Formoterol, 24 μg bid, and Serious Asthma Exacerbations*

Similar Rates Compared With Formoterol, 12 μg bid, With and Without Extra Doses Taken on Demand, and Placebo

James Wolfe, MD, FCCP; Craig LaForce, MD; Bruce Friedman, MD; William Sokol, MD; Denise Till, MSc; Giovanni Della Cioppa, MD; and Andre van As, MD, PhD, FCCP

Study objectives: **The primary objective was to determine whether high-dose formoterol, 24 μg bid, was associated with more asthma exacerbations compared with lower formoterol doses in patients with stable persistent asthma. Serious asthma exacerbations (life threatening or requiring hospitalization) were the primary end point. Secondary end points included significant exacerbations requiring systemic corticosteroids, all exacerbations, and changes in FEV_1.**

Design: **In a multicenter, placebo-controlled, parallel-group study, patients were randomized to 16 weeks of treatment with formoterol, 24 μg bid; formoterol, 12 μg bid, with up to two additional 12-μg doses daily on demand for worsening symptoms (12 μg bid plus on demand); formoterol, 12 μg bid; or placebo. The formoterol 12-μg-bid plus on-demand regimen was administered open label, while the other three regimens were double blind.**

Setting: **Outpatient clinics.**

Patients: **A total of 2,085 patients aged ≥ 12 years with stable, persistent asthma were enrolled and treated; 65% (n = 1,347) received regular concomitant antiinflammatory therapy during the study.**

Measurements and results: **Nine patients had respiratory-related serious adverse events (SAEs) requiring hospitalization: two patients (0.4%) in the 24-μg-bid group; one patient (0.2%) in the 12-μg-bid plus on-demand group; five patients (0.9%) in the 12-μg-bid group; and one patient (0.2%) in the placebo group. All of these events were asthma related, except for two SAEs in the 12-μg-bid group that were later considered not to be asthma related by independent reviewers who were not associated with the conduct of the study. The proportions of patients with significant asthma exacerbations (requiring systemic corticosteroids) were similar in the 24-μg-bid group (6.3%, 33 of 527 patients), 12-μg-bid group (5.9%, 31 of 527 patients) and placebo group (8.8%, 45 of 514 patients) and lower in the 12-μg-bid plus on-demand group (4.4%, 23 of 517 patients; $p = 0.0057$ vs placebo). All treatments were well tolerated. All formoterol treatment regimens had a significant effect on FEV_1 measured 2 h after dose during the study ($p < 0.0001$ vs placebo); and on predose trough FEV_1 measured at all visits after baseline ($p < 0.002$ vs placebo).**

Conclusions: **Treatment with formoterol, 24 μg bid, was not associated with an increase in serious asthma exacerbations compared with the lower formoterol doses or placebo.**

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Key words: adverse events; Aerolizer; asthma; bronchodilation; exacerbations; formoterol; high dose

Abbreviations: AE = adverse event; CI = confidence interval; DPI = dry powder inhaler; ED = emergency department; FDA = Food and Drug Administration; ICS = inhaled corticosteroids; ITT = intent to treat; LABA = long-acting β_2-agonist; SAE = serious adverse event

The use of inhaled corticosteroids (ICS) is recommended as a rational approach for the management of underlying airway inflammation that results in the many manifestations of asthma. This approach is often supplemented with short-acting, inhaled, β_2-agonist bronchodilators, which provide symptomatic relief. The introduction of long-acting β_2-agonists (LABAs; formoterol and salmeterol) has resulted in improved outcomes when they are used

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concurrently with ICS, compared with use of either monotherapy alone. Both LABAs are classified as controller medications for use in patients with persistent asthma and are usually recommended for use in conjunction with ICS.[1,2]

