

# Efficacy and safety of ciclesonide nasal spray for the treatment of seasonal allergic rhinitis

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**Background:** Allergic rhinitis (AR), an inflammatory disease of the nasal mucosa, affects approximately 25% of adults and 40% of children in the United States. Ciclesonide nasal spray is a corticosteroid being developed as a hypotonic formulation for AR.

**Objective:** We sought to evaluate the efficacy, safety, and tolerability of ciclesonide nasal spray in adult and adolescent patients with seasonal AR (SAR).

**Methods:** In this double-blind study patients (age,  $\geq 12$  years) were randomized to receive 200  $\mu$ g of intranasal ciclesonide (n = 164) or placebo (n = 163) once daily for 28 days. The primary measure was morning and evening patient-assessed reflective total nasal symptom score (TNSS). Additionally, instantaneous TNSSs, physician-assessed overall nasal signs and symptoms severity, and the results of the Rhinoconjunctivitis Quality of Life Questionnaire were evaluated. Adverse events were monitored throughout the study.

**Results:** Ciclesonide significantly improved average morning and evening reflective and instantaneous TNSSs compared with placebo over days 1 to 14 ( $P < .001$ ). Improvements were also noted over days 1 to 28 ( $P < .001$ ) and over days 15 to 28 ( $P = .011$ ). Ciclesonide was well tolerated.

**Conclusion:** Intranasal ciclesonide was superior to placebo in relieving nasal symptoms in adult and adolescent patients with SAR. These results confirm the dose range-finding study in patients with SAR and support the efficacy of ciclesonide in AR. **Clinical implications:** In a clinical setting ciclesonide was shown to be safe and effective in the treatment of SAR in adolescent and adult patients. (J Allergy Clin Immunol 2006;118:1142-8.)

**Key words:** Intranasal corticosteroid, hay fever, nasal symptoms, health-related quality of life

## Abbreviations used

|          |                                                              |
|----------|--------------------------------------------------------------|
| AE:      | Adverse event                                                |
| AR:      | Allergic rhinitis                                            |
| des-CIC: | Desisobutyl-ciclesonide                                      |
| INS:     | Intranasal corticosteroid                                    |
| PANS:    | Physician-assessed overall nasal signs and symptoms severity |
| PAR:     | Perennial allergic rhinitis                                  |
| RQLQ:    | Rhinoconjunctivitis Quality of Life Questionnaire            |
| SAR:     | Seasonal allergic rhinitis                                   |
| TNSS:    | Total nasal symptom score                                    |

An estimated 20 to 40 million Americans have allergic rhinitis (AR).<sup>1</sup> AR is the general term that encompasses seasonal AR (SAR), perennial AR (PAR), and PAR with seasonal exacerbations. SAR is easily identifiable by the appearance of symptoms that correlate with periods of pollen exposure. In contrast, PAR symptoms are commonly triggered by indoor allergens and are not usually affected by seasonality, except in the case of patients with PAR with seasonal exacerbations. SAR accounts for 20% of cases and PAR for 40% of cases, and another 40% of cases have a mixed cause.<sup>1</sup>

Current treatments for AR include antihistamines, decongestants, leukotriene modifiers, and intranasal corticosteroids (INSs). Oral antihistamines are an effective first-line pharmacologic treatment for the relief of itching, sneezing, and rhinorrhea associated with AR.<sup>2</sup> However, antihistamines do not adequately treat nasal congestion and are linked to class-specific side effects (eg, sedation, impaired cognitive function, and cardiac arrhythmias).<sup>2-4</sup> INSs are considered the most effective treatment for the management of AR symptoms.<sup>2</sup> Unlike antihistamines, INSs have a more profound effect on nasal congestion and the related sleep disturbance and daytime somnolence resulting from nasal congestion.<sup>5</sup> Patient preference and willingness to adhere to INS therapy are dependent on the sensory attributes of the nasal spray (eg, smell, taste, throat rundown, and nose runout) and might affect patient compliance.<sup>6</sup>

Ciclesonide is a corticosteroid with previously demonstrated efficacy in the treatment of asthma when delivered through a metered-dose inhaler.<sup>7,8</sup> Ciclesonide is also currently in clinical development as an intranasal formulation for use in the treatment of AR. Ciclesonide is administered as an inactive parent compound that is metabolized by endogenous esterases in the upper and lower airways to the pharmacologically active metabolite desisobutyl-ciclesonide

