

Evaluation of beclomethasone dipropionate (80 and 160 micrograms/day) delivered *via* a breath-actuated inhaler for persistent asthma

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ABSTRACT

Background: Breath-actuated inhalers (BAI) may simplify the delivery of inhaled medications compared with other devices.

Objective: To evaluate the efficacy and safety of beclomethasone dipropionate BAI versus matching placebo in adolescent and adult patients with persistent asthma.

Methods: This phase III, 12-week, double-blind study enrolled patients with asthma aged ≥ 12 years who were previously treated with a stable dose of inhaled corticosteroid or noncorticosteroid therapy. After a run-in period of 14 to 21 days, patients were randomly assigned in a 1:1:1 ratio to beclomethasone dipropionate BAI 80 or 160 micrograms/day (40 or 80 micrograms twice daily) or placebo BAI. The primary end point was the standardized baseline-adjusted trough morning forced expiratory volume in 1 second (FEV₁) area under the effect curve from time 0 to 12 weeks (AUEC_[0–12 weeks]). Secondary end points included peak expiratory flow, rescue medication use, asthma symptoms, and the time to withdrawal due to meeting predefined criteria for worsening asthma. Additional end points evaluated quality of life, instructions for use, and safety.

Results: The full analysis and the safety sets included 270 and 273 patients, respectively. Patients who received beclomethasone dipropionate BAI 80 or 160 micrograms/day had significant improvements in FEV₁ AUEC_(0–12 weeks) versus placebo ($p \leq 0.001$). Improvements in secondary end points were also apparent in patients who received beclomethasone dipropionate BAI 80 or 160 micrograms/day compared with placebo. Patients who received beclomethasone dipropionate BAI 80 or 160 micrograms/day had greater increases in Asthma Quality of Life Questionnaire scores versus placebo patients at week 12. Of 98 patients who participated in the instructions-for-use substudy, 87 (88.8%) used the inhaler successfully on their first attempt. Treatment was generally safe and well tolerated.

Conclusion: Beclomethasone dipropionate BAI 80 and 160 micrograms/day were effective and well-accepted treatments in patients with asthma, with safety comparable to beclomethasone dipropionate delivered via a metered-dose inhaler.

Clinical trial NCT02040779, www.clinicaltrials.gov

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Inhaled corticosteroids (ICS) are recommended in current treatment guidelines as the preferred daily medication for all patients with persistent asthma.¹ Depending on the patient's needs, ICS can be delivered by a variety of devices, including pressurized metered-

dose inhalers (MDI), dry powder inhalers, and, more recently, breath-actuated inhalers (BAI).² Patients must use these devices properly to ensure effective delivery of medication to the lungs.^{3,4} With MDIs, patients are required to coordinate inhalation and actuation for proper drug administration, but multiple studies indicate misuse commonly attributed to coordination errors.^{5,6} Of note, improper inhaler technique has been associated with uncontrolled asthma and increased emergency department visits.⁷ BAIs were developed to offer advantages compared with MDIs: they eliminate the need for hand-breath coordination necessary with MDIs and have been reported to be easier to use than the other devices.⁸

QVAR (beclomethasone dipropionate hydrofluoroalkane [HFA] Inhalation Aerosol (Teva Pharmaceutical Industries, Frazer, PA) is an ICS delivered via a pressurized MDI that was approved by the U.S. Food and Drug Administration in 2002 for maintenance treatment of asthma in patients aged ≥ 5 years.⁹ With QVAR, beclomethasone dipropionate is delivered

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in an ultrafine aerosol that allows it to reach the peripheral airways, an important site of inflammation in asthma.^{10,11} Beclomethasone dipropionate delivered *via* a new BAI (Teva Pharmaceutical Industries) has been developed to ensure that patients are able to consistently use the device properly and obtain treatment benefits. The current study evaluated the efficacy and safety of beclomethasone dipropionate (80 or 160 $\mu\text{g}/\text{day}$) administered *via* the BAI compared with a matching placebo BAI in adolescent and adult patients with persistent asthma.

METHODS

This phase III, 12-week, randomized, double-blind, placebo-controlled, parallel-group study evaluated the efficacy and safety of beclomethasone dipropionate administered *via* a BAI at dosages of 80 $\mu\text{g}/\text{day}$ and 160 $\mu\text{g}/\text{day}$ in patients aged ≥ 12 years with persistent asthma. The study was conducted at 44 centers in the United States, from December 2013 to December 2014, and consisted of a 2- to 3-week run-in period, a 12-week double-blind treatment period, and a follow-up visit or telephone call scheduled for 7 ± 3 days after the last treatment visit. During the run-in period, the patients were provided with a single-blind placebo BAI for use twice daily and instructed on its proper use. Albuterol/salbutamol HFA MDI (90 μg ex-actuator) was provided to all the patients and was permitted as rescue medication throughout the study. Patients who entered the study while on ICS monotherapy (fluticasone propionate ≤ 220 $\mu\text{g}/\text{day}$ or equivalent) or noncorticosteroid medications (NCS) (including leukotriene modifiers, theophylline, chromones, or short-acting beta agonists alone or in combination) continued to receive their medication during the run-in period. Patients who were receiving an ICS in combination with an NCS were required to discontinue the NCS for 7 to 30 days before entering the run-in period if, in the investigator's opinion, there would be no inherent harm to the patient.

Patients who continued to meet eligibility criteria at the end of the run-in period discontinued their previous asthma medication and were randomly assigned to one of three treatment groups: beclomethasone dipropionate BAI 80 $\mu\text{g}/\text{day}$ (one inhalation of 40 μg twice daily), beclomethasone dipropionate BAI 160 $\mu\text{g}/\text{day}$ (one inhalation of 80 μg twice daily), or matching placebo BAI device (one inhalation twice daily). Randomization was stratified according to the patient's current asthma therapy at screening and during run-in (ICS versus NCS), and treatment assignments were made through a qualified interactive response technology system. During the run-in and treatment periods, patients recorded their peak expiratory flow (PEF) value, use of albuterol/salbutamol, and asthma symptoms in a diary twice daily in the morning and evening.

