

Once-daily ciclesonide improves lung function and is well tolerated by patients with mild-to-moderate persistent asthma

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Background: Inhaled corticosteroids are recommended as first-line therapy for persistent asthma.

Objective: We sought to assess the efficacy and safety of ciclesonide once daily in patients with mild-to-moderate persistent asthma.

Methods: An integrated analysis of 2 identical, multicenter, double-blind, randomized, parallel-group, placebo-controlled trials was conducted. Patients ($n = 1015$; aged ≥ 12 years) with mild-to-moderate asthma (FEV_1 of 60% to 85% of predicted value) were randomized to ciclesonide 80 μg (CIC80), 160 μg (CIC160), or 320 μg (CIC320), once daily (exactuator doses) in the morning or placebo for 12 weeks.

Results: All ciclesonide groups showed significant improvements from baseline to week 12 in FEV_1 compared with the placebo group (CIC80, 0.12 L [$P = .0007$]; CIC160, 0.13 L [$P = .0004$]; and CIC320, 0.14 L [$P < .0001$]). Likewise, FEV_1 percent predicted, morning and evening peak expiratory flow, 24-hour asthma symptom score, daily albuterol use, and nighttime awakenings were significantly improved in all ciclesonide groups compared with the placebo group. Overall ciclesonide safety profile and rates of oropharyngeal adverse events for all groups were low and similar to those of the placebo group. Fewer ciclesonide-treated patients exhibited asthma-aggravated adverse events, and fewer ciclesonide-

treated patients discontinued the study for any reason or because of a lack of efficacy compared with those in the placebo group. No suppression of hypothalamic-pituitary-adrenal-axis function (as assessed by means of 24-hour urinary cortisol levels corrected for creatinine and peak serum cortisol levels after stimulation with low-dose [1 μg] cosyntropin) was observed with any dose of ciclesonide.

Conclusions: In this integrated analysis, ciclesonide once daily administered in the morning is effective and well tolerated. (J Allergy Clin Immunol 2005;116:1206-12.)

Key words: Asthma, ciclesonide, 24-hour asthma symptom score, daily albuterol use, nighttime awakenings

Asthma is a chronic inflammatory disorder defined by variable and reversible airway obstruction, inflammation, and hyperresponsiveness.^{1,2} In the United States, asthma prevalence has increased by 60% since the early 1980s.³ National and international guidelines advocate the use of inhaled corticosteroids (ICSs) as first-line therapy for persistent asthma.^{1,4,5} It is recommended that the degree of asthma severity and response to therapy be established according to pulmonary function measurements, as well as measures such as asthma symptom scores, daily albuterol use, and nighttime awakenings.¹ ICSs are considered the most efficacious long-term controller therapy for asthma.^{4,6} However, high-dose ICS regimens, prolonged exposure, and frequent daily administration have been associated with systemic and local (oropharyngeal) adverse events (AEs).⁷⁻¹²

Ciclesonide, a novel ICS under development, lacks appreciable activity itself and can be considered a pro-drug.^{13,14} On inhalation, ciclesonide is converted in the lungs by endogenous esterases to its active metabolite, desisobutryl-ciclesonide (des-CIC), which has high receptor affinity and forms reversible conjugates with lipids within the lung.¹³⁻¹⁷ Additionally, ciclesonide possesses other favorable pharmacokinetic-pharmacodynamic properties, such as a reported systemic bioavailability of less than 1%, which might help reduce the incidence of AEs.¹⁸⁻²¹

To assess the efficacy and safety of ciclesonide, 80 μg , 160 μg , and 320 μg , once daily in the morning, 2 identical 12-week studies were conducted in patients

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Supported by Aventis Pharmaceuticals, a member of the Sanofi-Aventis Group, and ALTANA Pharma.

