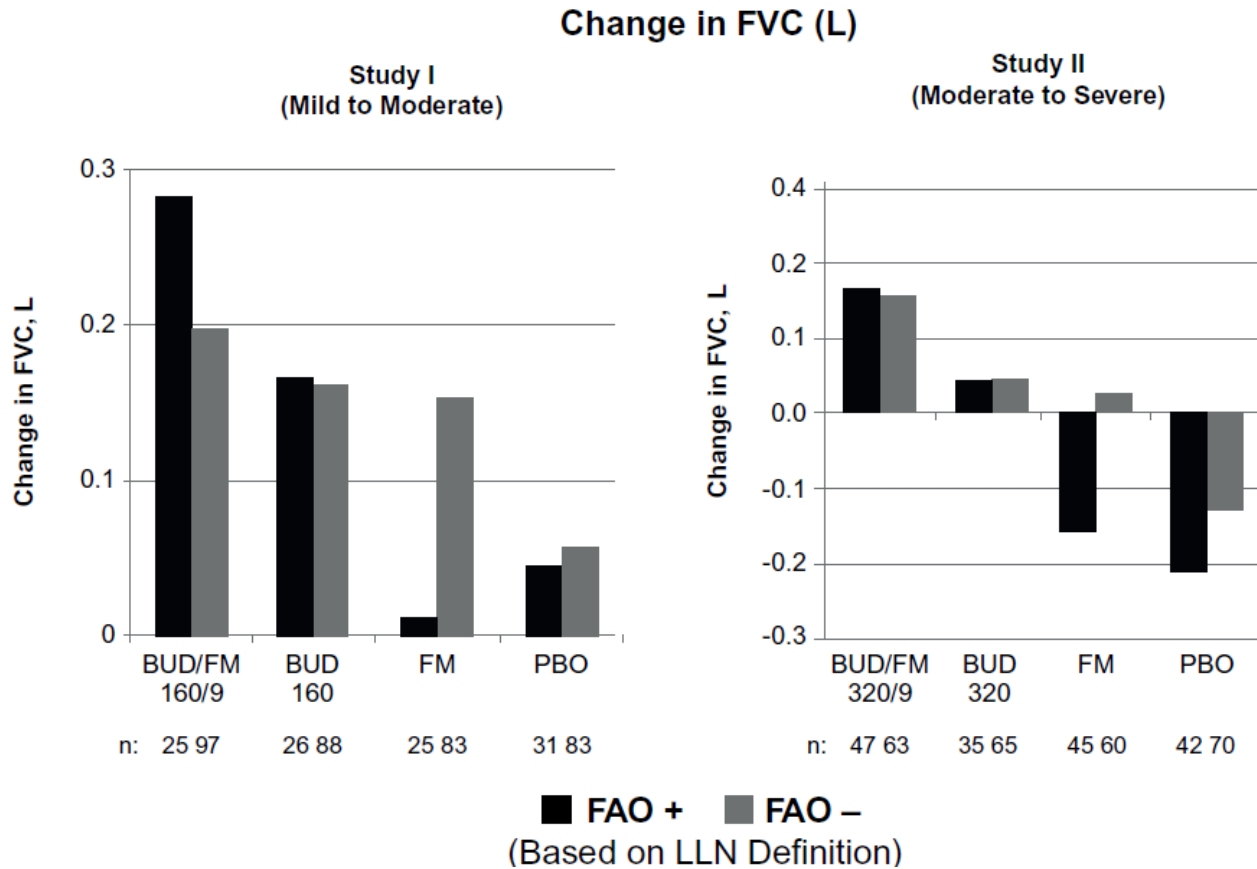
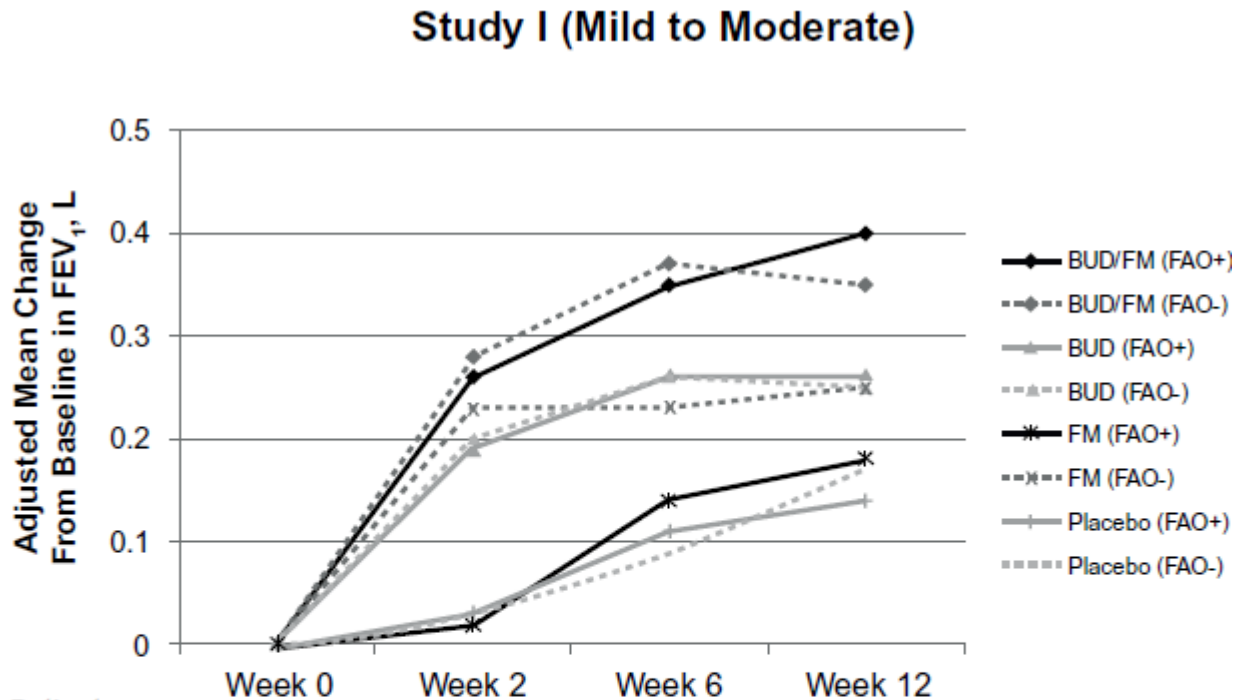
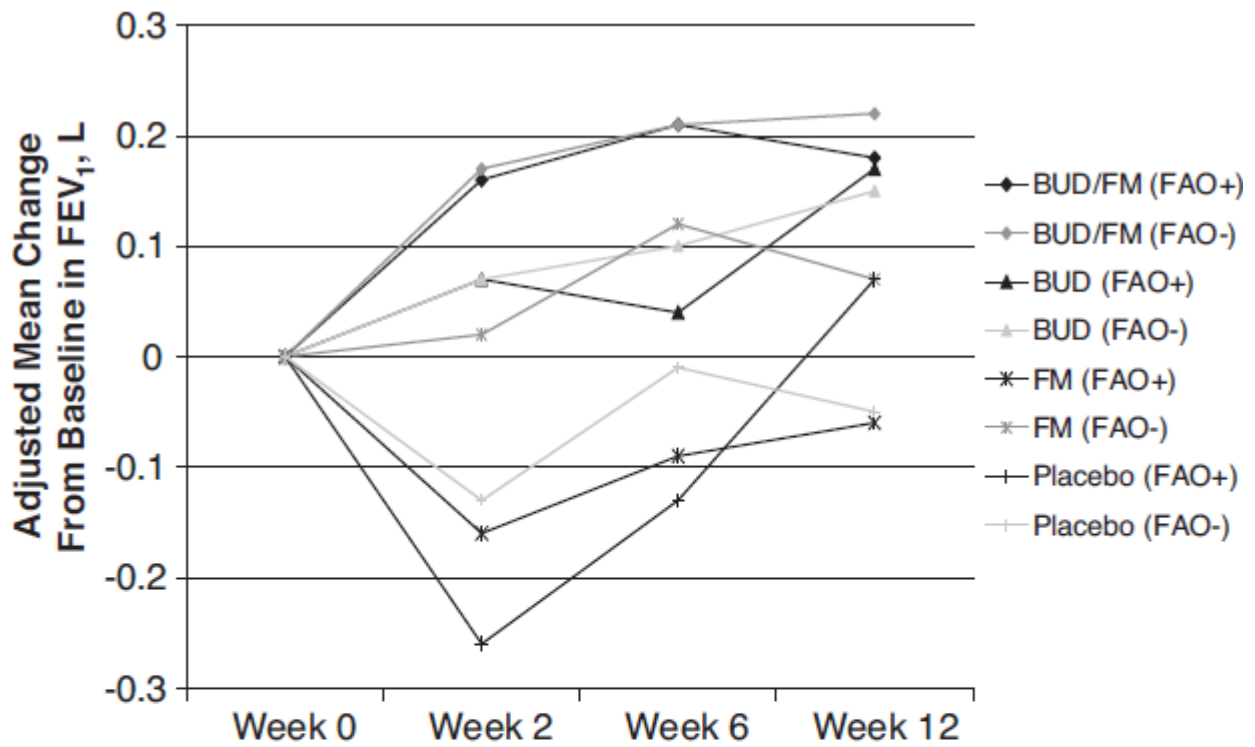


