

Efficacy and safety of ciclesonide hydrofluoroalkane nasal aerosol once daily for the treatment of seasonal allergic rhinitis

Craig LaForce, MD*; Julius van Bavel, MD†; Eli O. Meltzer, MD‡; and Mark A. Wingertzahn, PhD§

Background: Aerosol-based corticosteroid nasal formulations may be preferred over current aqueous nasal sprays by some patients because they traditionally cause less pharyngeal and anterior nose runoff.

Objective: To determine the optimal dose, safety, and tolerability of ciclesonide hydrofluoroalkane nasal aerosol in patients with seasonal allergic rhinitis (SAR).

Methods: Patients 12 years or older with a history of SAR received ciclesonide hydrofluoroalkane nasal aerosol to a total dose of 75, 150, or 300 μg or placebo once daily (half dose per nostril) for 2 weeks. The primary efficacy assessment was patient-reported average morning and evening reflective (24-hour) total nasal symptom scores (rTNSS). Secondary efficacy assessments included patient-reported average morning and evening instantaneous TNSS (iTNSS), patient-reported morning iTNSS, physician-assessed nasal signs and symptom severity, and Rhinoconjunctivitis Quality of Life Questionnaire responses. Safety and tolerability were also assessed.

Results: Ciclesonide hydrofluoroalkane nasal aerosol demonstrated a statistically significantly greater reduction from baseline in average morning and evening rTNSS (24-hour) vs placebo, with treatment differences as follows: 0.81 ($P = .001$; 300 μg), 0.90 ($P < .001$; 150 μg), and 0.66 ($P = .01$; 75 μg). Improvements in average morning and evening iTNSS and patient-reported morning iTNSS were also significantly improved regardless of dose ($P \leq .003$ for all ciclesonide groups vs placebo). The incidence of treatment-related adverse events was low ($<1.6\%$ for all) and similar among groups.

Conclusions: Ciclesonide hydrofluoroalkane nasal aerosol demonstrated statistically significant improvements in SAR symptoms vs placebo. On the basis of comparable efficacy and safety profiles observed for all doses, these results suggest that the 75- μg and 150- μg doses of ciclesonide hydrofluoroalkane appear appropriate for further evaluation of efficacy.

Ann Allergy Asthma Immunol. 2009;103:166–173.

INTRODUCTION

Allergic rhinitis (AR) is a chronic inflammatory disease of the upper airways characterized by nasal congestion, rhinorrhea, sneezing, and nasal itching. Among the approximately 40 million to 60 million people in the United States with

AR,^{1,2} most (80%) develop symptoms before the age of 20 years, with up to 40% of patients becoming symptomatic by the age of 6 years.³ Depending on allergen sensitivity, AR can be categorized as either seasonal (SAR) or perennial (PAR). Forty percent of US adults who have been diagnosed as having AR by a health care professional have PAR and 20% have SAR; an additional 40% have PAR with seasonal flares.³ AR has a substantial physical and emotional impact on patients and places a considerable economic burden on the US health care system.¹

Current treatment guidelines for AR recommend the use of intranasal corticosteroids (INCSs) as first-line treatment for moderate to severe AR in both adults and children.⁴ Although effective, aqueous corticosteroid nasal sprays may cause adverse effects (such as a wet feeling in the nose and postnasal drip), may be improperly used, and may not provide complete or long-term symptom relief; as a result, compliance with daily dosing is often poor.^{5,6} In addition, aqueous nasal sprays may not be the formulation of choice for all patients because some may prefer a drier INCS nasal aerosol. Therefore, formulations that address reasons for patient dissatisfaction may have practical benefit in clinical practice.

Ciclesonide is a corticosteroid approved in the United States as an aqueous nasal spray for treatment of adolescent and adult patients (≥ 12 years old) with SAR and PAR and

Affiliations: * North Carolina Clinical Research, Raleigh, North Carolina; † Allergy and Asthma Associates, PLLC, Austin, Texas; ‡ Allergy and Asthma Medical Group and Research Center, San Diego, California; § Nycomed, Florham Park, New Jersey.

Disclosures: Dr LaForce reports Research Support/Consultant/Speaker's Bureau: Alcon Inc, AstraZeneca, Genentech, GlaxoSmithKline, Inspire Pharmaceuticals Inc, Merck & Co Inc, Meda Pharmaceuticals Inc, Novartis Pharmaceuticals Corporation, Nycomed US Inc (Altana), Sanofi-Aventis US, LLC, Schering-Plough Corporation, Sepracor Inc, UCB S.A., Wyeth Pharmaceuticals. Dr van Bavel reports no conflict of interest. Dr Meltzer reports Research Support/Consultant/Speaker's Bureau: Alcon Inc, Amgen Inc, AstraZeneca, Boehringer Ingelheim Corporation, Dey L.P., Genentech, GlaxoSmithKline, Greer Laboratories, Inspire Pharmaceuticals Inc, Merck & Co Inc, Meda Pharmaceuticals Inc, Novartis Pharmaceuticals Corporation, Nycomed US Inc (Altana), Sanofi-Aventis US, LLC, Schering-Plough Corporation, Sepracor Inc, UCB S.A., Wyeth Pharmaceuticals. Dr Wingertzahn reports support from Nycomed (employment).

Funding Sources: Financial support for conducting the study was provided by Nycomed US. Financial support for editorial assistance was provided by Nycomed US and Sepracor Inc.

