

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Ducharme FM, Lemire C, Noya FJD, et al. Preemptive use of high-dose fluticasone for virus-induced wheezing in young children. *N Engl J Med* 2009;360:339-53.

**Table E1. Study Mechanics\***

	<b>Fluticasone (N=62)</b>	<b>Placebo (N=67)</b>	<b>P-value</b>
<b>Study duration</b>			
Follow-up period—weeks	40 (31 to 60)	40 (30 to 52)	0,81
Treatment period—weeks†	37 (24 to 55)	33 (20 to 41)	0,18
<b>Study drug use</b>			
Days of use/person-month‡	5.19 (3.67 to 7.91)	6.60 (4.09 to 8.62)	0,20
Cumulative days of use‡	46 (31.5 to 68)	40 (25 to 63)	0,25
Cumulative dose of fluticasone used (mg) ‡	50 (39 to 91)	—	
<b>Adherence per patient §</b>			
	N=57	N=63	
Diary—% ¶	88% (78% to 95%)	85% (75% to 93%)	0,59
	N=60	N=67	
Dose counter—% ¶	86% (79% to 95%)	91% (85% to 99%)	0,007
Overuse (≥6 puffs/day)—% of days ¶¶	3,30%	4,10%	<0.001
<b>Blinding</b>			
Parent	N=62	N=66	
Undecided—%	18 (29%)	20 (30%)	0,97
Correct guess—%	21 (34%)	23 (35%)	
Physician	N=62	N=66	
Undecided—%	42 (68%)	44 (67%)	0,65
Correct guess—%	11 (18%)	13 (20%)	
Nurse	N=60	N=66	
Undecided—%	32 (53%)	45 (68%)	0,18
Correct guess—%	20 (33%)	8 (12%)	

\* Raw values for each group are reported as median (interquartile range) or number (percentage), as indicated.

† Treatment duration was censored at study drug discontinuation, if applicable.

‡ Study drug use per patient-month of observation was computed as the cumulative number of days of use recorded, divided by number of person-month. The cumulative dose and days of use were not adjusted for person-month of observation. In all cases, the study drug use was documented on the dose counter, from randomization until the end of the follow-up (or study drug discontinuation, if applicable).

§ Adherence represents the ratio of the cumulative number of study drug inhalations on days of use, as reported on diary and documented on the dose counter, respectively, divided by six (the recommended daily dosage). Adherence was not censored to 100%, that is, the number of inhalations exceeding the recommended daily dose of 6 inhalations were included in the computation of adherence.

¶ The proportion of days of use where overuse (≥ 6 puffs/day) was documented on the dose counter.

**Table E2. Height and weight distribution at baseline and endpoint\***

<b>Z-score</b>	<b>Fluticasone</b>		<b>Placebo</b>	
	<b>Baseline (N=60)</b>	<b>Endpoint (N=60)</b>	<b>Baseline (N=66)</b>	<b>Endpoint (N=66)</b>
<b>Height</b>				
<b>Z &lt; -2</b>	1 (2%)	0 (0%)	1 (1%)	1 (2%)
<b>-2 ≤ Z &lt; -1</b>	4 (7%)	6 (10%)	5 (7%)	4 (6%)
<b>-1 ≤ Z &lt; 0</b>	18 (30%)	21 (35%)	17 (26%)	20 (30%)
<b>0 ≤ Z &lt; 1</b>	22 (37%)	22 (37%)	29 (44%)	25 (38%)
<b>1 ≤ Z &lt; 2</b>	15 (24%)	11 (18%)	7 (11%)	12 (18%)
<b>2 ≤ Z</b>	0%	0%	7 (11%)	4 (6%)
<b>Weight</b>				
<b>Z &lt; -2</b>	1 (1%)	2 (3%)	1 (2%)	1 (2%)
<b>-2 ≤ Z &lt; -1</b>	3 (5%)	5 (8%)	6 (9%)	8 (12%)
<b>-1 ≤ Z &lt; 0</b>	19 (31%)	16 (26%)	15 (22%)	11 (16%)
<b>0 ≤ Z &lt; 1</b>	21 (34%)	22 (35%)	27 (40%)	20 (30%)
<b>1 ≤ Z &lt; 2</b>	13 (21%)	14 (23%)	14 (21%)	21 (31%)
<b>2 ≤ Z</b>	5 (8%)	3 (5%)	4 (6%)	6 (9%)

