

Evaluation of the efficacy and safety of ciclesonide hydrofluoroalkane nasal aerosol, 80 or 160 μ g once daily, for the treatment of seasonal allergic rhinitis

Paul Ratner, MD*; Robert Jacobs, MD†; Dale Mohar, MD‡; Holly Huang, MS, MPH§; Shailesh Y. Desai, PhD§; and Joseph Hinkle, MD§

Background: A hypotonic aqueous nasal spray of ciclesonide is indicated for the treatment of allergic rhinitis (AR). A new nasal aerosol formulation of ciclesonide containing a hydrofluoroalkane propellant delivered via a metered-dose inhaler (CIC-HFA) is currently in clinical development as a potential treatment for AR.

Objectives: To study the efficacy and safety of once-daily administration of CIC-HFA 80 or 160 μ g compared with placebo in subjects 12 years and older with seasonal AR (SAR).

Methods: Subjects 12 years and older with a ≥ 2 -year history of SAR were randomized in a placebo-controlled, double-blind, parallel-group, multicenter study to receive CIC-HFA 80 or 160 μ g or placebo once daily in the morning for 2 weeks. Changes from baseline in reflective total nasal symptom scores (rTNSSs), instantaneous TNSSs (iTNSSs), and reflective total ocular symptom scores (rTOSSs) in subjects with a baseline rTOSS of ≥ 5.00 were evaluated. Treatment-emergent adverse events were monitored throughout the study.

Results: Seven hundred seven subjects were randomized. From baseline, CIC-HFA 80 or 160 μ g demonstrated 15.1% and 16.0% reductions in rTNSSs ($P < .0001$, 3.7% for placebo), 14.3% and 15.4% reductions in iTNSSs ($P < .0001$, 3.9% for placebo), and 15.7% and 15.0% reductions in rTOSSs ($P < .001$, 6.8% for placebo). The overall incidence of treatment-emergent adverse events was low and comparable between the CIC-HFA and placebo groups.

Conclusions: In this study, once-daily treatment with CIC-HFA 80 or 160 μ g demonstrated statistically significant improvements in nasal and ocular symptoms of SAR. Both doses of active treatment were well tolerated.

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INTRODUCTION

An estimated 60 million Americans suffer from allergic rhinitis (AR) every year.¹ Symptoms of AR include nasal congestion, nasal itching, runny nose, and sneezing.² Allergic rhinitis may significantly affect quality of life and productivity for allergy sufferers and may impose an economic burden in direct and indirect treatment costs.¹

Current treatments for AR include antihistamines, decongestants, leukotriene modifiers, and intranasal corticosteroids.³ Among these treatment options, intranasal corticosteroids are an effective therapy for the management of AR of

all severities, providing relief from allergy symptoms and reducing underlying inflammation.^{4,5}

Ciclesonide is a corticosteroid, is administered as a pro-drug, and is activated by esterases to the pharmacologically active metabolite desisobutyl-ciclesonide.⁶ A hypotonic aqueous nasal spray formulation of ciclesonide has demonstrated efficacy in the treatment of seasonal AR (SAR) and perennial AR^{7,8} and is approved in the United States for the treatment of SAR in patients 6 years and older and perennial AR in patients 12 years and older.⁹ A new nasal aerosol formulation of ciclesonide containing a hydrofluoroalkane propellant delivered via a metered-dose inhaler (CIC-HFA) is currently in development for the treatment of AR. The objective of this study was to determine the efficacy, safety, and tolerability of CIC-HFA 80 or 160 μ g once daily compared with placebo in subjects 12 years and older with SAR.

METHODS

Subjects

Subjects 12 years and older with a history of SAR to mountain cedar pollen for a minimum of 2 years immediately preceding the study screening visit were eligible. The SAR was to have been of sufficient severity to have required treatment (either continuous or intermittent) and, in the investigator's judgment, was expected to require treatment throughout the entire study period. Subjects must have demonstrated sensitivity to mountain cedar pollen through a stan-

Affiliations: * Sylvana Research Associates, San Antonio, Texas; † Biogenics Research Institute, San Antonio, Texas; ‡ Kerrville Research Associates, Kerrville, Texas; § Sunovion Pharmaceuticals Inc., Marlborough, Massachusetts.

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dard skin prick test. Subjects were excluded if they had a history of nasal abnormalities, including nasal polyps, clinically significant respiratory tract malformations, recent nasal biopsy, nasal trauma, nasal ulcers or perforations, nasal surgery, atrophic rhinitis, or rhinitis medicamentosa (all within 60 days before screening). Subjects with a known hypersensitivity to any corticosteroid or any of the excipients in the formulation of ciclesonide or with a history of a respiratory tract infection or disorder within 14 days preceding the screening were also excluded. Subjects who had a minimum cumulative subject-assessed reflective total nasal symptom score (rTNSS) of 47 (of 84) and a minimum cumulative subject-assessed reflective score for runny nose or nasal congestion of ≥ 10 (of 21) during any 3 of the last 4 days of the single-blind placebo run-in period were randomized to receive medication. This study was approved by the Quorum Review Institutional Review Board (Seattle, Washington) and was conducted in accordance with the principles of the most current Declaration of Helsinki.¹⁰ Written informed consent was obtained from subjects before study participation.