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(des-CIC).<sup>9,10</sup> The relative glucocorticoid receptor binding affinity of des-CIC is 100-fold greater than that of ciclesonide (relative glucocorticoid receptor binding affinities are 1200 and 12, respectively; dexamethasone reference is 100).<sup>11</sup>

Ciclesonide for intranasal use is formulated in a hypotonic suspension, which has been shown in preclinical *in vivo* models to provide enhanced tissue uptake when compared with a traditional isotonic formulation.<sup>12</sup> In addition, the intranasal formulation of ciclesonide is preserved with potassium sorbate rather than benzalkonium chloride, which is used in many INs. Benzalkonium chloride is believed to interfere with mucociliary transport and can lead to the development of hypersensitivity, rhinitis medicamentosa, and neutrophil dysfunction.<sup>13,14</sup> Furthermore, benzalkonium chloride has a bitter taste that might compromise patient adherence.<sup>6</sup>

This clinical study evaluated the efficacy of 200 µg of ciclesonide nasal spray administered once daily compared with that of placebo on nasal symptoms and signs of AR in adults and adolescents with SAR over a 28-day period. Additionally, health-related quality of life, safety, and tolerability of ciclesonide were assessed.

## METHODS

### Patients

Eligible patients were required to be 12 years of age or older, to be in good health with a history of SAR (requiring treatment) of 2 years or longer, and to have a demonstrated sensitivity to mountain cedar pollen, as determined by means of a skin prick test. Patients were excluded from the study if they had nasal pathology, including nasal polyps, within 60 days before study initiation or clinically relevant respiratory tract malformations; recent nasal biopsy (within 60 days); nasal trauma; nasal surgery; atrophic rhinitis; rhinitis medicamentosa (within 60 days); or active asthma requiring treatment with inhaled or systemic corticosteroids, routine use of β-agonists, or both. In addition, patients were excluded from the study if they had a known hypersensitivity to corticosteroids, had a history of respiratory tract infection or disorder within 14 days of the screening visit or had a respiratory tract infection during baseline, had used antibiotics for acute conditions within 14 days of the screening visit, were treated with systemic corticosteroids within 2 months of study initiation, or were treated with topical corticosteroids in concentrations in excess of 1% hydrocortisone for dermatologic conditions within 1 month of study initiation. Patients were not permitted to initiate immunotherapy or increase the dose of existing immunotherapy during the study. All patients provided written informed consent.

### Study design and treatment

This was a randomized, double-blind, parallel-group, placebo-controlled, multicenter clinical trial. After a 7- to 10-day baseline period, patients were randomized to receive 200 µg of ciclesonide or placebo administered intranasally (2 actuations per nostril) once daily in the morning for a 4-week treatment period. This study was approved by an institutional review board (Schulman Associates Institutional Review Board, Inc, Cincinnati, Ohio) and conducted in accordance with the principles of the revised version of the Declaration of Helsinki.

### Allergy testing

Histamine phosphate (1 mg/mL; ALK-Abelló, Hørsholm, Denmark), delivered epicutaneously by using the MultiTest testing

device (Lincoln Diagnostics, Inc, Decatur, Ill), was used as the positive histamine control in this study. Mountain cedar pollen extracts (1:20 wt/vol) were obtained from ALK-Abelló. The mountain cedar pollen skin test was approximately equal to the positive control (histamine phosphate) and represented a 3+ reaction on a 4+ scale.

### Pollen counts

Daily mountain cedar pollen counts were assessed through a collection device maintained at each investigative site.

### Treatment compliance

Patients recorded total nasal symptom scores (TNSSs) and the time of study medication use in patient diaries on a daily basis to assess treatment compliance.

### Efficacy assessments

The primary efficacy end point was the change from baseline in the average of morning and evening patient-assessed reflective TNSSs over the first 2 weeks of treatment. The reflective TNSS measures nasal symptom severity over the past 12 hours and is calculated as the sum of 4 nasal symptoms (runny nose, itchy nose, sneezing, and nasal congestion), each rated on a scale of 0 (no signs/symptoms evident) to 3 (signs/symptoms that interfere with daily activities). Secondary variables included patient-assessed instantaneous TNSSs, physician-assessed overall nasal signs and symptoms severity (PANS), total nonnasal symptom scores (sum of reflective itching/burning eyes, tearing/watery eyes, redness of eyes, and itching of ears or palate assessments measured on a 0- to 3-point scale), Rhinocconjunctivitis Quality of Life Questionnaire (RQLQ) results, individual nasal symptoms, and time to onset of effect. PANS and RQLQ results were assessed at baseline and on treatment days 15 and 29. Nasal and nonnasal symptoms were assessed by patients (recorded in a diary) during the baseline period and over 4 weeks of treatment.

