

Safety and efficacy of beclomethasone dipropionate delivered by breath-actuated or metered-dose inhaler for persistent asthma

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ABSTRACT

Background: Breath-actuated inhalers (BAI) have been developed to simplify the delivery of inhaled medication.

Objective: To evaluate the safety and efficacy of beclomethasone dipropionate hydrofluoroalkane BAI and metered-dose inhaler (MDI) versus placebo in patients who previously used a mid- to high-dose inhaled corticosteroid or inhaled corticosteroid/long-acting beta agonist for persistent asthma.

Methods: This phase III study included five treatment groups: placebo, and four beclomethasone dipropionate groups (BAI 320 µg/day, BAI 640 µg/day, MDI 320 µg/day, and MDI 640 µg/day). Efficacy over 12 weeks was assessed by spirometry, peak flow measurements, and other clinical end points. Safety was assessed by adverse events.

Results: Baseline-adjusted trough morning forced expiratory volume in 1 second area under the effect curve from time 0 to 12 weeks (primary end point) was increased in the BAI 320 and BAI 640 µg/day groups and the MDI 640 µg/day group versus placebo (not significant). Clinically important improvements were noted in morning and evening peak expiratory flow and decreased rescue medications. More patients who received placebo than patients in active treatment groups withdrew due to meeting the stopping criteria for worsening asthma. Patients in the active treatment groups experienced a greater decrease in asthma symptoms than patients in the placebo group. Quality of life and Asthma Control Test scores improved in the active treatment groups compared with the placebo group ($p \leq 0.0074$). The most common adverse events ($>5\%$ in any group) were oral candidiasis and upper respiratory tract infection.

Conclusion: Clinical benefits for patients who used BAI 320 and 640 µg/day and MDI 640 µg/day were demonstrated. The safety profiles of BAI 320 and 640 µg/day were comparable with that of the MDI. These benefits and the continued need for better symptom control among patients with asthma support the continued development of this controller medication. ClinicalTrials.gov identifier NCT02031640.

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The prevalence of asthma in the general population has continued to steadily climb. From 2001 to 2010, the number of people with asthma in the United States increased 27%, from 20.3 million to 25.7 million, including 7 million children and 3.1 million adults ages

≥ 65 years.^{1,2} In 2009, 12.8 million people had an asthma episode or attack, and >3300 people died of asthma.^{1,3}

According to the National Asthma Education and Prevention Program Expert Panel Report 3 guidelines,⁴ inhaled corticosteroids (ICS) are the preferred daily medication for controlling symptoms in patients with persistent asthma. Multiple types of devices are available for ICS delivery, *i.e.*, metered-dose inhalers (MDI), breath-actuated MDIs (or breath-actuated inhalers [BAI]), dry powder inhalers (DPI), and nebulizers, depending on the needs of the patient.⁵ Proper use of these inhaler devices by the patient is critical for effective delivery of the medication to the lungs.^{6,7} MDIs, which require the patient to coordinate inhalation and actuation for proper administration, are the most frequently prescribed devices.^{8,9} This coordination is an important limitation of MDIs; one study demonstrated that 48% of patients did not correctly use their MDI after physician instruction.^{8,9}

DPIs do not require coordination of actuation with inhalation; however, limitations of these devices in-

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clude loss of dose if exhalation occurs through the device after actuation, variable delivery dose, and difficulty of generating a sufficient inhalation flow for actuation.⁸⁻¹⁰ BAIs were developed to eliminate the need for the coordination of inhalation and actuation, and several studies reported that patients find them easier to use than pressurized MDIs or DPIs.¹¹ In addition, BAIs have been shown to produce higher lung deposition compared with DPIs, which may be due, in part, to a higher fine particle mass and significantly smaller mass median diameter.¹¹

QVAR (beclomethasone dipropionate hydrofluoroalkane) Inhalation Aerosol (Teva Respiratory, LLC; Horsham, PA), an ICS delivered *via* a pressurized MDI, was approved in 2000 for maintenance treatment of patients with asthma or patients with asthma who require systemic corticosteroids.¹² Results of studies demonstrated that the particle size generated from this MDI allowed for optimum lung deposition, with the drug reaching the peripheral as well as the central airways.^{13,14} Beclomethasone dipropionate delivered *via* a new BAI (Teva Pharmaceuticals, Inc., Frazer, PA) is being developed to help ensure that patients are able to consistently use the device correctly and benefit from therapy. The current study was designed to evaluate the efficacy and safety of beclomethasone dipropionate (320 or 640 $\mu\text{g}/\text{day}$) administered *via* BAI and MDI compared with placebo in patients currently using a mid to high dose of an ICS or any ICS/long-acting β agonist for persistent asthma.

METHODS

Study Design

This was a phase III, 12-week, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel-group study that evaluated the efficacy and safety of beclomethasone dipropionate treatment administered *via* BAI or MDI in male and female adolescents and adults ages ≥ 12 years with persistent asthma (ClinicalTrials NCT02031640). In the present study, 115 sites in the United States, Germany, Hungary, and Poland screened and 97 sites randomized at least one patient. The study consisted of three periods: a 2- to 3-week placebo run-in period, a 12-week double-blind treatment period with four treatment visits, and a follow-up visit or telephone call 7 ± 3 days after the last treatment visit.

