



Efficacy and safety of twice-daily and once-daily olopatadine-mometasone combination nasal spray for seasonal allergic rhinitis



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ARTICLE INFO

Article history:

Received for publication June 14, 2019.

Received in revised form November 1, 2019.

Accepted for publication November 6, 2019.

ABSTRACT

Background: GSP301 is an investigational fixed-dose combination nasal spray of olopatadine hydrochloride (antihistamine) and mometasone furoate (corticosteroid).

Objective: To evaluate efficacy and safety of GSP301 in patients with seasonal AR (SAR).

Methods: In this phase 2, double-blind, parallel-group study, patients (≥ 12 years of age) with SAR were equally randomized to twice-daily GSP301 (olopatadine 665 μg and mometasone 25 μg), once-daily GSP301 (olopatadine 665 μg and mometasone 50 μg), twice-daily or once-daily olopatadine monotherapy (665 μg), mometasone monotherapy (twice-daily 25 μg or once-daily 50 μg), or placebo for 14 days. The primary endpoint—mean change from baseline in morning and evening reflective Total Nasal Symptom Score (rTNSS)—was analyzed using analysis of covariance (ANCOVA; $P < .05$ = statistically significant). Average morning and evening 12-hour instantaneous TNSS (iTNSS), ocular symptoms, individual symptoms, onset of action, quality of life, and adverse events (AEs) were also assessed.

Results: A total of 1111 patients were randomized. Twice-daily GSP301 provided statistically significant and clinically meaningful rTNSS improvements vs placebo ($P < .001$), twice-daily olopatadine ($P = .049$), and mometasone ($P = .004$). Similar significant improvements in iTNSS were observed with twice-daily GSP301 vs placebo ($P < .001$) and twice-daily mometasone ($P = .007$); improvements were not significant vs olopatadine ($P = .058$). Once-daily GSP301 provided significant rTNSS and iTNSS improvements vs placebo and once-daily olopatadine ($P < .01$, all) but improvements were not significant vs mometasone. Treatment-emergent AEs rates were 10.8%, 9.5%, and 8.2%, with twice-daily GSP301, once-daily GSP301, and placebo, respectively.

Conclusion: Twice-daily GSP301 treatment was efficacious and well tolerated, providing statistically significant and clinically meaningful improvements in rTNSS (primary endpoint) vs placebo and both monotherapies.

Trial Registration: [Clinicaltrials.gov](https://clinicaltrials.gov) Identifier NCT02318303

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Introduction

Allergic rhinitis (AR) is a chronic disease caused by allergen-induced nasal inflammation that can occur within minutes after exposure.¹ An estimated 19.9 million adults² and 5.6 million children³ in the United States suffer from AR. In addition to the typical

nasal symptoms of congestion, rhinorrhea, itching, and sneezing,⁴ many patients have comorbidities such as asthma, obstructive sleep apnea, and sinusitis,^{5,6} all of which can be exacerbated by inadequate symptom control.⁶ AR also can negatively impact quality of life through depression, disturbed sleep, and impaired school or work productivity.^{7–9} Thus, it is not surprising that total annual US medical expenditures related to AR were estimated at \$11.2 billion (USD) in 2005, almost twice the costs estimated in 2000 (\$6.1 billion USD).¹⁰

The pathogenesis of AR involves both early- and late-stage immunoglobulin E-mediated responses to allergens, wherein numerous inflammatory cells are activated.¹¹ As such, effective AR

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Disclosures: CA and DM received compensation from Glenmark Specialty SA as site principal investigators on this study. YS and SKT are employees of Glenmark Pharmaceuticals Inc.

Funding Sources: Glenmark Specialty SA.

<https://doi.org/10.1016/j.anai.2019.11.007>

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symptom relief often requires multiple agents targeting different inflammatory cells and mediators. Indeed, patients with AR often experience inadequate symptom control from a monotherapy,^{6,9} with nearly half of patients on a prescription allergy treatment increasing the number of prescription treatments to 2 or more therapies.⁷ Combination nasal spray treatment with an antihistamine and a corticosteroid (azelastine hydrochloride [HCl] and fluticasone propionate) is more effective in reducing AR symptoms than either monotherapy agent alone.^{12,13}

GSP301 is an investigational fixed-dose combination (FDC) nasal spray containing an antihistamine (olopatadine HCl) and a corticosteroid (mometasone furoate) in a single device for the treatment of seasonal AR (SAR) symptoms. Intranasal olopatadine and mometasone are both efficacious and well-tolerated monotherapies for the treatment of AR.^{14–17} The US Food and Drug Administration–approved olopatadine and mometasone monotherapies are dosed twice daily and once daily, respectively.^{18,19} To combine both drugs into 1 FDC, the optimal dose and dosing regimen needed to be determined. In this phase 2 study, the objectives were to evaluate the efficacy, safety, and tolerability of twice-daily or once-daily GSP301 treatments vs placebo and vs the 2 monotherapy components of GSP301, olopatadine and mometasone, in patients with SAR.