The study was approved by an independent ethics committee or institutional review board, and conducted in accordance with the International Council for Harmonisation Good Clinical Practice Consolidated Guideline (E6) and all applicable national and local regulations. Written informed consent was obtained from adult patients and from the parent or legal guardian of adolescent patients (with written informed assent of the patient) before any study procedures or assessments were performed. The study was conducted and monitored by Pharmaceutical Product Development (Wilmington, NC).

Patients

Patients who were ≥ 12 years of age and had a documented history of persistent asthma were eligible for enrollment if they had a forced expiratory volume in 1 second (FEV_1) of 40 to 85% of the predicted value for age, height, sex, and race as per the National Health and Nutrition Examination Survey reference values at the screening visit¹²; were receiving a stable daily dose of ICS (fluticasone propionate ≤ 220 $\mu\text{g}/\text{day}$ or equivalent) or NCS therapy for at least 4 weeks; and demonstrated FEV_1 reversibility of $\geq 15\%$ within 30 minutes after two to four inhalations of albuterol/salbutamol HFA MDI. Eligible patients were able to perform acceptable and repeatable spirometry, consistent with American Thoracic Society/European Respiratory Society criteria,¹³ and were able to measure PEF using a handheld PEF meter.

Female patients of childbearing potential who had a negative urine pregnancy test result and who agreed to use acceptable contraception throughout the study and male patients, if sexually active, who also agreed to use acceptable contraception or exclusively had same-sex partners were eligible to participate in the study. Patients with a history of life-threatening asthma and those who had an asthma exacerbation that required oral corticosteroids within 1 month, had any hospitalization for asthma within the past 2 months, had received immunosuppressive medication within the past 4 weeks, had any known strong cytochrome P450 3A4 inhibitor within the past 30 days, or had a documented or suspected respiratory tract infection within the past 2 weeks were excluded. Patients who smoked (or had a ≥ 10 pack-year history of smoking), had a history of alcohol or drug abuse within the past 2 years, or a positive test result for human immunodeficiency virus or hepatitis B or C infection were also excluded.

At the end of the run-in period, the patients were randomized to study treatment if they continued to have an FEV_1 value within 40 to 85% of predicted; did not have a respiratory tract infection, asthma exacerbation, or any significant change in asthma medication during the run-in period; had no visual evidence of

oropharyngeal candidiasis; and had completed the daily asthma diary on at least 4 of the 7 days before randomization. In addition, patients were required to meet any of the following criteria or combination of criteria on at least 4 of the 7 days before randomization: daytime asthma symptom score of ≥ 1 , nighttime asthma symptom score of ≥ 1 , or rescue medication use on one or more occasions.

Assessments

The primary efficacy end point was the standardized baseline-adjusted trough morning (pre-dose and pre-rescue bronchodilator) FEV₁ area under the effect curve evaluated from time 0 to 12 weeks (AUEC_[0–12 weeks]). Pulmonary function was measured electronically using standardized equipment at approximately the same time of day (± 1 hour) and submitted to a central reading center for evaluation. The highest FEV₁ measurement from three acceptable and two repeatable maneuvers was used from a maximum of five attempts, consistent with American Thoracic Society/European Respiratory Society criteria.¹³ Baseline FEV₁ was defined as the last measurement recorded as the best attempt before the first dose of double-blind study treatment.

Secondary efficacy end points included the changes from baseline in the weekly average of daily trough morning and daily evening PEF, total daily use of albuterol/salbutamol, total daily asthma symptom score, and time to withdrawal due to meeting predefined criteria for worsening asthma symptoms. PEF was measured using a handheld peak flow meter, with the highest value of three measurements recorded in the diary. Daytime symptom scores were self-assessed in the evening on a scale that ranges from 0 to 5 (0, no symptoms during the day; 5, symptoms so severe that the patient could not go to work or perform normal daily activities). Nighttime symptom scores were assessed the following morning on a scale from 0 to 4 (0, no symptoms during the night; 4, symptoms so severe that the patient did not sleep at all). If any of the following predefined criteria for worsening asthma were met, then the investigator was to determine whether the patient should have been withdrawn from the study in the interest of the patient's safety: FEV₁ below the FEV₁ stability limit value calculated at the randomization visit; any of the following during any 7-day period: ≥ 4 days in which the highest morning PEF fell below the PEF stability limit calculated at the randomization visit, ≥ 3 days in which ≥ 12 inhalations/day of rescue medication were used, or ≥ 2 days in which the patient experienced a nighttime asthma symptom score of >2 ; or a clinical exacerbation.

Other efficacy end points included the changes from baseline in total daily albuterol/salbutamol use and

total daily asthma symptom score (defined as the average of daytime and nighttime scores) over the first 14 days on study treatment, and the changes from baseline in the percentage of rescue-free days (defined as 24-hour periods with no rescue medication use), symptom-free days (defined as 24-hour periods with asthma symptom scores of 0), and asthma control days (defined as 24-hour periods with asthma symptom scores of 0 and no rescue medication use).