Albuterol/salbutamol hydrofluoroalkane MDI was provided to all patients as rescue medication and was permitted to be used throughout the duration of the study. After the 2- to 3-week run-in period, the patients were randomized in a 1:1:1:1:1 ratio to one of five treatment groups: beclomethasone dipropionate 320 $\mu\text{g}/\text{day}$ *via* BAI, beclomethasone dipropionate 640 $\mu\text{g}/\text{day}$ *via* BAI, beclomethasone dipropionate 320 $\mu\text{g}/\text{day}$

via MDI, beclomethasone dipropionate 640 $\mu\text{g}/\text{day}$ *via* MDI, or placebo (matching either the BAI or MDI device). The study was approved by an independent ethics committee or institutional review board, and was conducted in accordance with the International Council for Harmonisation Good Clinical Practice Consolidated Guideline (E6). Written or oral informed consent was obtained from each patient or legal guardian before study procedures or assessments. The study was conducted and monitored by Pharmaceutical Product Development (Wilmington, NC).

Patients

The study included male and female patients, ages ≥ 12 years, with asthma, diagnosed at least 3 months before study enrollment but stable for at least 30 days, and with a forced expiratory volume in 1 second (FEV_1) result of 40 to 85% of the predicted normal value for age, height, sex, and race. All the patients were required to demonstrate a minimum FEV_1 reversibility of 12% within 30 minutes after two to four inhalations of albuterol/salbutamol within the previous year, at screening, or during run-in, and to have been on a stable dose of ICS (≥ 440 $\mu\text{g}/\text{day}$ of fluticasone propionate or equivalent) for a minimum of 4 weeks before the prescreening visit, or any ICS/long-acting β agonist for at least 4 weeks before the prescreening visit. The patient's current ICS/long-acting β agonist asthma treatment was changed, at a prescreening visit, to fluticasone propionate if, in the investigator's judgment, there was no inherent harm and the patient gave consent or assent (dose of 110 μg , two inhalations twice daily, for a total daily dose of 440 μg or 220 μg , two inhalations twice daily, for a total daily dose of 880 μg or the equivalent). The dose of fluticasone propionate was based on the ICS component of the patient's current therapy, and the patient then underwent screening procedures after 7 days but no more than 30 days.

Patients were excluded if they had a history of life-threatening asthma, were pregnant, were current smokers, had a 10 pack-year smoking history or had used tobacco in the past year, had a respiratory infection 2 weeks before the screening visit, had used immunosuppressive drugs 4 weeks before the screening visit, had untreated candidiasis at the screening visit (patients with clinical visual evidence of oral candidiasis who agreed to receive treatment and to comply with appropriate medical monitoring could enter the study), had a positive human immunodeficiency virus test result or active hepatitis B or C viral infection, or had any disease or condition deemed by the investigator to put the patient at risk.

Patients were required to continue to meet the entry criteria and to have no evidence of oropharyngeal candidiasis at the randomization visit, to have no asthma exacerbation during the run-in period, and to comply

with completion of the daily diary. In addition, patients' asthma symptoms and rescue medication usage were required to meet the following criteria or a combination of the criteria on at least 4 of the 7 days immediately preceding the randomization visit: any daytime asthma symptom score of 1 or more; any nighttime asthma symptom score of 1 or more; any albuterol/salbutamol use (one or more occasions).

Assessments

The primary efficacy end point was the standardized baseline-adjusted trough morning (predose and pre-rescue bronchodilator) FEV₁ area under the effect curve from time 0 to 12 weeks (AUEC_[0-12 weeks]). Spirometry was conducted consistently by using standardized equipment, time of day (± 1 hour), and posture. Pulmonary function tests were to be measured electronically by using the same spirometer on a patient throughout the study whenever possible. Pulmonary function measurements were obtained at the screening visit, the randomization visit (baseline), and at each treatment visit. For FEV₁ results, the highest value from three acceptable and two repeatable attempts was used. Secondary efficacy measures included change from baseline in the weekly average of daily trough morning peak expiratory flow (PEF) and evening PEF, total daily use of albuterol/salbutamol inhalation aerosol, total daily asthma symptom scores, and time to withdrawal over the 12-week treatment period due to meeting the stopping criteria for worsening asthma symptoms.

A twice-daily paper diary captured PEF results, rescue medication, and total daily asthma symptom scores. Daytime symptom scores were based on a scale that ranged from 0 to 5, in which 0 was defined as no symptoms during the day and 5 was defined as symptoms so severe that the patient could not go to work or perform normal daily activities. Nighttime symptom scores were based on a scale that ranged from 0 to 4, in which 0 was defined as no symptoms and 4 was defined as symptoms so severe that the patient did not sleep at all. Other outcomes and end points included change from baseline in the Asthma Quality of Life Questionnaire with standardized activities (AQLQ[S]) (patients ages ≥ 18 years only) at week 12 and end point, including the proportion of patients who achieved a clinically significant change from baseline (a minimum important difference of 0.5 in the AQLQ[S] score) at week 12 and end point (last non-missing postbaseline assessment); Asthma Control Test (ACT) over 12 weeks and at end point; and results of the Patient Satisfaction and Preference Questionnaire at week 12 and end point.

