



Outcome measures and serious asthma exacerbation in clinical trials of asthma controller medications

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ABSTRACT

Background: With the introduction and approval of several new asthma controller medications for pediatric use, the risk-benefit ratio of these medications has not been fully evaluated.

Objective: To determine whether physiologic pulmonary measurements are superior to other measures in evaluating outcomes and to determine whether asthmatic children have a higher risk of serious adverse events than adults.

Methods: We obtained data on asthma controller medications approved between 1997 and 2010 from the US Food and Drug Administration archives. Six medications were approved for use in children and adults during this time. Of these, we were able to analyze 23 trials of 5 medications. Nine of the trials were conducted in pediatric patients and 14 in adults.

Results: We determined whether the primary outcome measure was a physiologic pulmonary measure or another measure and compared trial outcomes. We also evaluated serious adverse events, including mortality rates for both adult and pediatric trials. The frequency of successfully demonstrating efficacy was far superior using physiologic pulmonary measures (13/14 [93%]) compared with other outcome measures (4/9 [44%]). The frequency of serious asthma exacerbations, although less than 1%, was higher in the pediatric group of patients (18/1,948 [0.9%]) compared with adults (4/2,460 [0.2%]), regardless of assignment to placebo or drug.

Conclusion: These results suggest that physiologic pulmonary function measures should be used in evaluating the efficacy of asthma controller medications. These data also indicate that pediatric patients may be more prone to serious asthma exacerbations during clinical trials.

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Introduction

With the advent of the Pediatric Exclusivity Act of 1997 and a new generation of asthma controller medications, it has become obvious that the risk-benefit ratio among the pediatric sample of patients and adults needs further evaluation. Specifically, are the methods used to evaluate pediatric trials the same as those used in adult trials? Is the safety profile of asthma control medications similar to the data from adult trials?

Many changes have been made in the methods to evaluate new asthma control medications. The introduction of nonphysiologic measures, such as Summary Symptom Score, percentage of symptom-free days, and worst symptom score, has provided researchers with more effective tools for monitoring patient outcomes. Furthermore, the classic forced expiratory volume in 1 second (FEV₁) has been replaced

by other measures, such as peak expiratory flow rate. It is unclear whether the physiologic or the nonphysiologic measures are more appropriate for the pediatric trials because children may have difficulties in executing physiologic pulmonary function tests.^{1,2}

Besides the methods of evaluating efficacy among pediatric patients compared with adult patients with asthma, there is a concern that the safety profile of the asthma controller medications may differ between the 2 groups.³ If such is the case, should these findings be included in product labeling and in the informed consents for the future trials?

On the basis of these factors, we hypothesized that the frequency of successful trials using physiologic methods compared with nonphysiologic methods of outcome evaluation would be different among pediatric asthma controller trials when compared with adult trials. Furthermore, we hypothesized that the profile of adverse events (AEs) and especially serious adverse events (SAEs) would be different among pediatric asthma controller trials compared with adult trials.

Although we could have evaluated our hypothesis using the published literature, we chose a different path. Specifically, we

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used the US Food and Drug Administration (FDA) website to access an abbreviated version of the agency's independent evaluations of all safety and efficacy data submitted to pharmaceutical companies. This method reduces the file drawer effects (publication is biased toward more positive findings). Also, the published literature may not reflect all of the AEs, especially the SAEs.

The aim of our study was to assess the frequency of successful outcome among the asthma controller medication trials using physiologic pulmonary function measures compared with other outcome measures among both the adult and pediatric clinical trials. We also aimed to evaluate the frequency of AEs, especially SAEs, among the pediatric and adult trials for asthma controller medications.

Methods

Selection of trials

Because of the concerns of publication bias and potential exaggerations of published reports, we decided to access data from the FDA website, available as part of the Freedom of Information Act (1996). We specifically accessed the efficacy and safety report sections for this study. This information was found at <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm> (DRUGS@FDA.org) and accessed on December 21, 2010. To determine the

medications approved for the treatment of asthma in children from the passage of the Pediatric Exclusivity Act in 1997 until 2010 we used data available from www.centerwatch.com.