Received for publication November 25, 2008; Received in revised form February 4, 2009; Accepted for publication March 14, 2009.

children (≥ 6 years old) with SAR.⁷ Ciclesonide is administered as an inactive parent compound that is converted to the pharmacologically active metabolite, desisobutyl-ciclesonide, by intracellular esterases within the nasal mucosa.^{8,9} Previous studies established safety, tolerability, and efficacy of ciclesonide aqueous nasal spray in adult, adolescent, and pediatric patients with AR.^{10–13} Ciclesonide is also available in the United States in an inhaled hydrofluoroalkane formulation for treatment of asthma. The current dose-ranging study was conducted to evaluate the efficacy and tolerability of 3 doses of ciclesonide hydrofluoroalkane nasal aerosol (solution) among adults and adolescents with SAR during a 2-week treatment period.

METHODS

Patients

Patients 12 years or older with a history of SAR for at least 2 years were included. Patients had to demonstrate (via standard skin prick test) sensitivity to grass or tree pollen known to induce SAR. Patients with clinically significant findings of nasal anatomical deformities (including nasal polyps or septal defects, recent nasal biopsy, nasal trauma, or surgery) or nonallergic rhinitis (eg, atrophic rhinitis or rhinitis medicamentosa) within 60 days of screening were excluded. Patients with active asthma requiring daily treatment with inhaled or systemic corticosteroids and/or β -agonists were also excluded. Patients were prohibited from taking AR medications (other than study medication) during or immediately before study drug administration. To qualify for randomization, patients had to achieve a minimum patient-reported reflective total nasal symptom scores (rTNSS) of an average of 6 (of a possible 12) and a patient-reported score of at least 2 for rhinorrhea or nasal congestion during the last 7 days of the run-in period.¹⁴

Study Design and Treatment

This was a double-blind, randomized, parallel-group, placebo-controlled, dose-ranging phase 2 study at 35 centers in the United States. Daily pollen counts were recorded by site throughout the study. After a 7- to 14-day (for patients using INCSs in the past) or 21-day washout period, patients were randomly assigned to receive ciclesonide hydrofluoroalkane nasal aerosol, 300 μ g, 150 μ g, or 75 μ g, or placebo (study vehicle only). At the screening visit, each patient received 1 placebo hydrofluoroalkane nasal aerosol device for use during the run-in period. During the treatment visit, a single dose of ciclesonide or placebo was administered via 1 actuation per nostril, once daily. Patients who met selection criteria were assigned to blinded treatment groups by means of a computer-generated randomization list. Investigators and patients remained blinded to the identity of each patient's assigned treatment. Study medications were packaged as to appear indistinguishable. This study was approved by Coast Institutional Review Board (Lake Forest, California) and conducted in accordance with the principles of the Declara-

tion of Helsinki. All patients provided written informed consent at the screening visit.

Efficacy and Safety Assessments

The primary efficacy end point was the change from baseline in the average of the morning (24 hours after dosing) and evening (12 hours after dosing) patient-reported rTNSS over the 2-week study period. Patient-reported rTNSS (24-hour) was calculated as the sum of 4 nasal symptoms (nasal congestion, runny nose, itchy nose, and sneezing), each rated on a scale of 0 (no signs or symptoms) to 3 (signs or symptoms that interfere with daily activities). Secondary efficacy end points included average morning and evening patient-reported iTNSS during the 2-week treatment period, morning patient-reported iTNSS during the 2-week treatment period (performed before administration of the next day's treatment dose to evaluate 24-hour drug effect), evaluation of the change in the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score at end point,¹⁴ morning patient-reported reflective (24-hour) nonnasal symptom score during the 2-week treatment period, and physician-evaluated nasal signs and symptoms severity (PNSS). Safety assessments included incidence of spontaneous and treatment-emergent adverse events (AEs); ear, nose, and throat examinations; vital sign measurements; and physical examinations.

Statistical Analyses

The intent-to-treat (ITT) analyses, used for all efficacy measures, were based on patients who received randomized study medication and had at least 1 postbaseline efficacy measurement. The planned sample size of 120 randomized patients per group was determined to provide 90% power to detect a difference of 0.9 among treatment groups in the change from baseline in TNSS, with a 2-sided α of .05, assuming an SD of 2.¹⁴

A sequential approach across measures was combined with a sequential approach across doses to control type I error rates. If the *P* value from the test of the average of morning and evening patient-evaluated rTNSS (days 1 to 14) was $\leq .05$ for ciclesonide, 300 μ g, vs placebo, then ciclesonide, 150 μ g, vs placebo was examined and the morning and evening patient-evaluated iTNSS (days 1 to 14) was evaluated for ciclesonide, 300 μ g, vs placebo.

Change from baseline in TNSS was measured using repeated-measures analysis of covariance (ANCOVA), with adjustments for baseline, day, treatment, and treatment-by-day interaction, using the ITT analysis set. Baseline was defined as the mean TNSS during the last 7 days before randomization. Changes from baseline in average morning and evening iTNSS and morning iTNSS were analyzed similarly to the primary efficacy measures. Change from baseline in average morning and evening rTNSS for each day and the average during the treatment period was analyzed using ANCOVA, with adjustment for baseline, treatment, and pooled center; change from baseline in PNSS and RQLQ score was analyzed similarly. The AEs were evaluated using descriptive

measures. All statistical analyses were performed with SAS statistical software (SAS Institute Inc, Cary, North Carolina).

