Long-term safety study of levalbuterol administered via metered-dose inhaler in patients with asthma

Daniel L. Hamilos, MD*; Anthony D'Urzo, MD†; Robin J. Levy, MD‡; Michael Marcus, MD§; Kenneth Tripp, MA‖; Merdad Parsey, MD, PhD‖; Rudolf A. Baumgartner, MD‖; and William K. McVicar, PhD‖

Background: Previous studies have raised concerns regarding the safety of regular use of β_2-agonists for treating asthma. Few studies have explored the safety of at least 1 year of use of racemic albuterol, and none have examined long-term dosing of levalbuterol.

Objective: To examine the long-term safety of levalbuterol hydrofluoroalkane (HFA) vs racemic albuterol HFA administered via metered-dose inhaler (MDI) in patients with stable asthma.

Methods: Patients with mild to moderate asthma (mean forced expiratory volume in 1 second [FEV_1], 68.3% of predicted) 12 years or older participated in a multicenter, parallel-group, open-label study. Patients were randomized to levalbuterol HFA MDI (90 μg; 2 actuations of 45 μg; n = 496) or racemic albuterol HFA MDI (180 μg; 2 actuations of 90 μg; n = 250) for 52 weeks of 4 times daily dosing. The primary end point was the incidence of postrandomization adverse events. Asthma exacerbations and pulmonary parameters were also assessed.

Results: The overall incidence of adverse events was similar for levalbuterol (72.0%) and racemic albuterol (76.8%). Rates of β-mediated adverse events, serious adverse events, and discontinuations because of adverse events were low (<15%) and were comparable between groups. Rates of asthma adverse events for levalbuterol and racemic albuterol were 18.3% and 19.6%, respectively. Mean percentage of predicted FEV_1 improved after dosing and was stable for both groups.

Conclusion: In this trial, up to 52 weeks of regular use of levalbuterol HFA MDI or racemic albuterol HFA MDI was well tolerated, and no deterioration of lung function was detected during the study period.

Ann Allergy Asthma Immunol. 2007;99:540–548.

INTRODUCTION

Asthma is a common chronic respiratory disease that has substantial medical and economic impact. Approximately 20 million people in the United States have asthma and 9 million American children younger than 18 years have been diagnosed as having the disease.[1,2] The prevalence of asthma increased by 75% from 1980 to 1994, and during this time the rates in children increased more than 160%.[3] In 2003, there were 12.7 million physician office visits and in 2002 1.9 million emergency department visits because of asthma.[1]

Short-acting β_2-agonists play a major role in asthma care. Racemic albuterol is a 1:1 mixture of (R)- and (S)-albuterol, with (R)-albuterol having bronchodilation activities.[4,5] Levalbuterol is the (R)-isomer of racemic albuterol and is available in solution for nebulization and as a metered-dose inhaler (MDI). Several preclinical studies suggest that (S)-albuterol may interfere with the effects of (R)-albuterol,[6–17] although the clinical relevance of this is unclear.

Previous studies indicate that regular use of β_2-agonists increases risks of deleterious effects, including asthma events and asthma exacerbations.[18–25] The National Heart, Lung, and Blood Institute currently recommends that β_2-agonists be used as needed to relieve symptoms.[26] However, because long-term dosing is still prevalent,[27] the potential health risks associated with long-term regular dosing with β_2-agonists warrant further investigation.

Only a few studies have investigated the safety of long-term (≥1 year) use of short-acting β_2-agonists administered via MDI,[28] and no previous studies have examined the regular dosing of levalbuterol during this time frame. This study evaluated the long-term safety of regular use of levalbuterol hydrofluoroalkane (HFA) MDI (12 months of 4 times daily dosing) compared with racemic albuterol HFA MDI.

* Massachusetts General Hospital, Boston, Massachusetts.
† Primary Care Lung Clinic, Toronto, Ontario, Canada.
‡ Family Allergy & Asthma Center, PC, Atlanta, Georgia.
§ Staten Island, New York.
‖ Sepracor Inc, Marlborough, Massachusetts.

Drs Hamilos, D'Urzo, Levy, and Marcus are Sepracor investigators who participated in this study. Dr McVicar is a Sepracor employee. Mr Tripp, Dr Baumgartner, and Dr Parsey are former Sepracor employees. Mr Tripp is currently at FoldRx Pharmaceuticals Inc, Cambridge, MA. Dr Parsey is currently at Genentech, San Francisco, CA. Dr Baumgartner is currently at Inotek Pharmaceuticals Corp, Beverly, MA.

This study was supported by Sepracor Inc, Marlborough, MA.
Received for publication January 29, 2007.
Received in revised form June 20, 2007.
Accepted for publication July 17, 2007.