The medications approved by the FDA to treat asthma in both pediatric and adult populations were mometasone furoate–formoterol fumarate dehydrate (Dulera; Merck and Co., Inc., Rahway, New Jersey), ciclesonide (Alvesco; Sunovion Pharmaceuticals inc., Marlborough, Massachusetts), beclomethasone dipropionate (Qvar; Teva Specialty Pharmaceuticals, Horsham, Pennsylvania), montelukast sodium (Singulair; Merck and Co., Inc.), fluticasone propionate (Flovent; Glaxo Wellcome, Research Park, North Carolina), and nedocromil sodium (Tilade; King Pharmaceuticals, Cary, North Carolina).

The medication mometasone furoate–formoterol fumarate dehydrate (Dulera) was excluded from our analysis because there were no primary trials available from the FDA used in the approval of this combination medication. The medication is a combination β_2 -agonist and inhaled corticosteroid composed of 2 previously approved medications and did not have any individual trials available for review from the FDA submission.

The remaining medications were all controller medications for persistent asthma administered to decrease baseline severity and decrease the number of asthma exacerbations. Although their mechanisms of action differed, every medication was dispensed in

Table 1

Summary of pivotal pediatric trials and efficacy results used for the FDA approval of asthma controller medications approved in 1997–2010

Medication	Study name (age range, y)	Treatment arm	No. (% complete)	Baseline score ^a	% Change ^b
Trials using a subjective asthma symptoms score survey as a primary efficacy end point					
Nedocromil inhalation aerosol	CR1978 (6–12) ^{c,d}	11 mg 3 times daily via nebulizer	48 (81)	3.23	–6.2
		Placebo	45 (80)	3.55	2.8
	CR2233 (2–5) ^{d,e}	11 mg 3 times daily via nebulizer	138 (90)	3.16	29.1
		Placebo	141 (89)	2.87	3.8
	CR3003 (6–12) ^{d,e}	11 mg 3 times daily via nebulizer	148 (91)	1.79	14.0
		Placebo	145 (89)	1.92	0.5
Summary	Investigational medication	334 (89)	2.57	17.3	
		Placebo	331 (88)	2.55	2.2
Trials using FEV ₁ as an efficacy end point					
Ciclesonide	343 (5–9) ^{d,f}	160 µg via MDI once daily	219 (83)	1.42	10.3
		40 µg via MDI twice daily	221 (85)	1.44	8.9
		Placebo	221 (82)	1.41	9.6
Fluticasone propionate	FLTA 2006 (4–11) ^{e,g}	50 µg via MDI	90 (77)	1.48	16.2
		100 µg via MDI	87 (82)	1.38	16.7
		50 µg via Diskhaler	91 (85)	1.45	15.2
		100 µg via Diskhaler	83 (76)	1.47	16.3
	FLTA 2007 (4–11) ^{e,g}	Placebo	86 (45)	1.47	6.8
		50 µg via Diskhaler twice daily	88 (72)	1.46	8.9
		100 µg via Diskhaler once daily	91 (68)	1.37	5.8
		Placebo	83 (53)	1.44	3.5
	FLTA 2008 (4–11) ^{e,g}	100 µg via MDPI twice daily	80 (73)	1.36	16.9
		200 µg via MDPI once daily	84 (62)	1.40	8.6
		Placebo	78 (41)	1.51	–2.6
		Montelukast sodium	049 (6–14) ^{g,h}	5-mg chewable tablet once daily	201 (94)
Placebo	135 (93)			NA	4.2
Nedocromil inhalation aerosol	CR1574 (6–12) ^{d,e}	11 mg 4 times daily via nebulizer	81 (84)	1.67	1.8
		Placebo	85 (91)	1.60	–1.3
Summary		Investigational medication	1,416 (81)	1.43	10.6
		Placebo	688 (72)	1.46	4.7

Abbreviations: FDA, US Food and Drug Administration; FEV₁, forced expiratory volume in 1 second; MDI, metered-dose inhaler; MDPI, multidose dry powder inhaler; NA, not available.

^aIndicates a mean score based on the 20-point Summary Severity Score.

^bNegative percentage change indicates a higher score and a worsening of reported symptoms; positive change indicates a lower score and a lessening of reported symptoms.

^cA 24-week trial.

^dPrimary outcome measure was a subjective assessment or other measure.

^eA 12-week trial.

^fA 52-week trial.

^gPrimary outcome measure was a pulmonary physiologic test.

