Zileuton added to low-dose inhaled beclomethasone for the treatment of moderate to severe persistent asthma

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Received 18 October 2006; accepted 26 January 2007
Available online 13 March 2007

KEYWORDS
Asthma; Zileuton; Beclomethasone; 5-lipoxygenase; 5-lipoxygenase inhibition; \( \text{Ltb}_4 \)

Summary
Objective: To assess the therapeutic effects of oral zileuton tablets combined with low-dose beclomethasone compared to doubling the dose of beclomethasone, in improving lung function and reducing asthma symptoms.

Methods: Randomized, active-control, double-blind, parallel, multi-center study of zileuton (400 or 600 mg QID)+200\( \mu \)g beclomethasone dipropionate (BDP) BID versus placebo+BDP 400\( \mu \)g BID in asthmatics with baseline FEV1 percent predicted values between 40% and 80% following a single-blind ICS (BDP 200\( \mu \)g BID) 2-week run-in. During the 3-month double-blind treatment period, assessments included safety, daytime and nighttime symptoms, acute asthma exacerbations, \( \beta_2 \)-agonist use, AM and PM peak expiratory flow (PEF) and FEV1.

Results: The addition of a 5-lipoxygenase (5-LO) inhibitor added to a low-dose of BDP showed no significant difference in FEV1 compared to doubling the dose of BDP. FEV1 improved in all 3 treatment groups, with mean increases of 10% with zileuton 600 mg QID+BDP 200\( \mu \)g BID, 12% with zileuton 400 mg QID+BDP 200\( \mu \)g BID, and 11% with BDP 400\( \mu \)g BID by study end. Within each treatment group, there were significant improvements in asthma symptoms and AM and PM PEF compared to baseline. No significant differences
were observed between groups with regards to salbutamol use, acute asthma exacerbations, the requirement for oral/parenteral corticosteroids and adverse clinical events. **Conclusions:** The addition of a 5-LO inhibitor added to low-dose beclomethasone may be an alternative to higher-doses of ICS in patients unable to achieve sufficient asthma control on low-dose ICS therapy. 

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### Introduction

Asthma is a heterogeneous chronic inflammatory disease requiring anti-inflammatory therapy to achieve asthma control.1,2 Responsiveness to treatment is heterogeneous, even among asthmatic patients with asthma of similar severity and this heterogeneity calls attention to the importance of assessing asthma control and adjusting treatment accordingly.3

Inhaled corticosteroids (ICS) are recommended as a first-line treatment for asthma not controlled by short-acting $\beta_2$-agonists alone (SABAs).1,2,4 Recent studies demonstrate that increasing doses of ICS result in increased systemic absorption while not necessarily improving lung function, with only a third of patients demonstrating greater than a 15% improvement in lung function.5,6 Furthermore, the potential for systemic side effects with higher doses of ICS and the relatively flat dose–response curves led to the universal asthma treatment guideline recommendation of using the lowest effective dose of ICS to control asthma.1,2

Current asthma treatment guidelines also suggest that patients uncontrolled on ICS therapy alone should receive additional therapy.4 The most common additional agents added to inhaled steroids are long-acting $\beta_2$-agonists (LABAs). The addition of a fixed-dose combination of an ICS and a LABA can result in reduced exacerbations, improved lung function and a reduction in the need for rescue medication.7

However, recent studies have suggested that 30% of asthmatics receiving combination therapy with a combination of an ICS and a LABA still remain inadequately controlled, even with specialty care.8–10 Reasons cited for these findings include insufficient patient education, poor medication compliance, environmental factors, poor inhalation technique and smoking. In addition, the presence of $\beta_2$-adrenergic receptor polymorphisms have been associated with deleterious responses to regular administration of both SABAs and LABAs.11,12 Importantly, inappropriate use of LABAs has also been associated with increased asthma-related mortality and cardiovascular effects in susceptible populations.8,9

Another complementary approach to asthma therapy is to modulate leukotriene production.13–14 Leukotrienes synthesized via the 5-LO pathway include the cysteinyl leukotrienes (LTC4, LTD4, and LTE4), 5-oxo-6,8,11,14-eicosatetraenoic acid (5-oxo-ETE) and leukotriene B4 (LTB4). While the leukotriene receptor antagonists, zafirlukast and montelukast, antagonize only the cysteinyl leukotriene receptor one (cysLT1R) and mediate the effects of the cysteinyl leukotrienes, the 5-LO inhibitor zileuton blocks the synthesis of the cysteinyl leukotrienes, 5-oxo-ETE and LTB4.23,36