The AQLQ(S) included 32 items with a 2-week recall period and used a 7-point Likert scale (1 [severely

impaired] to 7 [not impaired at all]); higher scores indicate better quality of life. Items were grouped to produce scores for symptoms, activity limitations, emotional function, and environmental function along with a total score, which was the mean sum of the individual subscores. Patients ages 12 to 17 years and non-English, non-German speaking patients were exempt from the Patient Satisfaction and Preference Questionnaire assessment procedure. Alert criteria for worsening asthma were met if an FEV₁ value was below the FEV₁ stability limit (80% of baseline FEV₁) calculated at the randomization visit, morning PEF fell below the PEF stability limit (80% of average morning PEF) calculated from the 7 days before randomization, ≥ 12 inhalations/day of rescue medication were used on at least 3 days in a 7-day period, nighttime asthma symptom score was >2 for at least 2 days in a 7-day period, and the overall clinical picture was consistent with worsening asthma as judged by the investigator. A clinical asthma exacerbation was defined as worsening asthma that required any significant treatment other than study drug or rescue medication. Safety was assessed by evaluating reported adverse events (AEs), treatment-emergent AEs, treatment-related AEs, laboratory test results, vital sign measurements, physical examination, and asthma exacerbation incidence; oropharyngeal examinations were completed at each visit to assess any possible oral candidiasis occurrence.

Statistical Analyses

A simulation study calculated that a sample size of ~ 500 patients (100 per treatment group) would provide a statistical power of 90% at the two-sided 0.05 level of significance for demonstrating efficacy. The simulation was carried out 2000 times with the following assumptions: true time averaged (*i.e.*, averaged over 12 weeks) treatment difference of 0.2 L between each active treatment and placebo, a common standard deviation of 0.42 L, four repeated postbaseline measurements of trough morning (predose and pre-rescue bronchodilator) FEV₁ for each patient, and a correlation coefficient of 0.7 among repeated observations within a patient.

Four analysis sets were defined: (1) the intent-to-treat (ITT) population, which included all randomized patients; (2) the per-protocol population, which included all data from randomized patients obtained before a major protocol violation; (3) the safety population, which included patients in the ITT population who took one or more doses of study drug and was used for all safety analyses; and (4) the full analysis set (FAS), which included patients in the ITT population who received at least one dose of study drug and had at least one postbaseline trough morning FEV₁ measurement. The FAS served as the primary population for