^hAn 8-week trial.

the form of a standing dose. Each medication had pivotal safety and efficacy trials submitted to the FDA and were included in our individual study selection process. These trials were conducted in the United States and other countries around the world. To test our hypothesis, we selected the randomized, placebo-controlled trials that measured the efficacy of the medication on a patient's baseline asthma.

We evaluated the 39 phase 3 pivotal adult or pediatric trials from the 5 remaining medications. Sixteen trials were excluded: 2 for missing data (beclomethasone dipropionate study 1081 and fluticasone study FLTA2016), 5 because they were not placebo controlled (beclomethasone dipropionate trials 1192, 1130, and 1163 and ciclesonide trials 3027 and 3028), 3 because they did not include FEV₁ data (beclomethasone dipropionate study 1162 and montelukast trials 039 and 036), 3 because they investigated the amount of steroid dose able to be withdrawn from the patient while receiving the investigative medicine (fluticasone study FLTA

2002 and montelukast trials 046 and 029), and 3 because they measured worsening of FEV₁ after a stimulus to induce asthma symptoms was implemented (montelukast trials 040, 015, and 042).

Of the 23 remaining placebo-controlled trials, 9 were used by the FDA for analysis in the pediatric population (Table 1), with age inclusion ranging from 4 to 14 years, 2 to 5 treatment arms per study (none included an active comparator), and lengths of 8 to 52 weeks. Only 1 trial lasted 52 weeks, and the rest lasted 8 to 24 weeks.

The remaining 14 trials were considered adult population trials (Table 2), with age of inclusion of 12 years or older, 2 to 5 treatment arms per study with an active comparator (beclomethasone dipropionate) in 3 trials, and lengths of 6 to 16 weeks. Included with each study was the number of participants and the percentage of participants who completed the study.

Table 2

Summary of pivotal adult trials and efficacy results used for the FDA approval of asthma controller medications approved in 1997–2010

Medication	Study name (age range, y)	Treatment arm	No. (% complete)	Baseline FEV ₁	% Change
Beclomethasone dipropionate	1083 (18–67) ^{a,b}	400 µg via 50-µg concentration	83 (88)	2.66	13.2
		400 µg via 100-µg concentration	88 (90)	2.47	9.7
		Placebo	85 (82)	2.44	3.7
	1129 (18–65) ^{b,c}	400 µg via HFA	113 (89)	2.80	2.1
		800 µg via CFC	117 (90)	2.86	2.8
		Placebo	117 (68)	2.81	–10.7
Ciclesonide	3031 (≥12) ^{b,d}	160 µg via MDI once daily	178 (93)	2.54	7.5
		80 µg via MDI twice daily	177 (88)	2.49	12.0
		80 µg twice daily for 4 weeks then 160 µg once daily for 12 weeks via MDI	175 (90)	2.39	7.9
	3030 (≥12) ^{b,c}	Placebo	178 (77)	2.45	2.4
		160 µg via MDI once daily	152 (88)	2.64	0.4
		80 µg via MDI twice daily	152 (89)	2.67	2.6
Fluticasone propionate	FLTA 2001 (≥12) ^{b,c}	Placebo	152 (68)	2.63	–5.2
		500 µg via Diskhaler twice daily	64 (84)	2.41	21.6
		500 µg via MDPI twice daily	79 (86)	2.49	16.5
	FLTA 2003 (≥12) ^{b,c}	Placebo	70 (47)	2.41	1.2
		100 µg via MDPI twice daily	73 (78)	2.60	18.8
		200 µg via MDPI once daily	77 (83)	2.58	14.3
	FLTA 2004 (≥12) ^{b,c}	Beclomethasone dipropionate 168 µg via MDI twice daily	76 (74)	2.56	18.8
		Placebo	73 (52)	2.62	8.0
		100 µg via MDPI twice daily	65 (65)	2.26	11.9
	FLTA 2005 (≥12) ^{b,c}	200 µg via MDPI once daily	65 (55)	2.38	4.6
		Beclomethasone dipropionate 168 µg via MDI twice daily	72 (67)	2.41	10.4
		Placebo	69 (38)	2.35	–3.4
Montelukast sodium	031 (15–85) ^{b,c}	250 µg via MDPI twice daily	86 (86)	2.42	17.4
		500 µg via MDPI once daily	83 (64)	2.46	5.7
		Placebo	84 (37)	2.45	–6.1
	020 (15–85) ^{b,c}	10-mg tablet once daily	408 (91)	2.47	13.0
		Placebo	273 (86)	2.54	3.9
		10-mg tablet once daily	387 (89)	2.15	7.4
Nedocromil inhalation aerosol	CR1408 (12–70) ^{c,e}	Beclomethasone dipropionate 200 µg via MDI spacer twice daily	251 (90)	2.10	12.9
		Placebo	257 (82)	2.21	0.9
		11 mg 4 times daily via nebulizer	60 (93)	2.40	4.2
	CR2333 (12–70) ^{c,e}	Placebo	63 (89)	2.59	2.3
		11 mg 4 times daily via nebulizer	94 (91)	2.49	5.2
		Placebo	95 (86)	2.42	5.0
	CR1409 (18–70) ^{c,e}	11 mg 4 times daily via nebulizer	59 (76)	2.26	–1.8
		Placebo	62 (77)	2.02	9.4
	CR1691 (12–67) ^{c,e}	11 mg 3 times daily via nebulizer	68 (94)	2.69	0.7
		Placebo	71 (79)	2.59	5.8
Summary	Investigational medication		2,903 (86)	2.48	8.5
	Active comparator medication		399 (83)	2.24	13.6
	Placebo		1,649 (73)	2.46	3.6