METHODS

Study Design

This was a randomized, open-label, active-controlled, multicenter, parallel-group study that evaluated the safety of 4 times daily dosing of 90 μg of levalbuterol HFA MDI (2 actuations; 45 μg per actuation; XOPENEX HFA; Sepracor Inc, Marlborough, MA) and 180 μg of racemic albuterol HFA (2 actuations; 90 μg per actuation; Proventil HFA; Schering-Plough Co, Kenilworth, NJ). The study was performed according to Declaration of Helsinki principles. The appropriate institutional review boards approved the protocol, and written informed consent was obtained from patients (or when necessary parents or guardians). All study sites were in the United States. Since this study primarily measured safety parameters, we followed the recommendations of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E9 Guidance for Industry document (Statistical Principles for Clinical Trials), which suggest that safety and tolerability data are best analyzed by descriptive analysis.[29] Significance testing was not performed on any comparisons except for the primary end point.

Study Patients

Eligible patients were 12 years or older; had stable asthma for at least 6 months, a forced expiratory volume in 1 second (FEV_1) of 50% or higher and 80% or lower of predicted, 12% or higher reversibility of airflow obstruction within 15 to 30 minutes after administration of 180 μg of racemic albuterol MDI, and used a β_2-adrenergic agonist, antiasthma anti-inflammatory medication, or over-the-counter asthma medication for at least 6 months before screening. Patients were ineligible if they had a history of life-threatening asthma within 3 months of screening or if they were hospitalized for acute asthma within 45 days of screening. Patients were ineligible if they had a greater than 10–pack-year history of cigarette smoking within 6 months of screening.

Patients could be removed from the trial if they had adverse events, had intercurrent illness, violated the protocol, or used disallowed medication, including adrenergic bronchodilators (other than study medication), nonprescription asthma medicine (such as inhaled epinephrine), ipratropium bromide, or parenteral or oral corticosteroids. However, up to three 5- to 10-day courses of oral corticosteroids could be administered at the investigator's discretion for treating any condition, including worsening of asthma.

The patient population consisted of both new and continuing patients who were rolled over from 2 completed phase 3 trials of levalbuterol HFA MDI. Both trials were multicenter, randomized, double-blind, placebo- and active-controlled studies of 8 weeks in duration. They investigated the efficacy (peak percentage change from predose visit in FEV_1—the primary end point), pharmacokinetics of (R)- and (S)-albuterol, and safety of 90 μg of levalbuterol HFA MDI (2 actuations; 45 μg per actuation) and 180 μg of racemic albuterol HFA MDI (2 actuations; 90 μg per actuation) in patients 12 years or older. Forty-four of 653 patients (7%) rolled over from the phase 3 trials. These patients were rerandomized into this long-term safety study, and observational profiles of adverse events were not significantly different between patients rolled over from the previous trials and those who were not (data not shown).

Protocol

The study consisted of 10 study visits during a 12-month period. After enrollment and before randomization, all new patients completed a 1-week, single-blind, placebo MDI (propellant containing ethanol and oleic acid; 2 actuations 4 times daily) run-in period. For rollover patients, the final study assessments from the previous trial served as baseline values, which were obtained before study drug allocation. All patients and parents or guardians were instructed in the use of the MDI device at screening, and appropriate use was reinforced at each clinic visit. Open-label pirbuterol MDI (0.2 mg per actuation) was used as rescue medication. Medical event calendars and study diary cards were completed daily at home.

End Points

The primary end point was the overall incidence of postrandomization adverse events reported during the treatment period. Secondary safety end points included the number of study discontinuations, asthma attacks, asthma adverse events, and expanded-definition asthma adverse events. Asthma attacks were defined a priori as worsening of asthma symptoms or pulmonary function that required an emergency department visit, hospitalization, therapeutic intervention with oral or parenteral corticosteroids, or an unscheduled visit to treat acute asthma symptoms. Expanded-definition asthma adverse events were defined post hoc as adverse events of asthma, combined with bronchitis, increased cough, or dyspnea. Other secondary safety end points included rescue medication use, daytime asthma control days (days in which patients used 2 or more puffs of rescue medication and had no asthma attacks), serum potassium and glucose levels, vital signs, electrocardiograms (ECGs), and serum (S)- and (R)-albuterol concentrations.

Serum potassium and glucose concentrations were determined before dosing and 1 hour after dosing at weeks 18, 26, 34, and 52. Serum levels of (R)- and (S)-albuterol were monitored before and 1 hour after dosing at weeks 1, 2, 26, and 52.

At all clinical visits, serial vital signs were measured at 20-minute intervals in the first hour after dosing and at discharge. ECGs were measured at baseline and at weeks 10, 26, 43, and 52 and were performed before and at 30 minutes after dosing. Pulmonary function testing was performed before dosing, immediately, and 60 minutes after dosing at every clinic visit. For pulmonary function testing, rescue medication was withheld for at least 7 hours and inhaled corticosteroids for at least 10 hours before testing. Leukotriene inhibitors were also withheld 12 hours before testing.