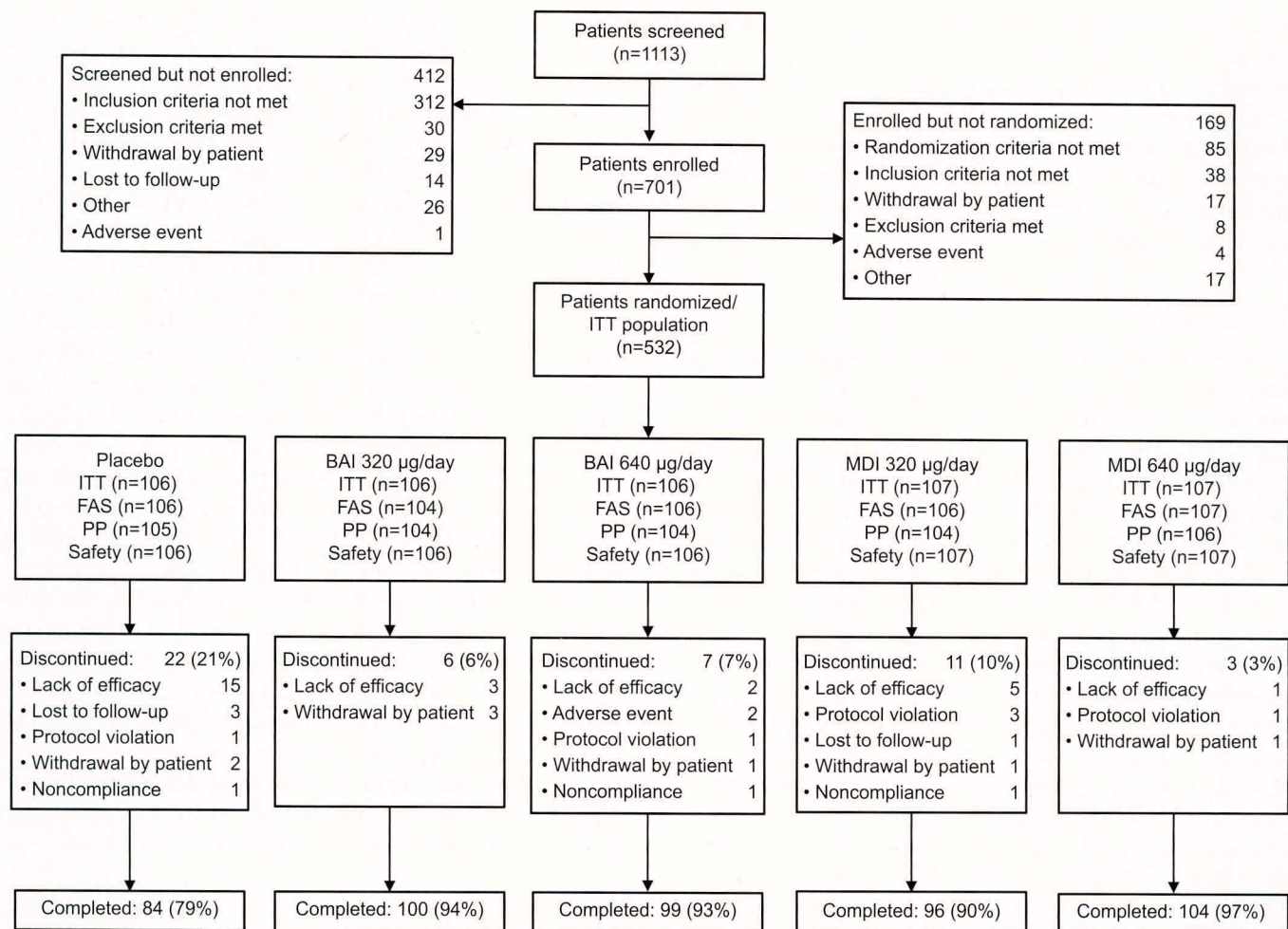


Figure 1. Patient disposition. BAI = Breath-actuated inhaler; ITT = intent-to-treat; FAS = full analysis set; MDI = metered-dose inhaler; PP = per protocol.

efficacy analysis. The primary efficacy variable was the standardized baseline-adjusted trough morning FEV_1 $AUEC_{(0-12 \text{ weeks})}$ and was analyzed by using analysis of covariance with effects due to baseline trough morning FEV_1 , sex, age, and treatment.

For analyses based on the primary efficacy variable, missing data caused by early dropout from the study were handled by penalizing the positive standardized baseline-adjusted trough morning (predose and pre-rescue bronchodilator) FEV_1 $AUEC_{(0-12 \text{ weeks})}$ by using a baseline-observation-carried-forward method. This method assigned these patients a standardized baseline-adjusted trough morning FEV_1 $AUEC_{(0-12 \text{ weeks})}$ of 0. Contrasts for pairwise comparisons of each beclomethasone dipropionate BAI and MDI dose versus placebo were constructed. The estimated treatment difference between active treatment groups and the placebo group was presented together with the two-sided 95% confidence interval for the difference and the p value. The FAS and per-protocol populations were used for secondary efficacy analyses.

RESULTS

The study was initiated in January 2014 and completed in November 2014. Overall, 1113 patients consented to participate in the study, 1001 patients attended the screening visit, and 532 patients were randomly assigned to treatment. All the patients who were randomized (ITT population) received at least one dose of study drug and were evaluated for safety (safety population); the FAS included 529 patients, and the per-protocol population included 523 patients. A total of 483 patients completed treatment, and 49 discontinued treatment (Fig. 1). Patient demographic and baseline characteristics are summarized in Table 1. Although similar numbers of patients (104–107 in the FAS) were randomized to each treatment arm, the placebo group showed a higher discontinuation rate, of 21% versus 3–10% of patients in the active treatment groups. Lack of efficacy withdrawals were higher with placebo ($n = 15$) compared with active treatment ($n = 1–5$) (Fig. 1). Baseline characteristics were well matched across the groups (Table 1).

Table 1 Patient demographics and baseline characteristics (FAS)

Demographic Variable	Placebo (n = 106)	BAI 320 µg/day (n = 104)	BAI 640 µg/day (n = 106)	MDI 320 µg/day (n = 106)	MDI 640 µg/day (n = 107)
Age, mean ± SD, y	43.7 ± 15.4	47.8 ± 15.7	46.2 ± 14.8	46.9 ± 15.1	46.2 ± 15.0
Patients 12–17 years old, no. (%)	4 (3.8)	5 (4.8)	7 (6.6)	3 (2.8)	6 (5.6)
Female patients, no. (%)	68 (64.2)	67 (64.4)	67 (63.2)	65 (61.3)	66 (61.7)
Race, no. (%)					
White	73 (68.9)	84 (80.8)	87 (82.1)	88 (83.0)	81 (75.7)
Black	27 (25.5)	17 (16.3)	14 (13.2)	16 (15.1)	24 (22.4)
Other	6 (5.7)	3 (2.9)	5 (4.7)	2 (1.9)	2 (1.9)
BMI, mean ± SD, kg/m ²	30.1 ± 8.9	29.9 ± 7.3	30.4 ± 7.2	29.1 ± 6.2	29.8 ± 6.5
Baseline pulmonary function					
FEV ₁ , mean ± SD, L	2.1 ± 0.6	2.1 ± 0.6	2.3 ± 0.6	2.1 ± 0.5	2.2 ± 0.6
Morning PEF, mean ± SD, L/min	356.3 ± 86.3	351.4 ± 89.8	364.4 ± 92.2	354.3 ± 95.9	361.3 ± 98.7
Evening PEF, mean ± SD, L/min	363.3 ± 88.6	357.5 ± 92.7	368.5 ± 92.1	360.2 ± 100.9	366.4 ± 100.3
Total AQLQ(S) score, mean ± SD	160.9 ± 32.2	161.3 ± 31.0	156.5 ± 39.4	156.8 ± 32.1	159.5 ± 29.2
ACT score, mean ± SD	16.6 ± 3.6	16.5 ± 3.3	16.0 ± 4.0	15.7 ± 3.9	16.2 ± 3.4
Key previous asthma medications, no. (%)					
Albuterol/salbutamol	77 (72.6)	88 (83.0)	86 (81.1)	87 (81.3)	92 (86.0)
Fluticasone propionate	71 (67.0)	79 (74.5)	72 (67.9)	78 (72.9)	81 (75.7)
Fluticasone propionate/salmeterol xinafoate	34 (32.1)	39 (36.8)	31 (29.2)	39 (36.4)	43 (40.2)
Budesonide/formoterol fumarate	18 (17.0)	16 (15.1)	14 (13.2)	22 (20.6)	21 (19.6)
Beclomethasone dipropionate	16 (15.1)	13 (12.3)	7 (6.6)	10 (9.3)	8 (7.5)