The instantaneous TNSS measures nasal symptoms at the time of evaluation and uses the same scale system as the reflective TNSS. The PANS assessment is the sum of nasal signs (intensity of discoloration of nasal passages, swollen nasal passages, presence of secretions, and evidence of postnasal drip, throat irritation, or both) and symptoms (runny nose, itchy nose, congestion, and sneezing) rated on a scale from 0 (none) to 3 (severe) for each sign or symptom. Nonnasal symptoms were assessed by the patient in the same manner as the reflective TNSS and included itching or burning eyes, tearing or watering eyes, redness of eyes, and itching of ears or palate.

The RQLQ is a disease-specific, validated quality-of-life questionnaire developed for the measurement of physical, emotional, and social problems common to adults and adolescents with allergies.<sup>15</sup> The version of the RQLQ administered depended on patient age, with patients 12 to 17 years assessed with the adolescent RQLQ and patients 18 years and older assessed with the adult RQLQ. Patients rated experiences over the past week for questions related to activities, sleep (adults only), non-nose/eye symptoms (adults only), practical problems, nasal symptoms, eye symptoms, emotions, and non-hay fever symptoms (adolescents only).

### Safety assessments

Physical examinations, including ear, nose, and throat assessments and hematology and laboratory tests were performed at the screening visit and on day 29. Vital signs and adverse events (AEs) were monitored throughout the study.

### Statistical methods

The intent-to-treat analyses were based on those patients who received at least 1 dose of study medication and who had 1 or more postbaseline efficacy variable measurements. The intent-to-treat

**TABLE I.** Patient demographics and baseline characteristics

| Parameter                                                         | Ciclesonide, 200 $\mu$ g<br>(n = 164) | Placebo<br>(n = 163) |
|-------------------------------------------------------------------|---------------------------------------|----------------------|
| Age (y)                                                           | 39 $\pm$ 14                           | 41 $\pm$ 15          |
| Male sex (n [%])                                                  | 58 (35.4)                             | 57 (35.0)            |
| Smoking history, n (%)                                            |                                       |                      |
| Never smoked                                                      | 117 (71.3)                            | 108 (66.3)           |
| Former smoker                                                     | 30 (18.3)                             | 35 (21.5)            |
| Current smoker                                                    | 17 (10.4)                             | 20 (12.3)            |
| Type of skin test, n (%)                                          |                                       |                      |
| Current skin prick test                                           | 125 (76.2)                            | 121 (74.2)           |
| Historical skin prick test                                        | 39 (23.8)                             | 42 (25.8)            |
| Antigen challenge results (mm)                                    | 10.19 $\pm$ 5.13                      | 9.18 $\pm$ 3.44      |
| Control results (mm)                                              | 0.93 $\pm$ 1.73                       | 0.85 $\pm$ 1.74      |
| Histamine results (mm)                                            | 9.13 $\pm$ 3.84                       | 8.85 $\pm$ 3.89      |
| Average baseline morning and evening reflective TNSS              | 8.96 $\pm$ 1.96                       | 8.83 $\pm$ 1.82      |
| Average baseline morning and evening instantaneous TNSS           | 8.40 $\pm$ 2.24                       | 8.33 $\pm$ 2.08      |
| Baseline PANS                                                     | 7.97 $\pm$ 1.58                       | 8.07 $\pm$ 1.44      |
| Combined adult and adolescent baseline RQLQ score                 | 3.96 $\pm$ 1.05                       | 3.78 $\pm$ 0.98      |
| Average baseline morning and evening reflective nonnasal symptoms | 7.64 $\pm$ 2.63                       | 7.50 $\pm$ 2.70      |

Data are presented as means  $\pm$  SD.

analyses were used for all efficacy measures. The planned sample size of 151 randomized patients per group was determined to provide 90% power to detect a difference of 0.9 between treatments in the change from baseline in the average of morning and evening reflective TNSSs over days 1 to 14 by using a 2-sided  $\alpha$  level of 5% and assuming an SD of 2.4.

