Fexofenadine is efficacious and safe in children (aged 6-11 years) with seasonal allergic rhinitis

Ulrich Wahn, MD,[a]*‡ Eli O. Meltzer, MD,[b]*‡ Albert F. Finn, Jr, MD,[c]*‡
Marek L. Kowalski, MD, PhD,[d]‡ Paola Decosta, MD,[e] Gunilla Hedlin, MD,[f]*
Pierre Scheinmann, MD,[g]* Claus Bachert, MD, PhD,[h]* Jose E. Rosado Pinto, MD,[i]*
Carlos Baena-Cagnani, MD,[j]‡ Paul Potter, MD,[k]‡ F. Estelle R. Simons, MD,[l]* and
Erik Ruuth, MD, PhD[e] *Berlin, Germany, San Diego, Calif, Charleston, SC, Lodz, Poland, Paris, France, Stockholm, Sweden, Ghent, Belgium, Lisbon, Portugal, Córdoba, Argentina, Mowbray, South Africa, and Winnipeg, Manitoba, Canada*

Asthma, rhinitis, other respiratory diseases

Background: This is the first prospective, randomized, double-blind, placebo-controlled study showing statistical improvement of an H_1-antihistamine in children with seasonal allergic rhinitis in all symptoms throughout the entire treatment period.
Objective: This randomized, placebo-controlled, parallel-group, double-blind study was performed to assess the efficacy and safety of fexofenadine in children with seasonal allergic rhinitis.
Methods: This study was conducted at 148 centers in 15 countries. Nine hundred thirty-five children (aged 6-11 years) were randomized and treated with either fexofenadine HCl 30 mg (n = 464) or placebo (n = 471) tablets twice a day for 14 days. Individual symptoms (sneezing; rhinorrhea; itchy nose, mouth, throat, and/or ears; itchy, watery, and/or red eyes; and nasal congestion) were assessed at baseline and then daily at 7:00 AM and 7:00 PM (±1 hour) during the double-blind treatment period. Each total symptom score was the sum of all symptoms, excluding nasal congestion. The primary efficacy variable was the change from baseline in the average of the daily 12-hour evening reflective total symptom scores throughout the double-blind treatment. Safety was evaluated from adverse-event reporting, vital signs, physical examinations, and clinical laboratory data at screening and study end point.

Results: Fexofenadine was significantly superior to placebo in the primary efficacy analysis ($P \leq .0001$). Individual symptom scores showed statistically significant superiority compared with placebo ($P < .05$), including nasal congestion in the evening reflective assessment ($P < .05$). There was no significant difference in adverse events between fexofenadine and placebo, either overall or by causality.
Conclusion: The efficacy and safety of the H_1-antihistamine fexofenadine has been confirmed in this multicenter, multinational study of children aged 6 to 11 years with seasonal allergic rhinitis. (J Allergy Clin Immunol 2003;111:763-9.)

Allergic rhinitis is the most common chronic condition in children.[1] Estimates of its prevalence in children, which varies from country to country, have been reported to be as high as 40%,[2] and it has been reported that the incidence of allergic rhinitis in children is rising.[3]

The symptoms of seasonal allergic rhinitis (SAR), including sneezing, rhinorrhea, nasal congestion, and the associated symptoms of itchy nose, palate, throat, and/or ears and itchy watery, and/or red eyes, can have a considerable impact on patients' quality of life and activities of daily living. Data indicate that almost a million school days are missed per year as a direct result of allergic rhinitis in the United States.[4] In addition, children with untreated allergy symptoms exhibit lower learning ability at school compared with nonallergic children.[5] Furthermore, if left untreated, allergic rhinitis can potentially exacerbate and contribute to asthma[6] as well as other comorbidities such as conjunctivitis, otitis, dental malocclusions, sinusitis, respiratory infections, and learning problems.[7-12]

Antihistamines have been a valuable allergic rhinitis treatment for decades, and data from studies in adult populations have been widely reported. Although some studies have assessed symptom relief of SAR in children using antihistamines,[13-18] including a postmarketing surveillance program,[19] only one study[13] has used the same end points as assessed in adult clinical studies. Fexofenadine (Allegra, Aventis) is a nonsedating, nonimpairing, selective H_1-receptor antagonist approved for the treat-