FIGURE E3. Adjusted* mean changes from baseline in predose FEV₁ over time by FAO category (LLN definition) in study I (mild-to-moderate asthma) and study II (moderate-to-severe asthma). The table below the figures reflects the number of patients at each time point. *Data presented as least-squares mean unless otherwise noted. BUD/FM = budesonide/formoterol; FAO = fixed airflow obstruction; FEV₁ = forced expiratory volume in 1 second; FM = formoterol; LLN = lower limit of normal.



Patient n:	Week 0	Week 2	Week 6	Week 12
BUD/FM (FAO+)	25	25	23	23
BUD/FM (FAO-)	98	97	91	83
BUD (FAO+)	28	26	23	23
BUD (FAO-)	91	88	81	81
FM (FAO+)	29	25	20	19
FM (FAO-)	89	83	71	64
Placebo (FAO+)	34	31	21	16
Placebo (FAO-)	93	83	64	50

Study II (Moderate to Severe)



Patient n:

BUD/FM (FAO+)	50	47	42	39
BUD/FM (FAO-)	66	63	59	55
BUD (FAO+)	36	35	29	24
BUD (FAO-)	65	65	54	48
FM (FAO+)	45	45	29	21
FM (FAO-)	67	60	47	41
Placebo (FAO+)	47	42	21	14
Placebo (FAO-)	74	70	46	40