

SUPPLEMENT

Table S1. The interval in weeks between the baseline visit (when randomisation occurred) and subsequent follow up assessments in the seven randomised clinical trials whose data are included in the present analysis.

	Follow up visit 1	Follow up visit 2	Follow up visit 3	Follow up visit 4	Follow up visit 5	Follow up visit 6	Follow up visit 7	Follow up visit 8
Fritsch[1]	6	13	18	26				
Peirsman[2]	13	26	39	52				
Petsky[3]	4	9	13	17	26	32	40	52
Pijnenburg[4]	13	26	39	52				
Pike[5]	9	17	26	34	40	52		
Szefler[6]	6	14	22	30	38	46		
Voorend-van Bergen[7]	17	34	52					

Table S2. Characteristics of participants in the five subgroups where outcomes are compared between those in the standard treatment and F_ENO guided treatment arms.

	ICS dose		Atopy		LTRA treatment		Obese		White	
	≤400 microg	>400 microg	Yes	No	Yes	No	Yes	No	Yes	No
Male gender	359/596 (60%)	284/516 (55%)	588/991 (59%)	36/86 (42%)‡	127/227 (56%)	515/880 (58%)	97/187 (52%)	535/898 (60%)	209/312 (66%)	311/587 (53%)‡
Mean age (SD), y	12.1 (3.3)	13.2 (2.8) ‡	12.6 (3.1)	12.8 (3.3)	12.0 (3.1)	12.7 (3.1) ‡	13.9 (2.5)	12.2 (3.0) ‡	10.5 (2.8)	14.0 (2.4) ‡
Any exacerbation	106/568 (19%)	190/479 (40%)‡	251/939 (27%)	27/78 (35%)	89/213 (42%)	207/829 (25%)‡	66/169 (39%)	226/857 (26%)‡	65/312 (21%)	183/524 (31%)‡
Loss of control*	186/378 (49%)	158/302 (52%)	305/607 (50%)	23/50 (44%)	80/149 (54%)	264/531 (50%)	76/127 (60%)	261/538 (49%)‡	107/221 (48%)	185/375 (49%)
LTRA treatment	77/595 (13%)	150/512 (30%)‡	204/986 (21%)	11/86 (13%)	n/a	n/a	40/187 (21%)	185/894 (21%)	106/312 (34%)	96/583 (16%)‡
LABA treatment	185/595 (31%)	449/512 (88%)‡	553/986 (56%)	53/86 (62%)	168/227 (74%)	466/880 (53%)‡	130/187 (70%)	491/894 (55%)‡	161/312 (52%)	374/583 (64%)‡
Baseline FENO median (IQR)	21 (11.4, 40.2)	23.6 (12, 47.8) ‡	23.6 (12.6, 46.1)	10 (7.8, 16.2)	22.5 (11.2, 42.3)	21.8 (11.6, 43.0)	16.8 (10, 31.6)	23 (12, 46.3) ‡	19.9 (10.2, 38.4)	20.7 (11.2, 41.3)
Median (IQR) ICS dose†	n/a	n/a	400 (400,1000)	400 (400,1000)	1000 (400,2000)	400 (400,1000) ‡	1000 (400, 2000)	400 (400, 1000) ‡	400 (400, 800)	800 (400, 2000) ‡
Proportion white	204/483 (42%)	108/416 (26%)‡	286/790 (36%)	9/75 (12%)‡	106/202 (53%)	206/693 (30%)‡	10/172 (6%)	301/707 (43%)‡	n/a	n/a
Proportion obese	81/583(14%)	106/502 (21%)‡	165/967 (17%)	18/83 (22%)	40/225(18%)	147/856 (17%)	n/a	n/a	10/311 (3%)	162/568 (29%)‡
Proportion atopic	527/879 (91%)	464/498 (93%)	n/a	n/a	204/215 (95%)	782/857 (91%)	165/183 (90%)	802/867 (92.5%)	286/295 (97%)	504/570 (88%)‡