Disclosure of potential conflict of interest: W. Berger has consultant arrangements with and has received research support from AstraZeneca, Merck, Pfizer, GlaxoSmithKline, Aventis, Alcon, Medpoint, Genentech, Novartis, Schering, and Altana. E. Kerwin has received research support from GlaxoSmithKline, Pfizer, Sanofi-Aventis, Altana, Bristol Myers Squibb, Novartis, Hoffman LaRoche, AstraZeneca, and others and is on the speakers' bureau of Sanofi-Aventis, GlaxoSmithKline, and Pfizer. D. Pearlman has consultant arrangements with Sanofi-Aventis. C. LaForce has consultant arrangements with Altana. D. Banerji and S. Kundu are both employed by Sanofi-Aventis.

Received for publication April 22, 2005; revised August 22, 2005; accepted for publication August 22, 2005.

Available online October 10, 2005.

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0091-6749/\$30.00

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doi:10.1016/j.jaci.2005.08.037

Abbreviations used

AE:	Adverse event
AQLQ:	Asthma Quality of Life Questionnaire
CIC:	Ciclesonide
des-CIC:	Desisobutyl-ciclesonide
DPI:	Dry powder inhaler
FP:	Fluticasone propionate
HPA:	Hypothalamic-pituitary-adrenal
ICS:	Inhaled corticosteroid
ITT:	Intent to treat
LOCF:	Last observation carried forward
PEF:	Peak expiratory flow

with mild-to-moderate persistent asthma. These studies were required by the US Food and Drug Administration registration to obtain marketing approval, and the results were combined to enhance the signal for differences in the groups analyzed. These studies are the first to assess once-daily morning administration of an ICS on the basis of FEV₁ measurement at the end of the 24-hour dosing interval (trough).

METHODS

Patients

Adolescents and adults (≥ 12 years of age) with mild-to-moderate persistent asthma⁴ for 6 months prior were eligible to participate in the study. Patients not receiving ICSs or those receiving any of the following low-to-moderate ICS doses 30 days before screening were eligible: 500 $\mu\text{g}/\text{d}$ or less fluticasone propionate (FP; GlaxoSmithKline, Research Triangle Park, NC) dry powder inhaler (DPI), 440 $\mu\text{g}/\text{d}$ or less FP pressurized metered-dose inhaler, 250 $\mu\text{g}/50 \mu\text{g}$ or less FP/salmeterol (GlaxoSmithKline) combination DPI twice daily, or 1000 $\mu\text{g}/\text{d}$ or less budesonide (AstraZeneca, Wilmington, Del), beclomethasone dipropionate (3M Pharmaceuticals, Northridge, Calif), flunisolide (Forest Pharmaceuticals, St Louis, Mo) or triamcinolone acetonide (Kos Pharmaceuticals, Cranbury, NJ), leukotriene receptor antagonists, cromones, or bronchodilators (short- or long-acting β_2 -agonists or xanthine derivatives). Patients were required to be nonsmokers for at least 1 year (<10 pack-year smoking history), with an FEV₁ of 60% or greater to 85% or less of predicted normal value at randomization after albuterol was withheld for at least 6 hours. This FEV₁ value must have been reduced by at least 10% from the actual FEV₁ value recorded at screening, or patients must have exhibited an asthma severity score of 3 or more, a peak expiratory flow (PEF) variability of greater than 20%, or albuterol use of 2 or more puffs per day for 3 or more of the last 7 days before randomization. Reversibility of FEV₁ by 12% or more ($\geq 200 \text{ mL}$) after 2 inhalations of albuterol (at randomization) or a documented history of 12% or greater reversibility within 1 year of screening was also required.

Female subjects were eligible if surgically sterilized or if they were practicing adequate birth control and had a negative serum pregnancy test result. Exclusion criteria included continual asthma or frequent nighttime symptoms, a history of life-threatening asthma, or 2 or more inpatient hospitalizations because of asthma exacerbations in the past year. Patients were excluded if they had received injectable or oral corticosteroids 3 months or less before screening, a serious concomitant disease (upper respiratory tract infection, lenticular opacities, or glaucoma), or a history of chronic bronchitis, chronic obstructive pulmonary disease, or emphysema. Patients on

maintenance allergen immunotherapy were allowed to enroll if they had not initiated or changed the regimen within 30 days before screening.