Adult patients completed the Asthma Quality of Life Questionnaire with Standardized Activities (AQLQ[S]) at the randomization and final visits; the change from baseline in the AQLQ(S) score and the proportion of patients who achieved a clinically significant change from baseline (minimum important difference of 0.5 in the AQLQ[S] score) at week 12 were determined. The AQLQ(S) includes 32 items scored on a scale that ranges from 1 to 7 (1, severely impaired; 7, not impaired at all) with a 2-week recall; higher scores reflect better quality of life. The items were grouped to produce subscores for symptoms, activity limitations, emotional function, and environmental function, along with a total score, which was the mean of the sum of the individual subscores.¹⁴ The ability of a subgroup of patients to comprehend and understand the instructions for use of the BAI device was evaluated during the screening visit at nine study centers. The patients who agreed to participate were asked to read the instructions for use. They were instructed to take two inhalations of the device with no additional training. Their ability to follow the instructions and demonstrate proper inhalation technique for the device was evaluated by the clinic staff.

Safety was assessed by evaluating adverse events (AE) and vital signs throughout the study, by physical examination at the screening and final visits, and by oropharyngeal examination for the presence for oral candidiasis at each visit. Asthma exacerbations with treatment details were recorded on the case report form but were not considered AEs unless they met criteria of a serious AE. All AEs were coded according to the Medical Dictionary for Regulatory Activities (version 16.1).¹⁵

Statistics

The sample size of 270 patients (90 patients per treatment group) would have 90% power at the two-sided 0.05 level of significance to detect a difference of 200 mL between each active treatment group and the placebo group in the change from baseline in the trough morning FEV₁ over the 12-week treatment period. The efficacy analysis was conducted in all intent-to-treat patients who received at least one dose of study drug and had at least one postbaseline trough morning FEV₁ assessment (defined as the full analysis set [FAS]).

Safety was assessed in all intent-to-treat patients who received one or more doses of study drug. All statistical analyses were conducted using SAS version 9.2 (SAS Institute, Inc., Cary, NC). The estimated treatment differences between each active treatment group and the placebo group were determined together with their two-sided 95% confidence intervals and *p* values.

The primary efficacy end point was analyzed using an analysis of covariance (ANCOVA) model with effects for baseline trough morning FEV₁, sex, age, and current asthma therapy (ICS or NCS) at screening and during the run-in, and treatment. Pairwise estimates were made between each active treatment group and the placebo group. A fixed-sequence multiple testing procedure was used while controlling the family-wise error rate at 5%. If the two-sided *p* value that resulted from the ANCOVA model for comparing beclomethasone dipropionate 160 µg/day versus placebo was <0.05, then the comparison of the 80 µg/day group versus placebo was interpreted inferentially.

Secondary efficacy end points were evaluated using a mixed model for repeated measures analysis with covariate adjustment for baseline values, sex, age, current asthma therapy at the time of the screening visit and run-in, treatment, week, and treatment-by-week interaction. Time to withdrawal from study treatment was evaluated using Kaplan-Meier estimates. For the secondary efficacy end points, comparisons of each active treatment versus placebo were conducted in a sequential order and interpreted inferentially if comparisons of the primary efficacy end points were statistically significant. This process was continued until either all comparisons of interest were interpreted inferentially or until the resulting two-sided *p* value for the comparison of interest was >0.05, at which point no further comparisons were to be interpreted inferentially. This approach allowed for control of a type I error for comparisons of a particular treatment over the five secondary end points as well as comparisons over treatment within a particular end point; however, this did not control for an overall type I error. Changes in AQLQ(S) were evaluated using an ANCOVA model with covariate adjustment for baseline value, age, sex, current asthma therapy, and treatment. All other end points were summarized descriptively.

RESULTS

Patients

A total of 273 patients were randomly assigned, received at least one dose of study medication, and were evaluable for safety (Fig. 1). Of these, 270 patients had a postbaseline trough morning FEV₁ assessment and were evaluable for efficacy. Twenty-three patients were discontinued from the study prematurely, includ-

ing 12 patients (13.2%) from the placebo group and 11 patients (6.0%) from the two beclomethasone dipropionate BAI groups combined. The most common reasons for discontinuation were withdrawal of consent by the patient (*n* = 8 [2.9%]) and lack of efficacy (*n* = 6 [2.2%]), the latter occurred mostly in the placebo group. The treatment groups were well balanced with respect to demographic and baseline characteristics. The study cohort had a mean age of 37.8 years; most patients (85.7%) were in the 18- to 64-year age group, and most (68.5%) had asthma for ≥15 years (Table 1). A majority of the patients (61.9%) were receiving NCS treatment rather than ICS treatment (38.1%) at study entry. The majority of the patients in the placebo, beclomethasone dipropionate BAI 80 µg/day, and beclomethasone dipropionate BAI 160 µg/day groups of the safety population were compliant with treatment. Of patients who received placebo or beclomethasone dipropionate BAI 80 µg/day, 95.6% were at least 80% compliant, and 100.0% of the patients who received beclomethasone dipropionate BAI 160 µg/day were at least 80% compliant.

Efficacy

In the primary efficacy analysis, patients in the beclomethasone dipropionate BAI 80 µg/day and 160 µg/day groups had significant improvements in trough morning FEV₁ AUEC_(0-12 weeks) compared with placebo (Table 2). In the ANCOVA model, the least squares mean difference between the 160 µg/day and placebo groups was 0.116 L (*p* = 0.001) and that between the 80 µg/day and placebo groups was 0.124 L (*p* = 0.0005). The patients in both active treatment groups had substantial improvements in trough morning FEV₁ compared with placebo starting at the first assessment at week 2 and continuing throughout the 12-week treatment period (Fig. 2).

In the secondary efficacy analyses, the patients in the beclomethasone dipropionate BAI 80 µg/day and 160 µg/day groups had substantial improvements in the weekly averages of trough morning PEF and evening PEF; the differences in change from baseline over 12 weeks compared with placebo were statistically significant for both the beclomethasone dipropionate BAI 80 µg/day and 160 µg/day dose groups for trough morning PEF (*p* = 0.0007 and *p* < 0.05, respectively). Improvements in morning PEF value were observed as early as day 1 and evident over the first 14 days of treatment with both doses of beclomethasone dipropionate BAI. Treatment with beclomethasone dipropionate BAI 80 µg/day significantly improved the evening PEF value from baseline over 12 weeks (*p* = 0.0112) compared with placebo, and improvements in patients treated with 160 µg/day were substantial compared with placebo but did not reach statistical significance (Table 3).