The effect of treatment on quality of life and health was evaluated with the adult or pediatric Asthma Quality of Life Questionnaire (AQLQ; QOL Technologies Ltd, Chichester, England) administered at baseline and at the end of the study. The adult AQLQ, administered to patients 18 years or older, included 32 items in 4 domains (activity limitations, symptoms, emotional functions, and exposure to environmental stimuli). The pediatric AQLQ, given to patients 12 through 17 years old, consisted of 23 items in 3 areas (symptoms, activities, and emotions). A 7-point scale was used, ranging from 1 (severe impairment) to 7 (no impairment).[30]

Statistical Analysis

Based on a 2:1 ratio for randomization (levalbuterol:racemic albuterol) and to achieve at least 6 months of levalbuterol exposure in at least 300 patients and 12 months of levalbuterol exposure in at least 100 patients, an estimated 650 patients were required. This number was based on Food and Drug Administration requirements and the ICH guidelines for a long-term safety study, which is required for approval of a drug. The study achieved these targets; of 496 patients randomized to levalbuterol, 330 (66.5%) completed at least 6 months of study and 171 (34.5%) completed the 12-month study.

The original study design was for 12 months. An amended study protocol reduced the study period to 6 months for newly enrolled patients; 137 of 496 patients who finished at least 6 months of the study ended at 6 months and were considered completed patients. The intent-to-treat population included all randomized patients who received at least 1 dose of open-label study medication. All adverse events were coded using the COSTART (Coding Symbols for Thesaurus of Adverse Reaction Terms)[31] preferred term. For the overall incidence of adverse events, significance testing was performed at a .05 level of significance, using 2-sided tests.

The numbers and percentages (with each patient counted once for a given category) of adverse events and potentially related adverse events were calculated for each treatment group. Treatment differences between drugs were evaluated using a Cochran-Mantel-Haenszel χ^2 test on data stratified by investigator. The number and percentage of patients with asthma adverse events, asthma attacks, and expanded-definition asthma adverse events were summarized by treatment overall and for each month during the study.

FEV_1, AQLQ, and plasma concentrations of (R)- and (S)-albuterol were summarized descriptively. Changes in FEV_1 were compared using an analysis of covariance model with the change variable as the dependent variable, treatment and site as the fixed effects, and study baseline as the covariate. Changes in potassium and glucose concentrations from predose were calculated at each visit, and changes from baseline at the end of the treatment period were calculated for each parameter. Vital signs, rescue medication, daytime asthma control days, and ECG parameters were descriptively summarized. Changes in ECG parameters were compared using an analysis of covariance model with the change variable as the dependent variable, treatment and site as the fixed effects, and study baseline as a covariate.

RESULTS

Demographics, Disposition, and Baseline Characteristics

Among 932 patients enrolled, 746 were randomized to treatment in a 2:1 ratio of levalbuterol (n = 496) to racemic albuterol (n = 250) (Fig 1). Of the 186 patients not randomized, the most common reasons were a failure to meet entry criteria (55.9%), voluntary withdrawal (23.7%), or adverse events (8.6%).

Demographic and baseline characteristics were similar between treatment groups (Table 1). Most patients in both groups were white. African American and Hispanic patients made up 16.3% and 7.9% of the levalbuterol group and 18.0% and 6.8% of the racemic albuterol group, respectively. The percentage of predicted FEV_1 and the FEV_1 percentage of reversibility after 2 puffs of racemic albuterol HFA MDI were comparable between the groups (Table 1). The percentage of patients taking inhaled corticosteroids and montelukast were 59% and 17.5% for levalbuterol and 64% and 16.4% for racemic albuterol, respectively.

Of the patients randomized to treatment, 416 (55.8%) completed the study, and 279 (37.4%) finished 12 months of treatment (Fig 1). Reasons for termination were voluntary withdrawal, protocol violation, and adverse events, with asthma adverse events being the most common (4.8% in the levalbuterol group and 6.0% in the racemic albuterol group). The rate that patients discontinued participation in the study was similar for both treatment groups and did not increase over time (data not shown).

By diary cards, the mean compliance rate during the 12-month period was similar between treatment groups (95.7% in the levalbuterol group and 96.1% in the racemic albuterol group). Most patients (94.4% in the levalbuterol group and 96.1% in the racemic albuterol group) had compliance rates of 80% or higher. The mean percentage of change in evening peak expiratory flow from before to after dosing was approximately 35 L/min throughout the study, and the mean predose plasma concentration of isomers was higher than baseline during the trial (Fig 2). These findings indicate that patients took their medication throughout the trial.

Adverse Events

The frequency of adverse events was 72.0% in the levalbuterol patients and 76.8% the racemic albuterol patients (P = .12; Table 2), and individual adverse events occurred with similar frequencies among treatment groups. Most patients reported at least 1 respiratory event (54.8% for the levalbuterol group and 56.4% for the racemic albuterol group), which included viral infection, asthma, rhinitis, and sinusitis. Other common adverse events were headache and pain (Table 3).