Study design

Two identically designed, 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, US phase III trials were conducted. The prescreening visit (visit 1) occurred 3 to 5 days before screening-baseline (visit 2), which occurred 5 to 28 days before randomization (visit 3). During baseline, patients received single-blind placebo. At visit 3, patients were randomized to once-daily ciclesonide 80 μg (CIC80), 160 μg (CIC160), or 320 μg (CIC320; exactuator), or placebo. Doses were administered as 2 puffs in the morning (6 to 9 AM) and after completing pulmonary function tests. After randomization, no asthma medications were allowed except the study medication and albuterol hydrofluoroalkane metered-dose inhaler (Schering/Key Pharmaceuticals, Kenilworth, NJ). Patients requiring disallowed medications for asthma exacerbations after randomization were discontinued from the study. Allowed concomitant medications included topical, low-potency corticosteroid (hydrocortisone) cream or ointment ($\leq 1\%$), intranasal or ocular cromolyn sodium, antihistamines, or decongestants for treating allergic rhinitis, and maintenance immunotherapy. At the investigators' discretion, intranasal glucocorticoids were also permitted, but these were prohibited at centers performing cortisol testing. Patients were issued daily diary cards at baseline to note efficacy and safety.

All patients provided written informed consent. Protocol and informed consent forms were reviewed and approved by an independent ethics review committee. The study was conducted in accordance with Good Clinical Practice and conformed to the ethical principles of the Declaration of Helsinki.

Efficacy assessments

Efficacy evaluations were performed at screening-baseline through week 12. All pulmonary function tests were conducted according to the guidelines between 7 and 9 AM after albuterol had been withheld for 6 or more hours and before the morning dose of the study medication (end of dosing interval [trough]).²² Patients were trained on the MiniWright peak flowmeter. PEF rates were measured and recorded within 15 minutes of awakening and before the morning dose and in the evening. Patients were instructed to withhold albuterol use for 6 or more hours before measuring morning and evening PEF (highest of 3 efforts recorded). If morning PEF measurements on any 2 consecutive days were less than 80% of screening-baseline PEF measurements or less than 70% of baseline measurements, the patient was to contact the investigator or present to the study center, respectively.

Patients recorded their overall asthma severity ratings (24-hour asthma symptom scores) twice daily before measuring morning and evening PEF by using a 0- to 4-point scale (0, no symptoms; 4, symptoms preventing patients from engaging in daily activities or sleep). Daily albuterol use (puffs per day) and nighttime awakenings caused by asthma symptoms were also recorded. A lack of efficacy was defined as study withdrawal of randomized patients because of asthma exacerbations requiring treatment with medications other than inhaled albuterol, inadequately controlled asthma (clinical exacerbation, intolerable or incapacitating symptoms, or frequent nighttime awakenings), morning PEF of less than 80% of screening level on any 2 consecutive days, PEF of less than 70% of screening level on any 2 consecutive days, or albuterol use of more than 8 actuations per day on more than 3 consecutive days. Each patient's quality of life was assessed with the Juniper Asthma Quality of Life Questionnaire (AQLQ),²³ self-administered by patients at randomization, week 4, and