Methods

This study was conducted at 10 study sites in the United States in compliance with Good Clinical Practice and in accordance of the Declaration of Helsinki and International Conference on Harmonization guidelines. The protocol received approval from Novum Independent Institutional Review Board (Pittsburgh, PA) and was carried out in accordance with applicable local regulatory requirements. All patients provided written informed consent. Assent was obtained from patients aged 12 to 18 years (inclusive), and parents/caregivers/legal guardians provided consent.

Study Design

This double-blind, double-dummy, randomized, parallel-group, placebo- and active-controlled study was conducted in adolescent

and adult patients with SAR during the winter/mountain cedar pollen season.²⁰ The study consisted of 2 outpatient periods: a single-blind placebo run-in period (7–10 days from the screening visit to the randomization visit) and the treatment period (15–17 days from the randomization visit to the final treatment visit; Fig 1). After completion of the placebo run-in, eligible patients were equally randomized to 1 of 7 sponsor-formulated treatments for 14 days (2 sprays per nostril): twice-daily GSP301 (olopatadine 665 µg and mometasone 25 µg); once-daily GSP301 (olopatadine 665 µg and mometasone 50 µg); olopatadine monotherapy (665 µg twice or once daily); mometasone monotherapy (25 µg twice daily or 50 µg once daily); or placebo (GSP301 vehicle containing the same inactive ingredients as the active treatments).

Patients

Eligible patients were 12 years of age or older, with a clinical history of SAR for at least 2 years and a positive skin prick test for mountain cedar allergen (wheal diameter 5 mm or greater than negative control). Patients were also required to have a minimum average 12-hour reflective Total Nasal Symptom Score (rTNSS) of at least 8 out of 12 and a morning congestion score of 2 or higher at the screening visit.

Key exclusion criteria included any known history or evidence of the following: nasal polyps or other clinically significant respiratory tract malformations/disorders; recent nasal biopsy, trauma or surgery; significant atopic dermatitis, significant chronic sinusitis, chronic purulent postnasal drip, or rhinitis medicamentosa; nasal structural abnormalities, including ulceration, mucosal erosion, or septal deviation that significantly interfere with nasal air flow, or any other significant nasal abnormality; or cold, upper/lower respiratory infection, otitis, or acute sinusitis (≤ 14 days before randomization visit). Additional key exclusion criteria, prohibited medications, and randomization criteria are provided in the eMethods.

Outcomes

The primary endpoint was the mean change from baseline to end of treatment in patient-reported average morning and evening

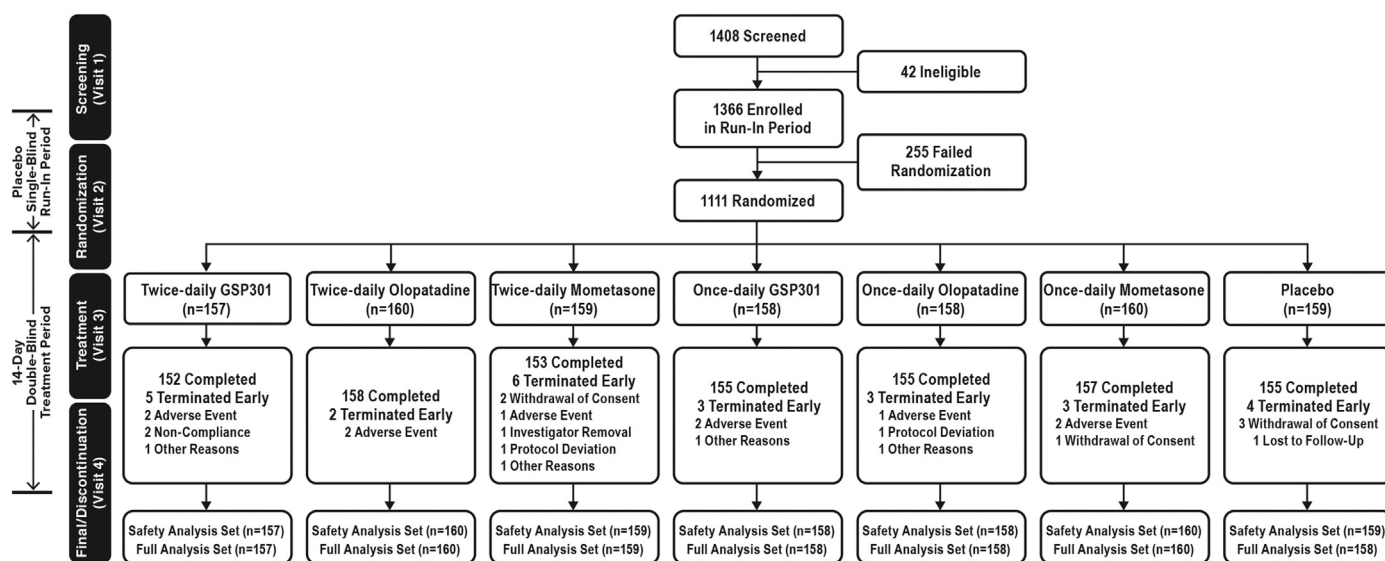


Figure 1. Patient disposition and study design. Twice-daily GSP301, olopatadine 665 µg, and mometasone 25 µg; once-daily GSP301, olopatadine 665 µg, and mometasone 50 µg; twice- or once-daily olopatadine 665 µg; twice-daily mometasone, 25 µg; once-daily mometasone, 50 µg. The screening visit (visit 1) occurred between day -10 and day -7 before the randomization visit on day 1 (visit 2). The treatment visit (visit 3) occurred on approximately day 8, and the final/discontinuation visit (visit 4) occurred on approximately day 15. No scheduled posttreatment follow-up visit was planned for this study. Patients who did not meet randomization criteria were ineligible for randomization.