Abbreviations: CFC, chlorofluorocarbon; FDA, US Food and Drug Administration; FEV₁, forced expiratory volume in 1 second; HFA, hydrofluoroalkane; MDI, metered-dose inhaler; MDPI, multidose dry powder inhaler; NA, not available.

^aA 6-week trial.

^bPrimary outcome measure was a pulmonary physiologic test.

^cA 12-week trial.

^dA 16-week trial.

^ePrimary outcome measure was a subjective assessment or other measure.

Table 3

Summary of pivotal pediatric trials and safety results used for the FDA approval of asthma controller medications approved in 1997–2010

Medication	Trial	Investigation medication and active comparator				Placebo			
		No.	No. (%) of SAEs	System	Asthma exacerbations	No.	No. (%) of SAEs	System	Asthma exacerbations
Ciclesonide ^a	343	480	18 (3.8)	9 RS, 9 Misc	7	221	6 (2.7)	4 RS, 2 Misc	4
Fluticasone ^a	FLTA 2006	351	2 (0.6)	1 RS, 1 GI	0	86	1 (1.2)	1 RS	1
	FLTA 2007	179	2 (1.1)	1 GI, 1 SS	0	83	2 (2.4)	2 RS	2
	FLTA 2008	164	1 (0.6)	1 GI	0	78	1 (1.3)	1 RS	1
Montelukast sodium ^a	049	201	4 (2.0)	3 RS, 1 GN	3	135	0 (0.0)	0	
Summary ^a		1,375	27 (2.0)	1 GN, 3 GI, 13 RS, 1 SS, 9 Misc	10	603	10 (1.7)	8 RS, 2 Misc	8
Nedocromil inhalation aerosol ^b	CR1574	80	6 (7.5)	6 RS	1	83	3 (3.6)	3 RS	1
	CR1978	48	1 (2.1)	1 NS	0	45	1 (2.2)	1 GI	0
	CR2233	136	4 (2.9)	NA	NA	140	5 (3.6)	NA	NA
	CR3003	148	2 (1.4)	NA	NA	144	7 (4.9)	NA	NA
Summary ^b		412	13 (3.2)	1 NS, 6 RS, 6 NA	1	412	16 (3.9)	1 GI, 3 RS, 12 NA	1

Abbreviations: FDA, US Food and Drug Administration; GI, gastrointestinal; GN, general complaint; NS, nervous system; RS, respiratory system; SAE, serious adverse event; SS, special senses; Misc, miscellaneous; NA, not available.

^aData provided as SAEs.

^bData provided as discontinuation due to an adverse event.