Change from baseline in TNSSs was analyzed by using a repeated-measures analysis of covariance, with covariate adjustment for baseline, treatment, day, treatment by day, and center and with patient treated as a random effect. Baseline was defined as the average reflective morning and evening TNSS over the last 7 days before randomization. Estimated treatment differences and 95% CIs for the treatment differences were provided. Change from baseline for individual time points of nasal and nonnasal symptoms and change from baseline in PANS and RQLQ results were analyzed by means of univariate analysis of covariance, with covariates of baseline, center, and treatment. Changes from baseline data are presented as least-squares means  $\pm$  SEM. AEs were assessed by using descriptive measures.

## RESULTS

### Patient disposition and baseline demographics

Four hundred ninety patients were screened, and 327 were randomized to receive ciclesonide (n = 164) or placebo (n = 163). Thirty-five patients withdrew from the study: 21 (12.8%) patients treated with ciclesonide and 14 (8.6%) patients treated with placebo. The primary reasons for discontinuation were AEs (4 patients treated with ciclesonide and 5 patients treated with placebo) and lack of efficacy (4 patients treated with ciclesonide and 5 patients treated with placebo). Mean treatment compliance, as

reported in patient diaries, was comparable between groups (94.3% and 95.4% for ciclesonide and placebo, respectively). Patient demographics and baseline characteristics were generally similar between treatment groups (Table I). The average patient age was 39 to 41 years, and the majority of patients were female (65%). Baseline averages of morning and evening reflective TNSS values were 8.96 and 8.83 for the ciclesonide and placebo groups, respectively, indicating a patient population with moderately severe SAR.

### Efficacy

Ciclesonide decreased the average of morning and evening reflective TNSSs from baseline more than placebo (Fig 1). Over the first 2 weeks of treatment, ciclesonide significantly improved the average of morning and evening reflective TNSSs by  $-2.40 \pm 0.16$  compared with  $-1.50 \pm 0.16$  observed with placebo treatment ( $P < .001$ ; Fig 2 and Table II). These changes corresponded to mean percentage changes from baseline of 27% and 17% in the ciclesonide and placebo treatment groups, respectively. Each symptom component of the TNSS contributed to this finding, with estimated treatment differences for nasal congestion, runny nose, sneezing, and nasal itching being 0.26, 0.24, 0.20, and 0.20, respectively ( $P \leq .003$ ). Ciclesonide maintained consistently greater symptom relief versus placebo, with a difference of 0.75 (95% CI, 0.17-1.32) over days 15 to 28 ( $P = .011$ ). Over the entire study period, the average of morning and evening reflective TNSSs decreased from baseline by  $2.69 \pm 0.17$  in the ciclesonide group and  $1.87 \pm 0.17$  in the placebo group ( $P < .001$  vs placebo, Fig 2 and Table III). Individual analysis of placebo-adjusted morning reflective TNSSs and evening reflective TNSSs revealed similar improvements from baseline in patients treated with ciclesonide relative to those treated with placebo during the first 2 weeks of treatment, which is suggestive of a 24-hour effect (Fig 3). This effect was also maintained throughout the study.

In addition, ciclesonide improved the average of morning and evening instantaneous TNSSs from baseline compared with placebo (Tables II and III). Improvements in the average of morning and evening instantaneous TNSSs over the first 2 weeks of treatment were significantly greater in the ciclesonide treatment group ( $-2.15 \pm 0.16$ ) versus the placebo group ( $-1.28 \pm 0.16$ ;  $P < .001$ , Table II). Improvements observed with ciclesonide versus placebo were maintained throughout the study, with differences of 0.73 (95% CI, 0.18-1.28) and 0.80 (95% CI, 0.35-1.25) over days 15 to 28 and days 1 to 28, respectively.