TABLE I. Baseline demographics and asthma characteristics of the ITT population

Variable	Placebo (n = 249)	CIC80 (n = 257)	CIC160 (n = 250)	CIC320 (n = 255)	Overall (n = 1011)
Sex, n (%)					
Male	99 (40)	105 (41)	97 (39)	112 (44)	413 (41)
Female	150 (60)	152 (59)	153 (61)	143 (56)	598 (59)
Mean age (y)	36.9	36.2	36.4	36.8	36.6
Race, n (%)					
White	217 (87.1)	224 (87.2)	214 (85.6)	224 (87.8)	879 (86.9)
Black	19 (7.6)	18 (7.0)	24 (9.6)	20 (7.8)	81 (8.0)
Other	13 (5.2)	15 (5.8)	12 (4.8)	11 (4.3)	51 (5.0)
Mean duration of asthma (y)	17.34	18.92	19.94	18.61	18.71
Mean (SE) FEV ₁ (L)	2.45 (0.04)	2.42 (0.04)	2.40 (0.03)	2.48 (0.04)	2.44 (0.02)
Mean (SE) FEV ₁ (% predicted)	71.42 (0.53)	70.82 (0.55)	70.90 (0.52)	70.64 (0.52)	70.94 (0.27)
Mean (SE) morning PEF (L/min)	367.43 (6.05)	362.26 (5.91)	354.80 (5.20)	371.41 (5.63)	364.01 (2.86)
Mean (SE) evening PEF (L/min)	384.56 (6.25)	379.32 (6.25)	368.64 (5.23)	388.02 (5.90)	380.16 (2.97)
Mean (SE) 24-h asthma symptom score*	2.70 (0.09)	2.62 (0.09)	2.52 (0.10)	2.67 (0.09)	2.63 (0.05)
Mean (SE) albuterol use (puffs per day)	3.17 (0.16)	3.21 (0.16)	3.05 (0.16)	3.20 (0.16)	3.16 (0.08)
Mean (SE) nighttime awakenings†	0.32 (0.03)	0.34 (0.04)	0.25 (0.03)	0.27 (0.03)	0.30 (0.02)
Mean AQLQ score	4.77	4.55	4.72	4.68	—

*Overall asthma symptom scores recorded twice daily before measuring morning and evening PEF.

†Nighttime awakenings caused by asthma symptoms and albuterol use.

week 12 (or last observation carried forward [LOCF]) at the clinic.

Safety assessments

Patients recorded AEs during the study until 14 days after the last dose of study medication. Oropharyngeal examinations were performed at baseline and each clinic visit. Cultures for *Candida* species were performed to confirm diagnosis of suspected fungal infection. Positive cultures were reported as oral candidiasis. Routine clinical laboratory tests and physical examinations were performed.

Patients at selected centers had to meet hypothalamic-pituitary-adrenal (HPA) axis eligibility criteria: screening morning serum cortisol level of 5 µg/dL or greater preceding low-dose (1 µg) cosyntropin stimulation and screening serum cortisol level of 18 µg/dL or greater at 20, 30, or 60 minutes after stimulation or, for female subjects taking oral contraceptives or hormone therapy, an increase in serum cortisol level of 7 µg/dL or greater at the same time intervals. Levels of 24-hour urine cortisol (n = 176) and serum cortisol (before and after stimulation with 1 µg of cosyntropin, n = 179) collected at screening-baseline and week 12 were evaluated by using standard methods.^{24,25}

Statistical analysis

Analysis was based on the intent-to-treat (ITT) population (randomized patients who received ≥1 dose of double-blind study medication with a valid baseline and ≥1 postbaseline measurement of the primary efficacy analysis variable, FEV₁). The primary variable was analyzed by using an analysis of covariance model of change from baseline to week 12 (or LOCF), with factors for treatment, pooled center, previous therapy, baseline FEV₁, age, and sex as covariates. Primary comparisons were performed between the ciclesonide doses and placebo in a step-down fashion, starting with the highest

dose at a level of significance of an α value of .05. Analyses of change from baseline at each visit and study end point (LOCF) and the analysis of covariance model were used for the secondary analysis variables (FEV₁ percent predicted, morning and evening PEF, 24-hour asthma symptom score, daily albuterol use, and nighttime awakenings). Analysis of withdrawal rates and the Kaplan-Meier analysis of time to withdrawal (days since date of randomization) were conducted by using the Fisher exact test and the log-rank test, respectively. AEs and other safety data were summarized by using the safety population (randomized patients who received ≥1 dose of study medication).

RESULTS

Demographics

Of the 2152 screened patients, 1015 (526 in one study and 489 in the other) were randomized. Four patients were excluded from the ITT population because of a lack of a baseline or postbaseline FEV₁ measurement. Baseline demographics were comparable between groups (Table I).

Forty-six patients from the ITT population had a baseline FEV₁ of less than 60% of predicted value: 15 receiving CIC80 (28.9% to 59.9%), 9 receiving CIC160 (54.3% to 59.8%), 10 receiving CIC320 (52.8% to 59.6%), and 12 receiving placebo (47.7% to 59.9%).