RESULTS

Patient Disposition and Baseline Demographics

A total of 513 patients were randomized to receive ciclesonide hydrofluoroalkane nasal aerosol, 300 μg ($n = 136$), 150 μg ($n = 125$), or 75 μg ($n = 122$), or placebo ($n = 130$); 498 patients completed the study. Two patients were misrandomized; 1 patient received placebo rather than ciclesonide, 300 μg , and 1 patient received ciclesonide, 75 μg , rather than placebo. These patients were included in the ITT and safety analysis sets but were excluded from the per-protocol analysis set. Patient demographics were similar among treatment groups (Table 1). The ITT analysis set consisted of 193 males (37.6%) and 320 females (62.4%) (age range, 12–77 years). Baseline average morning and evening patient-reported rTNSS scores were 9.20, 9.02, and 9.45 for ciclesonide, 300 μg , 150 μg , and 75 μg , respectively, and 9.02 for placebo, indicating that all groups tested had moderate to moderately severe SAR.

Morning and Evening rTNSS

The primary efficacy end point of the study was change from baseline in average morning and evening patient-reported rTNSS during the 2-week treatment period. Compared with placebo, all ciclesonide hydrofluoroalkane nasal aerosol doses examined significantly improved the average rTNSS during the study period ($P \leq .01$; Fig 1; Table 2). Treatment differences for the reduction from baseline for ciclesonide were 0.81 (95% confidence interval [CI], 0.32 to 1.29; $P =$

.001), 0.90 (95% CI, 0.40 to 1.39; $P < .001$), and 0.66 (95% CI, 0.16 to 1.16; $P = .01$) for the 300- μg , 150- μg , and 75- μg formulations of ciclesonide, respectively, compared with placebo.

Change in Average Morning and Evening rTNSS Over Time

Numerical improvements in morning and evening rTNSS for all ciclesonide hydrofluoroalkane nasal aerosol doses were observed by day 2. The numerical difference between ciclesonide and placebo continued to increase during the 14-day treatment period, reaching significance at day 2 for the 150- μg dose and at day 3 for the 300- μg and 75- μg doses of ciclesonide hydrofluoroalkane, suggesting an onset of efficacy within 2 to 3 days for patient-reported rTNSS (Fig 2).

Change in Average Morning and Evening iTNSS

All ciclesonide hydrofluoroalkane nasal aerosol doses significantly improved the average patient-reported morning and evening iTNSS during the study period ($P \leq .003$ for all groups vs placebo; Fig 3). Treatment differences for the reduction from baseline were 0.75 (95% CI, 0.26 to 1.23; $P = .002$), 0.86 (95% CI, 0.36 to 1.35; $P < .001$), and 0.75 (95% CI, 0.25 to 1.25; $P = .003$) for the 300- μg , 150- μg , and 75- μg formulations of ciclesonide, respectively, vs placebo.

Change in the Individual Morning and Individual Evening iTNSS

Compared with placebo, all ciclesonide hydrofluoroalkane nasal aerosol doses improved the patient-reported morning iTNSS during the study period ($P < .001$ for all groups; Fig 4). Treatment differences for the reduction from baseline in

Table 1. Patient Demographics and Baseline Characteristics^a

Characteristic	Ciclesonide hydrofluoroalkane nasal aerosol, 300 μg ($n = 136$)	Ciclesonide hydrofluoroalkane nasal aerosol, 150 μg ($n = 125$)	Ciclesonide hydrofluoroalkane nasal aerosol, 75 μg ($n = 122$)	Placebo ($n = 130$)
Age, y				
Mean (SD)	39.6 (15.2)	36.2 (13.3)	36.9 (14.0)	38.0 (14.6)
Median (range)	41.2 (12–77)	38.4 (12–64)	37.3 (12–65)	38.9 (12–77)
Sex, No. (%)				
Male	53 (39.0)	51 (40.8)	37 (30.3)	52 (40.0)
Female	83 (61.0)	74 (59.2)	85 (69.7)	78 (60.0)
Race, No. (%) ^b				
White	111 (81.6)	102 (81.6)	96 (78.7)	112 (86.2)
Black	23 (16.9)	19 (15.2)	21 (17.2)	14 (10.8)
Asian	1 (0.7)	3 (2.4)	1 (0.8)	4 (3.1)
Other	2 (1.5)	1 (0.8)	5 (4.8)	1 (0.8)
Type of skin test, No. (%)				
Current skin prick	52 (38.2)	52 (41.6)	35 (28.7)	46 (35.4)
Historical skin prick	81 (59.6)	71 (56.8)	84 (68.9)	81 (62.3)
Unknown	3 (2.2)	2 (1.6)	3 (2.5)	3 (2.3)
Antigen minus control challenge results, median (range), mm	8 (3–40)	9 (3–42)	8 (3–40)	10.0 (3–36)

^a Data are presented for the intent-to-treat population.

^b Patients were permitted to select more than 1 race.