FAS = Full analysis set; BAI = breath-actuated inhaler; MDI = metered-dose inhaler; SD = standard deviation; BMI = body mass index; FEV₁ = forced expiratory volume in 1 second; PEF = peak expiratory flow; AQLQ(S) = Asthma Quality of Life Questionnaire with standardized activities; ACT = Asthma Control Test.

Table 2 Baseline-adjusted trough morning FEV₁ area under the effect curve from week 0 to week 12 (FAS)

Parameter Statistic*	Placebo (n = 106)	BAI 320 µg/day (n = 104)	BAI 640 µg/day (n = 106)	MDI 320 µg/day (n = 106)	MDI 640 µg/day (n = 107)
LS mean ± SE	0.056 ± 0.022	0.090 ± 0.022	0.101 ± 0.022	0.041 ± 0.022	0.096 ± 0.022
p Value (compared with placebo)	—	0.272	0.142	0.636	0.193

FEV₁ = Forced expiratory volume in 1 second; FAS = full analysis set; BAI = breath-actuated inhaler; MDI = metered-dose inhaler; LS = least squares; SE = standard error.

*LS means and p values represent the results obtained from the analysis of covariance with covariate adjustment for baseline, sex, age, and treatment.

Primary Efficacy End Point

The primary efficacy analysis was conducted on the FAS (n = 529). Although patients treated with beclomethasone dipropionate BAI 320 and 640 µg/day, and beclomethasone dipropionate MDI 640 µg/day experienced increases in the least squares mean of the primary efficacy end point of baseline-adjusted trough morning FEV₁ AUEC_(0–12 weeks) compared with placebo, these differences were not statistically significant (Table 2, Fig. 2).

Secondary Efficacy End Points

Clinically important increases in the beclomethasone dipropionate BAI groups were observed for most of the secondary efficacy end points (Table 3). Over the 12-week treatment period, both the beclomethasone dipropionate BAI 320 µg/day and 640 µg/day groups demonstrated substantial improvements, of 4 to 12.5 L/min, compared with placebo in change from baseline in the weekly average of daily trough morning PEF and daily evening trough PEF, in addition to clinically meaningful decreases in the total daily use of albuterol/salbutamol inhalation aerosol. For BAI 320 µg/day only, the

total daily asthma symptom score improved (Table 3). For the MDI treatment groups, similar clinically meaningful changes in all four efficacy end points were also demonstrated in the MDI 640 µg/day group, but only the total daily use of albuterol/salbutamol and total daily asthma symptom scores achieved a p value of <0.05 in the MDI 320 µg/day group. Of the patients who discontinued treatment, more patients in the placebo group than in any of the active treatment groups withdrew due to meeting the stopping criteria for worsening asthma (Table 3).

Patient Assessments and Other Outcome Variables

Ratings of quality of life (AQLQ[S] total score) at the study end point increased from baseline in the active treatment groups compared with the placebo group (Table 4). The patients treated with beclomethasone dipropionate delivered *via* BAI or MDI experienced greater improvements in ACT scores compared with those in the placebo group (p ≤ 0.0014) (Table 4). Patient assessments of the BAI and MDI devices from the Patient Satisfaction and Preference Questionnaire scores were varied. Patients rated the MDI device