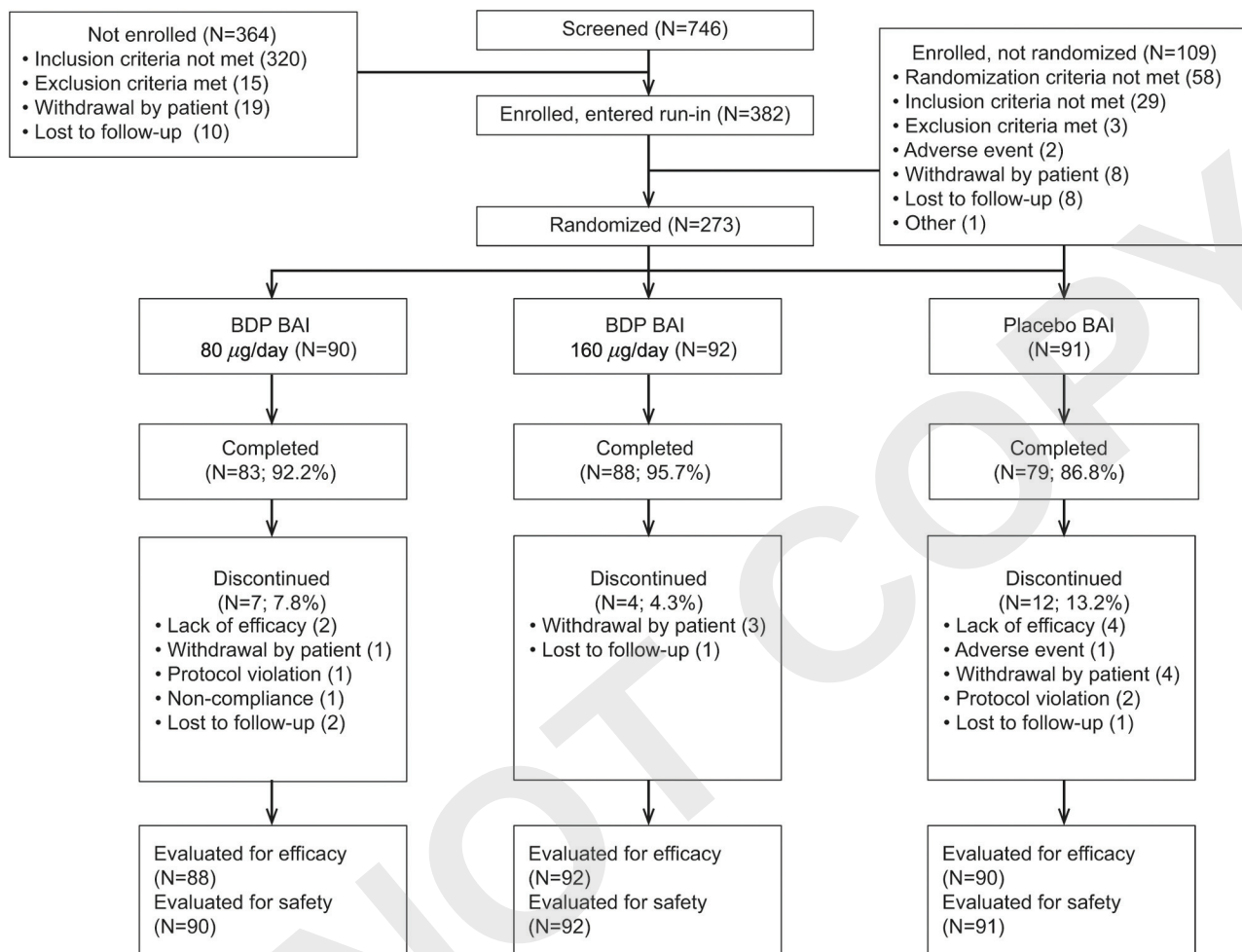


Figure 1. Patient disposition. BAI = Breath-actuated inhaler; BDP = beclomethasone dipropionate.

Improvements in the weekly averages of the total daily use of albuterol/salbutamol for the beclomethasone dipropionate BAI 80 µg/day dose compared with placebo were statistically significant ($p = 0.0285$). There were substantial improvements with the beclomethasone dipropionate BAI 160 µg/day dose ($p = 0.0175$); however, conclusions regarding statistical significance in the beclomethasone dipropionate BAI 160 µg/day group could not be reached due to the hierarchical statistical analysis used in this study (Table 3). Decreases in total daily asthma symptom scores were also apparent in both active treatment groups, and fewer patients in the active treatment groups withdrew from the study due to worsening asthma compared with patients in the placebo group (Table 3).

Beclomethasone dipropionate BAI 80 µg/day and 160 µg/day showed substantial improvements in other efficacy end points, including the change from baseline in the percentage of rescue-free days, asthma-control days, and symptom-free days during the 12-week treatment period (Table 4). Two additional end points

assessed efficacy over the first 14 days. Total daily use of albuterol/salbutamol over the first 14 days of study treatment decreased from baseline in both active treatment groups compared with an increase from baseline in the placebo group, and the decrease in total daily asthma symptom scores over the first 14 days was greater in the active treatment groups than in the placebo group (Table 4).