Study Design and Treatment

This was a phase 3, randomized, placebo-controlled, double-blind, parallel-group, multicenter study. It consisted of a 3- to 30-day screening period; a mean (SD) 7 (1)-day single-blind placebo run-in period; a mean (SD) 14 (2)-day treatment period, with an interim visit a mean (SD) of 7 (1) days after randomization; and a mean (SD) 7 (2)-day follow-up period. Subjects were randomized in a ratio of 1:1:1 to receive CIC-HFA 80 μg (1 actuation per nostril, 40 μg per actuation); CIC-HFA 160 μg (1 actuation per nostril, 80 μg per actuation); or placebo once daily in the morning for 2 weeks. Randomization was performed within each study site. Subjects were blinded to the study medication according to the randomization schedule, which was prepared by PPD Inc (Wilmington, North Carolina), the clinical research organization conducting the study, using the SAS PROC PLAN procedure (SAS Institute Inc, Cary, North Carolina). The treatment assignment procedure used a block size sufficient to maintain blinding and to balance the enrollment across treatment groups. We assigned the lowest randomization number to the first subject enrolled and proceeded in increasing sequential order within a block as subjects were qualified for the study.

Pollen Counts

Mountain cedar pollen counts were recorded daily by each study site throughout the study. Pollen counts were documented beginning the day of the site initiation and ending 2 weeks after the last subject's end-of-study visit. All pollen counts were obtained from within 50 miles of the study site. The single-blind placebo run-in period was scheduled for all the subjects when mountain cedar pollen counts in the vicinity of each study site were elevated to 50 grains/ m^3 or higher for ≥ 3 consecutive days.

Efficacy Assessments

The primary end point was change from baseline in subject-reported morning and evening rTNSSs averaged for the 2-week treatment period. Subject-reported diaries were used to record rTNSSs evaluating symptom severity during the 12 hours before the recording of the score. The rTNSS was calculated as a sum of 4 individual nasal symptoms: nasal congestion, runny nose, sneezing, and nasal itching, each rated on a scale from 0 (no signs/symptoms evident) to 3 (signs/symptoms that were hard to tolerate and interfered with daily activities).

Key secondary end points were change from baseline in subject-reported morning and evening instantaneous TNSSs (iTNSSs) averaged for the 2-week treatment period and change from baseline in subject-reported morning and evening reflective total ocular symptom scores (rTOSSs) averaged for the 2-week treatment period in subjects with a baseline rTOSS of ≥ 5.0 . Subject-reported diaries were used to record iTNSSs evaluating symptom severity during the past 10 minutes and were calculated as a sum of 4 individual nasal symptoms: nasal congestion, runny nose, sneezing, and nasal itching, each rated on a scale from 0 (no signs/symptoms evident) to 3 (signs/symptoms that were hard to tolerate and interfered with daily activities). Subject-reported diaries were also used to record rTOSSs evaluating symptom severity during the 12 hours before the recording of the score and was calculated as the sum of the 3 ocular symptoms: itchy eyes, tearing eyes, and redness of eyes, each individual rated on a scale from 0 (no signs/symptoms evident) to 3 (signs/symptoms that were hard to tolerate and interfered with daily activities). Another secondary end point included change from baseline in subject-reported morning and evening instantaneous TOSSs (iTOSSs), recorded in a diary, averaged for the 2-week treatment period in subjects with a baseline iTOSS of ≥ 5.0 . Subjects used diaries to record iTOSSs, evaluating symptom severity during the 10 minutes before the recording of the score and calculated using the same individual ocular symptoms and rating scale as used for the calculation of rTOSSs. Additional secondary end points were change from baseline in subject-reported individual morning and evening reflective and instantaneous nasal symptom scores of nasal congestion, runny nose, sneezing, and nasal itching (recorded in a diary) averaged for the 2-week treatment period and change from baseline in subject-reported individual morning and evening reflective and instantaneous ocular symptom scores of itchy eyes, tearing eyes, and redness of eyes (recorded in a diary) averaged for the 2-week treatment period. The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) was self-administered by subjects at baseline (before randomization) and at the end of the double-blind study medication period. Change in overall RQLQ scores was recorded for the intention-to-treat (ITT) population and was calculated in subjects with a baseline RQLQ score of ≥ 3.0 . Subjects were asked to recall their experiences during the previous week for the individual domains of the RQLQ: activities, sleep, non-nasal/

non-ocular symptoms, practical problems, nasal symptoms, and eye symptoms recorded on a scale from 0 (not troubled) to 6 (extremely troubled) and the emotional domain recorded on a scale from 0 (none of the time) to 6 (all of the time). Change from baseline in overall RQLQ scores was calculated as the average of the individual domain scores of the RQLQ for the 2-week treatment period.