The importance of LTB4 blockade stems from its role as a potent chemoattractant for inflammatory cells, such as T-effector cells, eosinophils, and neutrophils.24–26 Indeed, LTB4 is the major 5-LO product of neutrophils, monocytes, and alveolar macrophages.20 LTB4 stimulates leukocyte chemotaxis, chemokinesis and vascular endothelium adherence, delays neutrophil apoptosis and prolongs neutrophil survival.24

Another key 5-LO product, 5-oxo-6,8,11,14-eicosatetraenoic acid (5-oxo-ETE), is a chemoattractant for eosinophils, over 30 times more potent than the cysteinyl leukotrienes, and leads to the migration of eosinophils and prolonged eosinophil survival. 5-oxo-ETE also activates neutrophils, stimulates neutrophil degranulation and induces potent basophil migratory responses.37,38

Recent reports have suggested that neutrophils may play an important role in asthma, particularly severe and difficult-to-treat populations.31,32 Indeed, neutrophilic inflammation has been shown to be increased in multiple asthma phenotypes, including severe, acute, fatal, sudden-onset, occupational and smoking asthmatics with a corresponding increase in neutrophil numbers and activation states.28,32,39,41 Corticosteroids have been reported to suppress neutrophil apoptosis and their use may increase neutrophil numbers.38,42,43 LTB4, a potent neutrophil chemoattractant, is increased in the bronchoalveolar lavage (BAL) fluid, sputum and tissue of severe asthmatics and the levels remain high despite corticosteroid therapy.27,29,32,42 The relative insensitivity of the 5-LO pathway to corticosteroid therapy, increased 5-LO products in asthmatic inflammation and increased neutrophilic inflammation support the rationale for the combination of a 5-LO inhibitor added to an ICS.

Zileuton, a benzothiophene N-hydroxyurea, is a selective inhibitor of 5-LO. In controlled clinical studies in patients with persistent asthma, zileuton improved pulmonary function and asthma symptom scores significantly and reduced the need for $\beta_2$-agonist use and systemic corticosteroid rescue for acute asthma exacerbations.44,45

This randomized, active-control, double-blind, parallel, multi-center study was designed to evaluate the effect of zileuton plus low-dose beclomethasone compared with doubling the dose beclomethasone in asthmatics inadequately controlled with the regular use of ICS.

### Materials and methods

#### Patients

Asthmatics either not currently treated with ICS or those on a stable dose of BDP were recruited for enrollment in the
study. Inclusion criteria included: non-smokers between the ages of 16 and 70, baseline FEV₁ within 40–80% of predicted values on ICS and 15% reversibility after salbutamol. Exclusion criteria included the use of oral corticosteroids or ICS (>600 µg BDP or equivalent), inhaled cromolyn, nedocromil, theophylline products, long-acting antihistamines, aspirin or other non-steroidal anti-inflammatory agents, phenytoin or warfarin, anticholinergic eyedrops or inhalation therapy, oral salbutamol or LABAs. Patients were permitted to use nasal corticosteroids during the study and undergo immunotherapy if they entered the study on a stable dose/regimen.

Study protocol

This was a randomized, active-controlled multi-center study with a 2-week, single-blind run-in period followed by a 12-week double-blind treatment period. Efficacy assessments included FEV₁, morning (AM) and evening (PM) PEF, daily and nocturnal asthma symptom scores, β₂-agonist use, and the frequency of acute asthma exacerbations.

Patients had to meet the single-blind selection criteria to enter the study. Study drugs during the single-blind period were 2 matching placebo tablets, BDP (400 µg daily) and placebo inhalers. During the run-in period patients were required to complete patient diaries; patients who complied with the patient diary and pill regimen and who then met the double-blind selection criteria (including FEV₁, symptom scores, and rescue medication use) were randomized into the double-blind period.