At end point, although large changes from baseline in the ciclesonide group were observed, statistically significant differences from placebo were not observed in overall PANS and RQLQ scores because of the large changes in the placebo group occurring at the end of the study period (Table III). However, at study day 15, ciclesonide provided greater improvements in overall PANS and combined RQLQ scores compared with placebo ( $P \leq .002$ , Table II). Notably, at day 15, treatment differences were evident for the nasal symptom components but

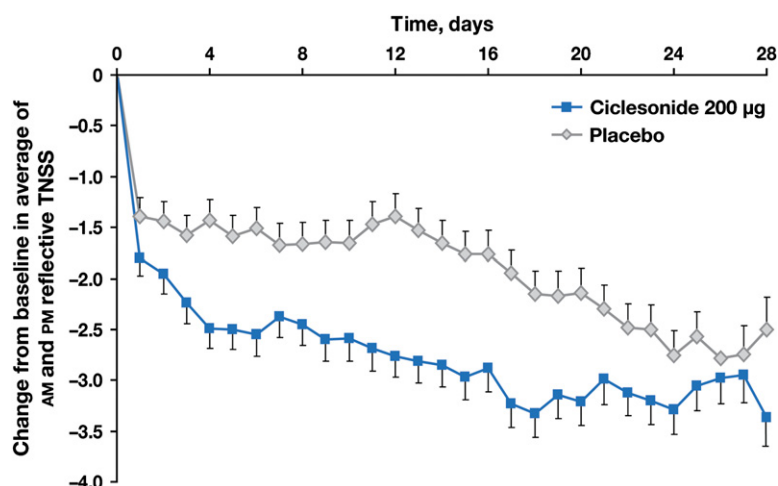


**FIG 1.** Ciclesonide improved patient-assessed average of morning and evening reflective TNSSs throughout the study. Change from baseline in average of morning and evening reflective TNSSs was measured over time. Data are presented as least-squares means and SEM. Average baseline morning and evening reflective TNSSs  $\pm$  SD were  $8.96 \pm 1.96$  in the ciclesonide group and  $8.83 \pm 1.82$  in the placebo group.

not for the nasal sign components of PANS ( $P \leq .001$ , ciclesonide vs placebo). In terms of quality of life at day 15, ciclesonide also improved all domains of the RQLQ, with the exception of eye symptoms, more than placebo ( $P \leq .001$ ). Interestingly, because patients were not required to have impaired quality of life at baseline, a post-hoc analysis of patients with higher baseline scores, indicating greater impairment, was conducted. This analysis demonstrated that a greater treatment difference (0.57 vs 0.45 for the all-patient analysis) was observed in patients with baseline RQLQ scores at or greater than the median level of 4.0. Reflective nonnasal symptoms were also assessed by using patient diaries and demonstrated a numerically larger response in the ciclesonide group versus the placebo group ( $-1.73$  vs  $-1.30$ ,  $P = .071$ ).

Ciclesonide nasal spray demonstrated a rapid onset of action, with a significant improvement in average of morning and evening reflective TNSSs versus that seen with placebo by the second day of treatment ( $P < .05$ ). In addition, hourly measurements of instantaneous TNSSs during day 1 revealed numerically greater improvements with ciclesonide compared with those seen with placebo at every hour assessed. However, the first time point with a  $P$  value of less than .05 for the difference in instantaneous TNSSs was at hour 12 (changes of  $-1.94$  and  $-1.22$  for ciclesonide and placebo,  $P = .022$  vs placebo). Therefore although encouraging, the formal definition requiring a confirmatory time point to establish an onset of action within 12 hours was not met.

## Safety

The frequency of AEs was similar between treatment groups, with 66 (40.2%) and 64 (39.3%) patients in the ciclesonide and placebo groups, respectively, experiencing 1 or more AEs. The most common AEs were nasal passage irritation (6.1%) and headache (5.5%) among patients treated with ciclesonide and nasal passage irritation (5.5%), pharyngitis (3.7%), and upper respiratory tract

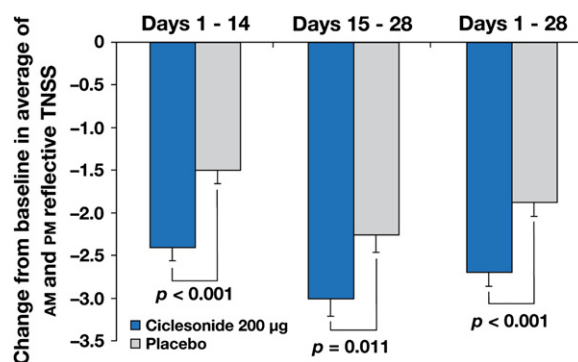


**FIG 2.** Ciclesonide improved patient-assessed average of morning and evening reflective TNSSs throughout the study. Data are presented as least-squares means and SEM. Average baseline morning and evening reflective TNSSs  $\pm$  SD were  $8.96 \pm 1.96$  in the ciclesonide group and  $8.83 \pm 1.82$  in the placebo group.