Efficacy

Pulmonary function. Ciclesonide provided superior and sustained control in FEV₁ versus placebo ($P \leq .0007$). Onset of action was observed by week 1 (Fig 1). FEV₁ improvements were noted at the end of the 24-hour dosing

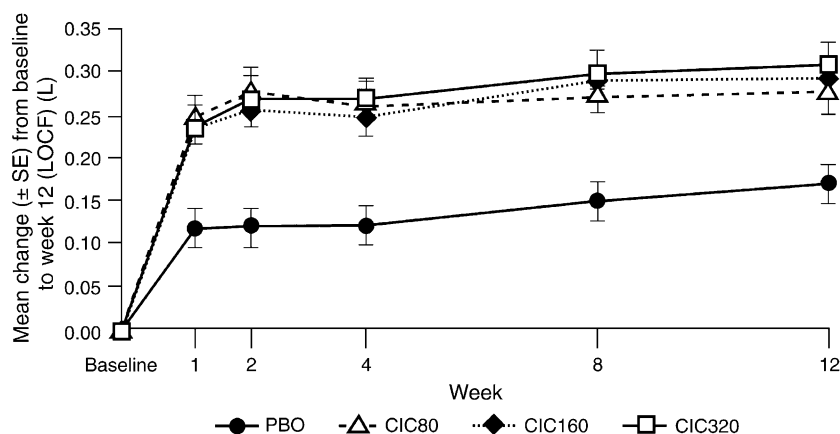


FIG 1. Mean change from baseline to week 12 (LOCF) in FEV₁ (ITT population). $P \leq .0007$ for all ciclesonide groups versus the placebo (PBO) group at week 1 through week 12.

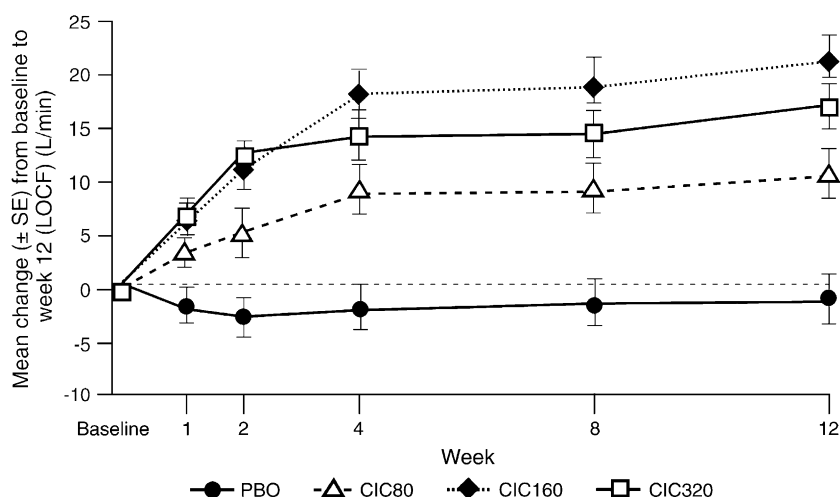


FIG 2. Mean change from baseline to week 12 (LOCF) in morning PEF (ITT population). $P \leq .0207$ for all ciclesonide groups versus the placebo (PBO) group at week 1 through week 8; $P \leq .0008$ for all ciclesonide groups versus the placebo group at week 12.

interval (trough) and before morning administration of study medication.

All ciclesonide groups showed statistically significant and early and sustained improvements at weeks 1 through 12 in morning PEF versus the placebo group ($P \leq .0207$), with onset of action by week 1 (Fig 2). The CIC160 group displayed greater numeric improvements in morning PEF than the CIC320 group, which were not statistically significant (Table II).

Improvements in FEV₁ percent predicted and evening PEF were consistent with those observed for FEV₁ and morning PEF, respectively, and demonstrated that ciclesonide was more effective than placebo (Table II). The CIC160 group displayed numerically greater improvements in evening PEF, which were not statistically different from those of the CIC320 group (Table II).