During the double-blind period patients received 1 of 3 treatments: zileuton 2400 mg taken as 600 mg tablets 4 times a day (QID) plus inhaled BDP 400 µg (200 µg [2 puffs] BID) daily; zileuton 1600 mg (400 mg QID) plus inhaled BDP 400 µg (200 µg BID) or placebo tablets plus inhaled BDP 800 µg (400 µg [4 puffs] BID) daily—hereafter referred to as Z 2400 mg+B 400 µg, Z 1600 mg+B 400 µg, and Pl+B 800 µg. Results from the initial zileuton phase I studies indicated that both of these doses of zileuton were well tolerated and would provide significant LTB₄ inhibition (70–90%).

Safety assessments included physical examination, medical history, chest radiograph, electrocardiogram, routine blood chemistry panel, vital signs, and hematology tests.

On the first day of the double-blind period zileuton or placebo was administered and FEV₁ measured at baseline and 30 min post-dose. At subsequent visits, FEV₁ was measured after the morning dose. AM PEF was measured each morning prior to the first dose of study drug and PM PEF measurements were obtained 2 h after the third dose each evening. Patients completed diaries and recorded morning and evening scores, based on wheezing, shortness of breath, cough, and nasal congestion. Patients also recorded their salbutamol use, other concomitant medication use, and any adverse events during the previous 24-h period. Study visits were scheduled for Days 15, 43, 71 and 85 of the double-blind treatment period.

The protocol permitted a 1-week course of oral prednisone at a tapered dose (≤60 mg/day for ≤7 days) for any acute asthma exacerbations not responding to salbutamol or antibiotics for suspected respiratory infections.

Compliance with dosing regimens was monitored. Patients were instructed to return all unused tablets and inhalers to the study center at every visit. Study personnel verified patient compliance through counts of the unused tablets and by the patient’s record of inhaler use in the patient’s diaries. At each visit, the study drug supplies were dispensed and the date and time of the first and last administered dose (for both tablets and inhalers) and the number of tablets remaining after the last dose were recorded on the case report form. Zileuton plasma levels provided an additional check of compliance.

Statistical analysis

The primary efficacy variable was the percent change from baseline to the final visit in morning FEV₁. Sample size requirements for a superiority study were calculated from a previous 1-month study of zileuton versus placebo in asthma that demonstrated an improvement in FEV₁ of 0.19 L with zileuton. Based on a calculated standard deviation of 0.48 L for the change from baseline in FEV₁, it was estimated that 100 patients per treatment group would be required to provide a power of 80% at the 2-sided 0.050 level for a pairwise comparison between a zileuton plus BDP group and the Pl+B 800 µg group, assuming that the expected difference between these 2 groups was 0.19 L for the change from baseline. The primary comparison for this study was Z 2400 mg+B 400 µg versus Pl+B 800 µg for mean percent change from baseline to the final visit.

Statistical analyses were performed using SAS for Windows. Unless otherwise noted, inferential treatment comparisons were declared statistically significant at the 5% level using 2-sided tests. Efficacy analyses were based on the intent-to-treat population using a last value carried forward convention. Data from investigative sites with less than 2 subjects for each treatment group were pooled into a single "site."

Baseline values for non-diary data were obtained by selecting the final measurement prior to the first administration of double-blind study drug. Baseline values of the diary data were obtained by computing the mean of the diary data collected during the single-blind lead-in phase. For all analyses, summary statistics were based only on patients for whom there was both a baseline value and a double-blind interval value.

Double-blind data best corresponding to the nominal visit day from the appropriate "intervals" were used, but data obtained more than 3 days after the end of double-blind dosing were not used. When more than 1 value was of equal proximity to the nominal visit day, the later value was selected. The "final" treatment measurement was obtained using the last data measurement not later than 3 days after the end of the double-blind dosing.

A 2-way analysis of variance was performed with effects for treatment and investigator in the model to test differences between treatment groups for efficacy endpoints. Additionally, a model with investigator, treatment and investigator–treatment interaction was fit to investigate whether the treatment effect was homogenous across investigative sites. If investigator–treatment interaction was significant (using α = 0.100) by-site analyses were
conducted. Adjustments for multiplicity were not performed on analyses of secondary outcomes.

Analysis of safety data was based on all data from all patients who entered the double-blind period. Adverse events were coded by COSTART body system, COSTART term and COSTART medical term. Adverse events having an onset later than 14 days after the end of treatment were not included in frequency tabulations (Table 1).