Formoterol and salmeterol have a similar duration of bronchodilation of at least 12 h, but formoterol has a fast onset of action of < 3 min, whereas salmeterol can take up to approximately 20 min to produce clinically relevant bronchodilation.[3–8] Formoterol has been available for > 10 years, originally as a pressurized metered-dose inhaler and subsequently as a dry powder inhaler (DPI), and has been shown to be well tolerated and effective in long-term studies.[9,10] Formoterol was approved in Europe and worldwide in the mid-1990s; subsequently, a single-dose DPI (Foradil Aerolizer; Novartis Pharmaceuticals; East Hanover, NJ) was approved in 2001 by the US Food and Drug Administration (FDA) for use as maintenance treatment of asthma and COPD at a dose and schedule of 12 μg (one capsule) inhaled bid. Treatment with formoterol DPI has been shown to be effective and well tolerated in children and adults with asthma in studies up to 1 year in duration.[11–15]

*From Allergy and Asthma Associates of Santa Clara Valley Research Center (Dr. Wolfe), San Jose, CA; North Carolina Clinical Research (Dr. LaForce), Raleigh, NC; Allergy, Asthma, Bronchitis and Immunology Associates (Dr. Friedman), Fountain Valley, CA; Health Research Institute (Dr. Sokol), Newport Beach, CA; Novartis Horsham Research Centre (Ms. Till and Dr. Della Cioppa), Horsham, UK; and Novartis Pharmaceuticals (Dr. van As), East Hanover, NJ.
Ms. Till has a declared conflict of financial interest in that she is an employee of Novartis and owns Novartis shares.
Dr. Della Cioppa has a declared conflict of financial interest in that he is an employee of Novartis and owns Novartis shares.
Dr. van As has a declared conflict of financial interest in that he was an employee of Novartis and owns Novartis shares.
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Correspondence to: James Wolfe, MD, Allergy and Asthma Associates of Santa Clara Valley Research Center, 4050 Moorpark Ave, San Jose, CA 95117; e-mail: aaascv@asthmaresearch.com

The safety of LABAs has been the focus of much recent discussion after a placebo-controlled study in approximately 26,000 patients revealed a small but significant increase in asthma-related deaths among patients receiving salmeterol.[16] In the case of formoterol, concerns were raised about a possible link between the use of higher doses of this agent (24 μg bid via single-dose DPI) and an increase in serious asthma exacerbations, based on findings from two 12-week studies and a 1-year study.[11–13,17] Using the frequency of the serious asthma exacerbations in these three studies, the present study in more than 2000 asthma patients was designed and powered to answer the latter question. We therefore evaluated the safety and efficacy of the 24-μg-bid dose (approved in most countries, but not in the United States) taken for 16 weeks in adolescents and adults with stable persistent asthma compared with the 12-μg-bid regimen (approved in the United States) and an open-label arm that allowed use of formoterol, 12 μg bid, with up to two additional 12-μg doses taken as needed (12 μg bid plus on demand) and placebo. The primary end point was the percentage of patients with serious asthma exacerbations.

Materials and Methods

Study Design

This was a 2,085-patient, multicenter, randomized, parallel-group, double-blind, placebo-controlled study with a 2-week run-in and a 16-week treatment period during which patients visited the clinic at 4-week intervals. At baseline, patients were evaluated for medical history, vital signs, physical examination, history of asthma treatment and asthma exacerbations, bronchodilator reversibility testing, and ECG. Blood and urine samples were collected for laboratory testing. At each visit, vital signs and physical examination were repeated and information was gathered on medication use, adverse events (AEs), and emergency department (ED) visits. FEV_1 was measured at each visit before the administration of study drug or placebo, and 2 h after dose. Patients completed a questionnaire on their satisfaction with their asthma management prior to and at the end of the treatment period.

Inclusion/Exclusion Criteria

Male and female patients aged ≥ 12 years with persistent asthma were enrolled at 194 outpatient asthma clinics across the United States. Among the inclusion criteria were appropriate treatment for asthma according to management guidelines[2]; $FEV_1 \geq 40\%$ of predicted normal following washout from inhaled bronchodilator treatment; and FEV_1 reversibility $\geq 12\%$ after inhalation of up to four puffs of albuterol (360 μg) at screening or documented within the past year.

Exclusion criteria included pregnancy, nursing, or child-bearing potential and absence of reliable contraception; clinically significant cardiovascular disease; malignancy; history of insulin-dependent diabetes mellitus; upper respiratory tract infection 1 month before and during the run-in period; a recent or > 10

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