Symptoms. All ciclesonide groups demonstrated significant and sustained improvements in 24-hour asthma symptom scores versus the placebo group ($P \leq .0002$,

Table II). Daily albuterol use was significantly reduced in all ciclesonide groups but increased in the placebo group ($P < .0001$, Table II). Likewise, ciclesonide groups exhibited significant and sustained reductions in nighttime awakenings versus the placebo group ($P \leq .0001$, Table II). Statistically significant increases in overall AQLQ scores from baseline to study end (LOCF) were also observed for all 3 ciclesonide doses versus placebo ($P < .0001$, Table II).

Significantly fewer ciclesonide-treated patients discontinued because of a lack of efficacy (6.7% to 9.7%) versus placebo-treated patients (25%) ($P < .0001$); time to withdrawal because of a lack of efficacy was longer for patients in the ciclesonide groups ($P < .0001$ vs placebo, Fig 3).

Safety

AEs. The frequency of overall treatment-emergent AEs was comparable between groups (ciclesonide, 57.6% to 59.5%; placebo, 59.9%). Likewise, the frequency of

TABLE II. Primary efficacy and key secondary variables: Mean $\pm$ SE change from baseline to end of study (ITT population)*

Variable	Placebo group (n = 249)	CIC80 group (n = 257)†	CIC160 group (n = 250)†	CIC320 group (n = 255)†
FEV ₁ (L)	0.17 $\pm$ 0.03	0.28 $\pm$ 0.03‡	0.29 $\pm$ 0.03‡	0.31 $\pm$ 0.03‡
FEV ₁ (% predicted)	4.47 $\pm$ 0.69	8.07 $\pm$ 0.68§	8.24 $\pm$ 0.69§	8.45 $\pm$ 0.68§
Morning PEF (L/min)	-1.70 $\pm$ 2.74	10.93 $\pm$ 2.70	21.06 $\pm$ 2.74	17.22 $\pm$ 2.71
Evening PEF (L/min)	1.48 $\pm$ 2.54	9.89 $\pm$ 2.50¶	18.06 $\pm$ 2.54¶	14.59 $\pm$ 2.51¶
24-h asthma symptom score	-0.15 $\pm$ 0.08	-0.58 $\pm$ 0.08#	-0.70 $\pm$ 0.08#	-0.61 $\pm$ 0.08#
Albuterol use (puffs per day)	0.42 $\pm$ 0.14	-0.86 $\pm$ 0.14**	-1.02 $\pm$ 0.14**	-1.04 $\pm$ 0.14**
Nighttime awakenings (n/night)††	0.07 $\pm$ 0.03	-0.08 $\pm$ 0.03**	-0.16 $\pm$ 0.03**	-0.13 $\pm$ 0.03**
AQLQ score (overall)	0.14 $\pm$ 0.06	0.50 $\pm$ 0.06**	0.61 $\pm$ 0.06**	0.69 $\pm$ 0.06**

*Values are presented as least-squares mean $\pm$ SE.†n values reflect FEV₁ population (n values for other parameters were comparable).‡ $P \leq .0007$; § $P \leq .0002$; || $P \leq .0008$; ¶ $P \leq .0162$; # $P \leq .0002$; ** $P \leq .0001$ (all P values vs placebo).

††Nighttime awakenings caused by asthma symptoms and albuterol use; overall asthma symptom scores recorded twice daily before measuring morning and evening PEF.

possibly related treatment-emergent AEs was low and comparable between treatment groups (ciclesonide, 1.9% to 5.2%; placebo, 5.2%). Frequencies of oral candidiasis (ciclesonide, 0% to 1.6%; placebo, 0.4%), pharyngitis (ciclesonide, 4.0% to 5.4%; placebo, 5.2%), cough (ciclesonide, 0.8% to 1.6%; placebo, 2.0%), and hoarseness (ciclesonide, 0% to 0.8%; placebo, 0.4%) were low and comparable between groups.

Fewer ciclesonide-treated patients exhibited asthma-aggravated AEs versus placebo-treated patients (ciclesonide, 2.4% to 6.2%; placebo, 16.7%). More patients in the placebo group (14.3%) discontinued because of asthma-aggravated AEs compared with those in any of the ciclesonide groups (2.7% to 3.9%).