Safety Assessments

Treatment-emergent adverse events (TEAEs), including local AEs of the nasal cavity, were recorded throughout the study. Serious AEs and discontinuations due to AEs were also recorded. All the TEAEs were coded for analysis using the Medical Dictionary for Regulatory Activities version 11.1.

Statistical Methods

The ITT population was used for analysis of all efficacy and safety end points. The ITT population consisted of all randomized subjects who received ≥ 1 dose of study medication. The primary end point (rTNSS) was analyzed using the ITT population, and treatment groups were compared using analysis of covariance (ANCOVA), with treatment and study

center as fixed effects and baseline as the covariate. Comparison of each active treatment group with placebo was performed at a significance level of $\alpha = .025$ (2-sided).

Each of the key secondary end points was analyzed using an ANCOVA model, with treatment and study center as fixed effects and baseline as the covariate. To address multiple comparisons, the primary end point and the first and second key secondary end points were analyzed using the Dmitrienko gatekeeping method based on the Bonferroni test,¹¹ a closed testing procedure used to control the error rate for multiple comparisons.

For iTNSS, if the comparison of the 160- μg treatment group with the placebo group for the primary end point (rTNSS) was statistically significant at the $\alpha = .025$ level, then the comparison of the 160- μg treatment group with the placebo group for iTNSS was performed at the $\alpha = .025$ significance level, with the P value for the first key secondary end point being the larger of the 2 comparisons. If the primary end point comparison was not statistically significant, then the comparison of the first key secondary end point was not performed for the 160- μg treatment

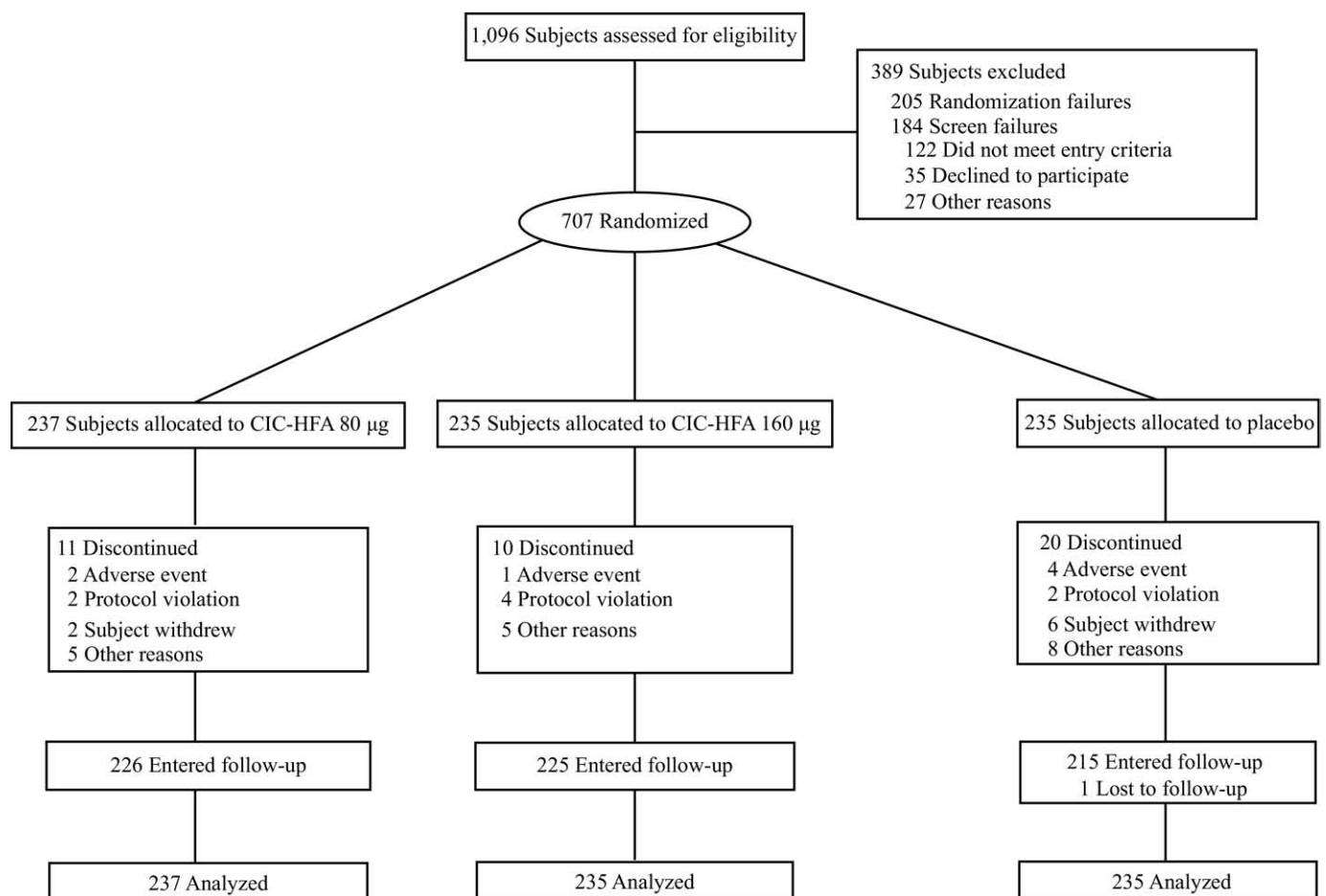


Figure 1. Study flow and disposition of study subjects. CIC-HFA indicates ciclesonide hydrofluoroalkane nasal aerosol.