12-hour rTNSS for: twice-daily GSP301 compared with placebo, twice-daily olopatadine, and twice-daily mometasone; and once-daily GSP301 compared with placebo, once-daily olopatadine, and once-daily mometasone. Secondary endpoints included: the mean changes from baseline to end treatment in average morning and evening 12-hour instantaneous TNSS (iTNSS) and average morning and evening 12-hour reflective Total Ocular Symptom Score (rTOSS), onset of action, and mean change from baseline to end of treatment in the overall Rhinoconjunctivitis Quality-of-Life Questionnaire—Standardized Activities (RQLQ(S))²¹ score for the same comparisons as the primary endpoint.

Additional efficacy assessments included mean change from baseline in: average morning and evening 12-hour reflective and instantaneous individual nasal symptoms over the treatment period; average morning and evening 12-hour iTNSS to the end of treatment; average morning and evening 12-hour reflective and instantaneous TNSS on each day of treatment; and mean change from baseline to end of treatment in Physician-assessed Nasal Symptom Score (PNSS).²² Treatment comparisons for additional assessments were the same as those for the primary endpoint. For the TNSS, a treatment difference of 0.23 units (defined as the minimal clinically important difference [MCID]²³) using direct anchor-based methodology was considered clinically meaningful.

Onset of action was defined as the first post-dose time point at which significant differences in iTNSS change from baseline between the active treatments and placebo were observed as long as the significant difference was sustained.²⁴ The mean change from baseline in iTNSS vs placebo was assessed at study clinics for a total of 4 hours after the first dose of study treatment (visit 2) at the following time points: predose (0 minutes) and at 15, 30, 45, 60, 90, 120, 150, 180, 210, and 240 minutes post-dose. Baseline was defined as the pre-dose time point at randomization (visit 2). Further efficacy assessment details are provided in the eMethods.

Safety was monitored via adverse events (AEs), physical examinations, focused ear, nose, and throat (ENT) examinations, vital signs, electrocardiograms (ECGs), and laboratory assessments. Physical examinations, ECGs, and laboratory assessments were conducted at the screening and final visits; AEs, focused ENT examinations, and vital signs were monitored throughout the study.

Statistical Analysis

Efficacy analyses were based on the full analysis set (FAS) population, defined as all randomized patients who received at least 1 dose of study drug and completed 1 or more post-baseline primary efficacy assessments. Safety assessments were based on the safety analysis set (SAS), which included all patients who received at least 1 dose of study drug. The primary efficacy endpoint was examined via analysis of covariance (ANCOVA) adjusting for treatment, study site, and baseline score as a linear, continuous covariate. Comparisons between the 2 monotherapy treatments (olopatadine and mometasone) and placebo were performed as exploratory analyses. To adjust for multiplicity, a gatekeeping strategy was used (see eMethods).

Secondary and additional efficacy outcomes were assessed using a similar ANCOVA model and gate-keeping strategy as those used for the primary outcome. Onset of action was analyzed using an ANCOVA model adjusting for study treatment group, center, and baseline iTNSS, which was a linear, continuous covariate. The RQLQ(S) was analyzed using an ANCOVA model similar to that used for analysis of the efficacy endpoints using the RQLQ(S) population (adult patients [≥ 18 years] with an RQLQ score of ≥ 3.0 at the randomization visit [visit 2]). Baseline was defined as the score at visit 2, and the MCID was defined as a treatment difference of 0.50 units on the overall score.²⁵ Descriptive statistics were used to summarize baseline demographic variables and symptom scores, and AEs by treatment group.

Table 1
Patient Demographic Characteristics (SAS) and Baseline Symptom Scores (FAS)^a