Analysis of efficacy data

As a first step in the data analysis, we evaluated the frequency of physiologic pulmonary measures (FEV₁ and peak expiratory flow rate) vs other types of primary outcome measures, such as subjective assessments. We then determined the frequency of positive outcome ($P < .05$) for the primary outcome measure. When evaluating the trials, FEV₁ was not only the most common primary outcome measure but also a measured outcome for 20 of the 23 trials. Therefore, we used this to further evaluate the differences in outcome among adult and pediatric asthma controller medication trials.

Within these trials, the baseline FEV₁ and the FEV₁ at the patient's last visit were recorded. We then determined the percentage change in FEV₁ from baseline to last visit. The percentage change of FEV₁ was then weighted for the number of participants in each group. The results of this weighting were then combined together to investigate overall placebo and investigational medication responses within the pediatric and adult subgroups.

An analysis of variance was performed on the data using the percentage change in FEV₁ as the dependent variable. The independent variables were the age group of the population (adult or pediatric) and treatment given (pharmacologic or placebo). This was then weighted for the number of patients in each arm analyzed. The statistical tests were conducted using SPSS statistical software, version 19.0 (SPSS Inc., Chicago, Illinois).

After determining the overall percentage of successful trials for all 23 trials, we performed a χ^2 analysis looking at differences between the pediatric and adult groups to determine whether the primary outcome measure was a pulmonary physiologic test or a subjective evaluation or a nonpulmonary physiologic outcome.

Analysis of safety data

We looked at the safety data from each trial submitted to the FDA to determine the number of participants in each arm who completed the study and the number of deaths and SAEs. All efficacy trials had specific data about the number of deaths in each study.

As a note, all nedocromil trials were included separately because those trials did not report SAEs, only discontinuations due to an AE. Also, the adult safety data for montelukast were a combination of the data from all phase 2b and 3 clinical trials, which added a significant number of patients to the adult safety sample size.

For the trials where SAEs were available, we categorized the SAEs into the following subgroups based on body systems for com-

parison: general complaints; cardiovascular system; gastrointestinal system; endocrine system; hematologic and lymphatic systems; metabolic, immunologic, and nutritional; nervous system; respiratory system; skin; special senses; genitourinary system; musculoskeletal system; and miscellaneous. The respiratory system was further categorized into asthma exacerbations.

These data are included in Tables 3 and 4 as a comparison to the other medications. The number of asthma exacerbations is included in these data because it was commonly the most frequent SAE reported in the pediatric trials. It is also shown in the adult trials for comparison. The percentage of SAEs was then compared between investigational and active medications and placebo.

To analyze this safety data, we used the χ^2 test with Yates correction to evaluate the frequency of AEs and SAEs within the pediatric and adult populations.

Results

Pediatric trials

A total of 2,769 children between the ages of 2 and 14 years were enrolled in 9 pivotal trials for 4 asthma controller medications approved between 1997 and 2010 (Table 1). There were 2 separate methods of evaluation used for these trials. Six trials used FEV₁ as the primary or secondary outcome measurement. The 3 remaining trials for nedocromil used a 20-point summary symptom score that involved domains, including daytime symptoms, nighttime awakenings, cough, and rescue inhaler use.

The total number of participants included in the pediatric safety population was 2,802. These participants were divided into 2 groups. The first was trials reporting SAEs, and the second was those reporting withdrawals due to an AE (Table 3). No deaths occurred in any of the pediatric trials.

Adult trials

A total of 4,951 adults and adolescents 12 years and older were enrolled in 14 pivotal trials (Table 2). All of these trials used FEV₁ as a primary or secondary outcome measure.

The total population included for the safety analysis was 6,764 participants. In terms of SAEs, the active comparator groups were combined with the investigational drug groups to create a pharmacologic group. These data sets were then separated into 2 categories of reporting: those trials reporting SAEs and those reporting withdrawals due to an AE (Table 4). There was 1 death in the montelukast group of the adult trials. The patient was a 50-year-old man

Table 4

Summary of pivotal adult trials and safety results used for the FDA approval of asthma controller medications approved in 1997–2010