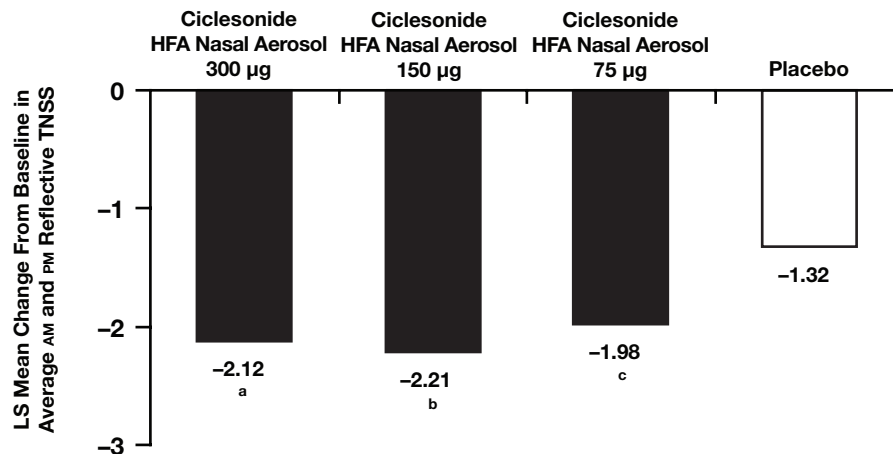


Figure 1. Change from baseline in average morning and evening reflective total nasal symptom scores (rTNSS) during the 2-week treatment period. Baseline values were 9.20, 9.02, and 9.45 for the 300-µg, 150-µg, and 75-µg groups, respectively, and 9.02 for the placebo group. HFA indicates hydrofluoroalkane. ^a*P* = .001, ^b*P* < .001, and ^c*P* = .01 vs placebo.

Table 2. Average Morning and Evening Patient-Reported Reflective Total Nasal Symptom Severity and Individual Symptoms During the 2-Week Treatment Period^a

	Ciclesonide hydrofluoroalkane nasal aerosol, 300 µg (n = 136)	Ciclesonide hydrofluoroalkane nasal aerosol, 150 µg (n = 125)	Ciclesonide hydrofluoroalkane nasal aerosol, 75 µg (n = 122)	Placebo (n = 130)
TNSS overall results				
Baseline, mean (SD)	9.20 (1.55)	9.02 (1.61)	9.45 (1.55)	9.02 (1.60)
Change from baseline, LS mean (SE)	-2.12 (0.17)	-2.21 (0.18)	-1.98 (0.18)	-1.32 (0.18)
Treatment difference (95% CI) vs placebo	0.81 (0.32-1.29)	0.90 (0.40-1.39)	0.66 (0.16-1.16)	
<i>P</i> value	.001	<.001	.01	
Nasal congestion				
Baseline, mean (SD)	2.59 (0.35)	2.52 (0.40)	2.60 (0.38)	2.53 (0.38)
Change from baseline, LS mean (SE)	-0.47 (0.05)	-0.52 (0.05)	-0.43 (0.05)	-0.28 (0.05)
Treatment difference (95% CI) vs placebo	0.19 (0.07-0.32)	0.24 (0.11-0.37)	0.15 (0.01-0.28)	
<i>P</i> value	.003	<.001	.03	
Nasal itching				
Baseline, mean (SD)	2.24 (0.60)	2.31 (0.52)	2.35 (0.54)	2.25 (0.53)
Change from baseline, LS mean (SE)	-0.52 (0.05)	-0.54 (0.05)	-0.51 (0.05)	-0.31 (0.05)
Treatment difference (95% CI) vs placebo	0.21 (0.06-0.35)	0.23 (0.08-0.37)	0.20 (0.06-0.35)	
<i>P</i> value	.004	.002	.006	
Sneezing				
Baseline, mean (SD)	2.01 (0.61)	1.95 (0.63)	2.05 (0.64)	1.93 (0.70)
Change from baseline, LS mean (SE)	-0.58 (0.05)	-0.56 (0.05)	-0.51 (0.05)	-0.34 (0.05)
Treatment difference (95% CI) vs placebo	0.24 (0.10-0.38)	0.22 (0.07-0.36)	0.17 (0.03-0.31)	
<i>P</i> value	<.001	.003	.02	
Runny nose				
Baseline, mean (SD)	2.36 (0.49)	2.24 (0.53)	2.45 (0.51)	2.31 (0.49)
Change from baseline, LS mean (SE)	-0.54 (0.05)	-0.57 (0.05)	-0.53 (0.06)	-0.34 (0.05)
Treatment difference (95% CI) vs placebo	0.20 (0.05-0.34)	0.23 (0.08-0.38)	0.19 (0.04-0.34)	
<i>P</i> value	.008	.002	.01	

Abbreviations: CI, confidence interval; LS, least squares; TNSS, total nasal symptom score.

^a Data are presented for the intent-to-treat population.

the morning iTNSS were 0.86 (95% CI, 0.36 to 1.35; *P* < .001), 1.03 (95% CI, 0.52 to 1.53; *P* < .001), and 0.88 (95% CI, 0.37 to 1.39; *P* < .001) for the 300-µg, 150-µg, and

75-µg formulations of ciclesonide vs placebo, respectively, and confirmed 24-hour effect. Similarly, compared with placebo, all ciclesonide doses improved the patient-reported