group. An analogous algorithm was followed for the 80- μg treatment group comparisons. The significance or lack of significance for 1 dose group did not affect the testing of the other dose group.

Analysis of the secondary end points (iTOSS and rTOSS) was performed in an identical manner as for the first key secondary end point using treatment and study center as fixed effects and baseline as a covariate. Other secondary end points, including change in reflective and instantaneous individual nasal symptoms, change in reflective and instantaneous individual ocular symptoms, change in overall RQLQ scores, and change in individual domain scores of the RQLQ in subjects with a baseline RQLQ score of ≥ 3.0 were analyzed using the ANCOVA model, with baseline as a covariate. No adjustments for multiple comparisons were used for any of the other statistical analyses except for the primary and key secondary end points. This study was not designed or powered for a comparison of the 80- μg dose with the 160- μg dose of CIC-HFA. No statistical comparisons were performed between the 80- and 160- μg treatment groups.

RESULTS

Subject Disposition and Baseline Characteristics

A total of 1,096 subjects were screened for study participation, and 912 were enrolled; 184 subjects were screen failures and did not meet 1 or more of the entry criteria (Fig 1). Of the 912 subjects enrolled, 707 were randomized to receive study medication and were included in the ITT population. The remaining 205 subjects did not qualify for randomization and were discontinued from study participation. Of the 707 subjects in the ITT population, 665 (94.1%) completed the study and 42 (5.9%) discontinued before study completion. The most common reasons for discontinuation were protocol violations or AEs.

The mean mountain cedar pollen counts for all study sites combined and for each of the individual sites were elevated for ≥ 3 consecutive days at levels of 50 grains/ m^3 or greater, as required by the protocol, at the start of the single-blind placebo run-in period. For all sites combined and in the vicinity (ie, within a 50-mile radius) of each individual study site, pollen counts remained elevated (mean raw pollen counts, 1,826–4,313 grains/ m^3) for the duration of the double-blind treatment period.

The demographic and baseline characteristics were similar across treatment groups. The mean subject age was 42 years (range, 13–72 years). Most subjects were white (93.1%) and female (66.0%). Mean baseline rTNSSs were similar across the 3 treatment groups (range, 9.10–9.46), indicating a moderately severe SAR subject population (Table 1).

Efficacy Assessments

The CIC-HFA 80 or 160 μg treatment groups demonstrated 15.1% and 16.0% reductions in rTNSSs compared with a 3.7% reduction for the placebo group and 14.3% and 15.4% reductions in iTNSSs compared with a 3.9% reduction for the placebo group from baseline (Table 2). The daily improvement observed in rTNSSs was consistent across the 2-week double-blind treatment period (Fig 2).

The CIC-HFA 80 or 160 μg treatment groups also demonstrated 15.7% and 15.0% reductions in rTOSSs compared with a 6.8% reduction for the placebo group from baseline. The daily improvement observed in rTOSSs was consistent across the 2-week double-blind treatment period (Fig 3). The CIC-HFA treatment groups also demonstrated improvements in iTOSSs in subjects with baseline iTOSSs ≥ 5.0 averaged for the 2-week treatment period (Table 3).

The CIC-HFA 80 and 160 μg treatment groups demonstrated improvements in individual reflective and instantaneous

Table 1. Subject Demographics and Baseline Characteristics (ITT Population)

	CIC-HFA 80 μg (n = 237)	CIC-HFA 160 μg (n = 235)	Placebo (n = 235)
Age, mean (SD), y	41 (13)	42 (13)	42 (14)
Sex, No. (%)			
Male	78 (32.9)	80 (34.0)	80 (34.0)
Female	159 (67.1)	155 (66.0)	155 (66.0)
Race, No. (%)			
White	218 (92.0)	220 (93.6)	220 (93.6)
Black	13 (5.5)	8 (3.4)	14 (6.0)
Asian	4 (1.7)	3 (1.3)	1 (0.4)
Other	2 (0.8)	4 (1.7)	0
Skin prick allergy test, No. (%) positive	237 (100)	235 (100)	235 (100)
Baseline rTNSS, mean (SD)	9.32 (1.77)	9.46 (1.67)	9.10 (1.80)
Baseline iTNSS, mean (SD)	8.68 (2.05)	8.94 (2.00)	8.61 (2.06)
Baseline rTOSS, mean (SD) ^a	6.89 (1.19)	7.01 (1.11)	6.95 (1.23)

Abbreviations: CIC-HFA, ciclesonide hydrofluoroalkane nasal aerosol; iTNSS, instantaneous total nasal symptom score; ITT, intention-to-treat; rTNSS, reflective total nasal symptom score; rTOSS, reflective total ocular symptom score.