\* Values are provided at baseline (randomization) and endpoint (at the end of follow-up, irrespective of study drug discontinuation)

**Table E3. Adverse health events**

Adverse Health Event	Placebo		Fluticasone		P-value*
	Events	Patients	Events	Patients	
	N	N (%)	N	N (%)	
<b>All adverse health events†</b>		<b>N=67</b>		<b>N=62</b>	
Otitis media	44	23 (34%)	55	27 (44%)	0,28
Fever	28	20 (26%)	32	18 (29%)	0,69
Gastroenteritis	13	11 (16%)	15	14 (23%)	0,38
Pneumonia	10	10 (15%)	14	13 (21%)	0,37
Sinusitis	12	9 (13%)	11	10 (16%)	0,67
Injuries	12	9 (13%)	7	5 (8%)	0,33
Chickenpox	6	6 (9%)	9	9 (15%)	0,32
Croup	4	4 (6%)	8	5 (8%)	0,74
Vomiting	7	4 (6%)	4	4 (7%)	1
Pharyngitis	5	4 (6%)	6	6 (10%)	0,52
Streptococcal infection	5	4 (6%)	3	2 (3%)	0,68
Conjunctivitis	4	3 (5%)	3	2 (3%)	1
Eczema	1	1 (2%)	6	6 (10%)	0,06
Rash	2	2 (3%)	5	5 (8%)	0,26
Serous otitis media	2	2 (3%)	4	4 (7%)	0,43
<b>Serious adverse health events‡</b>		<b>N=67</b>		<b>N=62</b>	
Pneumonia‡	2	2 (3%)	3	3 (5%)	0,67
Febrile seizure	1	1 (2%)	0	0 (0%)	1
Afebrile seizure	0	0 (0%)	1	1 (2%)	0,48
Admission to ICU	2	2 (3%)	0	0 (0%)	0,5
Burn	1	1 (2%)	0	0 (0%)	1
Respiratory syncythial virus infection	1	1 (2%)	0	0 (0%)	1
Atelectasis	1	1 (2%)	0	0 (0%)	1
Kawasaki	1	1 (2%)	0	0 (0%)	1
Total	9	9 (13%)	4	4 (6%)	0,26

\* Significance level for the group difference in the number of patients experiencing an event

† Most frequent adverse health events, with an incidence of  $\geq 5\%$  in either group

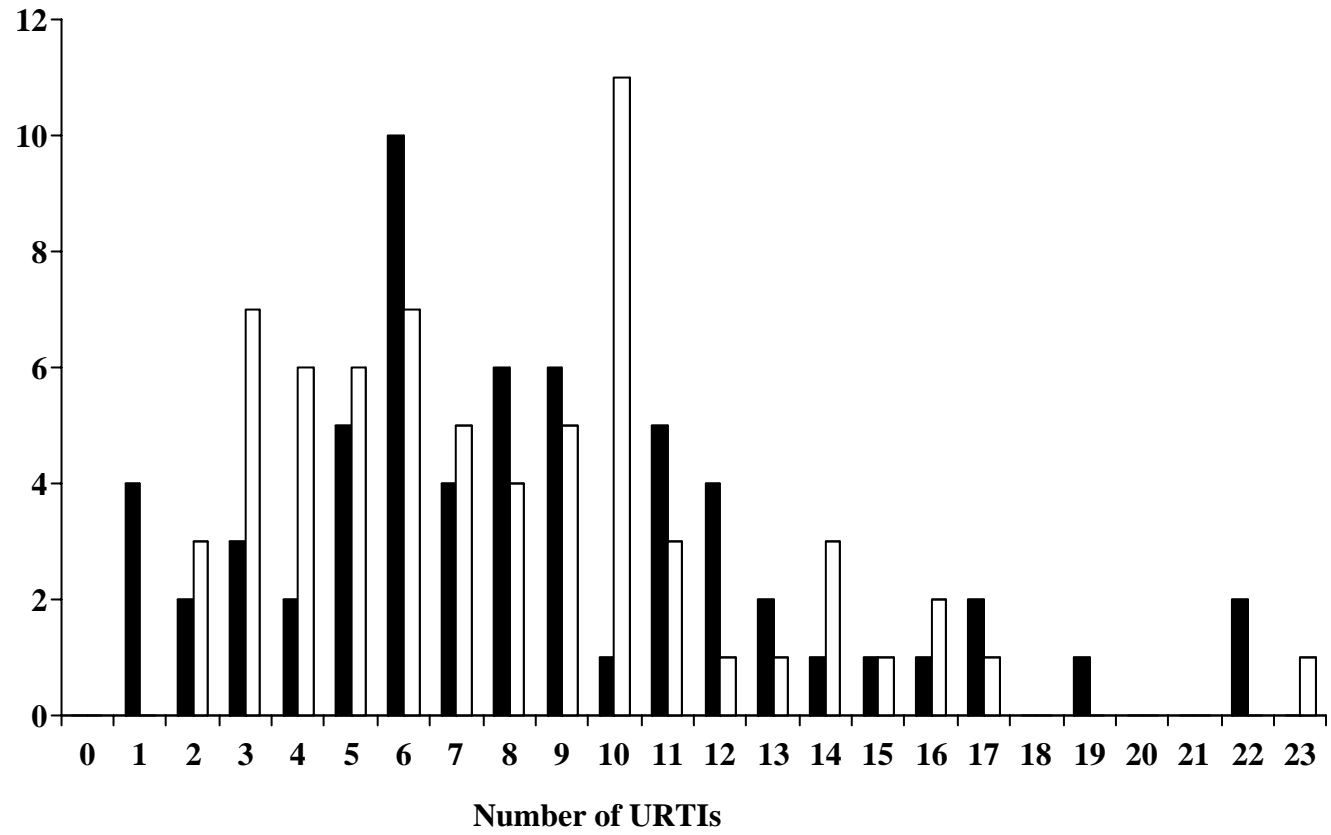
‡ Defined as one requiring or prolonging hospital admission