During the study, asthma adverse events, asthma attacks, or expanded definition of asthma adverse events occurred in 18.3%, 16.3%, and 26.4% of the levalbuterol patients, respec-

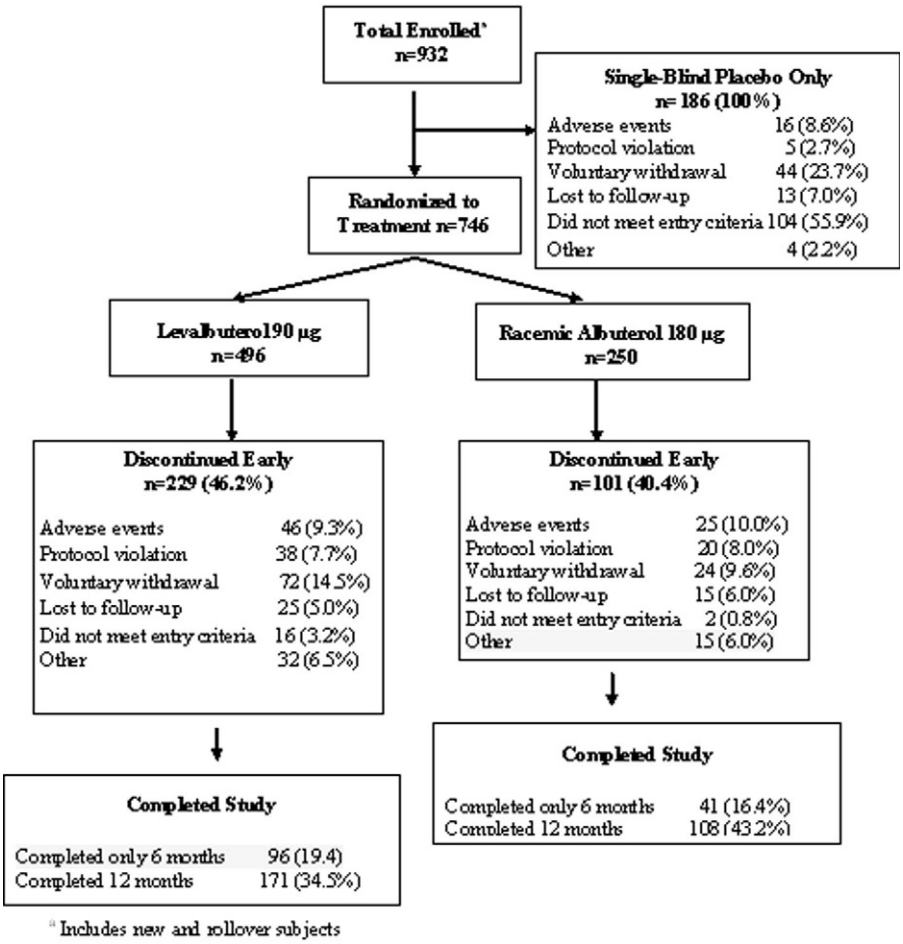

Figure 1. Patient disposition throughout the study.

tively, and 19.6%, 18.4%, and 33.2% of the racemic albuterol patients, respectively, without a noticeable difference between groups (Table 2). Most asthma adverse events were single events that lasted longer than 24 hours (Table 4). An analysis of the time to onset of adverse events across study groups revealed no differences for asthma and asthma-related events (data not shown).

The incidence of serious adverse events was comparable between the treatment groups (Table 2). No deaths occurred in either group. The most common serious adverse events were asthma (1.0% in the levalbuterol group and 0.8% in the racemic albuterol group) and cholelithiasis (0.2% in the levalbuterol group and 0.4% in the racemic albuterol group).

β-Mediated Adverse Events

The incidence of β-mediated adverse events was similar for the 2 treatment groups (Table 2). Potassium and glucose levels and heart rate and $QT_{c\text{-}F}$ interval changes varied little during the study period and were comparable between groups. After 12 months, for levalbuterol and racemic albuterol, the mean ± SD change from predose visit for serum potassium levels was −0.02 ± 0.31 mEq/L and −0.06 ± 0.29 mEq/L, respectively, and the mean ± SD change from predose in serum glucose levels was 2.83 ± 16.78 mg/dL and −1.21 ± 14.04 mg/dL, respectively. The predose mean ± SD change for the $QT_{c\text{-}F}$ interval from study baseline was −5.3 ± 13.5 milliseconds for the levalbuterol group and −4.4 ± 14.4 milliseconds for the racemic albuterol group.

Disease Control Measurements and Pharmacokinetics

Overall, 72.6% of the patients taking levalbuterol and 68.4% of those taking racemic albuterol used rescue medication during the study, and for both groups on average less than 0.6 puffs were used per day and were used an average of 3 to 5 days per month. The daytime asthma control days were similar between treatment groups (27.8 to 29.4 days per month and 28.2 to 29.4 days per month for the levalbuterol and racemic albuterol groups, respectively) and stable during the study.