HPA-axis evaluations. Mean baseline values of peak serum cortisol were comparable between groups, including the placebo group (ciclesonide, 24.66-27.78 μ g/dL; placebo, 26.93 μ g/dL). Ciclesonide had no effect on peak serum cortisol levels after low-dose (1 μ g) cosyntropin stimulation after 12 weeks of treatment versus levels observed in the placebo group ($P = .3673$, Fig 4). No trend for greater reduction in cosyntropin response was observed in the ciclesonide groups versus the placebo group.

Likewise, mean baseline 24-hour urinary-free cortisol levels corrected for creatinine were comparable between groups, including the placebo group (ciclesonide, 0.0129-0.0179 μ g/mg; placebo, 0.0151 μ g/mg). Ciclesonide had no effect on 24-hour urinary-free cortisol levels after 12 weeks versus the placebo group (ciclesonide, -0.0013 ± 0.003 to 0.0033 ± 0.003 μ g/mg; placebo, 0.0009 ± 0.003 μ g/mg; all mean $\pm$ SE; $P \geq .5118$).

Laboratory evaluations. For all groups, mean baseline and end point values for all laboratory analyses were within the normal range.

DISCUSSION

Ciclesonide, 80 to 320 μ g, administered once daily in the morning improved lung function in patients with mild-to-moderate persistent asthma. Significant improvements

of 110 to 140 mL were observed in FEV₁ change from baseline to end point in all ciclesonide groups compared with the placebo group. Changes in FEV₁ were observed by week 1 (the first data point after treatment initiation) and were sustained throughout the study. Significant improvements were also noted in FEV₁ percent predicted (3.60% to 3.98%), morning PEF (12.63-22.76 L/min), and evening PEF (8.41-16.58 L/min) versus the placebo group.

Symptomatic relief, assessed by nighttime awakenings, was superior for the ciclesonide groups versus the placebo group. Furthermore, all ciclesonide groups showed a reduction in 24-hour asthma symptom scores (0.43-0.55) and daily albuterol use (1.28-1.46 puffs) versus the placebo group. Ciclesonide-treated patients also experienced improvements in the overall AQLQ score. Parallel to these results, morning or evening administration of ciclesonide has been found to be equally efficacious in a separate study of patients with mild-to-severe asthma.²⁶ Findings from similar studies with subjective parameters have also been observed with FP at doses up to 500 μ g twice daily and budesonide at doses up to 400 μ g twice daily in patients with mild-to-moderate asthma.^{27,28} With the exception of budesonide (a step down to once-daily dosing) and mometasone furoate (recently approved), there are no other approved ICSs with this type of dosing.

The efficacy of ciclesonide once-daily dosing reported here might reflect a combination of notable pharmacokinetic and pharmacodynamic properties of this particular corticosteroid. The active metabolite, des-CIC, has high receptor affinity and forms reversible lipid conjugates within the lung.^{13,15-17} Lipid conjugation is speculated to prolong lung residence time, leading to a longer duration of action and possibly less frequent dosing. Budesonide liposomal DPI also undergoes lipid conjugation and has been reported to have a prolonged lung residence time.²⁹

Many of the currently available ICSs are associated with systemic and oropharyngeal AEs, which can add to

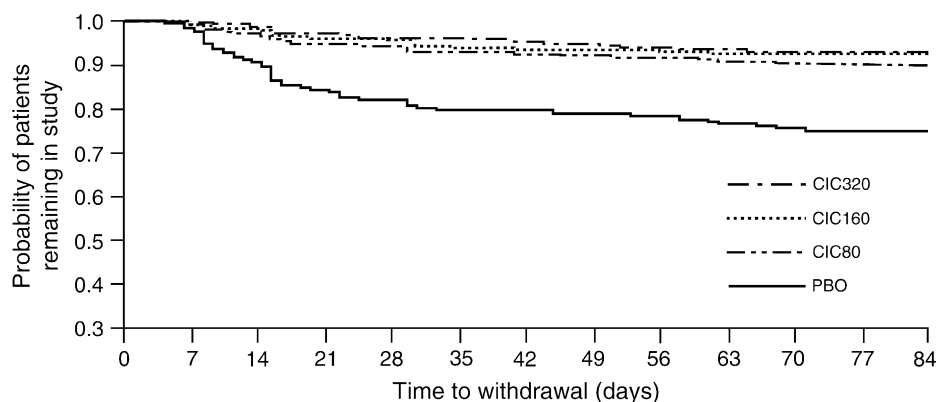


FIG 3. Kaplan-Meier plot of subject discontinuation from the study because of a lack of efficacy (ITT population). *PBO*, Placebo.