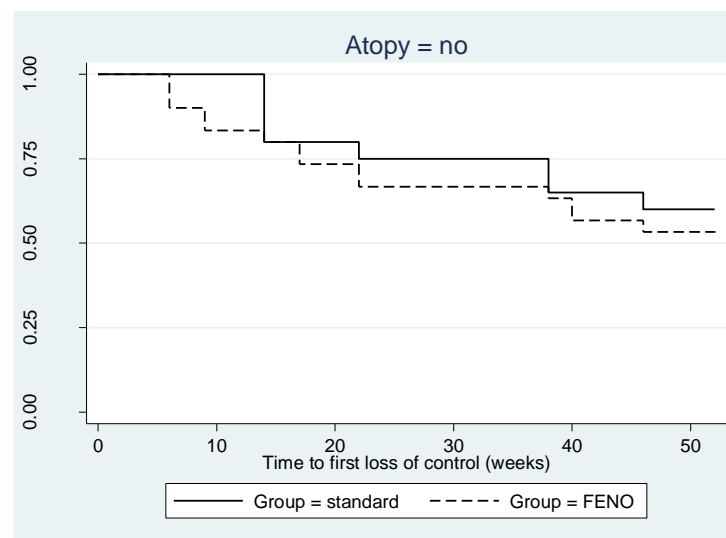
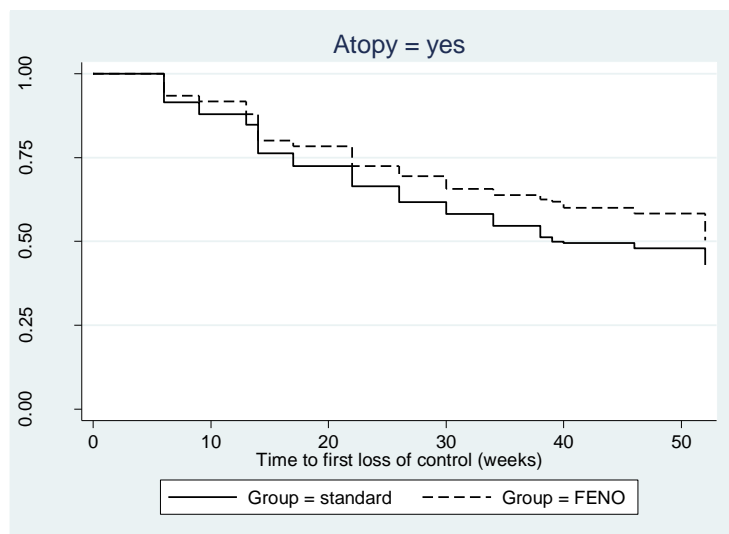
*After being controlled at baseline. †microg budesonide or equivalent. ‡ p<0.05.

Table S3. Proportion of individuals who were initially controlled who lost control in F_ENO -guided and standard management arms of clinical trials with stratification for patient characteristics. ICS=inhaled corticosteroids, presented as ≤400 or >400 micrograms budesonide equivalent. Obesity was defined by International Obesity Task Force criteria.

Baseline characteristic		% with loss of control during follow-up [#] in each treatment arm		F _E NO vs standard		p value for interaction*
		F _E NO guided management	Standard management	OR	95% CI	
LTRA treatment	Yes	39/74 (53%)	41/75 (55%)	0.94	(0.48, 1.87)	0.453
	No	118/261 (45%)	146/270 (54%)	0.70	(0.49, 1.00)	
ICS dose	≤400 microg	88/191 (46%)	98/187 (52%)	0.80	(0.52, 1.22)	0.652
	>400 microg	69/144 (48%)	89/158 (56%)	0.69	(0.43, 1.99)	
Obese	Yes	40/66 (61%)	36/61 (59%)	1.08	(0.53, 2.22)	0.274
	No	116/264 (44%)	145/274 (53%)	0.69	(0.48, 0.99)	
Atopic	Yes	133/291 (46%)	172/316 (54%)	0.73	(0.52, 1.02)	0.457
	No	14/30 (47%)	8/20 (40%)	1.15	(0.36, 3.69)	
Ethnic group	White	48/106 (45%)	59/115 (51%)	0.76	(0.42, 1.37)	0.946
	Non-white	89/191 (47%)	96/184 (52%)	0.78	(0.52, 1.18)	

*adjusted for age, ICS at baseline (except ICS dose model) and RCT population; # from those controlled at baseline

Figure S1. Kaplan Meier curves showing time to loss of control for patients who were initially controlled and whose asthma treatment was guided by either fractional exhaled nitric oxide (“FENO”) or by symptoms only (“standard”) and stratified by atopy. The difference between treatment arms was significant for those who were atopic ($p=0.050$) but not for the non-atopic patients ($p=0.566$).



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