The median (interquartile range) 1-hour postdose (R)-albuterol serum levels for the levalbuterol and racemic albuterol groups were similar throughout the study and increased

Table 1. Demographics and Baseline Disease Characteristics[a]

Characteristics	Levalbuterol (n = 496)	Racemic albuterol (n = 250)
Age of intent-to-treat population		
Mean (SD), y	38.0 (15.0)	39.0 (14.8)
12–17 y, No. (%)	59 (12)[b]	25 (10)[b]
≥18 y, No. (%)	437 (88)[c]	225 (90)[c]
Male, No. (%)	175 (35.3)	83 (33.2)
Race, No. (%)		
White	360 (72.6)	180 (72.0)
African American	81 (16.3)	45 (18.0)
Hispanic	39 (7.9)	17 (6.8)
Asian	11 (2.2)	5 (2.0)
Other	5 (1.0)	3 (1.2)
FEV_1 percent predicted, mean (SD)	68.4 (8.4)	68.0 (8.1)
Percent FEV_1 reversibility, mean (SD)	22.5 (11.6)	22.8 (11.3)
Screening FEV_1, mean (SD)	2.25 (0.5)	2.20 (0.5)
Asthma duration, No. (%)		
6 months to <1 y	7 (1.4)	1 (0.4)
1 y to <5 y	53 (10.7)	35 (14.0)
5 y to <10 y	96 (19.4)	39 (15.6)
10 y to <15 y	86 (17.3)	36 (14.4)
≥15 y	254 (51.2)	139 (55.6)
Exacerbations before 60 days, mean (SD)	0.3 (1.4)	0.2 (0.6)
Inhaled corticosteroid users, %	59	64

Abbreviation: FEV_1, forced expiratory volume in 1 second.
[a] All *P* values were >.05.
[b] The mean (SD) age of patients in the 12- through 17-year-old group was 14.1 (1.6) years for the levalbuterol group and 14.2 (1.6) years for racemic albuterol group.
[c] The mean (SD) age of patients in the group 18 years or older was 41.2 (12.9) years for the levalbuterol group and 41.7 (13.0) years for the racemic albuterol group.

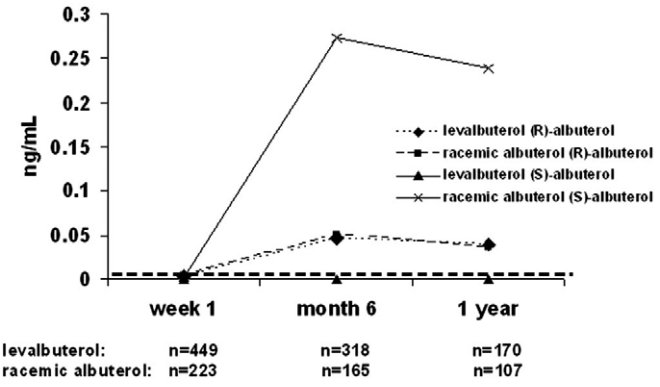

Figure 2. The median predose concentration of (R)- and (S)-albuterol in the plasma of patients treated with levalbuterol or racemic albuterol at week 1, month 6, and 1 year. The dotted horizontal line indicates the detection limit of the assay. Only the values of the new patients (nonrollover) are presented at week 1.

Table 2. Summary of Adverse Events Reported During the Open-Label Treatment Period[a]

Adverse events	No. (%) of patients	
	Levalbuterol (n = 496)	Racemic albuterol (n = 250)
At least 1 adverse event	357 (72.0)	192 (76.8)
Serious adverse events[b]	18 (3.6)	13 (5.2)
Discontinued study because of adverse events	45 (9.1)	24 (9.6)
Asthma adverse events	91 (18.3)	49 (19.6)
Asthma attack[c]	81 (16.3)	46 (18.4)
Expanded-definition asthma adverse events[d]	131 (26.4)	83 (33.2)
β-Mediated adverse events[e]	67 (13.5)	47 (18.8)
Potentially treatment-related adverse events[f]	81 (16.3)	42 (16.8)

[a] Adverse events included adverse events on study enrollment to on or before the last clinical visit or early termination visit for all patients. Patients with multiple adverse events were counted only once.
[b] Serious adverse events included any event that was fatal or life threatening, was permanently disabling, required hospitalization, was a congenital anomaly, or required intervention to prevent permanent damage.
[c] Defined as an asthma adverse event that required hospitalization, emergency department visit, treatment with oral burst or parenteral corticosteroids, or an unscheduled clinic visit.
[d] Defined as adverse events of asthma, combined with adverse events of bronchitis, cough increase, dyspnea, or lung disorder.
[e] Includes tachycardia, palpitation, chest pain, arrhythmia, hypertension, dyspepsia, nausea, leg cramps, dizziness, insomnia, nervousness, anxiety, and tremor.
[f] The combination of adverse events with possible, probable, definite, and unknown relationship to study medication.

from baseline to a comparable extent (60 minutes after dosing, visit 1: 0.10 ng/mL [0.07–0.15 ng/mL] and 0.12 ng/mL [0.08–0.17 ng/mL], respectively; 60 minutes after dosing, 12-month visit: 0.13 ng/mL [0.09–0.19 ng/mL] and 0.13 ng/mL [0.09–0.20 ng/mL], respectively). The median (interquartile range) 1-hour postdose (S)-albuterol plasma concentrations also increased from baseline during the study for the racemic albuterol group and were approximately 2.5- to 3.5-fold higher than the mean (R)-albuterol plasma concentration (60 minutes after dosing, visit 1: 0.30 ng/mL [0.18–0.46 ng/mL]; and 60 minutes after dosing, 12-month visit: 0.45 ng/mL [0.31–0.64 ng/mL]).