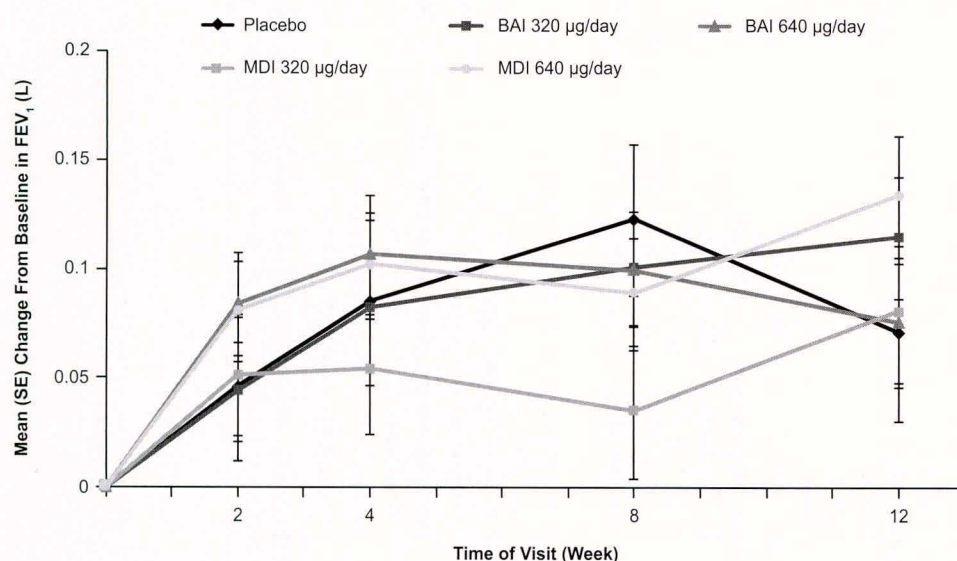


Figure 2. Change from baseline (mean ± SE) in trough morning FEV₁ (L) From week 0 to week 12 (FAS). BAI = Breath-actuated inhaler; FAS = full analysis set; FEV₁ = forced expiratory volume in 1 second; MDI = metered-dose inhaler; SE = standard error.

Table 3 Change from baseline in weekly average of secondary efficacy end points over the 12-week treatment period (FAS)

Parameter Statistic*	Placebo (n = 106)	BAI 320 µg/day (n = 104)	BAI 640 µg/day (n = 106)	MDI 320 µg/day (n = 106)	MDI 640 µg/day (n = 107)
Daily trough morning PEF, L/min					
LS mean ± SE	−5.524 ± 2.59	5.092 ± 2.56	2.895 ± 2.56	0.480 ± 2.56	6.988 ± 2.53
p Value (compared with placebo)	—	0.004	0.020	0.098	0.001
Daily evening PEF, L/min					
LS mean ± SE	−4.708 ± 2.65	4.439 ± 2.62	4.462 ± 2.61	−0.620 ± 2.61	5.594 ± 2.58
p Value (compared with placebo)	—	0.014	0.013	0.270	0.005
Total daily use of albuterol/salbutamol inhalation aerosol, no. of inhalations					
No. patients	101	96	99	97	101
LS mean ± SE	0.478 ± 0.12	−0.226 ± 0.12	−0.213 ± 0.12	−0.173 ± 0.12	−0.323 ± 0.12
p Value (compared with placebo)	—	<0.0001	<0.0001	0.0002	<0.0001
Total daily asthma symptom score#					
LS mean ± SE	−0.058 ± 0.04	−0.207 ± 0.04	−0.159 ± 0.04	−0.247 ± 0.04	−0.274 ± 0.04
p Value (compared with placebo)	—	0.012	0.085	0.002	<0.001
Patient withdrawals from the study due to meeting stopping criteria for worsening asthma					
Patients, no. (%)	15 (14.2)	3 (2.9)	3 (2.8)	5 (4.7)	1 (0.9)
p Value (compared with placebo)	—	0.003	0.003	0.020	<0.001

FAS = Full analysis set; BAI = breath-actuated inhaler; MDI, metered-dose inhaler; PEF, peak expiratory flow; LS, least squares; SE, standard error.

*LS means and p values were obtained from the Mixed Model for Repeated Measures analysis with covariate adjustment for baseline, sex, age, treatment, week, and treatment by week interaction.

#Based on the average of the daytime and nighttime scores. Daytime symptom scores were based on a 0–5 point scale, in which 0 was defined as “no symptoms” and 5 was defined as “symptoms so severe that the patient could not go to work or perform normal daily activities.” Nighttime symptom scores were based on a 0–4 point scale, in which 0 was defined as “no symptoms” and 4 was defined as “symptoms so severe that the patient did not sleep at all.”

higher for total satisfaction than the BAI device; however, more patients preferred the BAI device to the MDI device (Table 5). The MDI device, however, had a higher “willingness to continue with inhaler” score than the BAI device (Table 5).

Safety

AE reporting was similar across all active treatment groups, with roughly a third of each treatment group

reporting at least one AE. The most frequently reported AEs (which occurred in ≥2% of patients in any treatment group) are summarized in Table 6. The patients were actively monitored for oral candidiasis at every visit. Approximately 3–10% of patients across active treatment groups were noted to have evidence of oral candidiasis, but only 0–3% reported these as infections. Other AEs were balanced across treatment groups. Treatment-related AEs are summarized in

Table 4 Additional study end points (FAS)

Parameter	Placebo (n = 106)	BAI 320 µg/day (n = 104)	BAI 640 µg/day (n = 106)	MDI 320 µg/day (n = 106)	MDI 640 µg/day (n = 107)
Change from baseline in AQLQ(S) total mean score at study end point*					
No. patients	99	98	99	103	99
Model-adjusted change from baseline, LS mean ± SE	-0.018 ± 0.09	0.376 ± 0.09	0.324 ± 0.09	0.336 ± 0.09	0.448 ± 0.09
p Value (compared with placebo)	—	0.0022	0.0074	0.0052	0.0003
Change from baseline in ACT score over weeks 1 to 12					
No. patients	106	103	105	105	106
Model-adjusted change from baseline, LS mean ± SE	0.051 ± 0.28	1.583 ± 0.28	1.318 ± 0.28	1.452 ± 0.28	1.571 ± 0.28
p Value (compared with placebo)	—	0.0001	0.0014	0.0004	0.0001

FAS = Full analysis set; BAI = breath-actuated inhaler; MDI = metered-dose inhaler; AQLQ(S) = Asthma Quality of Life Questionnaire with standardized activities; LS = least squares; SE = standard error; ACT = Asthma Control Test.