Abbreviations used
AE: Adverse event
bid: Two times per day
mITT: Modified intention-to-treat
PP: Per protocol
qid: Four times per day
SAR: Seasonal allergic rhinitis
TEAE: Treatment-emergent adverse event
TSS: Total symptom score

ment of SAR. Large, randomized trials have been performed in adults to show the efficacy and safety of this agent in SAR.[20-23] Previous studies have shown that doses of fexofenadine HCl up to 60 mg 2 times per day (bid) are safe and well tolerated in children aged 6 through 11 years.[24,25] The present study was conducted to confirm the efficacy and safety of twice-daily dosing of fexofenadine HCl (30 mg bid) compared with placebo in the treatment of SAR in children.

METHODS

Patients

Children aged 6 through 11 years with spring or fall SAR (allergic to pollens of the appropriate season) and an approximate 1-year history of SAR were enrolled. A positive skin prick test result (wheal diameter ≥3 mm compared with diluent within 15 minutes of the skin prick) to at least 1 allergen indigenous to the study site area or, when relevant, to a child's site of residence, which must have been positive in serum allergen-specific IgE testing, was required. In addition, the appropriate sensitizing allergen was required to be present at visit 1 and likely to be present for 3 weeks from visit 1. Children also needed to satisfactorily demonstrate that they could swallow the study medication.

At visit 1 (baseline), each child (with the help of his or her caregiver) provided a 12-hour reflective assessment of the severity of the allergy symptoms. Symptoms included the following: sneezing; rhinorrhea; itchy nose, palate, throat, and/or ears; itchy, watery, and/or red eyes; and nasal congestion. Each symptom was evaluated on a 5-point scale: 0 = absent; 1 = mild; 2 = moderate; 3 = severe; and 4 = very severe. A total symptom score (TSS) was calculated by adding the individual symptom scores, excluding nasal congestion (maximum possible TSS = 16). A reflective TSS of ≥6 at the initial visit, with 2 or more symptoms with a minimum score of 2 (moderate), was necessary for entry into the trial. Blood samples were taken at visit 1 for allergen-specific assays of IgE of the individual allergen(s) from the skin prick test or for each individual allergen in a mixture. As far as possible, individual allergens were tested. Serum-specific IgEs were determined by the Fluoro Enzyme Immuno Assay technique (UNICAP, Pharmacia), and a positive serum allergen-specific IgE was defined as IgE class ≥2 (≥0.7 kUA/L).

Exclusion criteria included (but were not limited to) the following: an upper respiratory tract infection within 30 days of the study; purulent conjunctivitis or rhinitis of any type other than SAR; obstructive deviated nasal septum or obstructive nasal polyposis; active perennial allergic rhinitis; cystic fibrosis; immunotherapy to treat SAR; and clinically significant cardiovascular, hepatic, neurologic, psychiatric, endocrine, or other major systemic disease. Drugs that were excluded included oral, nasal, and inhaled corticosteroids for 30, 14, and 30 days, respectively, before visit 1, and inhaled or oral cromolyn sodium for 14 days before the visit. Children were also excluded from the trial if nasal congestion was con-

sidered very severe. Between visits 1 and 2, the following drugs were excluded: (a) the H_1-receptor antagonists astemizole, loratadine, fexofenadine, and cetirizine; (b) leukotriene modifiers, such as montelukast and zafirlukast.

The study protocol was approved by institutional review boards, and an informed-consent form was obtained from the parent/guardian and the child before inclusion.

Study design

This double-blind, randomized, parallel-group, placebo-controlled study was conducted at 148 centers in 15 countries, as follows: Argentina (16), Australia (9), Austria (1), Chile (3), Finland (3), France (12), Germany (5), Israel (3), Italy (7), Poland (10), Portugal (2), South Africa (18), Spain (6), Uruguay (2), and the United States (51).