Quality of Life

The AQLQ(S) total score at week 12, which reflects quality of life over the preceding 2-week period, increased from baseline in each treatment group; the improvement was greater in the beclomethasone dipropionate BAI 80 µg/day and 160 µg/day groups compared with the placebo group ($p = 0.0095$ and $p = 0.0559$ respectively) (Table 5). Similar trends were observed on each of the AQLQ(S) subscores, particularly the symptom subscore. Most patients in each treatment group achieved a clinically significant change from baseline in the AQLQ(S) total score at week 12 (defined

Table 1 Patient demographic and baseline characteristics (ITT population)

Characteristic	Placebo (N = 91)	Beclomethasone Dipropionate		Total (N = 273)
		BAI 80 µg/day (N = 90)	BAI 160 µg/day (N = 92)	
Age, mean ± SD, y	37.2 ± 14.82	38.8 ± 15.02	37.4 ± 16.05	37.8 ± 15.27
Age group, no. (%)				
12–17 y	9 (9.9)	8 (8.9)	13 (14.1)	30 (11.0)
18–64 y	80 (87.9)	79 (87.8)	75 (81.5)	234 (85.7)
≥65 y	2 (2.2)	3 (3.3)	4 (4.3)	9 (3.3)
Sex, no. (%)				
Male	45 (49.5)	36 (40.0)	36 (39.1)	117 (42.9)
Female	46 (50.5)	54 (60.0)	56 (60.9)	156 (57.1)
Race, no. (%)				
White	73 (80.2)	64 (71.1)	72 (78.3)	209 (76.6)
Black	13 (14.3)	17 (18.9)	14 (15.2)	44 (16.1)
Asian	3 (3.3)	2 (2.2)	1 (1.1)	6 (2.2)
Other	2 (2.2)	7 (7.8)	5 (5.4)	14 (5.1)
Weight, mean ± SD, kg	82.3 ± 23.85	85.3 ± 22.38	80.3 ± 20.58	82.6 ± 22.32
Duration of asthma, no. (%)				
<1 y	1 (1.1)	2 (2.2)	0	3 (1.1)
1 to <5 y	4 (4.4)	4 (4.4)	2 (2.2)	10 (3.7)
5 to <10 y	9 (9.9)	8 (8.9)	10 (10.9)	27 (9.9)
10 to <15 y	12 (13.2)	16 (17.8)	18 (19.6)	46 (16.8)
≥15 y	65 (71.4)	60 (66.7)	62 (67.4)	187 (68.5)
Current asthma therapy, no. (%)				
ICS	35 (38.5)	34 (37.8)	35 (38.0)	104 (38.1)
NCS	56 (61.5)	56 (62.2)	57 (62.0)	169 (61.9)
Trough morning FEV ₁ , mean ± SD, L*	2.42 ± 0.608	2.34 ± 0.648	2.35 ± 0.564	
Trough morning PEF value, mean ± SD, L/min*	380.54 ± 96.28	357.66 ± 92.10	369.49 ± 83.61	
Total asthma symptom score, mean ± SD*	1.03 ± 0.610	1.04 ± 0.666	1.07 ± 0.617	

ITT = Intent to treat; BAI = breath-actuated inhaler; SD = standard deviation; ICS = inhaled corticosteroid; NCS = noncorticosteroid medication; FEV₁ = forced expiratory volume in 1 second; PEF = peak expiratory flow.

*Data from the full analysis set population (N = 88 – 90 in the placebo group; N = 88 in the beclomethasone dipropionate BAI 80 µg/day group, and N = 92 in the beclomethasone dipropionate BAI 160 µg/day group).

as a minimum important difference of 0.5), including 80 and 74% of patients in the beclomethasone dipropionate BAI 80 µg/day and 160 µg/day groups, respectively, compared with 66% of those in the placebo group.

Ease of Use of BAI Device

The substudy that evaluated the instructions for use of the BAI device included 98 patients (mean age, 39.2 years; range, 12–68 years). Of these, 87 patients (88.8%) successfully administered two inhalations from a placebo BAI on their first attempt after reading the instructions for use; 10 patients (10.2%) were successful on their second attempt, and 1 patient (1.0%) did not successfully complete the task. The majority of the

patients indicated that the BAI was very easy (84.7%) or somewhat easy (12.2%) to use for delivering medication.

Safety

The incidence of AEs during the 12-week treatment period was generally similar across the three treatment groups, which ranged from 28.3% in the beclomethasone dipropionate BAI 160 µg/day group to 35.6% in the 80 µg/day group (Table 6). Overall, the most common AEs were upper respiratory tract infection, nasopharyngitis, and headache; no single AE occurred at an incidence of ≥5% in any treatment group. One patient in the placebo group experienced a serious AE (pneumonia and asthma exacerbation, which re-

Table 2 Baseline-adjusted trough morning FEV₁ AUEC_(0–12 weeks) (full analysis set)

Parameter Statistic*	Placebo (N = 90)	Beclomethasone Dipropionate	
		BAI 80 µg/day (N = 88)	BAI 160 µg/day (N = 92)
Model-adjusted ANCOVA			
No. patients	88	88	92
LS mean ± SE	0.048 ± 0.0252	0.171 ± 0.0254	0.164 ± 0.0248
95% CI	−0.002 to 0.097	0.121 to 0.222	0.115 to 0.213
Difference from placebo			
Difference of LS means	—	0.124	0.116
95% CI	—	0.054 to 0.193	0.048 to 0.185
p Value	—	0.0005	0.0010

FEV₁ = Forced expiratory volume in 1 second; AUEC_(0–12 weeks) = area under the effect curve from time 0 to 12 weeks; BAI = breath-actuated inhaler; ANCOVA = analysis of covariance; LS = least squares; SE = standard error; CI = confidence interval.

*Data from the ANCOVA model with covariate adjustment for baseline, sex, age, current asthma therapy, and treatment.