Demographics	Twice-daily GSP301 (n = 157)	Twice-daily olopatadine (n = 160)	Twice-daily mometasone (n = 159)	Once-daily GSP301 (n = 158)	Once-daily olopatadine (n = 158)	Once-daily mometasone (n = 160)	Placebo (n = 159)
Age, mean (SD), y	43.4 (14.1)	43.5 (13.9)	44.6 (13.7)	43.8 (13.6)	41.9 (12.5)	44.4 (14.3)	45.4 (15.0)
Sex, n (%)							
Male	46 (29.3)	59 (36.9)	63 (39.6)	58 (36.7)	53 (33.5)	45 (28.1)	47 (29.6)
Female	111 (70.7)	101 (63.1)	96 (60.4)	100 (63.3)	105 (66.5)	115 (71.9)	112 (70.4)
Race, n (%)							
White	129 (82.2)	132 (82.5)	126 (79.2)	132 (83.5)	131 (82.9)	127 (79.4)	133 (83.6)
Black	23 (14.6)	24 (15.0)	27 (17.0)	20 (12.7)	26 (16.5)	28 (17.5)	24 (15.1)
Asian	3 (1.9)	3 (1.9)	5 (3.1)	4 (2.5)	1 (0.6)	4 (2.5)	1 (0.6)
Other ^b	2 (1.3)	1 (0.6)	1 (0.6)	2 (1.3)	0 (0)	1 (0.6)	1 (0.6)
Ethnicity, n (%)							
Non-Hispanic or Latino	78 (49.7)	88 (55.0)	93 (58.5)	98 (62.0)	90 (57.0)	99 (61.9)	101 (63.5)
Hispanic or Latino	79 (50.3)	72 (45.0)	66 (41.5)	60 (38.0)	68 (43.0)	61 (38.1)	58 (36.5)
Baseline symptom and QoL scores, mean (SD)							
Average morning and evening rTNSS	10.4 (1.2)	10.3 (1.2)	10.5 (1.1)	10.4 (1.2)	10.3 (1.3)	10.4 (1.3)	10.3 (1.2)
Average morning and evening iTNSS	9.9 (1.7)	9.7 (1.7)	10.0 (1.4)	9.8 (1.7)	9.7 (1.7)	9.9 (1.7)	9.6 (1.7)
Average morning and evening rTOSS	7.4 (1.3)	7.3 (1.4)	7.5 (1.3)	7.2 (1.4)	7.4 (1.3)	7.4 (1.4)	7.3 (1.4)
Average morning and evening iTOSS	7.2 (1.5)	7.1 (1.5)	7.3 (1.4)	6.9 (1.5)	7.1 (1.5)	7.2 (1.5)	7.0 (1.6)
RQLQ(S) score ^c	4.7 (0.8)	4.7 (0.8)	4.7 (0.8)	4.7 (0.8)	4.6 (0.8)	4.6 (0.8)	4.7 (0.8)
PNSS	9.6 (2.0)	9.4 (2.1)	9.8 (1.9)	9.7 (2.0)	9.7 (2.1)	9.7 (2.1)	9.4 (2.1)

FAS, full analysis set; iTNSS, instantaneous Total Nasal Symptom Score; iTOSS, instantaneous Total Ocular Symptom Score; PNSS, Physician-assessed Nasal Symptoms Score; RQLQ(S), Rhinoconjunctivitis Quality-of-Life Questionnaire—Standardized Activities; rTNSS, reflective Total Nasal Symptom Score; rTOSS, reflective Total Ocular Symptom Score; SAS, safety analysis set; SD, standard deviation.

^aTwice-daily GSP301, olopatadine 665 μ g, and mometasone 25 μ g; once-daily GSP301, olopatadine 665 μ g, and mometasone 50 μ g; twice- and once-daily olopatadine, 665 μ g; twice-daily mometasone, 25 μ g; once-daily mometasone, 50 μ g.

^bIncludes American Indian or Alaska native, native Hawaiian, or other Pacific Islander.

^cRQLQ(S) population: Adult patients (≥ 18 years) with an RQLQ score of ≥ 3.0 at the randomization visit (visit 2); twice-daily GSP301 n = 128; twice-daily olopatadine n = 131; twice-daily mometasone n = 137; once-daily GSP301 n = 129; once-daily olopatadine n = 138; once-daily mometasone n = 134; placebo n = 133.

Statistical significance was set at $P < .025$ for comparisons of twice- and once-daily GSP301 vs placebo; for all other treatment comparisons, statistical significance was set at $P < .05$. Additional analysis details can be found in the [eMethods](#).

Sample Size

A sample size of 134 patients per treatment group would have a 90% power to detect a between-treatment group difference of 1.3 units with a standard deviation of 3.0 (assuming a 2-sided $\alpha = 2.5\%$) in the absolute change from baseline in average morning and evening 12-hour rTNSS over the treatment period. Therefore, a total of 1106 patients (158 per treatment group) were to be randomized, assuming a dropout rate of 15%.

Results

Patients

A total of 1111 patients were randomized, and 1085 (97.7%) completed the study, with 1110 included in the FAS and 1111 in the SAS ([Fig 1](#)). Most were female and white, with a mean age ranging from 41.5 to 45.4 years. Patients reported moderate to severe nasal and ocular symptoms at baseline. Demographic and symptom scores were comparable among the treatment groups at baseline ([Table 1](#)).