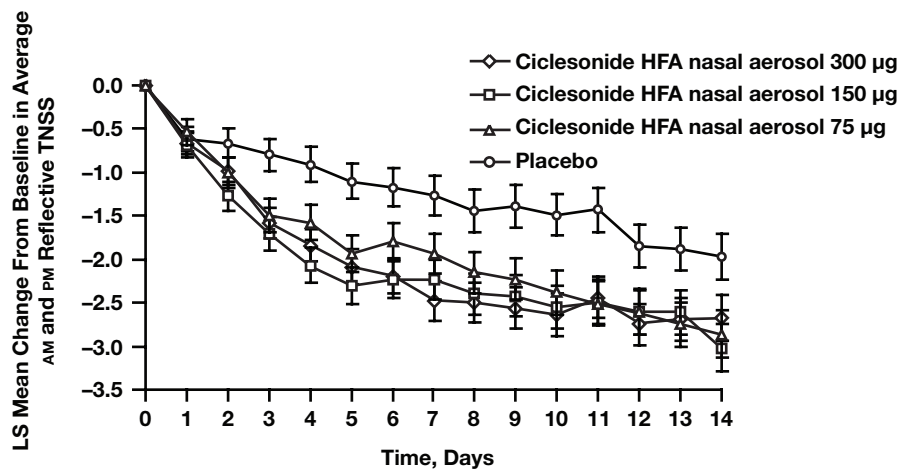


Figure 2. Time course of change from baseline in average morning and evening reflective total nasal symptom scores (rTNSS) during the 2-week treatment period. For ciclesonide, 300 µg, $P \leq .02$ between days 3 and 13; for ciclesonide, 150 µg, $P \leq .04$ from day 2 through day 14; and for ciclesonide, 75 µg, $P \leq .04$ from day 3 through day 14 vs placebo. HFA indicates hydrofluoroalkane.

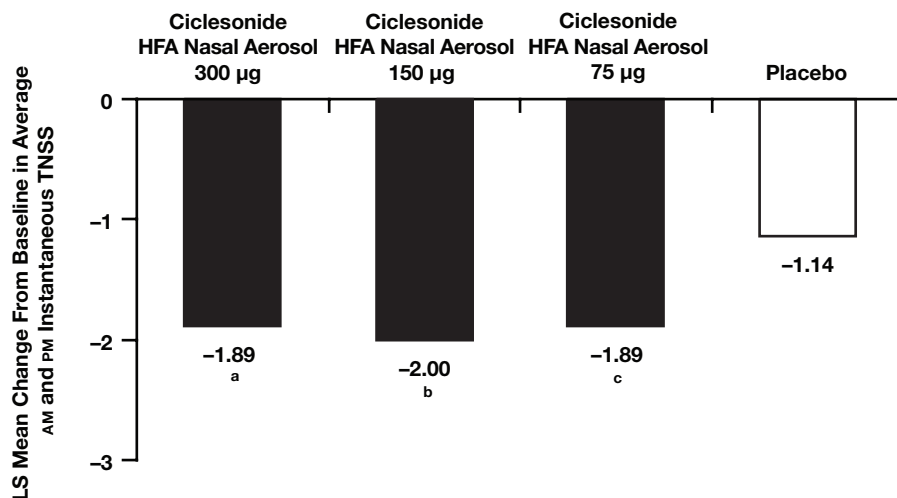


Figure 3. Change from baseline in average morning and evening instantaneous total nasal symptom scores (TNSSs) during the 2-week treatment period. Baseline values were 8.16, 7.96, and 8.30 for the 300-µg, 150-µg, and 75-µg groups, respectively, and 8.10 for the placebo group. HFA indicates hydrofluoroalkane; LS, least squares. ^a $P = .002$, ^b $P < .001$, and ^c $P = .003$ vs placebo.

evening iTNSS during the study period. Treatment differences for the reduction from baseline in evening iTNSS were 0.70 (95% CI, 0.19 to 1.20; $P = .01$), 0.76 (95% CI, 0.24 to 1.27; $P = .004$), and 0.68 (95% CI, 0.16 to 1.20; $P = .01$) for the 300-µg, 150-µg, and 75-µg formulations of ciclesonide, respectively, vs placebo.

Rhinoconjunctivitis Quality of Life Questionnaire

Although appreciable treatment differences between ciclesonide hydrofluoroalkane nasal aerosol and placebo were not observed in most individual domains of the RQLQ, improvements in the nasal symptom domain occurred, with treatment differences of 0.54 (95% CI, 0.10 to 0.98; $P = .02$), 0.38 (95% CI, -0.06 to 0.81; $P = .09$), and 0.61 (95% CI,

0.16 to 1.06; $P = .008$) for the 300-µg, 150-µg, and 75-µg formulations of ciclesonide, respectively, vs placebo. In patients with impaired quality of life at baseline (RQLQ score >3.0), appreciable improvements in RQLQ values over baseline were reported (mean baseline values ranged from 4.05 to 4.25; change from baseline least-squares means ranged from -1.24 to -1.5); however, these improvements were not significantly different from placebo.