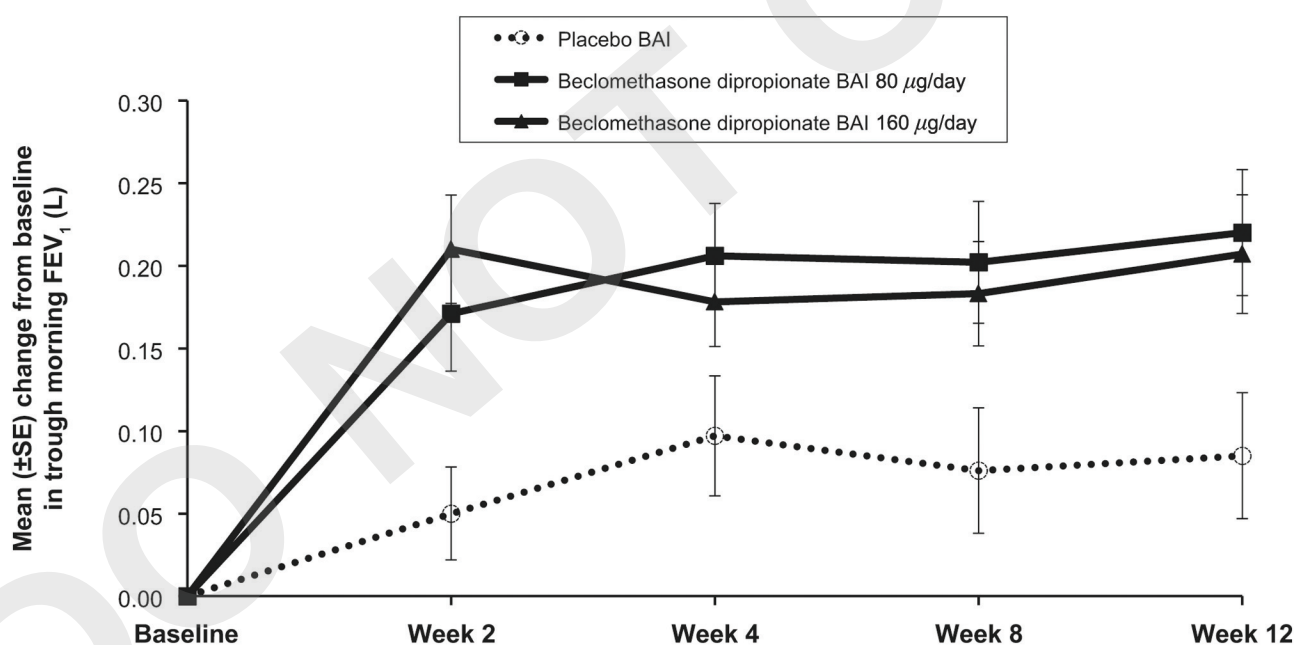


Figure 2. Mean ± SE change from baseline in trough morning FEV₁ during the 12-week treatment period (full analysis set). SE = standard error; FEV₁ = Forced expiratory volume in 1 second; BAI = breath-actuated inhaler.

solved but led to study discontinuation and was not considered related to study medication. There were no deaths, and the incidence of treatment-related AEs was low: two patients in the beclomethasone dipropionate BAI 160 µg/day group experienced oral candidiasis, one patient in the 80 µg/day group experienced sinus congestion and a sinus headache, and one patient in the placebo group experienced throat irritation. No patients in the beclomethasone dipropionate BAI 80 µg/day or placebo groups had oral candidiasis on oropharyngeal examination. Asthma exacerbations were reported in six patients

(6.6%) in the placebo group and in two patients (2.2%) in the beclomethasone dipropionate BAI 80 µg/day group. None of the patients in the 160 µg/day group had an asthma exacerbation.

DISCUSSION

Beclomethasone dipropionate BAI 80 µg/day and 160 µg/day significantly improved the primary efficacy end point of baseline-adjusted trough morning FEV₁ AUEC_(0–12 weeks) compared with placebo BAI in adolescent and adult patients with persistent asthma

Table 3 Change from baseline in weekly averages of secondary efficacy end points over the 12-week treatment period (full analysis set)

Parameter Statistic	Placebo (N = 90)*	Beclomethasone Dipropionate	
		BAI 80 µg/day (N = 88)*	BAI 160 µg/day (N = 92)*
Trough morning PEF value, L/min#			
LS mean ± SE	−0.80 ± 2.822	12.85 ± 2.824	7.12 ± 2.774
Difference of LS means vs placebo (95% CI)	—	13.65 (5.843 to 21.446)	7.91 (0.202 to 15.261)
p Value	—	0.0007	0.0443
Evening PEF value, L/min#			
LS mean ± SE	−0.80 ± 3.038	10.11 ± 3.051	4.61 ± 2.991
Difference of LS means vs placebo (95% CI)	—	10.90 (2.500 to 19.303)	5.41 (−2.905 to 13.715)
p Value	—	0.0112	0.2014
Total daily use of albuterol/salbutamol#			
LS mean ± SE	−0.01 ± 0.116	−0.37 ± 0.116	−0.40 ± 0.115
Difference of LS means vs placebo (95% CI)	—	−0.36 (−0.678 to −0.038)	−0.39 (−0.708 to −0.068)
p Value	—	0.0285	0.0175
Total daily asthma symptom scores#			
LS mean ± SE	−0.17 ± 0.046	−0.29 ± 0.046	−0.30 ± 0.045
Difference of LS means vs placebo (95% CI)	—	−0.13 (−0.255 to 0.001)	−0.14 (−0.263 to −0.011)
p Value	—	0.0509	0.0335
Proportion of patients who withdrew due to worsening asthma§			
Patients who met the stopping criteria, no. (%)	5 (5.6)	2 (2.3)	0
p Value	—	0.2384	0.0208

BAI = Breath-actuated inhaler; PEF = peak expiratory flow; LS = least squares; SE = standard error; CI = confidence interval.