Average morning and evening rTNSS

Both twice- and once-daily GSP301 treatments demonstrated statistically significant and clinically meaningful improvements in average morning and evening 12-hour rTNSS from baseline to the end of 14-day treatment vs placebo ($P < .0001$, both; [Table 2](#)). Twice-daily GSP301 treatment resulted in significant and clinically meaningful improvements compared with twice-daily olopatadine ($P = .049$) and twice-daily mometasone ($P = .004$; [Table 2](#)). Once-daily GSP301 treatment also resulted in significant and clinically meaningful improvements vs once-daily olopatadine ($P = .002$), but

Table 2

Treatment Comparisons of Average Morning and Evening Reflective and Instantaneous TNSS Over 14 Days of Treatment (FAS)^a

Average morning and evening rTNSS				
Treatment groups (1 vs 2)	No. GSP301, comparator	LSMD	95% CI	P value
Twice-daily				
GSP301 vs placebo	157, 158	-1.17	-1.73, -0.61 ^b	<.001 ^c
GSP301 vs olopatadine	157, 160	-0.49	-0.98, 0.00	.049 ^d
GSP301 vs mometasone	157, 159	-0.71	-1.20, -0.22	.004 ^d
Once-daily				
GSP301 vs placebo	158, 158	-1.11	-1.67, -0.55 ^b	<.001 ^c
GSP301 vs olopatadine	158, 158	-0.77	-1.26, -0.28	.002 ^d
GSP301 vs mometasone	158, 160	-0.36	-0.84, 0.13	.152
Average morning and evening iTNSS				
Treatment groups (1 vs 2)	No. GSP301, comparator	LSMD	95% CI	P value
Twice-daily				
GSP301 vs placebo	157, 158	-1.11	-1.65, -0.57 ^b	<.001 ^c
GSP301 vs olopatadine	157, 160	-0.45	-0.92, 0.02	.058
GSP301 vs mometasone	157, 159	-0.65	-1.12, -0.18	.007 ^d
Once-daily				
GSP301 vs placebo	158, 158	-1.11	-1.64, -0.57 ^b	<.001 ^c
GSP301 vs olopatadine	158, 158	-0.86	-1.33, -0.40	<.001 ^d
GSP301 vs mometasone	158, 160	-0.35	-0.82, 0.12	.145

Abbreviations: CI, confidence interval; FAS, full analysis set; iTNSS, instantaneous Total Nasal Symptom Score; LSMD, least squares mean difference; No, number; rTNSS, reflective Total Nasal Symptom Score; TNSS, Total Nasal Symptom Score.

^aTwice-daily GSP301, olopatadine 665 μ g, and mometasone 25 μ g; once-daily GSP301, olopatadine 665 μ g, and mometasone 50 μ g; twice- and once-daily olopatadine, 665 μ g; twice-daily mometasone, 25 μ g; once-daily mometasone, 50 μ g.
^b97.5% CI.

^cIndicates a significant difference ($P < .025$) vs treatment group 2.

^dIndicates a significant difference ($P < .05$) vs treatment group 2.

clinically meaningful improvements compared with once-daily mometasone did not reach statistical significance ($P = .152$; [Table 2](#)).

Exploratory analyses of olopatadine and mometasone compared with placebo showed that twice-daily olopatadine provided significant and clinically meaningful improvements vs placebo (least squares mean difference [LSMD] [95% confidence interval]: -0.68 [-1.17, -0.19], $P = .007$). Once-daily olopatadine provided clinically meaningful improvement vs placebo, but this comparison did not reach statistical significance (-0.34 [-0.83, 0.15], $P = .177$). Improvement with twice-daily mometasone vs placebo was clinically meaningful but did not reach statistical significance (-0.46 [-0.95, 0.03], $P = .067$). However, once-daily mometasone provided significant and clinically meaningful improvements vs placebo (-0.75 [-1.24, -0.26], $P = .003$).

Twice- and once-daily GSP301 significantly improved rTNSS vs placebo from day 1 and on each subsequent day up to day 14 (twice-daily: $P < .01$, all; [Fig 2A](#); once-daily: $P < .01$, all; [Fig 2B](#)), suggesting sustained daily symptom improvement. Exploratory analyses showed that twice-daily olopatadine provided significant improvements compared with placebo on days 1 through 3 and 7 through 14 ($P < .05$, all; data not shown) and once-daily olopatadine on day 2 ($P < .05$; data not shown); twice-daily mometasone provided significant improvements vs placebo on days 2, 12, and 14 ($P < .05$, all; data not shown) and once-daily mometasone on days 2, 3, and 7 through 14 ($P < .05$, all; data not shown).

Average morning and evening iTNSS

Similar to the primary endpoint, twice- and once-daily GSP301 treatments demonstrated significant and clinically meaningful improvements in average morning and evening 12-hour iTNSS from baseline to the end of treatment compared with placebo ($P < .001$, both; [Table 2](#)). Twice-daily GSP301 treatment resulted in significant and clinically meaningful improvement versus twice-daily mometasone ($P = .007$), but the comparison with twice-daily olopatadine showed only clinically meaningful improvement ($P = .058$; [Table 2](#)). Treatment with once-daily GSP301 demonstrated significant and clinically meaningful improvement vs once-daily olopatadine ($P < .001$) but resulted in only clinically meaningful improvement compared with once-daily mometasone ($P = .145$; [Table 2](#)).

In the exploratory analyses of olopatadine and mometasone vs placebo, twice-daily olopatadine provided significant and clinically meaningful improvements in iTNSS vs placebo (-0.66 [-1.12, -0.19], $P = .006$). Improvement with once-daily olopatadine was clinically meaningful compared with placebo, but this difference did not reach significance (-0.24 [-0.71, 0.22], $P = .306$). Similarly, twice-daily mometasone also provided clinically meaningful improvements vs placebo, but this did not reach significance (-0.46 [-0.93, 0.01], $P = .056$). Treatment with once-daily mometasone did provide significant and clinically meaningful improvements vs placebo (-0.76 [-1.23, -0.29], $P = .002$).

