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 prodrug.[13,14] On inhalation, ciclesonide is converted in the lungs by endogenous esterases to its active metabolite, desisobutyryl-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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Abbreviations used
AE: Adverse event
AQLQ: Asthma Quality of Life Questionnaire
CIC: Ciclesonide
des-CIC: Desisobutyryl-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 FEV_1 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 asthma[4] 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 μg/d or less fluticasone propionate (FP; GlaxoSmithKline, Research Triangle Park, NC) dry powder inhaler (DPI), 440 μg/d or less FP pressurized metered-dose inhaler, 250 μg/50 μg or less FP/salmeterol (GlaxoSmithKline) combination DPI twice daily, or 1000 μg/d or less budesonide (AstraZeneca, Wilmington, Del), beclomethasone dipropionate (3M Pharmaceuticals, Northridge, Calif), flunisolide (Forest Pharmaceuticals, St Louis, Mo) or triamcinolone acetonide (Kos Pharmaceuticals, Cranburg, 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 FEV_1 of 60% or greater to 85% or less of predicted normal value at randomization after albuterol was withheld for at least 6 hours. This FEV_1 value must have been reduced by at least 10% from the actual FEV_1 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 FEV_1 by 12% or more (≥200 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 (≤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