Spirometry Results

Mean percentage of predicted FEV_1 for both treatment groups improved from the visit predose FEV_1 during the active treatment period of the study (Fig 3A-C). By month 12, the percentage change in predose percentage of predicted FEV_1 from study baseline was 5.1% in the levalbuterol group and 5.2% in the racemic albuterol group (Fig 3C). Throughout the study, both groups had similar predose mean percentage of predicted FEV_1 values, which increased comparably after

Table 3. Most Frequent Postrandomization Adverse Events (≥5% in Frequency)[a]

Adverse events	No. (%) of patients	
	Levalbuterol (n = 496)	Racemic albuterol (n = 250)
Body as a whole	180 (36.3)	104 (41.6)
Abdominal pain	18 (3.6)	17 (6.8)
Unintentional injury	37 (7.5)	26 (10.4)
Flu syndrome	19 (3.8)	17 (6.8)
Headache	67 (13.5)	38 (15.2)
Pain	48 (9.7)	33 (13.2)
Respiratory system	272 (54.8)	141 (56.4)
Asthma	91 (18.3)	49 (19.6)
Bronchitis	36 (7.3)	18 (7.2)
Cough increased	40 (8.1)	24 (9.6)
Pharyngitis	49 (9.9)	25 (10.0)
Rhinitis	48 (9.7)	39 (15.6)
Sinusitis	56 (11.3)	31 (12.4)
Viral infection	150 (30.2)	71 (28.4)

[a] Patients may have had more than 1 adverse event per body system. Other categories of adverse events reported by less than 5% of patients included cardiovascular, digestive, musculoskeletal and nervous systems, skin and appendages, and special senses.

Table 4. Summary of Asthma Adverse Events, Asthma Attacks, and Expanded-Definition of Asthma Adverse Events

Variable	No. (%) of patients	
	Levalbuterol (n = 496)	Racemic albuterol (n = 250)
Asthma adverse events		
Overall	91 (18.3)	49 (19.6)
No. of single events	70 (14.1)	33 (13.2)
Duration >24 hours	83 (16.7)	43 1(7.2)
Asthma attack		
Overall	81 (16.3)	46 (18.4)
No. of single of events	61 (12.3)	34 (13.6)
Duration >24 hours	74 (14.9)	41 (16.4)
Expanded-definition asthma adverse events		
Overall	131 (26.4)	83 (33.2)
No. of single events	71 (14.3)	48 (19.2)
Duration >24 hours	123 (24.8)	77 (30.8)

dosing and increased further 60 minutes after dosing throughout the study. The changes in percentage of predicted FEV_1 were stable during the study period.

Quality-of-Life Evaluation

Both groups improved to a similar extent on the adult AQLQ. The mean improvement in the pediatric AQLQ was greater in the overall score and each domain score in the levalbuterol group compared with the racemic albuterol group (Fig 4). At 12 months, the mean ± SD change for the overall pediatric AQLQ score was 0.96 ± 0.92 for the levalbuterol group and −0.02 ± 1.18 for the racemic albuterol group.

DISCUSSION

We found that long-term regular dosing with levalbuterol HFA MDI or racemic albuterol HFA MDI in patients 12 years or older was equally safe and showed no evidence for declining efficacy or deterioration in lung function. The overall incidence of adverse events was similar between levalbuterol and racemic albuterol, and the 2 treatments were comparable in frequency of adverse events, asthma adverse events, and potential treatment-related adverse events. The rates of serious adverse events, β-mediated adverse events, asthma attacks, and expanded-definition of asthma adverse events were also low and similar between groups.

Levalbuterol was associated with slightly fewer β-mediated adverse events than racemic albuterol (13.3% vs 18.4%). Other parameters associated with β_2-agonist mediated adverse effects, such as serum potassium and glucose levels and increases in heart rate, changed little from baseline during the study and were similar between treatment groups. β-Mediated effects are dependent on the dose of (R)-albuterol administered. A previous study found a lower frequency of β-mediated effects with levalbuterol vs racemic albuterol; however, in this study the doses of (R)-albuterol in the levalbuterol and racemic albuterol treatment arms were not equivalent and the drugs were administered in higher doses by nebulization.[32] A study that compared comparable doses of levalbuterol and racemic albuterol via nebulization found no differences in β-mediated effects.[33]

The exposure to (R)-albuterol was similar between levalbuterol and racemic albuterol and rose similarly across the treatment period. This finding is comparable to other work that found no apparent difference in the pharmacokinetics of (R)-albuterol after administration of levalbuterol or racemic albuterol via nebulizer.[32,34] The increased concentration of (S)-albuterol with long-term dosing of racemic albuterol was 2.6-fold to 3.4-fold higher than (R)-albuterol concentrations, consistent with previous findings.[32,34,35]