^a Subjects with a baseline rTOSS of ≥ 5.0 .

Table 2. Changes in Reflective and Instantaneous Nasal Symptom Scores Averaged for the 2-Week Treatment Period (ITT Population)

	CIC-HFA 80 μ g (n = 237)	CIC-HFA 160 μ g (n = 235)	Placebo (n = 235)
rTNSS			
LS mean change from baseline	−1.45	−1.59	−0.51
Difference (95% CI) vs placebo	0.94 (0.57–1.32)	1.08 (0.70–1.45)	NA
P value	<.0001	<.0001	NA
Individual reflective nasal symptom scores			
Congestion			
LS mean change from baseline	−0.35	−0.36	−0.11
Difference (95% CI) vs placebo	0.24 (0.15–0.33)	0.25 (0.15–0.34)	NA
P value ^a	<.0001	<.0001	NA
Runny nose			
LS mean change from baseline	−0.32	−0.36	−0.11
Difference (95% CI) vs placebo	0.21 (0.10–0.31)	0.25 (0.14–0.35)	NA
P value ^a	.0001	<.0001	NA
Nasal itching			
LS mean change from baseline	−0.38	−0.43	−0.16
Difference (95% CI) vs placebo	0.22 (0.11–0.32)	0.27 (0.16–0.38)	NA
P value ^a	<.0001	<.0001	NA
Sneezing			
LS mean change from baseline	−0.40	−0.44	−0.12
Difference (95% CI) vs placebo	0.28 (0.17–0.39)	0.32 (0.21–0.43)	NA
P value ^a	<.0001	<.0001	NA
iTNSS			
LS mean change from baseline	−1.34	−1.47	−0.47
Difference (95% CI) vs placebo	0.87 (0.50–1.25)	1.0 (0.63–1.37)	NA
P value	<.0001	<.0001	NA
Individual instantaneous nasal symptom scores			
Congestion			
LS mean change from baseline	−0.32	−0.33	−0.10
Difference (95% CI) vs placebo	0.22 (0.13–0.31)	0.23 (0.14–0.32)	NA
P value ^a	<.0001	<.0001	NA
Runny nose			
LS mean change from baseline	−0.30	−0.33	−0.10
Difference (95% CI) vs placebo	0.20 (0.10–0.31)	0.23 (0.12–0.33)	NA
P value ^a	.0001	<.0001	NA
Nasal itching			
LS mean change from baseline	−0.37	−0.43	−0.15
Difference (95% CI) vs placebo	0.22 (0.11–0.33)	0.28 (0.17–0.39)	NA
P value ^a	<.0001	<.0001	NA
Sneezing			
LS mean change from baseline	−0.35	−0.38	−0.12
Difference (95% CI) vs placebo	0.23 (0.12–0.34)	0.27 (0.16–0.37)	NA
P value ^a	<.0001	<.0001	NA

Abbreviations: CI, confidence interval; CIC-HFA, ciclesonide hydrofluoroalkane nasal aerosol; iTNSS, instantaneous total nasal symptom score; ITT, intention-to-treat; LS, least squares; NA, not applicable; rTNSS, reflective total nasal symptom score.

^a P values for individual nasal symptom scores were not adjusted for multiplicity.

neous nasal symptom scores of runny nose, itchy nose, sneezing, and congestion (Table 2) and in individual reflective and instantaneous ocular symptom scores of itchy eyes, red eyes, and tearing eyes compared with the placebo group in subjects with baseline rTOSSs and iTOSSs ≥ 5.0 , respectively (Table 3).

The CIC-HFA 80 and 160 μ g treatment groups also demonstrated improvements in overall RQLQ scores and in individual domain scores of the RQLQ in subjects with a baseline RQLQ ≥ 3.0 (Table 4).

Safety Assessments

The overall incidence of TEAEs was low (range, 18.7%–24.7% across groups) and comparable between the ciclesonide treatment and placebo groups (Table 5). The TEAEs were judged to be mild in intensity. A total of 153 subjects (21.6%) reported 215 TEAEs. Events of the nasal cavity were the most frequently reported TEAEs, and epistaxis, nasal discomfort, and nasal septum disorder (nonulcerative lesions of the nonseptal mucosa) were the most frequently reported individual AEs.