‡ One pneumonia in the placebo group occurred following an adenotonsillectomy and was associated with an urinary tract infection

**Figure E1 – Distribution of upper respiratory tract infections and courses of systemic corticosteroids per group**

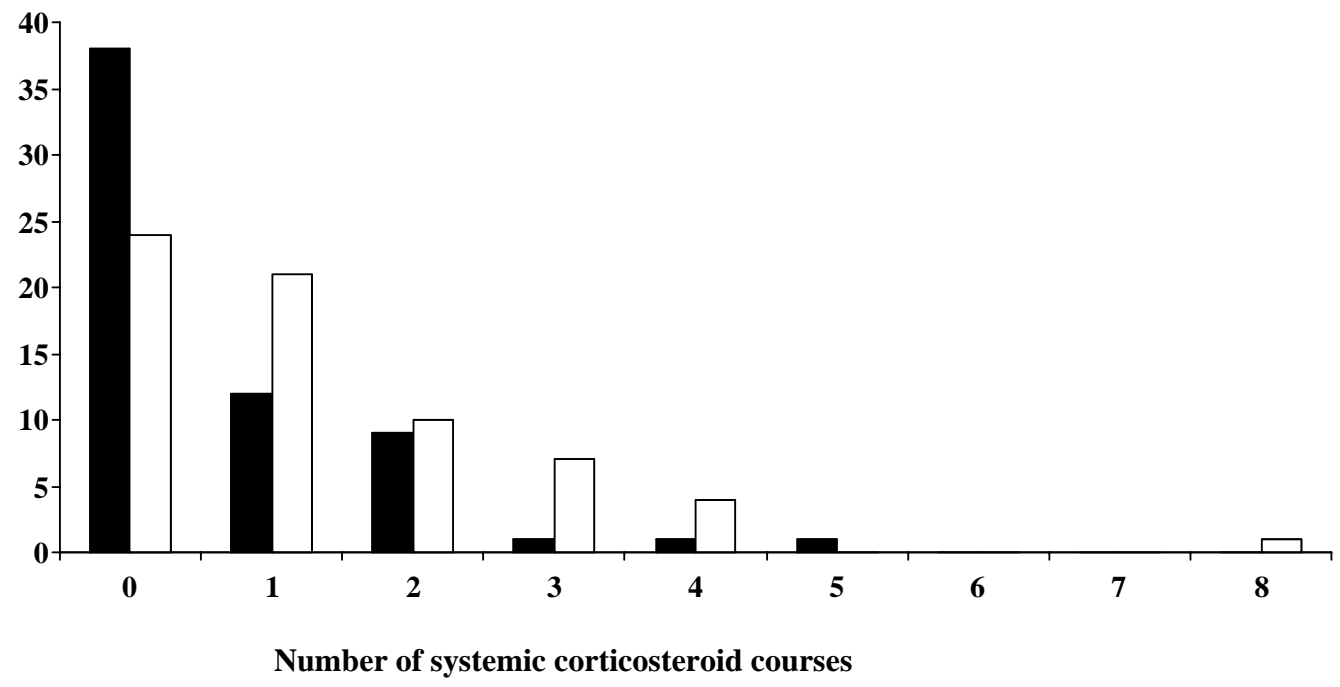
**A. Upper respiratory tract infections (URTIs) per patient**