Results

Subjects

Three hundred and eighty-eight patients entered the double-blind period. These patients were randomized to 3 groups across 32 centers: Z 1600 mg+400 μg BDP (n = 108), Z 2400 mg+B 400 μg (n = 110) and Pl+B 800 μg (n = 102). Two hundred and seventy patients (84%) completed the study. Fifty patients discontinued the double-blind treatment prematurely: 14 in the Z 1600 mg+400 μg BDP group, 20 in the Z 2400 mg+400 μg B group and 16 in the Pl+B 800 μg groups, respectively.

There were no clinically significant differences between treatment groups (Table 2) with respect to demographic characteristics. Baseline values (prior to randomization) for pulmonary function, symptom scores and salbutamol use were similar among groups, although the Z 2400 mg+B 400 μg group had lower baseline AM and PM PEF rates than both the Z 1600 mg+B 400 μg and the B 800 μg+Pl treatment groups. At the time of randomization, patients still had reduced lung function and were symptomatic.

Pulmonary function

All the 3 treatment groups demonstrated statistically significant improvement from baseline in FEV₁ at all visits (p ≤ 0.050). In the Z 2400 mg+400 μg treatment group, the greatest mean percent improvement occurred at Day 85 (10%); in the Z 1600 mg+B 400 μg group and the Pl+B 800 μg group, the greatest mean percent improvements occurred at Day 71 (11% and 13%, respectively) (Fig. 1). There were no statistically significant differences in FEV₁ between any pair of treatment groups at any visit.

Both of the zileuton groups, Z 2400 mg+B 400 μg and Z 1600 mg+B 400 μg, had statistically significant mean improvements from baseline in AM and PM PEF values at all study intervals (p ≤ 0.050). The mean improvements from baseline in PM PEF for the Z 2400 mg+B 400 μg group were statistically significant at almost all intervals except Day 30–57. Generally, the mean improvements from baseline in AM and PM PEF rates were higher for the Z 2400 mg+B 400 μg and the Z 1600 mg+B 400 μg treatment groups than for the Pl+B 800 μg group. The mean improvement from baseline in PM PEF was lower for the Z 1600 mg+B 400 μg than for the Pl+B 800 μg only during the double-blind Day 30–57 interval. There was a statistically significant difference between the Z 2400 mg+B 400 μg and Pl+B 800 μg treatment groups in AM PEF during the double-blind Day 79–99 interval (31.14 versus 16.31 L/min, p = 0.033). In addition, there were statistically significant differences between Z 2400 mg+B 400 μg and the Pl+B 800 μg treatment groups in PM PEF during the double-blind Day 1–29 (15.35 versus 6.68 L/min, p = 0.046), 58–78 (23.43 versus 9.90 L/min, p = 0.036) and 79–99 (24.52 versus 8.94 L/min, p = 0.019) intervals (Fig. 3).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Assessments of daily asthma symptoms completed by patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daytime symptoms (recorded each evening)</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>No Symptoms, unrestricted activity</td>
</tr>
<tr>
<td>1</td>
<td>Symptoms present but produce little or no discomfort; activity unrestricted</td>
</tr>
<tr>
<td>2</td>
<td>Symptoms present, sometimes causing annoyance or impairing routine activity such as dressing, walking, etc.</td>
</tr>
<tr>
<td>3</td>
<td>Symptoms severe, improving little after inhaled use and requiring the use of additional medication and/or doctor’s visit</td>
</tr>
<tr>
<td><strong>Nocturnal symptoms (recorded each morning)</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Slept well, no asthma symptoms</td>
</tr>
<tr>
<td>1</td>
<td>Spent restless night, may have awakened due to asthma symptoms; may have used inhaler</td>
</tr>
<tr>
<td>2</td>
<td>Awakened more than once due to symptoms, inhaler used</td>
</tr>
<tr>
<td>3</td>
<td>Awake all night due to symptoms, inhaler used</td>
</tr>
<tr>
<td><strong>Criteria for diagnosis of asthma exacerbations (1 or more required)</strong>*</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Decrease in PEF of ≥ 20% from previous visit</td>
</tr>
<tr>
<td>2</td>
<td>Increase of ≥ 25% in daily PEF variations</td>
</tr>
<tr>
<td>3</td>
<td>Daily use of ≥ 12 puffs of salbutamol</td>
</tr>
<tr>
<td>4</td>
<td>Relief provided by administered medications did not last at least 3 h</td>
</tr>
<tr>
<td>5</td>
<td>Score of 35 exceeded on four asthma assessment scores over 3-day period</td>
</tr>
<tr>
<td>6</td>
<td>Maximum score of 3 on daytime and 2 on nocturnal symptoms over any 24-h period</td>
</tr>
</tbody>
</table>