Regular treatment improved the quality of life for each treatment group. For adults (≥18 years) treated with levalbuterol or racemic albuterol, the mean change from baseline of the AQLQ scores increased slightly and to similar extents. However, in children (12 to <18 years) treated with levalbuterol, the mean changes from baseline for the different AQLQ scores improved, whereas that for the racemic albuterol group did not. In fact, most domains of the pediatric AQLQ for patients in the racemic albuterol group decreased from baseline (indicating a worsening in quality of life). The increase in the pediatric AQLQ scores exceeded 0.5 from baseline (the minimal clinically important difference that could mandate a change in a patient's management) at 12 months for levalbuterol. Although these results are limited by the open-label design and the small sample size (n = 19 for levalbuterol and n = 12 for racemic albuterol), they are consistent with those of a large, multicenter, randomized,

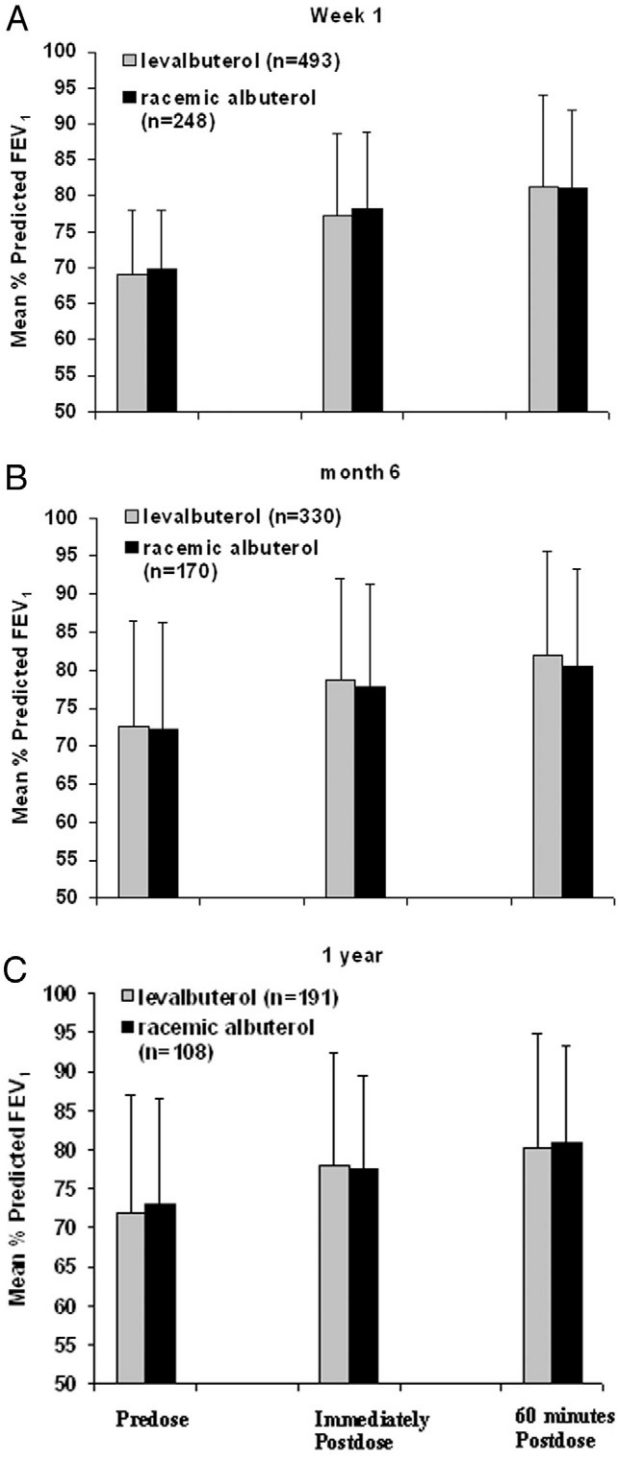

Figure 3. Forced expiratory volume in 1 second (FEV_1) as percentage of the predicted predose values determined at baseline before dosing, immediately after dosing, and 60 minutes after dosing in the levalbuterol and racemic albuterol treatment arms. The mean values are presented, and error bars indicate the SD. Percentage of predicted FEV_1 at week 1 (A), month 6 (B), and 1 year (C).