Twice- and once-daily GSP301 treatments significantly improved iTNSS vs placebo from day 1 and on each following day up to day 14 (twice-daily: $P \leq .001$, all; [Figure 2C](#); once-daily: $P \leq .01$, all; [Figure 2D](#)), indicating sustained daily improvement of symptoms. Twice-daily olopatadine was significant vs placebo on days 1 through 3 and 8 through 14 ($P < .05$, both; data not shown) and once-daily olopatadine on days 1 and 2 ($P < .05$, all; data not shown). Twice-daily mometasone provided significant improvements compared with placebo on days 2, 12, and 14 ($P < .05$, all; data not shown) and once-daily mometasone on days 2 through 4 and 6 through 14 ($P < .05$, all; data not shown).

Average morning and evening individual nasal symptoms

Twice- and once-daily GSP301 significantly improved all reflective and instantaneous individual nasal symptoms vs placebo

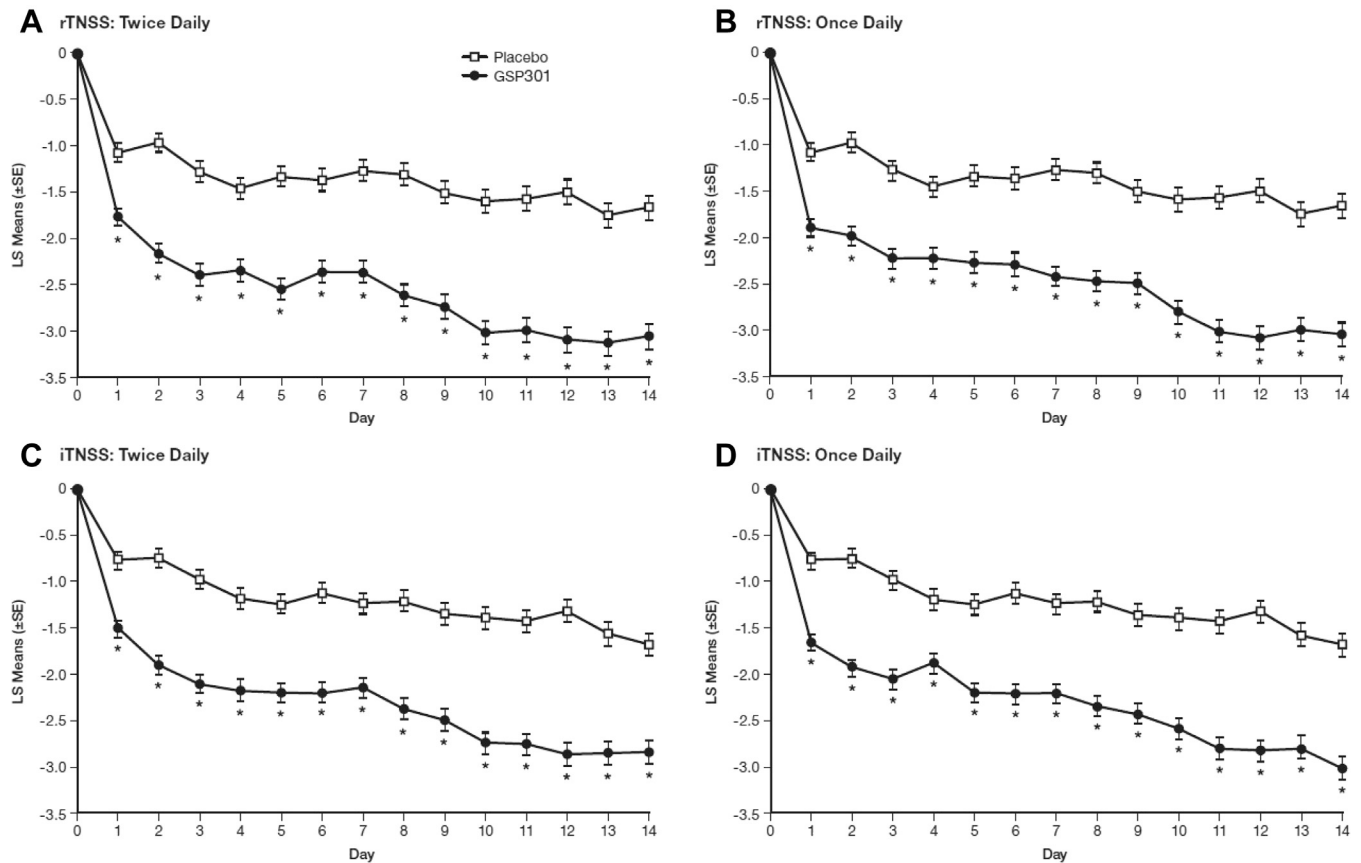


Figure 2. Treatment comparisons of average morning and evening rTNSS (A, B) and iTNSS (C, D) for twice-daily and once-daily GSP301 vs placebo over 14 days (FAS). Twice-daily GSP301, olopatadine 665 μg , and mometasone 25 μg ; once-daily GSP301, olopatadine 665 μg , and mometasone 50 μg . *Indicates a significant difference ($P < .025$) vs placebo. FAS, full analysis set; iTNSS, instantaneous Total Nasal Symptom Score; LS, least squares; rTNSS, reflective Total Nasal Symptom Score; SE, standard error.