infection (3.7%) among patients treated with placebo (Table IV). Epistaxis rates were low, affecting 4.3% and 2.5% of patients treated with ciclesonide and placebo, respectively. The majority (85%) of AEs were mild to moderate in intensity. AEs considered by the investigator to be at least likely related to study medication occurred in 11.0% and 9.8% of patients in the ciclesonide and placebo groups, respectively. Only 1 serious AE (increased heart rate) was reported. This event occurred in a patient treated with ciclesonide and was considered by the investigator to be unrelated to study medication. Four (2%) patients in the ciclesonide treatment group and 5 (3%) patients in the placebo treatment group withdrew from the study because of AEs.

## DISCUSSION

Ciclesonide, an investigational corticosteroid in development for the treatment of AR and asthma, is

**TABLE II.** Change from baseline in efficacy parameters (days 1-14)

| Parameter                                                   | Ciclesonide, 200 µg<br>(n = 164) | Placebo<br>(n = 163) |
|-------------------------------------------------------------|----------------------------------|----------------------|
| Average of morning and evening reflective TNSSs             |                                  |                      |
| Change from baseline                                        | -2.40 ± 0.16                     | -1.50 ± 0.16         |
| Difference from placebo                                     |                                  |                      |
| LS mean (95% CI)                                            | 0.90 (0.45 to 1.36)              | —                    |
| P value                                                     | <.001                            | —                    |
| Average of morning and evening instantaneous TNSSs          |                                  |                      |
| Change from baseline                                        | -2.15 ± 0.16                     | -1.28 ± 0.16         |
| Difference from placebo                                     |                                  |                      |
| LS mean (95% CI)                                            | 0.88 (0.44 to 1.31)              | —                    |
| P value                                                     | <.001                            | —                    |
| PANS score at week 2                                        |                                  |                      |
| Change from baseline                                        | -1.69 ± 0.15                     | -0.92 ± 0.15         |
| Difference from placebo                                     |                                  |                      |
| LS mean (95% CI)                                            | 0.77 (0.35 to 1.18)              | —                    |
| P value                                                     | <.001                            | —                    |
| RQLQ score at week 2                                        |                                  |                      |
| Change from baseline                                        | -1.17 ± 0.10                     | -0.72 ± 0.10         |
| Difference from placebo                                     |                                  |                      |
| LS mean (95% CI)                                            | 0.45 (0.16 to 0.73)              | —                    |
| P value                                                     | .002                             | —                    |
| Average of morning and evening reflective nonnasal symptoms |                                  |                      |
| Change from baseline                                        | -1.73 ± 0.17                     | -1.30 ± 0.17         |
| Difference from baseline                                    |                                  |                      |
| LS mean (95% CI)                                            | 0.43 (-0.04 to 0.90)             | —                    |
| P value                                                     | .071                             | —                    |

Data are presented as least-squares means ± SEM.

LS, Least squares.

administered as an inactive parent compound that is converted by esterases in the upper and lower airways to the pharmacologically active metabolite, des-CIC.<sup>9,10</sup> des-CIC subsequently forms fatty acid esters that act as a slow-release pool of anti-inflammatory activity.<sup>16</sup> High glucocorticoid receptor binding affinity (relative glucocorticoid receptor binding affinities of des-CIC and ciclesonide are 1200 and 12, respectively; dexamethasone reference is 100) and high lipophilicity contribute to the clinical efficacy of ciclesonide.<sup>7,8,11</sup> Low oral bioavailability (oral bioavailability of des-CIC is approximately 1%), high protein binding (99%), and high hepatic clearance (396 L/h) contribute to the favorable safety profile of ciclesonide.<sup>17-20</sup>

Once-daily intranasal administration of 200 µg of ciclesonide was shown to be effective for the treatment of SAR, as demonstrated by a statistically significant improvement from baseline compared with that seen in the placebo group in the primary efficacy variable of the average of morning and evening reflective TNSSs over days 1 to 14. Interestingly, although INS products are typically perceived as having the greatest effect on nasal congestion, this study demonstrated that ciclesonide nasal spray showed a similar magnitude of effect on all 4 components of the TNSS, namely nasal congestion, rhinorrhea, nasal itching, and sneezing. Although no direct head-to-head trials between ciclesonide and other AR products have been performed to date, indirect comparisons across studies suggest that the treatment-effect size of 0.90

observed between ciclesonide and placebo is larger than that generally seen with the leukotriene inhibitor montelukast, as well as nonsedating oral histamines, such as desloratadine, in the treatment of SAR.<sup>21,22</sup> Additionally, the magnitude of effect observed in this study appears comparable with what has been demonstrated previously with mometasone in trials using a similar measurement scale.<sup>23</sup>