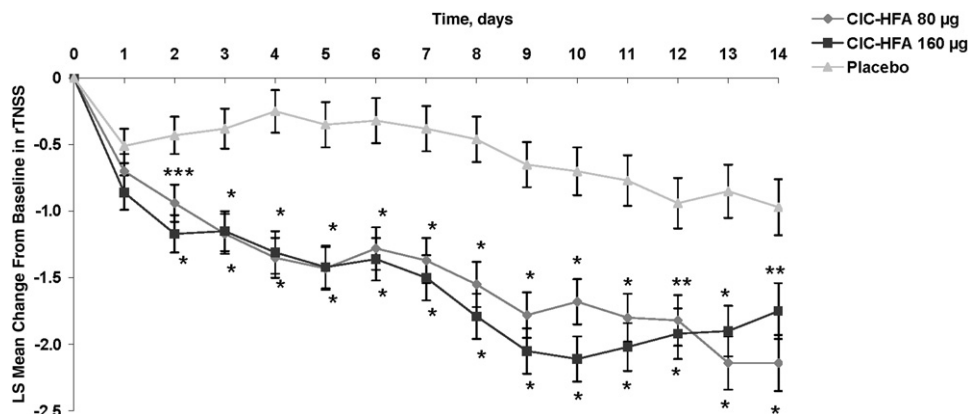


Figure 2. Daily change in reflective total nasal symptom scores (rTNSSs) for the 2-week double-blind treatment period for the intention-to-treat population. Error bars represent standard errors of the least squares (LS) means. CIC-HFA indicates ciclesonide hydrofluoroalkane nasal aerosol. * $P < .001$ vs placebo, ** $P < .01$ vs placebo, *** $P < .05$ vs placebo.

All cases of epistaxis across all the treatment groups were mild or moderate in severity, were assessed as related to the use of study medication, and resolved without intervention. Erosions of the septal mucosa were reported in 3 subjects (1.3%) receiving CIC-HFA 80 μg , 2 (0.9%) receiving CIC-HFA 160 μg , and 1 (0.4%) receiving placebo. No nasal septal perforations were reported in this study. One subject in the CIC-HFA 160 μg group experienced 1 serious TEAE of acute gastroesophageal reflux, which was assessed as not likely to be related to study medication. No dose effect or signal of safety concern was apparent in subject discontinuations due to AEs. Two subjects (0.8%) with bronchitis and papular rash in the CIC-HFA 80 μg group, 1 (0.4%) with insomnia in the CIC-HFA 160 μg group, and 4 (1.7%) with influenza, otitis media, sinusitis, conjunctivitis, upper respiratory tract infection, and viral upper respiratory tract infection in the placebo group discontinued from the study. Dis-

continuation due to the development of papular rash in the CIC-HFA 80 μg group and insomnia in the CIC-HFA 160 μg group was assessed as possibly related to study medication.

DISCUSSION

This is the first evaluation of the efficacy and safety of CIC-HFA 80 or 160 μg in a phase 3 study in subjects 12 years and older with SAR. In this study, once-daily CIC-HFA 80 or 160 μg reduced the nasal and ocular symptoms of SAR compared with placebo in subjects 12 years and older.

Both CIC-HFA doses (80 and 160 μg) demonstrated statistically significant improvements in rTNSSs and iTNSSs and improvements in the individual reflective and instantaneous nasal symptoms of runny nose, itchy nose, sneezing, and congestion. Improvements in rTOSSs and iTOSSs in subjects with a baseline rTOSS of ≥ 5.0 and a baseline iTOSS of ≥ 5.0 and in the individual reflective and instantaneous

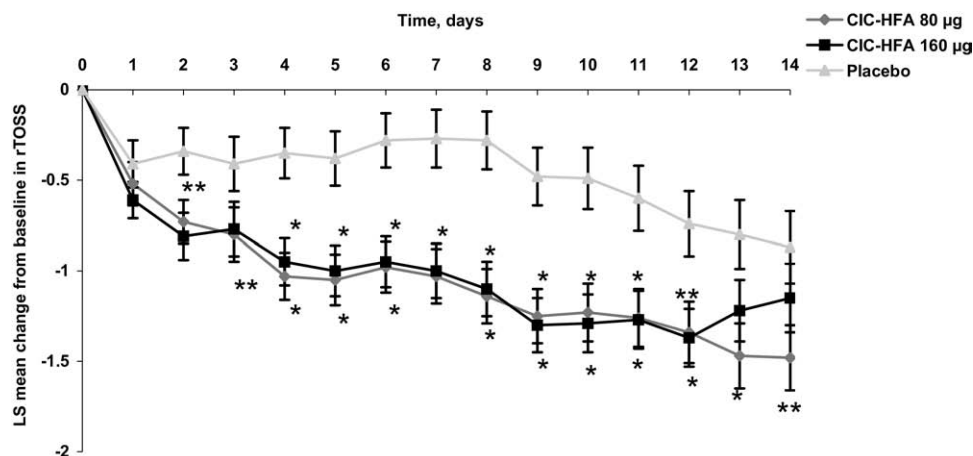


Figure 3. Daily change in reflective total ocular symptom scores (rTOSSs) for the 2-week double-blind treatment period for the intention-to-treat population. Error bars represent standard errors of the least squares (LS) means. CIC-HFA indicates ciclesonide hydrofluoroalkane nasal aerosol. * $P < .001$ vs placebo, ** $P < .01$ vs placebo, *** $P < .05$ vs placebo.