Physician-Evaluated Nasal Symptom Severity

Ciclesonide hydrofluoroalkane nasal aerosol demonstrated improvements from baseline in PNSS at end point, resulting in treatment differences of 0.91 (95% CI, 0.25 to 1.58; $P = .007$), 0.73 (95% CI, 0.05 to 1.40; $P = .04$), and 0.94 (95%

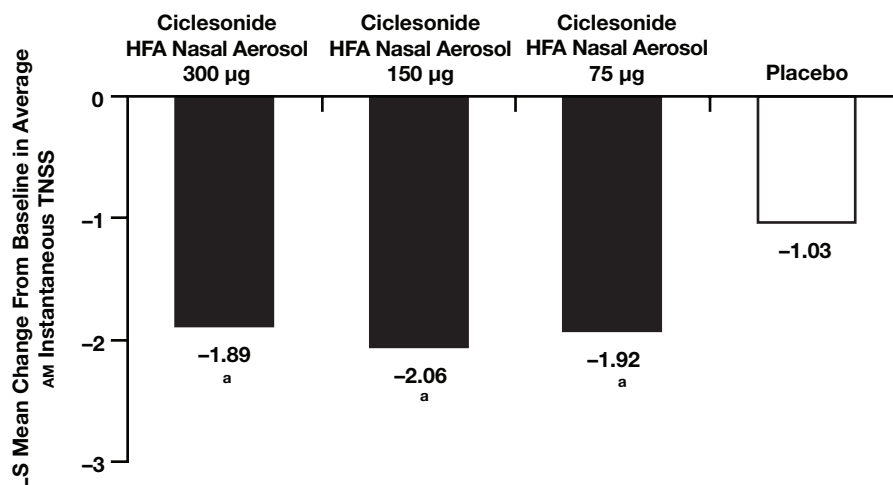


Figure 4. Change from baseline in morning instantaneous total nasal symptom scores (TNSSs) during the 2-week treatment period. Baseline values were 8.35, 8.17, and 8.59 for the 300-µg, 150-µg, and 75-µg groups, respectively, and 8.22 for the placebo group. HFA indicates hydrofluoroalkane; LS, least squares. ^a*P* < .001 vs placebo.

CI, 0.25 to 1.62; *P* = .007) for the 300-µg, 150-µg, and 75-µg formulations of ciclesonide, respectively, compared with placebo (Table 3).

Treatment-Emergent AEs

No clinically meaningful differences were found between the ciclesonide hydrofluoroalkane nasal aerosol and placebo groups in terms of the incidence, type, or severity of AEs. The most frequently reported AEs were headache and nasal discomfort (Table 4). The AEs judged to be treatment related or likely treatment related by the investigator were reported by 8 patients (5.9%) in the ciclesonide, 300 µg, group, 2 patients (1.6%) in the 150-µg group, 8 patients (6.5%) in the 75-µg group, and 4 patients (3.1%) in the placebo group and were of mild to moderate severity. Headache, the most frequently reported AE, occurred in 3 patients (2.2%) in the 300-µg group, 2 patients (1.6%) in the 150-µg group, 6 patients (4.9%) in the 75-µg ciclesonide group, and 2 patients (1.5%) in the placebo group. Epistaxis occurred in 1 patient (<1%) in each of the ciclesonide treatment groups. No severe AEs were reported during the study; however, nasal perfora-

tion was reported in 1 patient treated with ciclesonide, 75 µg, during the single-blind run-in period. Although initially considered by the investigator to be treatment or device related, this was later determined to be a nasal erosion rather than a perforation and not related to study treatment. Few abnormalities were observed in physical or nasal examinations, and almost all were considered by the investigator to not be clinically relevant. Vital signs were similar among the treatment groups.

DISCUSSION

Hydrofluoroalkane-based formulations have widely replaced, with some exceptions, chlorofluorocarbon-based aerosolized delivery systems for many products, including inhaled corticosteroids and albuterol used for asthma management. This effort emerged as a response to the Montreal Protocol on Substances That Deplete the Ozone Layer, which has been credited with successfully reducing the global production, consumption, and emissions of ozone-depleting substances.¹⁵ In part on the basis of this protocol, the Food and Drug

Table 3. Physician-Assessed Nasal Symptom Severity Score^a

	Ciclesonide hydrofluoroalkane nasal aerosol, 300 µg (n = 136)	Ciclesonide hydrofluoroalkane nasal aerosol, 150 µg (n = 125)	Ciclesonide hydrofluoroalkane nasal aerosol, 75 µg (n = 120)	Placebo (n = 130)
Baseline, mean (SD)	9.09 (2.23)	8.92 (2.33)	8.93 (2.36)	8.95 (2.00)
Change from baseline, LS mean (SE)	-2.98 (0.24)	-2.80 (0.25)	-3.01 (0.25)	-2.07 (0.24)
Treatment difference (95% CI) vs placebo	0.91 (0.25-1.58)	0.73 (0.05-1.40)	0.94 (0.25-1.62)	
<i>P</i> value	.007	.04	.007	

Abbreviations: CI, confidence interval; LS, least squares.

^a Data are presented for the intent-to-treat population.

Table 4. Treatment-Emergent Adverse Events Occurring in 2% or More of Any Treatment Group^a

Adverse event	Ciclesonide hydrofluoroalkane nasal aerosol, 300 µg (n = 135)	Ciclesonide hydrofluoroalkane nasal aerosol, 150 µg (n = 125)	Ciclesonide hydrofluoroalkane nasal aerosol, 75 µg (n = 123)	Placebo (n = 130)
Patients with ≥1 treatment-emergent adverse events, No. (%)	19 (14.1)	12 (9.6)	17 (13.8)	14 (10.8)
Headache, No. (%)	3 (2.2)	2 (1.6)	6 (4.9)	2 (1.5)
Nasal discomfort, No. (%)	3 (2.2)	1 (0.8)	1 (0.8)	3 (2.3)

^a Data are presented for the safety analysis population.

Administration mandated that most chlorofluorocarbon-based products be phased out of the US market. Because many prescriptions for intranasal chlorofluorocarbon-based products were written before their discontinuation in the market, a treatment gap in the area of AR now exists.