*These criteria were applied at Canadian sites only. At European sites, asthma exacerbation was determined by the subjective clinical judgment of the investigator, i.e., whether the patient had a worsening of symptoms sufficiently pronounced to be considered an acute exacerbation of asthma.
Asthma symptom scores and concurrent treatment

There were statistically significant improvements from baseline in mean daytime symptom assessments in all the 3 study groups ($p < 0.001$). There were no statistically significant differences between any 2 treatment groups at any interval (Fig. 4).

While baseline mean nocturnal symptom scores were mild in all the 3 treatment groups, (ranging from 0.45 to 0.56) there were no statistically significant differences between any 2 treatment groups in mean changes at any interval.

While there were no statistically significant differences between any 2 treatment groups in mean number of symptom-free days (mean values ranged from 19 to 22), there was a statistically significant difference in mean number of symptom-free nights between the Z 2400 mg+B 400 µg group (45 nights) and Pl+B 800 µg treatment groups (59 nights; $p < 0.050$).

The mean daily number of occasions of salbutamol use generally decreased from baseline values in all treatment groups during all study intervals, although the differences were not statistically significant for the Z 2400 mg+B 400 µg group until the Day 58–99 interval.

Twelve patients required a single course of oral or injected corticosteroids for asthma exacerbations during the study; 5 in the Z 2400 mg+B 400 µg group, 4 in the Z

Table 2  Demographic and baseline* characteristics of asthma patients.†

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Z 2400 mg+B 400 µg</th>
<th>Z 1600 mg+B 400 µg</th>
<th>Pl+B 800 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>39 ± 1.3</td>
<td>36 ± 1.3</td>
<td>37 ± 1.3</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>57 (53)</td>
<td>44 (40)</td>
<td>43 (42)</td>
</tr>
<tr>
<td>Male</td>
<td>51 (47)</td>
<td>66 (60)</td>
<td>59 (58)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>102 (94)</td>
<td>101 (92)</td>
<td>101 (99)</td>
</tr>
<tr>
<td>Black</td>
<td>2 (2)</td>
<td>5 (5)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (4)</td>
<td>4 (4)</td>
<td>0</td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td>2.18±0.08†</td>
<td>2.42±0.08</td>
<td>2.36±0.08</td>
</tr>
<tr>
<td>FEV1 (% predicted)</td>
<td>62.3±1.3</td>
<td>64.3±1.3</td>
<td>63.1±1.3</td>
</tr>
<tr>
<td>AM PEF (L/min)</td>
<td>346±11‡</td>
<td>388±12</td>
<td>380±12</td>
</tr>
<tr>
<td>PM PEF (L/min)</td>
<td>376±11†</td>
<td>417±12</td>
<td>407±12</td>
</tr>
<tr>
<td>Daily Symptoms [0 (none) to 3 (worst)]</td>
<td>1.19±0.04</td>
<td>1.18±0.04</td>
<td>1.14±0.04</td>
</tr>
<tr>
<td>Nocturnal Symptoms [0 (none) to 3 (worst)]</td>
<td>0.57±0.06</td>
<td>0.64±0.06</td>
<td>0.43±0.06</td>
</tr>
<tr>
<td>Salbutamol use (puffs/day)</td>
<td>2.67±0.3</td>
<td>3.32±0.3</td>
<td>2.84±0.3</td>
</tr>
</tbody>
</table>

*Baseline values prior to first administration of double-blind study drug.
†Values are presented as no. (%) or mean±SE.
‡$p<0.050$ vs. Z 1600 mg+B 400 µg.
§$p<0.050$ vs. Z 2400 mg+B 400 µg; $p<0.050$ vs. Pl+B 800 µg.
*Statistically significant at $p = 0.050$ vs. Pl+B 800 µg.

Figure 1  Mean (± SE) percent change in FEV1 from baseline to each double-blind visit.