*No. of patients in the analysis for placebo, beclomethasone dipropionate BAI 80 µg/day, and beclomethasone dipropionate BAI 160 µg/day groups were 89, 88, and 92, respectively, for trough morning PEF and evening PEF; 86, 88, and 89, respectively, for total daily use of albuterol/salbutamol; and 90, 88, and 92, respectively, for asthma symptom score and time to withdrawal. #Data from the mixed model for repeated measures analysis with covariate adjustment for baseline, sex, age, current asthma therapy, treatment, week, and treatment-by-week interaction.

§Comparisons vs placebo based on the log-rank test.

who were previously treated with either a low-dose ICS or NCS. Improvement in the trough morning FEV₁ was apparent at the first spirometry assessment at week 2 of the treatment period. The results of the primary efficacy analysis were supported by the analyses of the secondary efficacy end points. The improvements in most efficacy end points were generally similar in the beclomethasone dipropionate BAI 80 µg/day and 160 µg/day groups. It is important to recognize that the study was designed to compare the efficacy of each active treatment versus placebo and was not powered statistically to compare the efficacy between the two active treatments; therefore, no conclusions should be drawn about the relative efficacy.

In addition, the study was not designed to compare the BAI with an MDI. Because the two doses seemed to provide a similar benefit relative to placebo, beclomethasone dipropionate BAI 80 µg/day may be a reasonable starting dose for patients who are beginning ICS therapy or are switching from low-dose ICS therapy.

AQLQ(S) provides a separate and reliable evaluation of asthma symptoms and asthma-related activity limitations.¹⁶ Consistent with the improvements in efficacy end points, increases in AQLQ(S) scores were observed in both beclomethasone dipropionate BAI groups at week 12 compared with baseline. This observation reflected an improvement in asthma-related quality of

Table 4 Change from baseline in other efficacy end points during the 12-week treatment period (full analysis set)

Parameter Statistic	Placebo (N = 90)	Beclomethasone Dipropionate	
		BAI 80 µg/day (N = 88)	BAI 160 µg/day (N = 92)
Rescue-free days,* no. patients	83	86	89
Mean ± SE, %	0.3 ± 3.23	11.4 ± 3.27	10.1 ± 3.43
p Value#	—	0.0141	0.0296
Symptom-free days,* no. patients	87	86	92
Mean ± SE, %	9.5 ± 2.61	20.1 ± 2.95	21.6 ± 3.27
p Value#	—	0.0186	0.0147
Asthma-control days,* no. patients	85	86	92
Mean ± SE, %	6.8 ± 2.37	17.2 ± 2.70	20.6 ± 3.24
p Value#	—	0.0056	0.0051
Total daily use of albuterol/salbutamol over the first 14 days on study treatment,§ no. patients	85	88	89
LS mean ± SE¶	0.14 ± 0.121	−0.17 ± 0.121	−0.27 ± 0.120
Difference of LS means vs placebo (95% CI)	—	−0.311 (−0.644 to 0.023)	−0.409 (−0.742 to −0.076)
p Value	—	0.0682	0.0163
Total daily asthma symptom score over the first 14 days on study treatment,§ no. patients	89	88	92
LS mean ± SE¶	−0.07 ± 0.042	−0.13 ± 0.043	−0.16 ± 0.042
Difference of LS means vs placebo (95% CI)	—	−0.06 (−0.175 to 0.060)	−0.08 (−0.198 to 0.034)
p Value	—	0.3367	0.1669

BAI = Breath-actuated inhaler; SE = standard error; LS = least squares; CI = confidence interval.

*Baseline was defined as the percentage of days over the 7-day period before the randomization visit, in which criteria were met for rescue-free days, asthma control days, and symptom-free days.

#The p value determined by the Wilcoxon-Mann-Whitney test in pairwise comparison vs the placebo group.

§Baseline was defined as the average of daily albuterol/salbutamol usage or the total daily asthma symptom score over the 7-day period before the randomization visit.

¶Data from the mixed model for repeated measures analysis with covariate adjustment for baseline, sex, age, current asthma therapy, treatment, day, and treatment-by-day interaction.

life during the last 2 weeks of the treatment period and appeared to be mainly attributable to improvements in the asthma symptom subscore. For most patients in all three treatment groups, the improvement in AQLQ(S) scores from baseline at week 12 was greater than the minimum important difference of 0.5.¹⁶

The instructions-for-use substudy illustrated the ease of use of the BAI device. After reading the instructions for use and without further training, a large majority of the patients (88.8%) were able to successfully administer two inhalations of placebo on their first try. Proper use of inhaler devices is important because misuse has been associated with poor asthma control and increased exacerbation risk.^{7,17} Moreover, nearly all the patients indicated that the BAI was “very easy” or “somewhat easy” for

delivering medication. These findings were consistent with previous reports that patients find BAIs easier to use than MDIs or dry powder inhalers.⁸

Current asthma treatment guidelines recommend ICS as the preferred single agent for daily use for symptom control.¹ Guidelines also recommend a stepwise approach to asthma management to maintain long-term control of asthma with the least amount of medication and the lowest amount of risk for adverse effects.¹ In the present study, both doses of beclomethasone dipropionate BAI provided consistent improvements in pulmonary function and asthma symptoms in patients with persistent asthma. The availability of both the 80 and 160 µg doses of beclomethasone dipropionate allows for dosing flexibility of patients' ICS in accordance with treatment guidelines, which recommend titrating to

Table 5 Change from baseline in AQLQ(S) scores during the last 2 weeks evaluated at week 12 (full analysis set)