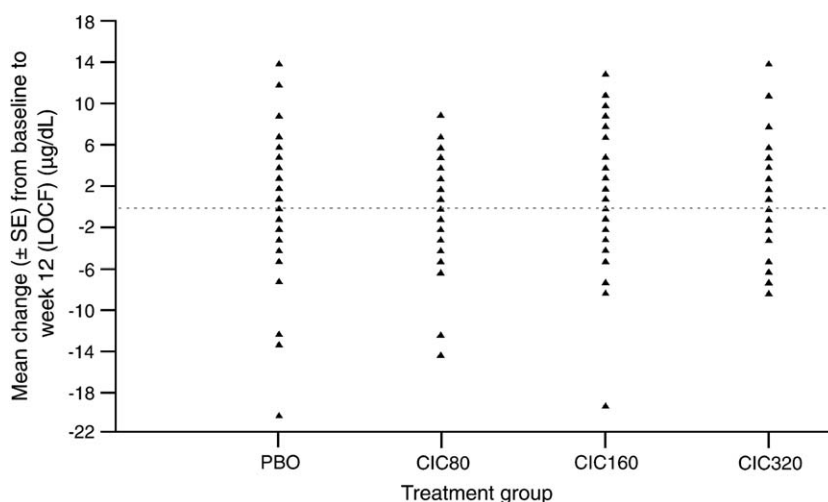


FIG 4. Mean change from baseline to week 12 (LOCF) in peak serum cortisol levels after stimulation with low-dose (1 µg) cosyntropin. No trend for greater reduction in cosyntropin response in the ciclesonide groups was observed compared with placebo (*PBO*).

the disease burden and further increase the risk of long-term treatment nonadherence.^{7-12,30} In this study safety measurements of ciclesonide at all doses were comparable with placebo, with no effect on the HPA axis, as assessed on the basis of urinary or stimulated cortisol levels after 12 weeks of treatment. These findings support results from studies of patients with asthma and healthy volunteers with ciclesonide, including doses of up to 640 µg twice daily.³¹⁻³⁴ The lack of HPA-axis suppression is consistent with the low oral bioavailability (<1%), high serum protein binding (approximately 99%), high apparent systemic clearance, and high first-pass metabolism of des-CIC.¹⁹⁻²¹

The incidence of oropharyngeal AEs after 12 weeks of treatment with ciclesonide was comparable with that observed with placebo. Similar results have been reported in previous studies, including ciclesonide at doses of up to 640 µg.^{35,36} This might be due to ciclesonide's reduced oral deposition of and its low conversion rate to des-CIC in the oropharynx.^{11,37}

Fewer ciclesonide-treated patients discontinued the study for any reason, including a lack of efficacy versus placebo ($P < .0001$). Ciclesonide-treated patients exhibited fewer asthma-aggravated AEs compared with those in the placebo group, who were more likely to drop out because of a worsening of disease. Furthermore, a dose-ordered trend was observed, with the highest ciclesonide group (CIC320) exhibiting the fewest asthma-aggravated AEs.

In this study once-daily morning administration of ciclesonide 80 to 320 µg improved lung function and asthma symptoms in patients with mild-to-moderate persistent asthma. Ciclesonide treatment was well tolerated and resulted in a low incidence of oropharyngeal AEs, with no effect on HPA-axis function at any dose level.

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Correction

With regard to the September 2005 editorial entitled "Are inhaled corticosteroids taken during pregnancy harmless?" (2005;116:501-2): In the first lines of the second and third paragraphs, Dr Ludmila Bakhireva's last name was misspelled. Our apologies to Dr Bakhireva.