Table 3. Changes in Reflective and Instantaneous Ocular Symptom Scores in Subjects With Baseline rTOSSs and iTOSSs ≥ 5.0 Averaged for the 2-Week Treatment Period

	CIC-HFA 80 μg (n = 164)	CIC-HFA 160 μg (n = 160)	Placebo (n = 148)
rTOSS			
LS mean change from baseline	−1.06	−1.05	−0.44
Difference (95% CI) vs placebo	0.61 (0.28–0.95)	0.60 (0.27–0.94)	NA
P value	.0007	.0009	NA
Individual reflective ocular symptom scores			
Redness of eyes			
LS mean change from baseline	−0.33	−0.32	−0.14
Difference (95% CI) vs placebo	0.19 (0.06–0.31)	0.18 (0.06–0.30)	NA
P value ^a	.0030	.0044	NA
Tearing eyes			
LS mean change from baseline	−0.38	−0.38	−0.16
Difference (95% CI) vs placebo	0.22 (0.10–0.34)	0.23 (0.11–0.34)	NA
P value ^a	.0003	.0002	NA
Itching eyes			
LS mean change from baseline	−0.35	−0.34	−0.14
Difference (95% CI) vs placebo	0.21 (0.09–0.33)	0.20 (0.08–0.31)	NA
P value ^a	.0004	.0009	NA
	CIC-HFA 80 μg (n = 149)	CIC-HFA 160 μg (n = 150)	Placebo (n = 134)
iTOSS			
LS mean change from baseline	−1.0	−1.07	−0.40
Difference (95% CI) vs placebo	0.61 (0.25–0.96)	0.68 (0.33–1.03)	NA
P value ^a	.0008	.0002	NA
Individual instantaneous ocular symptom scores			
Redness of eyes			
LS mean change from baseline	−0.34	−0.35	−0.12
Difference (95% CI) vs placebo	0.22 (0.09–0.35)	0.23 (0.10–0.36)	NA
P value ^a	.0008	.0004	NA
Tearing eyes			
LS mean change from baseline	−0.33	−0.38	−0.12
Difference (95% CI) vs placebo	0.22 (0.09–0.34)	0.27 (0.14–0.39)	NA
P value ^a	.0007	<.0001	NA
Itching eyes			
LS mean change from baseline	−0.34	−0.34	−0.15
Difference (95% CI) vs placebo	0.19 (0.07–0.31)	0.19 (0.07–0.31)	NA
P value ^a	.0026	.0026	NA

Abbreviations: CI, confidence interval; CIC-HFA, ciclesonide hydrofluoroalkane nasal aerosol; iTOSS, instantaneous total ocular symptom score; LS, least squares; NA, not applicable; rTOSS, reflective total ocular symptom score.

^a P values for iTOSS and individual reflective and instantaneous symptom scores were not adjusted for multiplicity.

ocular symptoms of redness of eyes, itchy eyes, and tearing eyes were also observed. In addition to significant improvements in ocular and nasal symptoms of SAR following treatment with CIC-HFA, improvements in the overall RQLQ score and in individual domain scores of the RQLQ in subjects with a baseline RQLQ score of ≥ 3.0 were also observed in both active treatment groups. The magnitude of improvement in nasal and ocular symptoms after treatment with CIC-HFA 80 or 160 μg compared with placebo observed in this study is similar to that reported for other intranasal corticosteroids at comparable doses for the treatment of SAR.^{12–19} Compared with placebo, once-daily dosing of CIC-HFA 80 or 160 μg was well tolerated in subjects with SAR,

and the frequency of TEAEs was comparable with that in the placebo group.

The reported incidence of nasal erosions in this study is of concern. However, there was no evidence of dose effect because the incidence of nasal erosions between the CIC-HFA 80 μg (1.3%) and 160 μg (0.9%), treatment groups was similar. In addition, these erosions were assessed as mild in intensity and did not lead to discontinuation from the study.

In a previously reported randomized, open-label, single-dose, 3-period crossover pharmacokinetic study²⁰ of 30 healthy volunteers, systemic exposure of CIC-HFA was evaluated and compared with that of the hypotonic aqueous nasal spray of ciclesonide and orally inhaled CIC-HFA metered-dose inhaler.