The study included 5 visits, as follows: screening (visit 1, day –8 to day –4), randomization (visit 2, day 1), during double-blind treatment (visit 3, day 6 to day 10), end of double-blind treatment (visit 4, day 15 to day 17), and follow-up (visit 5, day 22 to day 24). Children who met symptom criteria at visit 1 entered a 5- to 9-day, single-blind, placebo lead-in phase. After completion of this phase, each child was required to have an average TSS of ≥5 for the last 2 7:00 PM reflective TSSs (excluding nasal congestion) to qualify for randomization to the double-blind phase of the study. Each child was also required to have a concordant positive IgE skin prick test result and positive serum IgE test result for randomization, in addition to the presence of the appropriate pollen at visit 1 and its likely presence for 3 weeks. Compliance was assessed by tablet counts at visit 2 (day 1) for the single-blind medication and at visit 3 (days 6-10) and visit 4 (days 15-17) for the double-blind treatment; any child who had either missed >1 dose or taken an extra dose was excluded from the study. The caregiver was instructed to administer or supervise the administration of the study medication.

Children were randomized to receive either fexofenadine HCl 30 mg bid or matching placebo. Tablets were taken at 7:00 PM and 7:00 AM (±1 hour) for 2 weeks, with no dosing instructions regarding food intake. SAR symptoms were assessed daily at 7:00 AM and 7:00 PM (±1 hour) for the previous 12-hour period (hereafter referred to as *AM-reflective* and *PM-reflective*, respectively) by the child and caregiver immediately before dosing. Diary cards were collected at visits 2, 3, and 4 (though visit 3 was not mandatory).

Assessments: efficacy analysis

The primary efficacy variable was the mean change from baseline in the average PM-reflective TSS throughout the double-blind treatment period (also calculated as mean percentage change from baseline). The secondary efficacy variables were the AM-reflective TSS, the PM- and AM-reflective individual SAR symptom scores, and the daily PM-reflective TSS.

Assessments: safety analysis

Children recorded any adverse events (AEs) that occurred during the study. The investigator also assessed the children for AEs and instructed the children to report any events that occurred during the study. Laboratory tests were performed at visits 1 and 4. Physical examinations, including vital signs measurements, were performed at visits 1, 2, and 4. (In those cases in which visit 3 was made, AEs as well as vital signs were recorded.) Vital signs included systolic and diastolic blood pressure, respiratory rate, and heart rate.

Statistical analysis

Analyses were undertaken on the modified intention-to-treat (mITT) population. This was defined as all randomized children who received at least 1 dose of double-blind treatment and had a
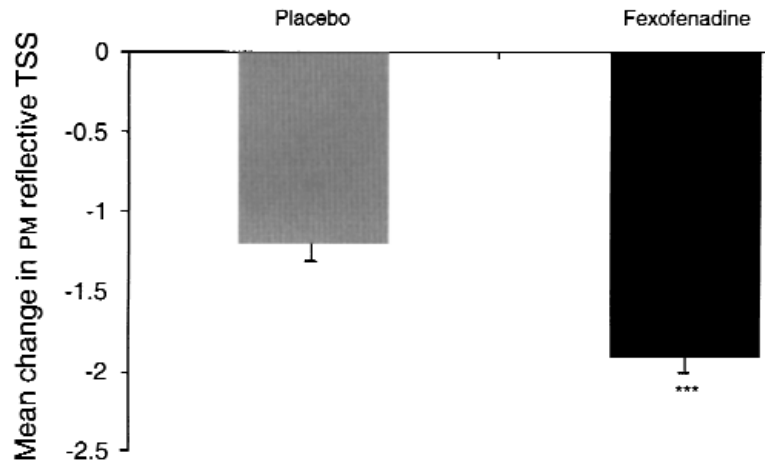
FIG 1. Mean (± SE) change in PM-reflective total symptom score *(TSS)* with modified intention-to-treat (mITT) population. ***$P \leq$ .0001 versus placebo.

baseline and at least 1 double-blind period PM-reflective assessment. Demographic and baseline characteristics were compared between treatment groups by Wilcoxon rank-sum tests for continuous variables and Fisher exact tests for categoric variables. Analysis of covariance was used to compare the effects of fexofenadine HCl 30 mg bid with those of placebo. For the primary efficacy analysis, the baseline score (randomization baseline TSS for AM and PM was defined as the average of assessments during the placebo single-blind period on day –2, day –1, and day 1 before double-blind treatment) was included as a continuous covariate, and treatment and pool center were included as fixed effects. A 2-sided 95% CI of the treatment difference was derived by adjusted (least-squares) mean from the analysis of covariance. Secondary efficacy variables were analyzed by the same model. The number of children with at least 1 treatment-emergent AE (TEAE) was compared between the treatment groups by Fisher exact test.