Figure 2  Mean (± SE) changes in the morning PEF (L/Min) values from baseline to each double-blind interval; *Statistically significant at $p = 0.050$ vs. Pl+B 800 µg.
Eight patients withdrew from the study due to an asthma exacerbation; 3 in the Z 2400 mg+B 400 µg group, 3 in the Z 1600 mg+B 400 µg group and 2 in the Pl+B 800 µg group. There were no statistically significant differences in the number of acute exacerbations or the number of patients requiring corticosteroids (oral or injected) between any of the treatment groups.

Safety

Adverse events (Table 3) were similar across all groups. Results of laboratory tests physical examinations, electrocardiograms, and chest radiographs were unremarkable with the exception of liver function abnormalities.

Five patients had alanine aminotransferase (ALT) values of ≥ 2 times the upper limit of normal (≥ 2 × ULN); 2 in the Z 2400 mg+B 400 µg group, 2 in the Z 1600 mg+B 400 µg group, and 1 in the Pl+B 800 µg group. Of the 4 patients taking zileuton who had ALT values ≥ 2 × ULN, 2 (1 in each group) had values that returned to normal while patients continued treatment and in the other 2 cases (1 in each group), resolution occurred within 20 days after discontinuation of the study drug. Only 1 patient (Z 2400 mg+B 400 µg treatment group) had an increase that was ≥ 3 × ULN and this elevation resolved upon discontinuation of the study drug.

Discussion

While the addition of a 5-LO inhibitor, zileuton (400 or 600 mg QID), to a low-dose ICS, BDP (200 mg BID), did not show significant differences in FEV₁ when compared to doubling the dose of BDP after 3 months of therapy, there were significant improvements in lung function and asthma symptoms within each treatment group compared to baseline values. The additive effect of zileuton to low-dose inhaled BDP resulted in rapid and sustained improvements in all the subjective and objective treatment outcomes evaluated throughout the study.

Table 3  Treatment-related adverse events occurring in ≥5% of any treatment group during the double-blind phase of the study.*

<table>
<thead>
<tr>
<th>Adverse event (COSTART terms)</th>
<th>Z 2400 mg+B 400 µg (n = 108)</th>
<th>Z 1600 mg+B 400 µg (n = 110)</th>
<th>Pl+B 800 µg (n = 102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>25 (23)</td>
<td>14 (13)</td>
<td>17 (17)</td>
</tr>
<tr>
<td>Aggravation reaction</td>
<td>20 (19)</td>
<td>26 (24)</td>
<td>17 (17)</td>
</tr>
<tr>
<td>Headache</td>
<td>22 (20)</td>
<td>22 (20)</td>
<td>18 (18)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>12 (11)</td>
<td>6 (6)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Flu syndrome</td>
<td>11 (10)</td>
<td>7 (6)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>7 (7)</td>
<td>1 (1)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (6)</td>
<td>3 (3)</td>
<td>5 (5)</td>
</tr>
</tbody>
</table>

*Values are presented as no. (%)

†The adverse event described by the COSTART term, “Aggravation Reaction,” were exacerbations of asthma in all cases but one, which was an exacerbation of eczema.
The rapid and continuous symptom relief in all 3 groups was associated with a reduction in the use of concomitant medications including rescue \( \beta_2 \)-agonists and systemic corticosteroids for needed for asthma exacerbations. While the study did not demonstrate significant differences between treatment groups in the primary outcome of FEV\( _1 \), significant improvements in PEF were found in the 2400 mg zileuton group. Thus, the addition of zileuton to low-dose BDP may be an alternative to using higher-doses of ICS in patients unable to achieve asthma control on low-dose ICS therapy.

The treatment effects are comparable to the effects seen in studies with the combination of ICS and LABA in symptomatic asthmatics.\(^7\) Cysteinyl leukotriene receptor antagonists (LTRA’s) have also shown benefit when added to inhaled steroids in similarly designed studies\(^13,34\) and the improvements with the 5-LO inhibitor zileuton compare favorably with those results. Another group has demonstrated that in a well-controlled, aspirin-intolerant asthmatic population, in which patients were on medium to high doses of inhaled and, in some cases, oral steroids, the addition of zileuton for 6 weeks resulted in acute and sustained improvements in pulmonary function and improved symptom control similar to the results seen in this study.\(^47\) Additionally a year-long, uncontrolled, open-label study and several case-reports have demonstrated additional symptom control and lung function improvement when zileuton was added to the patients’ current steroid therapy.\(^34,43,48,52\) These data suggest a complimentary effect between corticosteroids and agents that modulate leukotriene production.