Parameter Statistic*	Placebo (N = 90)	Beclomethasone Dipropionate	
		BAI 80 µg/day (N = 88)	BAI 160 µg/day (N = 92)
No. patients with AQLQ(S) data at week 12	71	75	74
Total AQLQ(S) score			
LS mean ± SE	8.57 ± 2.963	19.37 ± 2.944	16.55 ± 2.977
Difference of LS means vs placebo (95% CI)	—	10.81 (2.664 to 18.951)	7.98 (−0.204 to 16.171)
p Value	—	0.0095	0.0559
Symptom subscore			
LS mean ± SE	3.51 ± 1.270	8.78 ± 1.260	7.48 ± 1.273
Difference of LS means vs placebo (95% CI)	—	5.27 (1.779 to 8.754)	3.97 (0.468 to 7.472)
p Value	—	0.0033	0.0265
Activity limitation subscore			
LS mean ± SE	2.80 ± 0.995	5.48 ± 0.989	4.71 ± 0.999
Difference of LS means vs placebo (95% CI)	—	2.69 (−0.048 to 5.425)	1.91 (−0.838 to 4.658)
p Value	—	0.0542	0.1721
Emotional function subscore			
LS mean ± SE	1.13 ± 0.541	2.99 ± 0.538	2.58 ± 0.543
Difference of LS means vs placebo (95% CI)	—	1.85 (0.364 to 3.338)	1.45 (−0.050 to 2.941)
p Value	—	0.0149	0.0582
Environmental subscore			
LS mean ± SE	1.26 ± 0.471	2.12 ± 0.468	1.88 ± 0.474
Difference of LS means vs placebo (95% CI)	—	0.86 (−0.433 to 2.157)	0.62 (−0.686 to 1.927)
p Value	—	0.1908	0.3499

AQLQ(S) = Asthma Quality of Life Questionnaire with Standardized Activities; BAI = breath-actuated inhaler; LS = least squares; SE = standard error; CI = confidence interval.

*Data from an analysis of covariance model with covariate adjustment for baseline, sex, age, current asthma therapy, and treatment.

the lowest ICS dose that allows for control of the patient's disease.

QVAR MDI and the new BAI device both contain beclomethasone dipropionate uniformly dissolved in an HFA propellant with a mass median aerodynamic diameter of 1.1 µm.¹⁰ This small particle size allows for the delivery of the ICS to the central and peripheral airways.¹⁰ The effective delivery of beclomethasone dipropionate to the central and peripheral airways, the ease of use that the BAI provides because patients do not have to coordinate inhalation with actuation, combined with the efficacy and safety demonstrated in the present study, indicate that this new product has the potential to provide patients with an effective asthma maintenance medication

that is easy to use for patients with persistent asthma.

The safety profiles of beclomethasone dipropionate BAI 80 µg/day and 160 µg/day were comparable with the established profile for the drug delivered by MDI, with no new safety signals observed.^{18–20} The most frequently observed AEs were upper respiratory tract infection, nasopharyngitis, and headache. Notably, oral candidiasis and asthma exacerbations were reported infrequently in the beclomethasone dipropionate groups. The main limitation of this study was the continuation of the patient's current therapy during the run-in period, which may have minimized the observed treatment benefits of the beclomethasone dipropionate BAI compared with placebo. However, this

Table 6 AEs that occurred in $\geq 2\%$ of patients in any treatment group during the 12-week treatment period (safety population)

System Organ Class Preferred Term*, no. (%)	Placebo (N = 91)	Beclomethasone Dipropionate	
		BAI 80 $\mu\text{g/day}$ (N = 90)	BAI 160 $\mu\text{g/day}$ (N = 92)
Patients with ≥ 1 AE	28 (30.8)	32 (35.6)	26 (28.3)
Infections and infestations			
Upper respiratory tract infection	1 (1.1)	3 (3.3)	3 (3.3)
Nasopharyngitis	0	4 (4.4)	2 (2.2)
Viral upper respiratory tract infection	1 (1.1)	3 (3.3)	0
Bronchitis	4 (4.4)	0	0
Sinusitis	0	3 (3.3)	0
Oral candidiasis	0	0	2 (2.2)
Urinary tract infection	0	2 (2.2)	0
Gastroenteritis	0	2 (2.2)	0
Respiratory, thoracic, and mediastinal disorders			
Oropharyngeal pain	1 (1.1)	2 (2.2)	2 (2.2)
Allergic rhinitis	0	0	3 (3.3)
Epistaxis	2 (2.2)	0	1 (1.1)
Injury, poisoning, and procedural complications			
Ligament sprain	2 (2.2)	0	1 (1.1)
Muscle strain	2 (2.2)	1 (1.1)	0
Nervous system disorders			
Headache	3 (3.3)	0	3 (3.3)
Skin and subcutaneous disorders			
Contact dermatitis	3 (3.3)	1 (1.1)	0
Gastrointestinal disorders			
Abdominal discomfort	0	2 (2.2)	0
General disorders and administration-site conditions			
Local swelling	0	2 (2.2)	0

AE = Adverse event; BAI = breath-actuated inhaler.

*The AEs are shown in order of overall frequency within each system organ class.

design reflects real-world clinical practice, in which symptomatic patients on NCS may be switched to low-dose ICS therapy, and those on an ICS may be switched to an equivalent ICS with an easier-to-use inhalation device.

CONCLUSION

This study demonstrated that beclomethasone dipropionate BAI 80 $\mu\text{g/day}$ and 160 $\mu\text{g/day}$ provided significant improvements in pulmonary function over 12 weeks compared with placebo in patients with persistent asthma previously treated with low-dose ICS or NCS therapy. These benefits were accompanied by decreases in rescue medication usage and asthma symptoms, and improvements in health-related quality of life as measured by using the AQLQ(S). Of importance, the BAI device was easy to use and well accepted by the patients, as shown in the instructions-for-use substudy, with no new safety findings.

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