RESULTS

Demographics

Of 1961 children screened, 935 received study medication (n = 464 fexofenadine; n = 471 placebo). The most common reasons for nonrandomization (visit 1 and visit 2) were positive IgE test results (n = 499), a low TSS (n = 383), and the lack of a positive skin prick test result (n = 219). Three children were excluded from the mITT population because of the lack of postbaseline PM-reflective TSS data, leaving a total of 932 children in the mITT population (n = 469 placebo; n = 463 fexofenadine). Of these 932 children, 781 had no major protocol violations and were classified as protocol-correct (per protocol [PP] population). Nine hundred children completed the study. Seven children withdrew from the study because of treatment failure (fexofenadine, n = 3; placebo, n = 4). In all instances the frequency of withdrawals was similar across treatment groups. Treatment duration in the mITT population was also comparable between groups, with a median of 15 days and a mean of 15.3 days for each treatment group. The mean number of doses of double-blind treatment taken by the children in the mITT population was 28.5 (fexofenadine, 28.6; placebo, 28.4).

There were no statistically significant differences in baseline characteristics (including baseline PM-reflective individual symptom scores and TSS), between treatment groups apart from sex (P = .0417; Table I). Children in the mITT population had a median age of 9 years (mean, 8.8 years; range, 5-12 years). The numbers of children who had histories of allergy other than SAR were 271 (58.5% of 463) for the fexofenadine-treated group and 273 (58.2% of 469) for the placebo-treated group. The numbers of children who had histories of asthma were 133 (28.7% of 463) for the fexofenadine-treated group and 141 (30.1% of 469) for the placebo-treated group. Concordant positive serum allergen-specific IgE test and IgE skin prick test results were observed in 928 (99.6%) of the 932 children in the mITT population.

Primary efficacy analysis

Fexofenadine was significantly superior to placebo in the PM-reflective TSS ($P \leq$ .0001; Fig 1). The mean change from baseline was 1.94 for the fexofenadine-treated group and 1.21 for the placebo group.

Secondary efficacy analysis

Fexofenadine HCl 30 mg bid significantly improved the average AM-reflective TSS compared with placebo ($P \leq$ .0001). The change from baseline was –1.67 for the fexofenadine-treated group and –0.93 for the placebo group. The mean changes from baseline and treatment difference were consistent with those seen in the PM-reflective TSS assessment. In the fexofenadine HCl 30 mg bid group, all PM-reflective individual symptom scores, including nasal congestion, were significantly reduced compared with placebo (sneezing, $P \leq$ .0001; rhinorrhea, P = .0005; itchy nose, palate, throat, and/or ears, $P \leq$ .0001; itchy, watery, red eyes, $P \leq$ .0001; nasal congestion P = .0079; Fig 2). The AM-reflective assessment individual symptom scores were significantly reduced compared with placebo and were comparable to those observed when measured for the PM-reflective assessments (sneezing, $P \leq$ .0001; rhinorrhea, P = .0006;
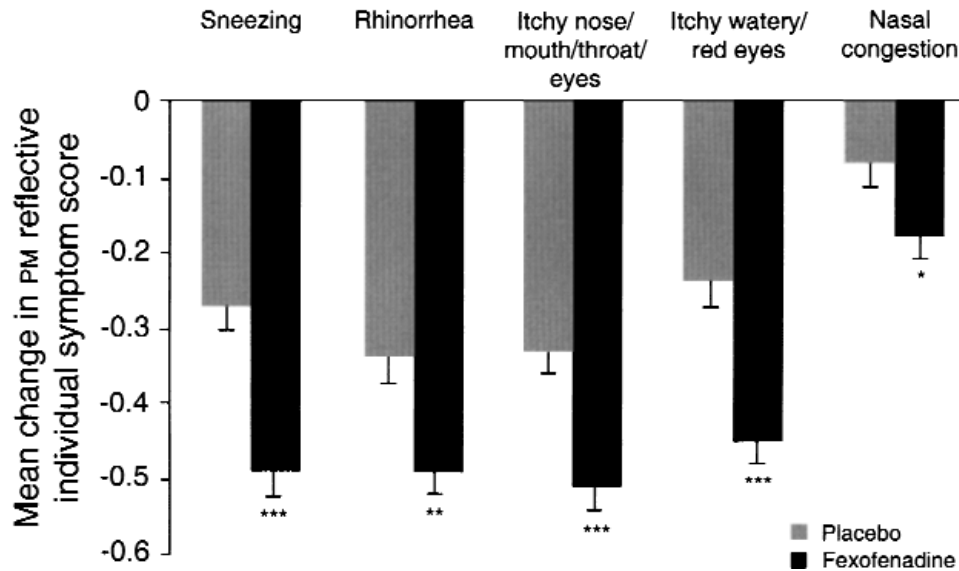
FIG 2. Twelve-hour PM-reflective individual symptom scores with modified intention-to-treat (mITT) population. All *P* values are for the treatment group versus placebo. *P < .01. **P < .001. ***P ≤ .0001.