An additional point to consider is the beneficial effects of the vehicle on overall improvement in AR symptomatology. Over days 1 to 14, the mean change from baseline in the TNSS was 1.5 for the vehicle (placebo) and 2.4 for the ciclesonide nasal spray group. The improvements in efficacy parameters with ciclesonide in this study were significant, despite the large improvements in patients treated with placebo. These large improvements observed in the placebo group of this study are consistent with published data indicating that placebo nasal sprays can alleviate symptoms associated with AR through keeping nasal tissues moist, relieving nasal irritation, and assisting in mucus drainage and clearance.<sup>24,25</sup> Studies using either saline or propylene/polyethylene glycol nasal sprays as placebo controls have reported significant improvements in nasal symptoms in patients treated with placebo alone.<sup>26</sup> Moreover, the hypotonic formulation of the placebo used in the current study might provide better symptom relief than would be achieved with a traditional isotonic formulation.

During the second 2-week period, daily changes from baseline in the ciclesonide-treated group essentially remained constant, whereas the mean changes in the placebo

**TABLE III.** Change from baseline in efficacy parameters (days 1-28)

| Parameter                                                   | Ciclesonide, 200 µg<br>(n = 164) | Placebo<br>(n = 163) |
|-------------------------------------------------------------|----------------------------------|----------------------|
| Average of morning and evening reflective TNSSs             |                                  |                      |
| Change from baseline                                        | -2.69 ± 0.17                     | -1.87 ± 0.17         |
| Difference from placebo                                     |                                  |                      |
| LS mean (95% CI)                                            | 0.81 (0.34 to 1.28)              | —                    |
| P value                                                     | <.001                            | —                    |
| Average of morning and evening instantaneous TNSSs          |                                  |                      |
| Change from baseline                                        | -2.43 ± 0.16                     | -1.63 ± 0.16         |
| Difference from placebo                                     |                                  |                      |
| LS mean (95% CI)                                            | 0.80 (0.35 to 1.25)              | —                    |
| P value                                                     | <.001                            | —                    |
| PANS score                                                  |                                  |                      |
| Change from baseline*                                       | -1.98 ± 0.16                     | -1.99 ± 0.16         |
| Difference from placebo                                     |                                  |                      |
| LS mean (95% CI)                                            | -0.01 (-0.44 to 0.43)            | —                    |
| P value                                                     | .982                             | —                    |
| Combined adult and adolescent RQLQ scores                   |                                  |                      |
| Change from baseline*                                       | -1.39 ± 0.11                     | -1.21 ± 0.11         |
| Difference from placebo                                     |                                  |                      |
| LS mean (95% CI)                                            | 0.18 (-0.13 to 0.49)             | —                    |
| P value                                                     | .244                             | —                    |
| Average of morning and evening reflective nonnasal symptoms |                                  |                      |
| Change from baseline                                        | -2.07 ± 0.17                     | -1.70 ± 0.17         |
| Difference from placebo                                     |                                  |                      |
| LS mean (95% CI)                                            | 0.38 (-0.09 to 0.85)             | —                    |
| P value                                                     | .117                             | —                    |

Data are presented as least-squares means ± SEM.

LS, Least squares.

\*At end point.

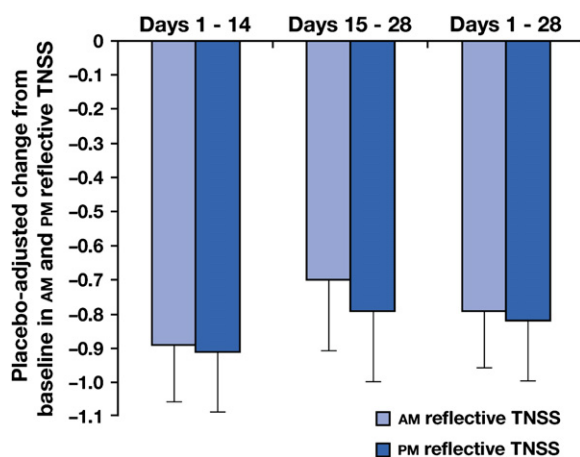


**FIG 3.** Ciclesonide improved patient-assessed morning reflective TNSSs and evening reflective TNSSs to a similar extent. Data are estimated differences between ciclesonide and placebo. Average baseline morning reflective TNSSs ± SD were 8.83 ± 2.11 in the ciclesonide group and 8.70 ± 1.97 in the placebo group. Average baseline evening reflective TNSSs ± SD were 9.09 ± 1.92 in the ciclesonide group and 8.97 ± 1.84 in the placebo group.