($P < .001$, all; Table 3). Twice- and once-daily GSP301 also improved all symptoms compared with the twice- and once-daily monotherapies, but only twice-daily GSP301 vs twice-daily mometasone and once-daily GSP301 vs once-daily olopatadine reached statistical significance on all 4 reflective and instantaneous symptoms ($P < .05$, all; data not shown).

Onset of action

Compared with placebo, change from baseline in iTNSS for once-daily GSP301 treatment group was significantly different at 150 minutes after the first dose (LSMD [95% CI]: -0.64 [-1.18, -0.09], $P = .022$), and at all subsequent time points with the exception of 180 minutes (180 min: $P = .055$; 210 min: $P = .011$; 240 min: $P = .006$). The once-daily olopatadine group had a significant difference in change from baseline vs placebo in iTNSS at 180 minutes after the first dose (-0.57 [-1.13, -0.01], $P = .045$) and all subsequent time points (210 min: $P = .035$; 240 min: $P = .01$). There was no time point up to 240 minutes after the first dose that was significantly different vs placebo for the twice-daily GSP301 and twice-daily olopatadine groups, or for once- or twice-daily mometasone groups (data not shown).

Average morning and evening rTOSS

Treatment with twice-daily GSP301 provided improvements in rTOSS vs placebo that did not reach statistical significance (LSMD [97.5% CI]: -0.42 [-0.86, 0.02], $P = .033$) per the gate-keeping strategy (a priori significance of $P < .025$ required). Once-daily GSP301 treatment resulted in significant improvements vs placebo (LSMD [97.5% CI]: -0.55 [-0.99, -0.12], $P = .005$). Twice- and once-daily GSP301 provided improvements compared with twice-

and once-daily monotherapies, respectively, but these comparisons did not reach statistical significance (data not shown). For the exploratory analyses of twice- and once-daily olopatadine and mometasone vs placebo, no comparisons reached statistical significance (data not shown).

Average morning and evening iTOSS

Treatment with twice-daily GSP301 resulted in improvements compared with placebo that did not reach statistical significance (LSMD [97.5% CI]: -0.39 [-0.81, 0.03], $P = .039$; a priori significance set at $P < .025$). All further twice-daily GSP301 comparisons were not statistically significant per the gate-keeping strategy (data not shown). Once-daily GSP301 provided significant improvements in iTOSS vs placebo (LSMD [97.5% CI]: -0.55 [-0.97, -0.13], $P = .003$) and vs once-daily olopatadine (LSMD [95% CI]: -0.44 [-0.80, -0.07], $P = .020$) and once-daily mometasone (LSMD [95% CI]: -0.40 [-0.77, -0.03], $P = .032$). For the exploratory analyses of twice- and once-daily olopatadine and mometasone vs placebo, only twice-daily olopatadine versus placebo reached statistical significance (LSMD [95% CI]: -0.39 [-0.76, -0.03], $P = .036$; other data not shown).

RQLQ(S)

Twice- and once-daily GSP301 provided significant and clinically meaningful improvements in overall quality of life from baseline to end of treatment in adult patients compared with placebo (twice-daily $P < .001$; once-daily $P = .002$; Table 4). Twice- and once-daily GSP301 also improved quality of life vs twice- and once-daily monotherapies, but no comparisons reached statistical significance per the gatekeeping strategy (data not shown). Twice- and once-daily GSP301 treatment resulted in

Table 3Treatment Comparisons of Individual Reflective and Instantaneous Nasal Symptom Scores for Twice- and Once-Daily GSP301 vs Placebo Over 14 Days (FAS)^a

	Twice-daily GSP301		Once-daily GSP301	
	LSMD (97.5% CI)	P value	LSMD (97.5% CI)	P value
Reflective				
Rhinorrhea	-0.27 (-0.42, -0.12)	<.001 ^b	-0.26 (-0.40, -0.11)	<.001 ^b
Nasal congestion	-0.24 (-0.38, -0.10)	<.001 ^b	-0.22 (-0.37, -0.08)	<.001 ^b
Nasal itching	-0.27 (-0.43, -0.11)	<.001 ^b	-0.26 (-0.42, -0.10)	<.001 ^b
Sneezing	-0.39 (-0.57, -0.22)	<.001 ^b	-0.37 (-0.55, -0.20)	<.001 ^b
Instantaneous				
Rhinorrhea	-0.27 (-0.42, -0.13)	<.001 ^b	-0.27 (-0.42, -0.13)	<.001 ^b
Nasal congestion	-0.24 (-0.37, -0.10)	<.001 ^b	-0.22 (-0.36, -0.09)	<.001 ^b
Nasal itching	-0.27 (-0.42, -0.12)	<.001 ^b	-0.28 (-0.43, -0.13)	<.001 ^b
Sneezing	-0.33 (-0.50, -0.16)	<.001 ^b	-0.33 (-0.50, -0.17)	<.001 ^b

Abbreviations: CI, confidence interval; FAS, full analysis set; LSMD, least squares mean difference.