Negative sensory attributes of some of the currently available aqueous INCS formulations (eg, postnasal drip, wet feeling in the nose, strong odor, bitter taste)^{6,16,17} may reduce patient satisfaction and lead to discontinued use of their medication.^{5,6,17} The effort to improve patient satisfaction and adherence to AR therapy has led to the development of a hydrofluoroalkane nasal aerosol formulation of ciclesonide. Hydrofluoroalkane formulations provide a greater mass of fine particles in a reduced volume (<4 µL per actuation), thereby offering a drier delivery method than aqueous nasal formulations, which may reduce the perceived negative attributes of INCS therapy and, possibly, improve patient adherence with therapy.

In this dose range-finding study, all doses of ciclesonide hydrofluoroalkane nasal aerosol elicited significant improvements in both the primary end point (patient evaluation of reflective nasal symptoms) and 2 secondary efficacy measures (average morning and evening patient-reported iTNSS during the 2-week treatment period and individual morning patient-reported iTNSS during the 2-week treatment period). All ciclesonide doses significantly improved the overall TNSS (primary end point) and the individual symptoms (nasal congestion, runny nose, itchy nose, and sneezing) of the TNSS from baseline compared with placebo.

Although the 300-µg dose of ciclesonide does not elicit any additional benefit in any efficacy measure beyond the 2 lower doses of ciclesonide, a dose-dependent effect is noted between the 75-µg and 150-µg doses with regard to the primary and first 2 secondary efficacy measures. These data demonstrate that the 150-µg dose of intranasal ciclesonide is numerically superior to the 75-µg dose and suggest that the 150-µg dose of ciclesonide appears to be more consistently effective in the amelioration of the symptoms associated with SAR. Of note, this finding is also consistent with data from the 14-day phase 2 dose range-finding study with the aqueous formulation of ciclesonide, which demonstrated that although statistically significant differences were not observed between the 2 highest doses of ciclesonide aqueous nasal spray, the 200-µg dose of ciclesonide aqueous nasal spray

was numerically superior to the 100-µg dose for the primary and most secondary efficacy measures.¹⁸

The treatment-effect size observed for the primary efficacy variable (average of patient-reported morning and evening rTNSS during the 14-day treatment period) in all ciclesonide hydrofluoroalkane nasal aerosol groups is clinically important. A difference of 0.5 units in TNSS has been argued to be clinically important because it was the effect size seen with several approved products for SAR, such as montelukast sodium.^{19,20} Treatment differences observed in this study are larger than this clinically important difference.

Twenty-four hour effect ranks high among patient expectations for efficacy of AR medications; INCSs that have 24-hour duration of effect may lead to greater patient satisfaction and improved adherence to prescribed therapy.⁵ Notably, in a national survey, lack of 24-hour effect was cited as a reason for discontinued use in adults with AR.⁵ The statistically significant improvement in symptom scores immediately before dosing (at the end of the dosing interval; morning iTNSS) was clinically relevant in magnitude and may lead to greater patient satisfaction and/or compliance by meeting patient expectations for a perceived 24-hour effect. These results are consistent with findings for previous studies of ciclesonide aqueous nasal formulation.^{11,13,21}

Improvement in RQLQ at end point demonstrated numeric improvements from baseline for all treatment groups; however, the overall results for RQLQ were not statistically significantly improved over placebo. When individual domains of the RQLQ were examined, the nasal symptoms domain was significantly improved for the 300-µg ($P = .02$) and 75-µg doses ($P = .01$) and the practical problems domain was numerically improved compared with placebo. Clinically, the change from baseline of 1.5 units for the nasal symptoms domain and 1.4 units for the practical problems domain represents large changes in patient-perceived health-related quality of life.^{22,23} Furthermore, despite a lack of statistical significance vs placebo in the other domains, all ciclesonide treatment groups demonstrated changes from baseline of 0.5 units or more (considered the minimally important difference)^{22,23} for each of the 7 RQLQ domains; all active doses exceeded the placebo treatment group. It is possible that variable pollen counts (ie, decreasing tree pollen and increasing grass pollen throughout the study) or the wide variability of pollen counts observed during the different

study centers could have played a role in the lack of statistically significant improvement in RQLQ scores. Overall PNSS scores at end point demonstrated appreciably greater improvements over baseline for all ciclesonide treatments compared with placebo.

Ciclesonide hydrofluoroalkane nasal aerosol was well tolerated at all doses tested, with a low incidence of local AEs, no severe AEs, and a safety profile similar to placebo. The AEs that typically occur with INCSs are generally local and include nasal discomfort and epistaxis.²² The occurrences of nasal discomfort and epistaxis were low and similar among treatment groups in this study, although the ability of a 2-week study to meaningfully evaluate these outcomes, especially epistaxis, is limited. Nonetheless, these findings compare favorably with historic epistaxis occurrence frequencies reported in short-duration aqueous and aerosol INCS studies.²⁴

In conclusion, the hydrofluoroalkane formulation of ciclesonide is both effective and safe in a 2-week treatment protocol for SAR. In addition, based on the comparable efficacy and safety profiles observed for all treatment groups, these results suggest that the 75- μ g and 150- μ g doses (half dose per nostril) of ciclesonide hydrofluoroalkane nasal aerosol appear appropriate for further evaluation of efficacy.