TABLE I. Demographic and baseline characteristics for modified intention-to-treat population

Characteristic	Placebo		Fexofenadine HCl	
Total treated (%)	469 (100.0)		463 (100.0)	
Age (y)				
Mean ± SD	8.8 ± 1.6		8.8 ± 1.6	
Median (range)	9 (5-12)		9 (6-12)	
Race				
White N (%)	373 (79.5)		377 (81.4)	
Black N (%)	33 (7.0)		34 (7.3)	
Asian/Oriental N (%)	7 (1.5)		6 (1.3)	
Multiracial N (%)	56 (11.9)		46 (9.9)	
Randomization baseline PM				
TSS (mean ± SD)	7.07 ± 0.103		6.80 ± 0.097	
Sneezing (mean ± SD)	1.75 ± 0.035		1.69 ± 0.035	
Rhinorrhea (mean ± SD)	1.94 ± 0.034		1.89 ± 0.034	
Itchy nose, mouth, throat and/or ears (mean ± SD)	1.76 ± 0.036		1.68 ± 0.037	
Itchy, watery, red eyes (mean ± SD)	1.62 ± 0.041		1.53 ± 0.040	
Nasal congestion (mean ± SD)	1.79 ± 0.039		1.78 ± 0.038	
	Male	Female	Male	Female
Sex: N (%)	312 (66.5)	157 (33.5)	278 (60.0)	185 (40.0)
Weight (kg)				
N	311	156	278	185
Mean ± SD	34.6 ± 11.3	33.1 ± 10.6	33.9 ± 9.6	33.8 ± 11.7
Median (range)	33.0 (15.5-83.9)	30.8 (16.0-68.9)	32.0 (17.5-60.3)	32.0 (19.0-114.8)
Height (cm)				
N	312	157	276	185
Mean ± SD	136.7 ± 12.1	135.5 ± 12.3	136.5 ± 10.7	135.2 ± 11.5
Median (range)	137.0 (102.0-172.7)	134.6 (107.0-164.0)	136.0 (111.0-164.0)	135.0 (110.0-162.0)

itchy nose, palate, throat, and/or ears, *P* ≤ .0001; itchy, watery, red eyes, *P* ≤ .0001). Nasal congestion showed a trend toward improvement in the AM-reflective assessment compared with placebo (*P* = .0952).

Assessment of the daily PM-reflective TSS showed that the improvement in TSS with fexofenadine HCl 30 mg bid was statistically superior to placebo for each day of the 14-day double-blind treatment period. A significant improvement compared with placebo was observed from the first day on treatment (*P* ≤ .0001) and was maintained throughout the entire treatment period (*P* < .0007, day 14; Fig 3).