*Last nonmissing postbaseline assessment.

Table 5 Patient satisfaction and preference of device in PASAPQ results at study end point

Parameter	BAI Device (n = 433)	MDI Device (n = 432)
Total satisfaction score, mean ± SD	79.7 ± 17.73	81.8 ± 13.99
Mean difference (p value)		-2.160 (0.0002)
Patients preferring specific inhaler, no. (%)	174 (40.1)*	170 (39.2)*
Willingness to continue with inhaler score, mean ± SD	74.6 ± 29.72	79.5 ± 26.42#
Mean difference (p value)		-4.864 (0.0054)

PASAPQ = Patient Satisfaction and Preference Questionnaire; BAI = breath-actuated inhaler; MDI = metered dose inhaler; SD = standard deviation.

*n = 434.

#n = 433.

Table 7. Similar percentages of patients in the beclomethasone dipropionate 320 µg/day BAI and MDI groups experienced treatment-related AEs and similar percentages of patients in the 640 µg/day BAI and MDI groups experienced treatment-related AEs. The majority of treatment-related AEs reported were *Candida* infections and oral candidiasis, with more episodes of oral candidiasis noted with the 640 µg/day dose.

Five patients in the beclomethasone dipropionate treatment groups experienced serious AEs. One of these serious AEs, a severe asthma exacerbation experienced by a patient in the BAI 640 µg/day group, resolved and did not require hospitalization but did lead to study discontinuation (one other patient in

the BAI 640 µg/day group withdrew from the study due to tremors, also considered related to the study drug). Four of the AEs scattered across treatment groups required hospitalization (BAI 320 µg/day, acute gastroenteritis with hypokalemia and acute kidney injury; MDI 320 µg/day, acute abdominal pain with cholelithiasis, gastropatia, and acute pancreatitis; MDI 640 µg/day, perforated diverticulitis; MDI 640 µg/day, retropharyngeal abscess), but none were related to the study drug. No deaths or serious AEs occurred during the follow-up period. Regarding other safety parameters, no clinically relevant changes from baseline were observed in hematology, chemistry, and urinalysis results, or in vital signs.

Table 6 Overall adverse events and adverse events that occurred in $\geq 2\%$ of any treatment group (safety population)

Patients, no. (%)	Placebo (n = 106)	BAI 320 $\mu\text{g/day}$ (n = 106)	BAI 640 $\mu\text{g/day}$ (n = 106)	MDI 320 $\mu\text{g/day}$ (n = 107)	MDI 640 $\mu\text{g/day}$ (n = 107)
Patients with ≥ 1 adverse event	29 (27.4)	31 (29.2)	37 (34.9)	33 (30.8)	45 (42.1)
Nasopharyngitis	2 (1.9)	2 (1.9)	3 (2.8)	2 (1.9)	4 (3.7)
Upper respiratory tract infection	2 (1.9)	4 (3.8)	1 (0.9)	7 (6.5)	4 (3.7)
<i>Candida</i> infection	0	0	3 (2.8)	2 (1.9)	0
Gastroenteritis	0	3 (2.8)	0	0	0
Oral candidiasis	0	5 (4.7)	10 (9.4)	3 (2.8)	9 (8.4)
Headache	5 (4.7)	2 (1.9)	2 (1.9)	0	3 (2.8)
Oropharyngeal pain	1 (0.9)	1 (0.9)	3 (2.8)	2 (1.9)	4 (3.7)

BAI = Breath-actuated inhaler; MDI = metered-dose inhaler.

Table 7 Treatment-related adverse events that occurred in any treatment group (safety population)

Patients, no. (%)	Placebo (n = 106)	BAI 320 $\mu\text{g/day}$ (n = 106)	BAI 640 $\mu\text{g/day}$ (n = 106)	MDI 320 $\mu\text{g/day}$ (n = 107)	MDI 640 $\mu\text{g/day}$ (n = 107)
Patients with ≥ 1 TRAE	2 (1.9)	5 (4.7)	16 (15.1)	6 (5.6)	13 (12.1)
Dysphonia	1 (0.9)	0	0	0	0
Oropharyngeal pain	1 (0.9)	0	0	1 (0.9)	0
Throat irritation	1 (0.9)	0	0	0	0
Asthma	0	0	1 (0.9)	0	0
Pharyngeal erythema	0	0	0	0	1 (0.9)
Headache	1 (0.9)	0	0	0	0
Tremor	0	0	1 (0.9)	0	0
Rash	1 (0.9)	0	0	0	0
Oral discomfort	0	0	0	0	1 (0.9)
<i>Candida</i> infection	0	0	3 (2.8)	2 (1.9)	0
Oral candidiasis	0	5 (4.7)	10 (9.4)	3 (2.8)	9 (8.4)
Oropharyngeal candidiasis	0	0	0	0	1 (0.9)
Blood bilirubin increased	0	0	1 (0.9)	0	0
Muscle spasms	0	0	0	0	1 (0.9)

BAI = Breath-actuated inhaler; MDI = metered-dose inhaler; TRAE = treatment-related adverse event.

