Serious Asthma Exacerbations in Asthmatics Treated With High-Dose Formoterol*

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Objective: To review three prospective, randomized, placebo-controlled, double-blind clinical studies of formoterol (Foradil Aerolizer; Novartis Pharmaceuticals; Basel, Switzerland) at dosages of 12 μg and 24 μg bid for the treatment of patients with asthma.

Data sources: Clinical studies submitted to the US Food and Drug Administration in support of the approval of Foradil Aerolizer for marketing in the United States.

Results: More patients treated regularly with formoterol, 24 μg bid, had a serious asthma exacerbation than did patients who had been treated with placebo. In the first study, 4 of 135 adult patients (3%) who had been treated with formoterol, 24 μg bid, had a serious asthma exacerbation compared to none of 136 placebo-treated patients. In the second study, 5 of 136 patients (3.7%) treated with formoterol, 24 μg bid, had a serious asthma exacerbation compared to 2 of 141 placebo-treated patients (1.4%). In the third study, 11 of 171 pediatric patients (6.4%) treated with formoterol, 24 μg bid, had a serious asthma exacerbation compared to none of 176 placebo-treated patients.

Conclusion: Regular use of high-dose inhaled formoterol (24 μg bid) may be associated with more frequent serious asthma exacerbations.

Key words: asthma; formoterol; long-acting β-agonist

Long-acting inhaled β2-agonists that are currently marketed in the United States allow for twice-daily dosing and are indicated for patients who require long-term control of asthma symptoms. The following two long-acting β2-agonists have been approved and are available in the United States for the long-term control of asthma: formoterol (Foradil Aerolizer; Novartis Pharmaceuticals; Basel, Switzerland) and salmeterol (Serevent Diskus and Serevent Inhalation Aerosol; GlaxoSmithKline; Research Triangle Park, NC). Despite their benefit in maintaining bronchodilation (eg, improved FEV1), some authors have voiced caution about the use of long-acting β2-agonists with regard to the potential development of airway subsensitivity.1 Bisgaard2 expressed concern about long-acting β2-agonists and the development of tolerance in the pediatric population, concluding that the role of these drugs in pediatric asthma as regular add-on therapy is questionable. Novartis Pharmaceuticals submitted a new drug application to the US Food and Drug Administration for marketing approval of Foradil Aerolizer at doses of 12 μg and 24 μg bid. Based on our review of the new drug application for Foradil Aerolizer, we concluded that this product has been shown to be safe and effective as a 12-μg bid dose (the US Food and Drug Administration-approved dose). However, our review of the clinical data presented showed a subtle signal for concern in those patients taking a dose of 24 μg bid3 in that a higher incidence of serious asthma exacerbations was noted. Based on this concern and pending any further clarifying data, the 24-μg bid dose of Foradil Aerolizer is not currently approved for US marketing.

Materials and Methods

Novartis Pharmaceuticals submitted data from clinical studies to support the use of orally inhaled formoterol (Foradil Aerolizer) twice daily for the long-term maintenance treatment of asthma. Three of the studies were placebo-controlled randomized clinical
studies evaluating multiple doses of formoterol. Two of these trials have been reported in the literature.4,5

There were two 12-week, double-blind, randomized, placebo-controlled, parallel-group studies performed in patients 12 to 75 years of age, with an FEV1 ranging from 40 to 80% of predicted values, and at least 15% β₂-agonist reversibility. Patients required therapy with daily doses of short-acting β₂-agonists for symptom control. Stable regimens of orally inhaled or intranasal corticosteroids, oral theophylline, short-acting antihistamines, or allergen immunotherapy were allowed. Patients were randomized to receive in a blinded fashion one of the following inhaled medications: placebo; albuterol, 180 µg qid; formoterol, 12 µg bid; or formoterol, 24 µg bid. All patients were allowed to use albuterol, 180 µg, for rescue therapy. Spirometry was performed at weeks 0, 2, 4, 8, and 12, with measurements performed prior to study drug administration, and at 5, 15, 30, and 60 min, and hourly for 12 h following drug administration. The primary efficacy end point was FEV1 at 12 h after study drug administration at week 12. An important secondary end point was asthma exacerbations, including those that met the criteria for being serious. An asthma exacerbation was considered to be serious if it resulted in a life-threatening experience, inpatient hospitalization or prolongation of hospitalization, persistent disability/incapacity, or death.