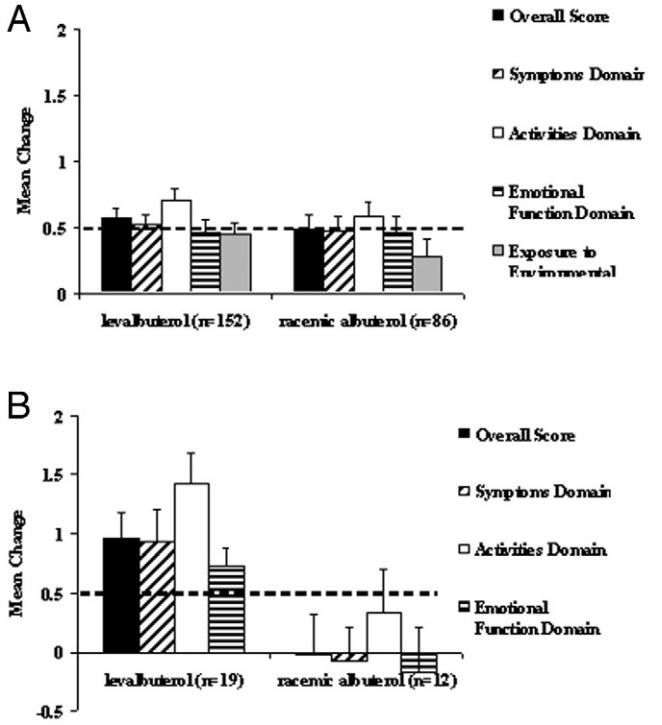

Figure 4. Mean change from baseline in the adult (A) and pediatric (B) Asthma Quality of Life Questionnaire (AQLQ) in terms of overall score and individual domain scores at 1 year. For the pediatric AQLQ, patients were 12 through 17 years in age. Changes in the overall score and each domain score were calculated by subtracting each patient's score at 12 months from the score at the day of randomization. Mean values are presented, and error bars indicate the SD. The dotted line indicates the minimal clinical important difference value of 0.5 that could mandate a change in a patient's management. Standard errors are indicated.

double-blind trial that compared levalbuterol MDI and racemic albuterol MDI in children aged 2 to 5 years that used a similar questionnaire to evaluate quality of life.[36]

The current study is one of the few to examine the safety of regular dosing with racemic albuterol for up to a year[28,37–39] and is the first, to our knowledge, to study levalbuterol HFA MDI in this way. Another open-label study explored the safety of regular dosing with racemic albuterol HFA MDI vs racemic albuterol chlorofluorocarbon MDI for 12 months in patients with stable asthma by monitoring the number of adverse events.[28] The incidence of adverse events and β-mediated adverse events was similar to that in our study: 86% of the patients treated with racemic albuterol experienced adverse events, 3% reported serious adverse events, and 25% reported β-mediated adverse events. By contrast, another 12-month study of regular nebulization with racemic albuterol reported a frequency of adverse events of 8% for the active treatment group and 5.1% for the placebo group.[37]

Potential deterioration of lung function that might be expected because of long-term β-agonist dosing was not de-

tected in this study. Clinically meaningful tolerance may manifest as a reduction in FEV_1, a reduction in responsiveness to β-agonists, or worsening of asthma and disease control, resulting in disease exacerbations. In this study, the mean percentage of predicted FEV_1 before dosing was stable and increased slightly during the 12 months. Similarly, the percentage of predicted FEV_1 either immediately or 60 minutes after dosing was also stable during the 12-month study. The number of asthma adverse events, asthma attacks, and expanded-definition asthma adverse events did not increase in either treatment group. The number of asthma control days did not decrease and was stable over time. The use of rescue medication was low and did not increase. In fact, the mean number of rescue puffs used per day decreased in both treatment groups. The consistent change from predose to postdose evening peak expiratory flow and measured predose isomer levels are evidence that the patients took medication throughout the study.

The finding of no significant deterioration in lung function during extended long-term dosing with racemic albuterol is in agreement with 2 previous studies.[37,38] However, other studies have detected a reduction in lung function[28] or an increase in bronchial hyperresponsiveness to histamine[40] after 12 months of treatment with racemic albuterol.

This study was an open-label trial, which may have influenced how patients and investigators judged treatment and changes in health status. Also, because there was no placebo control, it is not possible to draw conclusions on the effect of regular vs as-needed treatment with short-acting β-agonists. Finally, some patients were enrolled for only 6 months ($n = 96$ for the levalbuterol group and $n = 41$ for the racemic albuterol group), which may have influenced some findings. However, the FEV_1 results were similar between 6 months and a year, suggesting that this was not a problem. Genetic polymorphisms in the β_2-adrenergic receptor may influence a patient's response to β_2-agonists.[41,42] This study focused on the long-term safety of the regular use of levalbuterol or racemic albuterol, and genetic analysis of the β_2-adrenergic receptor was not performed; consequently, we do not know how our findings relate to genetic diversity in the β_2-adrenergic receptor. Except for the primary end point, no comparative statistical analyses were performed on the data. Statistical analyses of treatment differences for safety end points are difficult to interpret. The lack of statistically significant differences in safety end points between treatments is no assurance that there are not clinically relevant differences, because most studies (including this one) are not powered to detect clinically relevant differences.

In some trials, regular use of β_2-agonists had negative effects on lung function.[21,43] This finding has resulted in expert guidelines recommending that β-agonists be used on an as-needed basis. We agree with this recommendation. Nonetheless, long-term use is common; 25% to 33% of patients with mild asthma, 53% of patients with moderate asthma, and 73% of patients with severe asthma reported long-term use of β-agonists.[44] This provides a rationale for assessing the safety of regular (4 times a day), long-term use of β_2-agonists. Our study found that regular dosing of levalbuterol and racemic albuterol was well tolerated during a 12-month period and did not result in reduced lung function or deterioration of disease control.

ACKNOWLEDGMENTS

We thank E. Goodwin, PhD, of Sepracor Inc for her assistance in the preparation of the manuscript.

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Requests for reprints should be addressed to:
W. K. McVicar, PhD
Sepracor Inc
84 Waterford Dr
Marlborough, MA 01752
E-mail: william.mcvicar@sepracor.com