DISCUSSION

No significant improvement in the primary efficacy variable of baseline-adjusted trough morning FEV_1 AUEC_(0-12 \text{ weeks}) was apparent in this population of patients ages ≥ 12 years with asthma previously treated with ICS between any of the beclomethasone dipropionate BAI or MDI treatment groups and the placebo group over the 12-week treatment period. It is important to note that, when the data were evaluated at 12 weeks by using a last-observation-carried-forward or baseline-observation-carried-forward approach, a substantial treatment effect was noted for both BAI treatment groups

and the MDI 640 $\mu\text{g/day}$ treatment group. A study center effect was noted; when data from these sites were excluded from the analysis, all treatment groups demonstrated substantial improvement at 12 weeks (data on file). The results of the primary analysis were in contrast to the secondary efficacy variables, in which patients treated with beclomethasone dipropionate BAI 320 $\mu\text{g/day}$, BAI 640 $\mu\text{g/day}$, and MDI 640 $\mu\text{g/day}$ demonstrated consistent improvements in weekly average morning PEF and average evening PEF, and consistent decreases from baseline in albuterol/salbutamol use compared with patients who received placebo.

The patients in the placebo group were also three to five times more likely than the patients in the BAI or MDI groups to withdraw from the study because of worsening of asthma symptoms. The greater rate of discontinuation in the placebo group (21%) compared with the active treatment groups (3–10%) may have contributed to the lack of significance noted among the active groups and the placebo group for the FEV₁ results. Use of rescue medication and worsening asthma symptoms are clinically relevant over time and indicate that substantial and important treatment effects were observed in patients treated with beclomethasone dipropionate BAI and MDI compared with those who received placebo. In addition, positive effects of beclomethasone dipropionate BAI treatment were further supported in the results of the AQLQ(S) and ACT assessments completed during the study.

The contrast observed in the level of improvement seen from the primary as opposed to the secondary efficacy end points seemed to be driven in large part by the increase in FEV₁ AUEC_(0–12 weeks) demonstrated by the placebo group. As is common in similar studies of ICS therapy, all the patients were maintained on ICS therapy during the run-in period, and FEV₁ values would have been expected to decrease over time when ICS therapy was removed.^{15–17} In this study, FEV₁ values in the placebo group did not decline but improved by 0.056 L; this could explain the lack of statistical significance for the primary end point. The lack of significance may have been due, in part, to overtreatment of patients who were not dependent on ICS for asthma control at baseline before entering the study.

Step-down of controller therapy is recommended for patients after they have been stabilized for 3 months to allow for the lowest treatment dose to control asthma symptoms and exacerbations,¹⁸ with reevaluation every 1 to 6 months, depending on control⁴; however, to what degree this recommendation is practiced is unknown. In addition, it is possible that the patients with the most-severe disease in the placebo group dropped out early, before the 12-week analysis, which may have contributed to apparent improvements in FEV₁ in the placebo group. In addition, because physicians may have been reluctant to enroll patients who had more-severe asthma that may have worsened in a placebo-controlled study, the enrollment of patients with less-severe asthma may have allowed the patients on placebo to participate in the study without significant worsening. In recent ICS studies with a similar design, results for the placebo group were similarly improved.^{19,20}

Although both devices were generally well received by the patients, patient preference may have been affected because patients were more likely to have previously used an MDI and may have a preference for MDIs because of this familiarity. The safety profiles of

both beclomethasone dipropionate BAI 320 µg/day and BAI 640 µg/day were comparable with the established profile of the MDI, with no new safety signals observed.

Limitations of the study included the FEV₁ results of the patients on placebo, as noted above. This may have been a result of patient selection, which made it another potential study limitation. An additional potential limitation could have been the overtreatment of patients who were not dependent on ICS for asthma control at baseline before entering the study. Although the choice of FEV₁ as the primary efficacy end point has been proven to be a good measure of pulmonary function, some studies demonstrated a lack of correlation between pulmonary function measures and clinical outcomes such as asthma symptoms and quality of life measures.^{21–23} Strengths of the study included the double-blind, double-dummy protocol design, the rigorous completion of oral pharyngeal examinations at every visit, and the use of two doses of beclomethasone dipropionate (320 µg/day and 640 µg/day) for both the BAI and MDI devices. The lack of statistical significance of the primary efficacy end points of the study may be due to a combination of the lack of a decline in the placebo group when taken off ICS therapy and the lack of correlation between pulmonary function measures and clinical outcomes for beclomethasone dipropionate *via* BAI, given its clinical benefits and observed safety profile.

CONCLUSION

Based on the results of this study and the totality of the data, a treatment benefit was demonstrated for beclomethasone dipropionate delivered *via* the BAI or MDI device and would be expected to be similar for the treatment of asthma.

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