The third study was a 12-month, randomized, placebo-controlled safety study that was performed in children 5 to 12 years of age who were randomized to treatment with placebo, formoterol, 12 µg bid, or formoterol, 24 µg bid. Patients had an FEV1 between 50% and 85% of predicted, and at least 15% β₂-agonist reversibility. At study entry, patients were using inhaled bronchodilators daily and were receiving a stable regimen of either inhaled corticosteroids or Cromolyn sodium. Therapy with concomitant nasal corticosteroids, theophylline, and allergen immunotherapy was allowed if the regimens were stable. Rescue therapy with albuterol, 180 µg, was allowed. Spirometry was obtained with hourly measurements beginning just after drug administration and extending through 12 h on the first treatment day and after 3 weeks and 12 weeks of treatment. The primary efficacy end point was the FEV1 area under the curve after 3 months of treatment. An important secondary end point was asthma exacerbations. The definition of a serious asthma exacerbation in this pediatric study was identical to that used in the adult trials, and these events were recorded during the entire 12-month period of randomized treatment.

Results

The two adult/adolescent studies randomized 541 patients and 554 patients. Each study showed that both formoterol doses were statistically significantly better than placebo for the primary end point of FEV1 measurement taken at the 12th hour posttreatment (ie, FEV1 at trough) at the week 12 visit. The pediatric study randomized 518 patients. In children, both formoterol doses were also statistically significantly better than placebo for the primary end point of FEV1 area under the curve measurements (ie, the average of serial FEV1 measurements at hours 1 through 12) at the week 12 visit. None of the studies showed a statistically significant benefit for formoterol, 24 µg bid, compared to formoterol, 12 µg bid, although numerically an average gain in FEV1 at the end of the dosing interval of approximately 100 mL was noted in the two adult/adolescent studies.

There were no consistent differences among treatment groups with regard to the total overall number of asthma exacerbations. In the first adult/adolescent study, the total number of asthma exacerbations (regardless of severity) was 30, 30, 16, and 27 in the placebo, albuterol, 180 µg qid, formoterol, 12 µg bid, and formoterol, 24 µg bid, arms, respectively. In the second adult/adolescent study, the total number of asthma exacerbations (regardless of severity) was 33, 21, 24, and 16 in the placebo, albuterol, 180 µg qid, formoterol, 12 µg bid, and formoterol, 24 µg bid, arms, respectively. In the 1-year pediatric study, the overall total number of asthma exacerbations was 173, 171, and 171 in the placebo, formoterol, 12 µg bid, and formoterol, 24 µg bid, arms, respectively.

There were no consistent differences between the treatment groups in the three studies regarding premature discontinuations from the study. For the first study, premature discontinuations occurred in 9, 10, 7, and 9 patients in the placebo, albuterol, 180 µg qid, formoterol, 12 µg bid, and formoterol, 24 µg bid, arms, respectively. The most common reason for premature discontinuation was “asthma,” which accounted for three, five, three, and six patients continuing treatment in each respective treatment arm. For the second study, premature discontinuations occurred in 9, 4, 7, and 10 patients in the placebo, albuterol, 180 µg qid, formoterol, 12 µg bid, and formoterol, 24 µg bid, treatment arms, respectively. Asthma was the reason cited for treatment discontinuation in six, zero, four, and five patients within each treatment arm, respectively. In the pediatric study, a total of 10, 5, and 4 patients discontinued treatment prematurely in the placebo, formoterol, 12 µg bid, and formoterol, 24 µg bid, treatment arms, respectively. The most common reason for treatment discontinuation was asthma, involving seven, one, and three patients in each arm, respectively.

In all three randomized studies, serious asthma exacerbations occurred more frequently in the formoterol, 24 µg bid, arm compared to the placebo, albuterol, or formoterol, 12 µg bid, arms (Table 1). In the two 12-week studies in adults/adolescents, a total of nine patients had serious asthma exacerbations in the formoterol, 24 µg bid, treatment arm. All patients required hospitalization, and the events occurred between 10 days and 2.5 months after the initiation of treatment. One patient died due to a cardiorespiratory arrest, and two patients required intubation and mechanical ventilation. In comparison, two patients treated with placebo had serious asthma exacerbations, both of which required hospitalization but did not require intubation or result in fatality. In the 1-year pediatric study, 11 patients had serious but nonfatal asthma exacerbations in the
formoterol, 24 μg bid, arm, and these exacerbations occurred between day 50 and day 297 of treatment. In comparison, there were no serious asthma exacerbations reported in the placebo arm.