Medication	Trial	Investigation medication and active comparator				Placebo			
		No.	No. (%) of SAEs	System	Asthma exacerbations	No.	No. (%) of SAEs	System	Asthma exacerbations
Beclomethasone dipropionate ^b	1081	181	8 (4.4)	1 GN, 1 GU, 1 RS, 1 GI, 2 NS, 2 SK	0	87	2 (2.3)	1 NS, 1 RS	0
	1129	230	17 (7.4)	NA	NA	117	20 (17.1)	NA	NA
Ciclesonide ^b	3031	522	9 (1.7)	1 SK, 2 GU, 2 GN, 3 RS, 1 GI	0	178	1 (0.6)	1 RS	1
	3030	304	3 (1.0)	1 MSK, 1 SK, 1 GU	0	152	1 (0.6)	1 RS	1
Fluticasone ^b	FLTA 2003	226	2 (0.9)	1 GI, 1 GU	0	73	1 (1.4)	1 RS	1
	FLTA 2004	202	4 (2.0)	1 GI, 2 RS, 1 Misc	1	69	1 (1.4)	1 LM	0
	FLTA 2005	169	4 (2.4)	2 GI, 1 SK, 1 GN	0	84	0 (0.0)	0	0
	FLTA 2001	143	0 (0.0)	0	70	0 (0.0)	0	0	0
Montelukast sodium ^b	Combined safety data ^a	2206	19 (0.9)	2 GN, 1 CV, 4 GI, 3 MSK, 1 NS, 6 RS, 2 GU	NA	1,180	18 (1.5)	1 MT, 1 MSK, 1 NS, RS 11, 3 SK, 1 GU	NA
Summary ^b		3,772	66 (1.7)	6 GN, 1 CV, 10 GI, 3 NS, 12 RS, 5 SK, 7 GU, 1 Misc, 4 MSK, 17 NA	1	1,806	44 (2.4)	1 LM, 1 MT, 2 NS, 15 RS, 3 SK, 1 GU, 1 MSK, 20 NA	3
Nedocromil inhalation aerosol ^c	CR1408	60	2 (3.3)	1 RS, 1 NS	1	63	3 (4.8)	3 RS	1
	CR2333	94	5 (5.3)	3 NS, 2 RS	1	94	7 (7.4)	6 RS, 1 GU	3
	CR1409	59	7 (11.9)	2 RS, 2 GN, 2 NS, 1 MSK	2	62	10 (16.1)	10 RS	6
	CR1691	68	1 (1.5)	1 Misc	0	71	0 (0.0)	0	0
Summary ^c		281	15 (5.3)	2 GN, 6 NS, 5 RS, 1 Misc, 1 MSK	4	290	20 (6.9)	19 RS, 1 GU	10

Abbreviations: FDA, Food and Drug Administration; CV, cardiovascular; GI, gastrointestinal; GN, general complaint; GU, genitourinary system; LM, lymphatic system; Misc, miscellaneous; MSK, musculoskeletal system; MT, metabolic; NA, not available; NS, nervous system; RS, respiratory system; SAE, serious adverse event; SK, skin.

^aCombined safety data for all phase 2b/3 pivotal trials.

^bData provided as SAEs.

^cData provided as discontinuation due to an adverse event.

who was a passenger in a motor vehicle collision. The specific study was not designated.

Statistical analysis findings

As indicated in Table 5, the asthma controller medication trials using physiologic pulmonary outcome measures had a high frequency of demonstrating superiority to placebo (93% vs 44%). Moreover, no significant differences were found in the outcome of adult or pediatric asthma controller medication using the physiologic pulmonary function tests (Table 6).

Regarding the safety analysis, serious asthma exacerbations were significantly more common among the pediatric trials (0.9%) compared with adult trials (0.2%) (Table 7). Also, the frequency of

this type of asthma exacerbation was similar among the pediatric patients assigned to drug or placebo.

The frequency of serious asthma exacerbation was significantly higher among adults assigned to placebo (0.4%) than those treated with asthma controller medications (0.06%). Furthermore, the overall risk of serious asthma exacerbation was higher in the placebo group (0.8%) compared with the drug group (0.4%), when all of the data from the adult and pediatric trials were included (Table 7).