The improvements in symptom control with zileuton added to BDP occurred within 2–3 weeks and this relatively rapid improvement may lead to improved patient compliance with controller regimens. Lung function also improved throughout the study and this continued improvement may be due to both zileuton and BDP suggesting a potential synergism of these 2 therapies.

ICS provide effective long-term control for asthma patients, but they demonstrate a relatively flat dose-response with regard to lung function improvement; higher doses potentially lead to increased unwanted systemic effects.\(^5\) Therefore, optimizing safety and efficacy to achieve asthma control is ideal. Additionally, inhaled and oral corticosteroids do not inhibit the in-vivo synthesis of leukotrienes.\(^29,31,48,49\) Indeed, asthmatics on high-dose inhaled and oral corticosteroids have shown persistently elevated levels of key 5-LO products, including LT\( \beta \), LTC\( _4 \), LTD\( _4 \), and LTE\( _4 \).\(^27–29,42,50\) A recent report demonstrated that 2 weeks of treatment with a potent ICS (fluticasone 500 \( \mu \)g BID) reduced bronchial responsiveness to methacholine and decreased exhaled nitric oxide (eNO) levels but had no effect on bronchial responsiveness to inhaled LTD\( _4 \), suggesting that leukotriene-dependent parts of bronchoconstriction and airway inflammation are resistant to the effects of glucocorticosteroids.\(^51\) Because of the relative resistance of the 5-LO pathway to suppression by corticosteroids, the addition of a 5-LO inhibitor provides the possibility of additional asthma control.

Another complementary approach to the use of steroids in asthma therapy is to modulate leukotriene production.\(^13–32–34\) Leukotrienes are major mediators of the underlying inflammatory process in asthma. Leukotrienes can produce bronchoconstriction,\(^13\) increased microvascular permeability, mucus hypersecretion, smooth muscle hypertrophy and inflammatory cell infiltration including neutrophils and eosinophils.\(^14\) Leukotrienes are produced by multiple inflammatory cells, particularly mast cells, basophils, eosinophils, neutrophils, and macrophages, all of which have been implicated in asthma pathogenesis.\(^15–20\) The number and state of activation of eosinophils and mast cells, both rich sources of leukotrienes, correlate with asthma severity.\(^21,22\)

Leukotrienes are important mediators in asthma pathogenesis\(^3–17,23,53\) and 5-LO products have been shown to be increased in all severities of asthma, despite treatment with inhaled and oral corticosteroids.\(^27–30\)

Interestingly, steroid therapy has been shown to prolong the survival of neutrophils which have been suggested to be important in asthma pathology, especially in more severe and difficult-to-control patients.\(^27,28,31,32\) LT\( \beta \), a key product of the 5-LO pathway, is a potent neutrophil chemoattractant and levels of LT\( \beta \) remain high in the BAL fluid and urine from severe asthmatics, despite oral and inhaled steroid therapy.\(^27–31\) Therefore, modulating leukotriene production with 5-LO inhibition, in conjunction with ICS, may prove to be a useful complimentary therapeutic approach to achieving asthma control. This approach may allow for the blunting of leukotriene-mediated cellular inflammation, including the effects of LT\( \beta \) on neutrophil chemoattraction.

The incidence and types of adverse events were comparable in the 3 treatment groups. Five patients had elevations of ALT \( \geq \times 2 \) ULN, including 1 patient in the placebo group. Only 1 patient (Z 2400 mg+B 400 \( \mu \)g) had an increase \( \geq 3 \) ULN and this elevation resolved after discontinuation of the study drug. Similar findings were seen with zileuton treatment in previous placebo-controlled studies and routine ALT monitoring is recommended with zileuton therapy as well as avoidance in patients with a history of liver disease.\(^44,45\)

In conclusion, the addition of a 5-LO inhibitor, zileuton (400 or 600 mg QID), to a low-dose ICS, BDP (200 mg BID), may be an alternative to higher-doses of ICS in patients unable to achieve sufficient asthma control on low-dose ICS therapy.

Acknowledgements

The authors acknowledge Diane Bell, ScD, Monica Massaro, MPH, and Melissa De Chantd at Critical Therapeutics for their support of this manuscript. They thank the investigators and staff at all of the study sites and at Abbott Laboratories. This research was funded by Abbott Laboratories, North Chicago, IL.

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