**DISCUSSION AND CONCLUSIONS**

The three clinical studies reported on herein demonstrated that twice daily formoterol (at a dose of either 12 μg or 24 μg) was statistically superior to placebo in terms of improving FEV₁, which is an accepted end point for asthma control. The added benefit of formoterol, 24 μg bid, over formoterol, 12 μg bid, was considered to be marginal, and more patients who were randomized to receive formoterol, 24 μg bid, experienced serious asthma exacerbations compared to placebo, albuterol, 180 μg qid, or formoterol, 12 μg bid (Table 1). The finding of more serious asthma exacerbations does not merit statistical analysis since this was a post hoc, exploratory finding. Nonetheless, the consistency of this finding in three clinical trials was cause for concern. While Foradil Aerolizer is approved in other countries at doses of 12 μg and 24 μg bid, it is approved in the United States only at a dose of 12 μg bid.

Several pathophysiologic mechanisms have been proposed to support the hypothesis that the regular use of long-acting inhaled β-agonists may lead to an increased risk of serious asthma exacerbation. Chief among these is the development of desensitization of the β-receptor. The regular use of formoterol has been associated with decreased bronchoprotection as assessed by a variety of models, including methacholine challenge, adenosine monophosphate challenge, and exercise challenge.⁶⁻¹¹ Such findings have led to concern that patients who are treated regularly with a long-acting β-agonist may not respond optimally to a short-acting β-agonist during an acute asthma exacerbation, even if high rescue doses of a short-acting β-agonist (e.g., 1,600 μg inhaled albuterol) are used.⁶ Product labeling for Foradil Aerolizer describes 19 asthmatic patients who underwent methacholine challenge after an initial single dose of 24 μg formoterol and after 2 weeks of regular use of formoterol, 24 μg bid. Tolerance was observed after 2 weeks of regular dosing, with a diminished bronchoprotective effect on FEV₁ and a complete loss of protection at the end of the 12-h dosing period. There is some suggestion that a β₂-receptor polymorphism may influence the likelihood of a patient developing such desensitization, with homozygous Arg-16 patients being more susceptible.¹² The genotypic status of the patients with serious asthma exacerbation in the three controlled formoterol studies is unknown. Finally, there has been concern that a reliance on therapy with long-acting β₂-agonists may mask underlying inflammation and thus delay the patient’s awareness of deteriorating asthma, leading ultimately to more serious exacerbations.¹³

While pathophysiologic theories exist to support this concern, the clinical data regarding the regular use of long-acting β-agonists are largely supportive of their safety or, at most, show only subtle findings of concern. This summary of three placebo-controlled trials shows a subtle safety signal in that serious asthma exacerbations were more common in the formoterol, 24 μg bid, study arm when compared to the placebo arm. The most compelling data come from the pediatric study, which included a full year of follow-up data. However, it is important to note that formoterol is effective in all patients in improving FEV₁ measurements, symptom scores, and the requirement for rescue medication at night. Additionally, the total number of exacerbations was not worse (and in some instances was lower) with formoterol, 24 μg, compared to the lower dose and/or placebo. The pediatric study has been described in the literature.⁵ In this study, the authors concluded that asthmatic children treated with formoterol experience a benefit with improved airflow obstruction and reduced symptoms, but they caution that children should be closely monitored to detect early signs of acute exacerbation. In addition, they recommend that the amount of anti-inflammatory

### Table 1—Occurrence of Serious Asthma Exacerbations in Three Asthma Studies With Formoterol*  

<table>
<thead>
<tr>
<th>Variables</th>
<th>Placebo</th>
<th>Albuterol, 180 μg qid</th>
<th>Formoterol, 12 μg bid</th>
<th>Formoterol, 24 μg bid</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-wk randomized trial in adults and adolescents</td>
<td>0/136 (0)</td>
<td>2/134 (1.5)</td>
<td>0/136 (0)</td>
<td>4/135 (3)</td>
</tr>
<tr>
<td>12-wk randomized trial in adults and adolescents</td>
<td>2/141 (1.4)</td>
<td>0/138 (0)</td>
<td>1/139 (0.7)</td>
<td>5/136 (3.7)</td>
</tr>
<tr>
<td>1-yr randomized trial in children</td>
<td>0/176‡</td>
<td>NA</td>
<td>8/171§ (4.7)</td>
<td>11/171 (6.4)</td>
</tr>
</tbody>
</table>

*Values given as No. of patients with serious asthma exacerbations/total patients (%). NA = not applicable.
†One additional patient in the formoterol, 24 μg bid, arm experienced an exacerbation of sarcoidosis requiring corticosteroid therapy.
‡Two pediatric patients in the placebo arm developed pneumonia.
§One additional pediatric patient in the formoterol, 12 μg bid, arm developed pneumonia.
medication should not be reduced even if symptoms and pulmonary function improve.