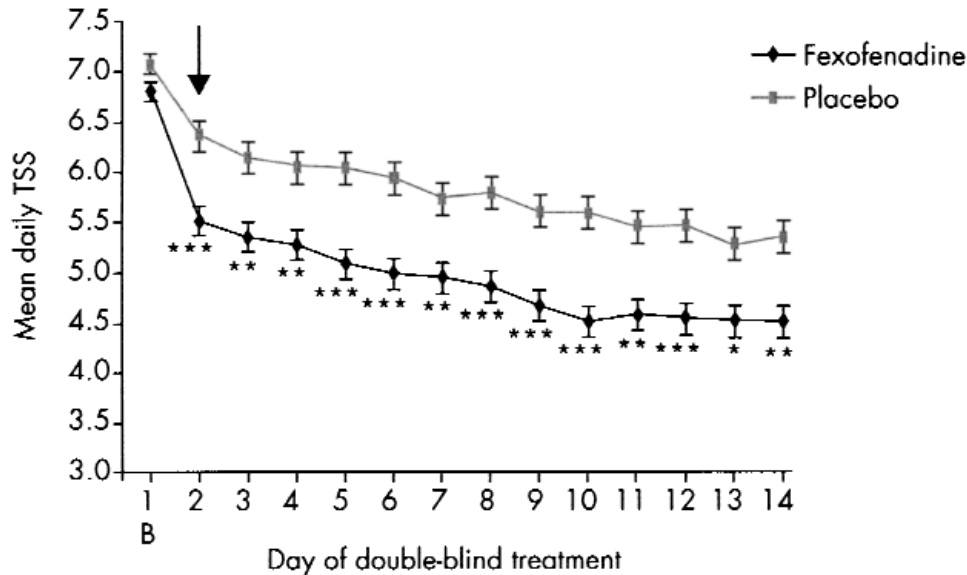For all efficacy variables, comparable results were obtained when the PP population was used for analysis.

FIG 3. Daily PM-reflective total symptom score *(TSS)* during double-blind treatment period—modified intention-to-treat (mITT) population. The *arrow* above the graph indicates the first point at which the effects of treatment would be observed (Day 2); Day 1 corresponds to the baseline *(B)*. *$P < .01$. **$P < .001$. ***$P \leq .0001$.

Safety analysis

In all, 935 children received at least 1 dose of the double-blind treatment and were therefore included in the safety analysis. The frequency of TEAEs was similar between the fexofenadine (85 of 464, 18.3%) and placebo (88 of 471, 18.7%) groups. The number of TEAEs possibly related to treatment was also comparable. A total of 2.7% (25) of the 935 children (fexofenadine, n = 14; placebo, n = 11) reported at least 1 TEAE possibly related to treatment. None of the possibly related TEAEs occurred in >1% of children (Table II).

Three children in the fexofenadine-treated group experienced TEAEs that led to withdrawal from the study, but these were not considered to be related to treatment (asthma, n = 1; upper respiratory infection, n = 1; vomiting, n = 1). One child experienced a serious adverse event, neutropenia, in the fexofenadine-treated group on routine evaluation that was thought to be related to treatment. Laboratory tests of the aforementioned child revealed decreased neutrophil levels on day 15 after 14 days of double-blind treatment: 0.4×10^9/L compared with 2.3×10^9/L at screening. This serious adverse event was reported as mild in intensity, and the child was asymptomatic and recovered without sequelae. Total leukocyte counts for this child remained stable during the follow-up but below the normal range of screening. Because serologic work was consistent with recent seroconversions for *Mycoplasma pneumoniae* and *Varicella* IgG, subclinical infections might offer an alternative explanation for the event.

There were no significant differences in changes in clinical laboratory and vital signs results between the fexofenadine- and placebo-treated groups.

TABLE II. Treatment emergent adverse events (>1%)—safety double-blind population

	No. of children (%)	
	Placebo	**Fexofenadine HCl**
Total in safety double-blind population	471 (100.0)	464 (100.0)
Total with TEAEs*	88 (18.7)	85 (18.3)
Headache	13 (2.8)	23 (5.0)
Epistaxis	5 (1.1)	7 (1.5)
Upper respiratory infection	5 (1.1)	7 (1.5)
Pharyngitis	1 (0.2)	6 (1.3)
Sinusitis	0 (0.0)	6 (1.3)
Nausea	1 (0.2)	5 (1.1)
Rash	3 (0.6)	5 (1.1)
Accidental injury	6 (1.3)	4 (0.9)
Asthma	9 (1.9)	3 (0.6)
Infection	5 (1.1)	1 (0.2)
Gastrointestinal pain	5 (1.1)	1 (0.2)

Treatment-emergent adverse events (TEAEs) were classified according to the HART coding system.

*$P = 1.00$ incidence of all TEAEs between fexofenadine and placebo by Fisher exact test.