ACKNOWLEDGMENTS

We thank John O'Flaherty, PhD, ProEd Communications Inc for his medical editorial assistance with the manuscript.

REFERENCES

- Nathan RA. The burden of allergic rhinitis. *Allergy Asthma Proc.* 2007;28:3–9.
- Settipane RA. Rhinitis: a dose of epidemiological reality. *Allergy Asthma Proc.* 2003;24:147–154.
- Skoner DP. Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis. *J Allergy Clin Immunol.* 2001;108:S2–S8.
- Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol.* 2001;108:S147–S334.
- HealthStar Communications, Inc., in partnership with Schulman, Ronca and Bucuvalas, Inc. Sponsored by Sepracor. *Allergies in America: A Landmark Survey of Nasal Allergy Sufferers.* Executive Summary: Adult. www.mmcpub.com/scsaia/AdultSummary.pdf. Accessed October 20, 2008.
- Naclerio RM, Hadley JA, Stoloff S, Nelson HS. Patient and physician perspectives on the attributes of nasal allergy medications. *Allergy Asthma Proc.* 2007;28:S11–S17.
- Omnaris [prescribing information]. Marlborough, MA: Sepracor Inc; 2007.
- Dietzel K, Engelstätter R, Keller A. Ciclesonide: an on-site-activated steroid. In: Hansel TT, Barnes PJ, eds. *New Drugs for Asthma, Allergy and COPD.* Progress in Respiratory Research, vol 31. Basel, Switzerland: Karger; 2001:91–93.
- Sato H, Nave R, Nonaka T, Mochizuki T, Takahama S, Kondo S. In vitro metabolism of ciclesonide in human nasal epithelial cells. *Biopharm Drug Dispos.* 2007;28:43–50.
- Berger WE, Nayak A, Lanier BQ, et al. Efficacy and safety of once-daily ciclesonide nasal spray in children with allergic rhinitis. *Pediatr Asthma Allergy Immunol.* 2008;21:73–82.
- Meltzer EO, Kunjibettu S, Hall N, et al. Efficacy and safety of ciclesonide, 200 microg once daily, for the treatment of perennial allergic rhinitis. *Ann Allergy Asthma Immunol.* 2007;98:175–181.
- Nave R, Wingertzahn MA, Brookman S, Kaida S, Matsunaga T. Safety, tolerability, and exposure of ciclesonide nasal spray in healthy and asymptomatic subjects with seasonal allergic rhinitis. *J Clin Pharmacol.* 2006;46:461–467.
- Ratner PH, Wingertzahn MA, van Bavel JH, Hampel F, Darken PF, Shah T. Efficacy and safety of ciclesonide nasal spray for the treatment of seasonal allergic rhinitis. *J Allergy Clin Immunol.* 2006;118:1142–1148.
- Meltzer EO, Hamilos DL, Hadley JA, et al. Rhinosinusitis: developing guidance for clinical trials. *J Allergy Clin Immunol.* 2006;118:S17–S61.
- Velders GJ, Andersen SO, Daniel JS, Fahey DW, McFarland M. The importance of the Montreal Protocol in protecting climate. *Proc Natl Acad Sci U S A.* 2007;104:4814–4819.
- Mahadevia PJ, Shah S, Leibman C, Kleinman L, O'Dowd L. Patient preferences for sensory attributes of intranasal corticosteroids and willingness to adhere to prescribed therapy for allergic rhinitis: a conjoint analysis. *Ann Allergy Asthma Immunol.* 2004;93:345–350.
- Mahr TA, Sheth KK, Boyle JM. Lack of efficacy and bothersome side effects decrease treatment adherence in children with allergic rhinitis [ACAAI abstract 3]. *Ann Allergy Asthma Immunol.* 2008;100:A3.
- Ratner PH, Wingertzahn MA, van Bavel JH, et al. Effectiveness of ciclesonide nasal spray in the treatment of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol.* 2006;97:657–663.
- Derebery M. Efficacy of mometasone furoate nasal spray in seasonal allergic rhinitis according to baseline symptom severity [abstract 245]. *J Allergy Clin Immunol.* 2007;119:S63.
- Kaiser H, Naclerio R, Given J, Toler T, Ellsworth A, Philpot E. Fluticasone furoate nasal spray: a single treatment option for the symptoms of seasonal allergic rhinitis. *J Allergy Clin Immunol.* 2007;119:1430–1437.
- Chervinsky P, Kunjibettu S, Miller DL, et al. Long-term safety and efficacy of intranasal ciclesonide in adult and adolescent patients with perennial allergic rhinitis. *Ann Allergy Asthma Immunol.* 2007;99:69–76.
- Juniper EF, Guyatt GH, Griffith LE, Ferrie PJ. Interpretation of rhinoconjunctivitis quality of life questionnaire data. *J Allergy Clin Immunol.* 1996;98:843–845.
- Meltzer EO. Quality of life in adults and children with allergic rhinitis. *J Allergy Clin Immunol.* 2001;108:S45–S53.
- Small P, Houle PA, Day JH, et al. A comparison of triamcinolone acetonide nasal aerosol spray and fluticasone propionate aqueous solution spray in the treatment of spring allergic rhinitis. *J Allergy Clin Immunol.* 1997;100:592–595.

Requests for reprints should be addressed to:
 Craig LaForce, MD
 North Carolina Clinical Research
 2615 Lake Dr
 Suite 301
 Raleigh, NC 27607
 E-mail: claforce@nccr.com