Some studies reported in the literature have demonstrated subtle findings of safety concern in patients who regularly use long-acting $\beta_2$-agonists. In a crossover study$^{14}$ of 165 asthmatic patients who received salmeterol, 50 $\mu$g bid, salbutamol, 400 $\mu$g qid, and placebo for 24 weeks, there were six asthma exacerbations requiring medical therapy during salmeterol treatment compared to two during salbutamol treatment and three during placebo treatment. Another signal for concern with salmeterol arose from the Serenvent Nationwide Surveillance study,$^{15}$ in which 12 of 16,787 patients (0.07%) treated with salmeterol died from asthma compared to 2 of 8,393 patients (0.02%) treated with salbutamol.

Two non-placebo-controlled trials for Foradil Aerolizer (submitted as part of the new drug application) did not show any evidence that a dose of 24 $\mu$g bid was worse than a dose of 12 $\mu$g bid with regard to serious asthma exacerbations.$^{3}$ Other studies, moreover, indicate that formoterol may actually decrease the rate of severe asthma exacerbations. For example, formoterol, 12 $\mu$g bid (Oxis Turbuhaler; AstraZeneca; London, UK [not approved in United States]) was shown to reduce the incidence of severe asthma exacerbations for $> 1$ year by 25% compared to placebo when added to a regimen that included inhaled budesonide (100 $\mu$g or 400 $\mu$g bid).$^{16}$ Formoterol, 4.5 $\mu$g bid, administered via inhaler (Oxis Turbuhaler) also has been reported$^{17}$ to show benefit in that it reduced the time to the first severe asthma exacerbation when added to a maintenance dose of budesonide in patients who previously had been receiving low doses of an inhaled corticosteroid. It did not, however, have any effect on serious asthma exacerbations when added to therapy with budesonide in patients who were previously steroid-naïve. This may lead some to questions about whether the patients in the three controlled trials of formoterol (Foradil Aerolizer) who had serious asthma exacerbations were (or were not) receiving concomitant inhaled corticosteroids. Unfortunately, this information is not available.

Studies with salmeterol, the only other long-acting bronchodilator that is approved for use in the United States, are also worthy of discussion. In one trial$^{18}$ comparing 24 weeks of treatment with salmeterol, 42 $\mu$g bid, to placebo, there were fewer asthma exacerbations with salmeterol (34 exacerbations) than with placebo (48 exacerbations). Salmeterol vs placebo was prospectively studied in 911 asthmatic patients who were allowed to take salbutamol as needed.$^{19}$ The results showed no significant difference in the proportion of patients experiencing serious asthma exacerbations (21% in both the salmeterol and placebo arms), although fewer salmeterol patients withdrew prematurely from the study (salmeterol, 18% of patients; placebo, 25% of patients). Therapy with salmeterol, 50 $\mu$g bid, for 6 months vs placebo for 6 months also was studied in a double-blind, randomized, crossover study of 101 patients with mild-to-moderate asthma who were concomitantly receiving inhaled corticosteroids.$^{20}$ Exacerbation rates were lower during salmeterol treatment (salmeterol, 16%; placebo, 25%), although this was not statistically significant.

In conclusion, the somewhat conflicting results noted in the literature on therapy with long-acting $\beta_2$-agonists may reflect differences in study design and duration, patient population, and definition of exacerbations, as well as differences in drugs or drug delivery. Our finding of more frequent serious asthma exacerbations with formoterol, 24 $\mu$g bid, compared to placebo was subtle yet consistent in three of three placebo-controlled, randomized clinical studies. None of these studies, however, was primarily designed nor powered to address the end point of serious asthma exacerbation. The Foradil Aerolizer is currently approved for use at a dose of 12 $\mu$g bid. Novartis Pharmaceuticals will perform a large placebo-controlled postmarketing study of Foradil Aerolizer, 24 $\mu$g bid, to better understand whether the safety concern raised in these trials is a real finding.

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