Table 4. Change in RQLQ in Subjects With Baseline RQLQ Scores ≥ 3.0 Averaged for the 2-week Treatment Period

	CIC-HFA 80 μg (n = 187)	CIC-HFA 160 μg (n = 183)	Placebo (n = 183)
Overall RQLQ			
LS mean change from baseline	-1.05	-1.07	-0.42
Difference (95% CI) vs placebo	0.62 (0.36–0.89)	0.64 (0.37–0.91)	NA
P value ^a	<.0001	<.0001	NA
Individual RQLQ domains			
Activities			
LS mean change from baseline	-1.00	-0.96	-0.28
Difference (95% CI) vs placebo	0.73 (0.44–1.01)	0.68 (0.40–0.97)	NA
P value ^a	<.0001	<.0001	NA
Sleep			
LS mean change from baseline	-1.01	-1.12	-0.41
Difference (95% CI) vs placebo	0.59 (0.29–0.90)	0.71 (0.39–1.02)	NA
P value ^a	.0002	<.0001	NA
Non-nasal/non-ocular symptoms			
LS mean change from baseline	-1.01	-0.91	-0.39
Difference (95% CI) vs placebo	0.63 (0.34–0.91)	0.53 (0.24–.82)	NA
P value ^a	<.0001	.0003	NA
Practical problems			
LS mean change from baseline	-1.16	-1.26	-0.54
Difference (95% CI) vs placebo	0.62 (0.31–0.92)	0.72 (0.40–1.03)	NA
P value ^a	<.0001	<.0001	NA
Nasal symptoms			
LS mean change from baseline	-1.15	-1.24	-0.46
Difference (95% CI) vs placebo	0.69 (0.40–0.98)	0.77 (0.48–1.07)	NA
P value ^a	<.0001	<.0001	NA
Eye symptoms			
LS mean change from baseline	-0.94	-0.99	-0.52
Difference (95% CI) vs placebo	0.43 (0.12–0.74)	0.48 (0.17–0.79)	NA
P value ^a	.0067	.0027	NA
Emotional			
LS mean change from baseline	-1.04	-0.95	-0.43
Difference (95% CI) vs placebo	0.61 (0.31–0.91)	0.52 (0.22–0.83)	NA
P value ^a	<.0001	.0007	NA

Abbreviations: CI, confidence interval; CIC-HFA, ciclesonide hydrofluoroalkane nasal aerosol; LS, least squares; NA, not applicable; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire.

^a P values were not adjusted for multiplicity.

In that study,²⁰ the systemic exposure of desisobutryl-ciclesonide after administration of a single dose of CIC-HFA 300 μg (59.1 ng/L), was found to be low and intermediate between that of orally inhaled CIC-HFA MDI 320 μg (586.2 ng/L), and intranasally administered ciclesonide aqueous nasal spray, 300 μg (15.2 ng/L). In another randomized, double-blind, parallel-group, placebo-controlled, dose-finding study²¹ of CIC-HFA in 513 subjects with SAR, the CIC-HFA 75- and 150- μg once-daily doses demonstrated effectiveness in the relief of nasal symptoms of SAR, whereas the 300- μg dose did not demonstrate any additional benefit in relief of nasal symptoms compared with the 2 lower doses of 75 and 150 μg .

In a randomized, double-blind, parallel-group, placebo-controlled study⁷ of 327 subjects with SAR, ciclesonide aqueous nasal spray, 200 μg once daily, was effective in reducing the nasal symptoms of SAR. Comparable results in the relief of nasal symptoms of SAR were observed studying the CIC-

HFA 80- and 160- μg doses in this study. The incidence of epistaxis observed in this study with CIC-HFA 80 μg (3.4%) and 160 μg (2.1%), was low and comparable with that observed with the ciclesonide aqueous nasal spray 200- μg (4.3%) formulation in a SAR study.⁷

Future studies comparing the nasal aerosol formulation of ciclesonide investigated in this study with a nasal aerosol formulation of another corticosteroid are required. These studies will be useful in comparing and distinguishing the efficacy, safety, and tolerability of the nasal aerosol formulations of corticosteroids with currently available aqueous corticosteroid formulations for the treatment of AR.

In conclusion, treatment with CIC-HFA 80 or 160 μg was effective in reducing the nasal and ocular symptoms of SAR compared with placebo in subjects 12 years and older in this study. Both doses of CIC-HFA were well tolerated.

Table 5. Treatment Emergent Adverse Events Reported by $\geq 2\%$ of Subjects in Any Treatment Group (ITT Population)

	Subjects, No. (%)		
	CIC-HFA 80 μ g (n = 237)	CIC-HFA 160 μ g (n = 235)	Placebo (n = 235)
Overall TEAEs	51 (21.5)	44 (18.7)	58 (24.7)
Epistaxis	8 (3.4)	5 (2.1)	10 (4.3)
Nasal discomfort	5 (2.1)	5 (2.1)	7 (3.0)
Nasal septum disorder ^a	5 (2.1)	1 (0.4)	3 (1.3)

Abbreviations: CIC-HFA, ciclesonide hydrofluoroalkane nasal aerosol; ITT, intention-to-treat; TEAE, treatment-emergent adverse event.

^a All 9 events of nasal septum disorder were reported as nasal irritations or abrasions.

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Requests for reprints should be sent to:

Paul H. Ratner, MD

Sylvana Research Associates

7711 Louis Pasteur Dr

Ste 406

San Antonio, TX 78229

E-mail: pratner@sylvanaresearch.com