Discussion

The results of our study support the suggestion that physiologic pulmonary measures are more sensitive in demonstrating the efficacy of asthma controller medications compared with other measures of outcome (93% vs 44%) regardless of the age group being tested. These physiologic measures are not meant to completely

Table 5

Frequency of success among adult asthma controller medication trials (n = 14) and pediatric asthma controller medication trials (n = 9) in relation to physiologic pulmonary primary outcome measures compared with other primary outcome measures^a

Measure	Adult trials	Pediatric trials
Physiologic pulmonary function outcomes		
FEV ₁	8/8	3/4
Morning PEF	2/2	0/0
Subjective and other outcome measures		
Summary Symptom Score	1/4	0/1
Percentage of symptom-free days	0/0	1/2
Worst symptom score	0/0	1/1
Growth velocity vs placebo	0/0	1/1

Abbreviations: FEV₁, forced expiratory volume in 1 second; PEF, peak expiratory flow.

^a93% vs 44% success rate ($\chi^2_1 = 4.38$, $P = .04$ with Yates correction).

Table 6

Analysis of variance evaluating the role of asthma controller medications compared with placebo using change in FEV₁ among the pediatric sample of patients compared with adult patients, weighted by the number of patients in the trials

Source	Type 3 sum of squares	df	Mean square	F	P value
Corrected model	89,566	4	22,392	7.30	<.001
Intercept	242,972	1	242,972	79.25	<.001
Age	7,947	1	7,947	2.59	.11
Assignment	73,755	2	36,878	12.03	<.001
Age × assignment	159	1	159	0.052	.82
Error	162,498	53	3,066		
Total	632,254	58			
Corrected total	252,064	57			

Adjusted $R^2 = 0.307$. Weighted least squares regression was weighted by the sample size.

Table 7

Frequency of asthma exacerbations of serious nature among the pediatric trials (n = 5) and adult trials (n = 7) including 4,438 patients with asthma

	No. of asthma exacerbations	No. without asthma exacerbations	Total
No. among adult trials	4 ^b	2,456	2,460
No. among pediatric trials ^a	18 ^c	1,960	1,978
Total	22 ^d	4,416	4,438

^aEighteen of 1,978 pediatric patients (0.9%) experienced serious exacerbation of asthma compared with 4 of 2,460 (0.2%) among adult patients ($\chi^2_1 = 10.95$, $P < .001$).

^bOne assigned to drug group (1/1,747, 0.06%) and 3 to placebo (3/713, 0.4%) (Yates $\chi^2_1 = 2.17$, $P = \text{NS}$).

^cTen assigned to drug group (10/1,375, 0.7%) and 8 to placebo (8/603, 1.3%) (Yates $\chi^2_1 = 1.045$, $P = \text{NS}$).

^dEleven of 3,122 patients assigned to drug group (0.4%) compared with 11 of 1,326 patients assigned to placebo (0.8%) ($\chi^2_1 = 4.26$, $P = .04$).

evaluate the disease severity but are limited to evaluating measurable physiologic changes.⁴

Overall, there were no deaths related to the study medications or study procedures among the adult and pediatric patients (n = 9,566). This finding is of significance and should be considered when designing and conducting asthma controller medications, especially when being reviewed by human subject protection committees.^{5–7}

However, serious asthma exacerbations were significantly more common among the pediatric trials (0.9%) compared with the adult trials (0.2%). This increased risk of asthma exacerbation was not related to assignment into the drug or placebo group in either the adult or pediatric populations. One pediatric trial, however, was 52 weeks long, which allowed the trial to have an effect on asthma exacerbations. However, when looking at overall time enrolled in the trials, the exposure time was 96 weeks for the pediatric patients and 82 weeks for the adult patients, thus illustrating that the proportionately longer time of enrollment by the pediatric patients does not make up for the large difference in the number of asthma exacerbations. These findings need to be considered in the future design and conduct of pediatric asthma controller medication trials.^{8–10}

All of these data are from short-term trials and cannot fully address the risk-benefit ratio of these treatments in the long term. Furthermore, these data do not fully establish the risk-benefit ratio of the various classes of asthma control medications. This concern is of significance among the pediatric group of patients who may be at risk after long exposures to treatments that may alter their growth or their immune system or metabolism. Such research should be conducted under the auspices of either the FDA or the National Institutes of Health.

The results of this study suggest that physiologic pulmonary function tests are far superior to other outcome measures among asthma controller medication trials, regardless of the age of the participants. Although serious asthma exacerbations are far more common among trials for pediatric patients compared with adult patients, regardless of treatment assignment to placebo or drug, they are still below 1%. These findings could help guide the design and conduct of future asthma controller medication trials.

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