DISCUSSION

Allergic rhinitis might exacerbate and contribute to the symptoms of several comorbid conditions. The high prevalence of concomitant rhinitis and asthma is reported in the ARIA guidelines,[26] which propose the concept that these might be local manifestations of "one-airway, one disease." Indeed, in patients with concomitant rhinitis and asthma, antihistamine treatment has shown significant improvement in both disorders.[27,28] Furthermore, previ-

ous studies have indicated that early intervention in the treatment of allergies could help prevent progression to other allergic disorders, such as asthma.[29,30]

Few studies in children with allergic rhinitis have involved objective efficacy end points.[31,32] No objective end points are currently required by the regulatory agencies for the assessment of drug efficacy for SAR treatment, and the efficacy of antihistamines in adults has been established with the standard and accepted TSS assessment. The measures of effectiveness in allergic rhinitis trials preferred by regulatory agencies are patients' self-related composite symptom scores and the resulting TSSs. The results of this study demonstrate that fexofenadine HCl (30 mg bid) is effective in reducing both the TSS and individual symptom scores of SAR compared with placebo. These effects were maintained throughout the entire 2-week, double-blind treatment period. The results of this study support previous data in which 30 or 60 mg fexofenadine HCl has been shown to suppress histamine-induced wheal and flare within 1 to 2 hours in children.[24]

A number of other studies have examined the effects of antihistamines in children with SAR.[13-19] However, only one of these studies, which investigated the effects of cetirizine (5 and 10 mg 4 times per day [qid]) in a randomized, double-blind, placebo-controlled trial of children with SAR aged 6 to 11 years, used symptom scoring similar to that used in adult studies.[13] This study showed that cetirizine (10 mg qid) is effective in the treatment of SAR (n = 209), as assessed by measurement of the TSS, in 2 of 4 weeks; the first week of treatment did not reach statistical significance. In this study the TSS corresponded to the sum of the individual symptoms of sneezing, nasal discharge, itchy eyes, itchy nose or mouth, and conjunctivitis but excluded nasal congestion. Assessment of individual symptoms showed that cetirizine (10 mg qid) demonstrated a significant decrease in the symptoms of itchy eye and itchy nose or mouth. There were no statistically significant differences from placebo for nasal discharge, conjunctivitis, sneezing, or nasal congestion with cetirizine (10 mg).

Traditionally, antihistamines have not been considered effective in relieving nasal congestion; accordingly, second-generation antihistamines are not indicated for the relief of nasal congestion. Nasal congestion is considered a vascular response involving a wide range of mediators, such as kinins, prostaglandin D_2, and leukotrienes. In the current study, fexofenadine HCl 30 mg bid showed statistically significant efficacy in relieving all symptoms of SAR, including ocular symptoms and nasal congestion. In the AM-reflective assessment, nasal congestion showed a trend toward improvement (P = .0952). Similarly, other studies in adults with SAR have shown significant efficacy with fexofenadine in relieving all symptoms of SAR.[20,22,33] The effect of fexofenadine on nasal congestion might reflect an activity that is broader than its antagonism at the H_1-receptor. Numerous in vitro studies with fexofenadine have highlighted the potential of this agent to produce significant anti-inflammatory effects at clinically relevant concentrations,[34-38] and it is hypothesized that these effects might contribute to inhibition of the late-phase response.[37]

In this large pediatric population, the incidence and severity of reported adverse events with fexofenadine were similar to those for placebo. The results of this trial confirm previous findings in which fexofenadine HCl at doses of up to 60 mg bid are safe and nonsedating in children aged 6 to 11 years.[25] This finding is further supported by the results of dose-response trials in healthy individuals, in which doses of up to 690 mg bid for 1 month were found to be safe and well-tolerated.[39,40] Extensive studies in children and adults have also shown no effect of fexofenadine on QT_c compared with placebo.[24,25,41] The proven efficacy of fexofenadine, in combination with its nonsedating and nonimpairing profile, evident even at doses in excess of those recommended by the manufacturer, offers validation for its use in the treatment of all symptoms of allergic rhinitis in children and adults.

In conclusion, previous studies have demonstrated that the pharmacokinetics and pharmacologic effects of fexofenadine in children are similar to those in adults and that fexofenadine is safe and well-tolerated in children aged 6 to 11 years. The results of this study clearly demonstrate that fexofenadine HCl 30 mg bid tablets are effective at reducing the symptoms of SAR, including nasal congestion, in children aged 6 to 11 years; this effect was maintained throughout the entire 2-week study period.

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