Number of Patients



**B. Courses of systemic corticosteroids per patient**

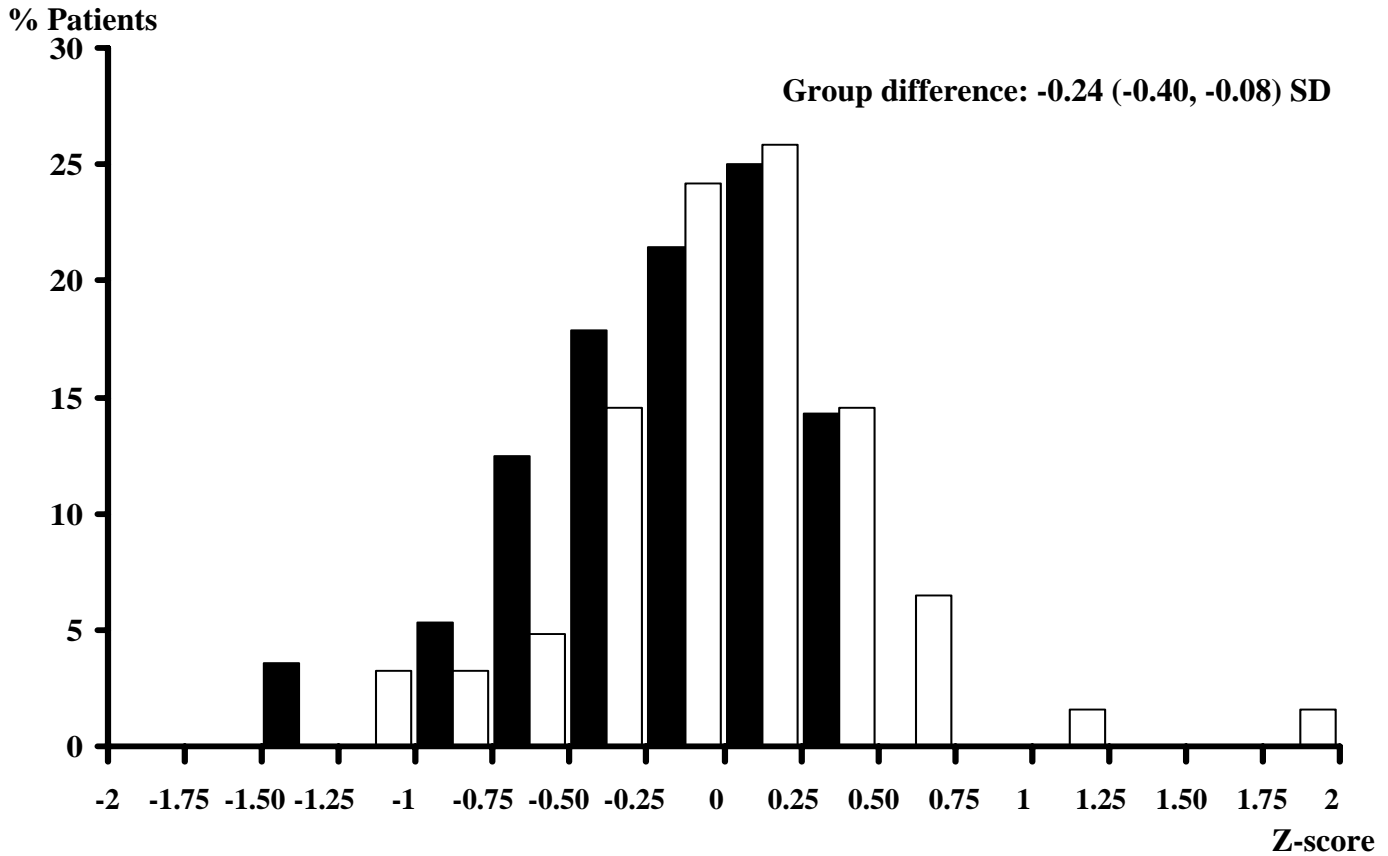
Number of Patients



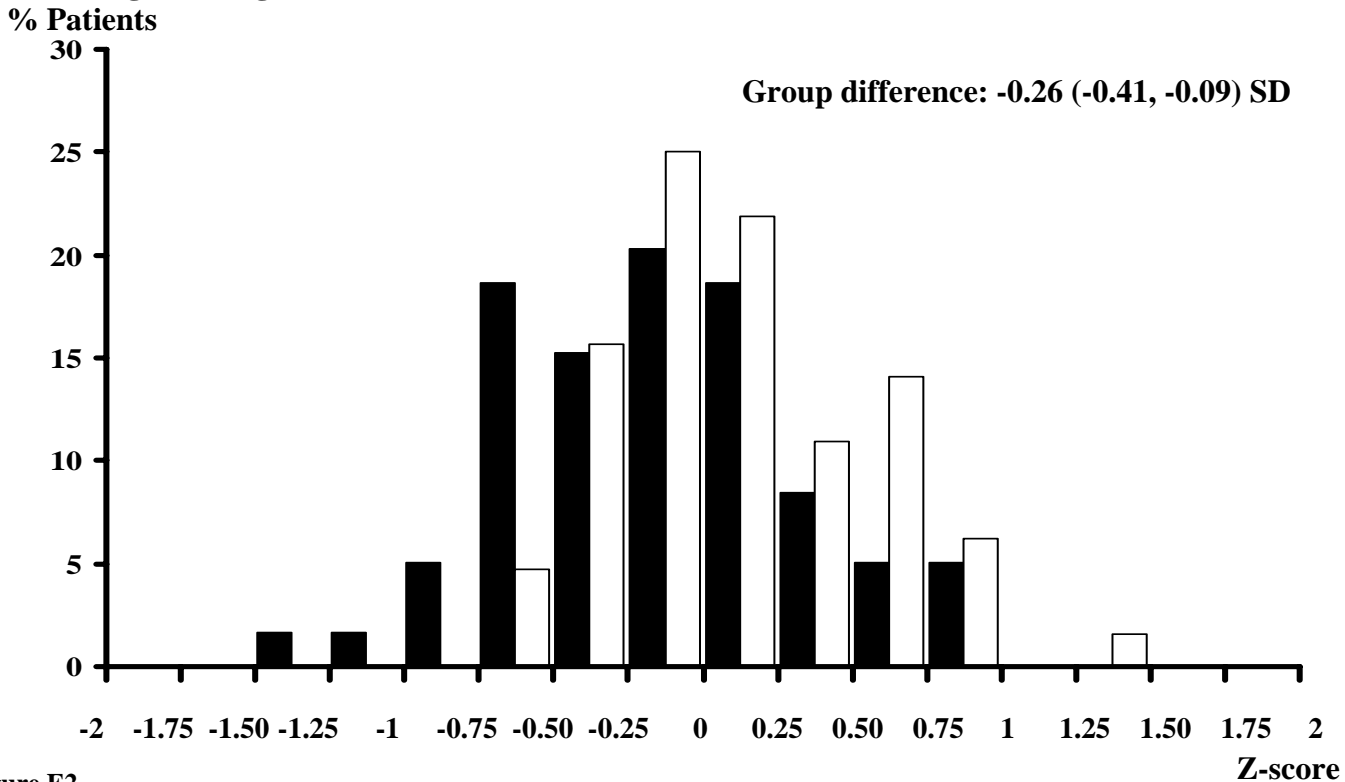
**Figure E1**  
This figure depicts the distribution of the number of upper respiratory tract infections (URTIs) (A) and short courses of rescue systemic corticosteroids (B) by patient in the fluticasone propionate (black bars) and the placebo (white bars) groups.

**Figure E2 – Distribution of the change from baseline in height and weight**

**A. Change in Height**



**B. Change in Weight**



**Figure E2**

This figure depicts the distribution and group difference in the change in height (A) and in weight (B) from baseline to endpoint in the fluticasone propionate (black bars) and the placebo (white bars) group, analyzed by intention-to-treat. Values were adjusted for age and gender, based on pediatric reference values<sup>31</sup> and presented as Z-score or standard-deviation units from the expected mean of zero. The y-axis indicates the percentage of patients. A change from baseline of zero indicates that children followed the same growth curve from baseline until the endpoint. Positive Z-score values represent a higher gain than expected; negative values, a lower gain than expected. A group difference in the change from baseline greater than 0.5 SD was considered *a priori* to be indicative of a clinically important difference.