group continued to decrease through day 28, resulting in a seemingly smaller effect size as the study progressed. Although the changes in TNSSs between the ciclesonide and placebo groups remained apparent through days 15

**TABLE IV.** AEs reported by 2% or more of patients in any treatment group\*

| AE                                    | Patients (n [%])              |                   |
|---------------------------------------|-------------------------------|-------------------|
|                                       | Ciclesonide, 200 µg (n = 164) | Placebo (n = 163) |
| Nasal passage irritation              | 10 (6.1)                      | 9 (5.5)           |
| Headache                              | 9 (5.5)                       | 4 (2.5)           |
| Epistaxis                             | 7 (4.3)                       | 4 (2.5)           |
| Pharyngitis                           | 5 (3.0)                       | 6 (3.7)           |
| Ear pain                              | 6 (3.7)                       | 2 (1.2)           |
| Upper respiratory tract infection NOS | 2 (1.2)                       | 6 (3.7)           |
| Nasopharyngitis                       | 5 (3.0)                       | 2 (1.2)           |
| Tympanic membrane disorder NOS        | 2 (2.4)                       | 1 (0.6)           |

NOS, Not otherwise specified.

\*Regardless of causality.

to 28, strong evidence for changes in PANS and RQLQ scores was apparent only at 2 weeks. One likely explanation for the increase in placebo response over time and the corresponding reduced difference between the ciclesonide and placebo groups is that the pollen counts appeared to have waned toward the end of the study. Because the majority of placebo-treated patients remained moderately symptomatic throughout the duration of the trial, the symptomatology in these patients also improved when pollen counts waned, leading to a readily observable

reduction in TNSSs toward the end of the study. In contrast, patients treated with ciclesonide nasal spray had their symptoms more adequately controlled over the course of the trial, and therefore little additional room for improvement remained when the pollen counts waned toward the end of the study. On average, daily pollen counts were approximately 3-fold lower during week 4 compared with weeks 1 to 3 and were similar to levels observed during the first part of the baseline period before the mountain cedar pollen season was at its peak.

The dosing posology was also assessed from the TNSS data. The data from this study showed that the effect size in the evening reflective TNSSs (0.9) over days 1 to 14 was similar to the effect size seen in the morning reflective TNSSs (0.89) assessed immediately before dosing and covering the second 12 hours of the 24-hour dosing interval. These data suggest that once-daily morning dosing is appropriate for ciclesonide nasal spray, which could theoretically lead to increased compliance compared with drugs that are dosed twice or more daily.

The safety and tolerability data from this study indicate that ciclesonide nasal spray was well tolerated. No clinically meaningful differences between the placebo and ciclesonide groups were observed in the incidence rate of AEs or other safety assessments during the study. Additionally, discontinuation rates because of AEs were similar for both groups. Although the incidence rates for headache, ear pain, and epistaxis were numerically higher in the ciclesonide nasal spray group, it appeared that the ciclesonide group had a lower incidence rate of upper respiratory tract infections compared with the placebo group. Most AEs, regardless of group, were reported to be mild to moderate in intensity, suggesting that ciclesonide nasal spray at the dose tested has an acceptable safety profile. The epistaxis rate for ciclesonide compared favorably with historic rates for other INSSs, with a placebo-adjusted epistaxis rate of 1.8%.

In conclusion, ciclesonide nasal spray provided substantial symptom relief, as measured by patients and physicians. Intranasal administration of ciclesonide was well tolerated, with an overall incidence rate of AEs comparable with that seen with placebo. The demonstrated efficacy and favorable safety and tolerability profile of ciclesonide suggest that ciclesonide nasal spray is an effective treatment option for patients with SAR and confirm the results of an earlier dose-dependent efficacy study in patients with SAR.<sup>27</sup>

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