Treatment group: twice-daily GSP301 n = 157; once-daily GSP301 n = 158; placebo n = 158.

^aTwice-daily GSP301, olopatadine 665 µg, and mometasone 25 µg; once-daily GSP301, olopatadine 665 µg, and mometasone 50 µg.^bIndicates a significant difference ($P < .025$) vs placebo.

significant improvements in all 7 individual domain scores vs placebo (twice-daily: $P < .01$, all), with the exception of sleep and eye symptoms for once-daily GSP301 ($P = .045$ and $P = .031$, respectively; per $P < .025$ significance level; Table 4).

PNSS

Treatment with twice- and once-daily GSP301 resulted in significant improvements in PNSS from baseline to end of treatment compared with placebo (twice-daily $P < .001$; once-daily $P < .001$; Table 5). Twice- and once-daily GSP301 also significantly improved PNSS vs twice- and once-daily monotherapies ($P < .05$, all; data not shown), with the exception of the comparison of once-daily GSP301 vs once-daily mometasone ($P = .696$; data not shown). Twice-daily GSP301 also provided significant improvements on all

Table 4Treatment Comparisons of RQLQ(S) Overall Score and Individual Domains for Twice- and Once-Daily GSP301 vs Placebo From Baseline to Treatment End (RQLQ[S] Population^a)

GSP301 vs Placebo	No. GSP301, Placebo	LSMD	97.5% CI	P value
Twice-daily				
Overall score	128, 133	-0.60	-0.98, -0.22	<.001 ^b
Domain scores				
Activities	127, 132	-0.62	-1.02, -0.21	<.001 ^b
Sleep	127, 132	-0.54	-0.98, -0.11	.005 ^b
Non-nose/eye symptoms	126, 132	-0.47	-0.87, -0.07	.009 ^b
Practical problems	127, 132	-0.78	-1.21, -0.35	<.001 ^b
Nasal symptoms	127, 132	-0.84	-1.25, -0.43	<.001 ^b
Eye symptoms	127, 132	-0.52	-0.94, -0.10	.006 ^b
Emotional	127, 132	-0.60	-1.02, -0.18	.002 ^b
Once-daily				
Overall score	129, 133	-0.53	-0.90, -0.15	.002 ^b
Domain scores				
Activities	129, 132	-0.53	-0.93, -0.13	.003 ^b
Sleep	129, 132	-0.39	-0.82, 0.05	.045
Non-nose/eye symptoms	129, 132	-0.54	-0.94, -0.14	.002 ^b
Practical problems	129, 132	-0.67	-1.10, -0.25	<.001 ^b
Nasal symptoms	129, 132	-0.72	-1.13, -0.31	<.001 ^b
Eye symptoms	129, 132	-0.40	-0.83, 0.02	.031
Emotional	129, 132	-0.50	-0.92, -0.08	.008 ^b

Abbreviations: CI, confidence interval; LSMD, least squares mean difference; RQLQ(S), Rhinoconjunctivitis Quality of Life Questionnaire—Standardized Activities.

^aAdult patients (≥ 18 years) with an RQLQ score of ≥ 3.0 at the randomization visit (visit 2); twice-daily GSP301, olopatadine 665 µg, and mometasone 25 µg; once-daily GSP301, olopatadine 665 µg, and mometasone 50 µg.^bIndicates a significant difference ($P < .025$) vs placebo.**Table 5**PNSS Overall Score and Individual Symptoms With Twice- and Once-Daily GSP301 vs Placebo From Baseline to Treatment End (FAS^a)

GSP301 vs Placebo	No. GSP301, Placebo	LSMD	97.5% CI	P value
Twice-daily				
Overall score	157, 158	-1.48	-2.15, -0.81	<.001 ^b
Individual symptoms				
Nasal congestion	157, 158	-0.31	-0.51, -0.11	<.001 ^b
Nasal itching	157, 158	-0.30	-0.52, -0.09	.001 ^b
Rhinorrhea	157, 158	-0.38	-0.58, -0.17	<.001 ^b
Sneezing	157, 158	-0.49	-0.71, -0.27	<.001 ^b
Once-daily				
Overall score	158, 158	-1.27	-1.94, -0.60	<.001 ^b
Individual symptoms				
Nasal congestion	158, 158	-0.40	-0.60, -0.20	<.001 ^b
Nasal itching	158, 158	-0.16	-0.38, 0.05	.081
Rhinorrhea	158, 158	-0.36	-0.56, -0.16	<.001 ^b
Sneezing	158, 158	-0.35	-0.57, -0.13	<.001 ^b

Abbreviations: CI, confidence interval; FAS, full analysis set; LSMD, least squares mean difference; PNSS, physician-assessed nasal symptom score.

^aTwice-daily GSP301, olopatadine 665 µg, and mometasone 25 µg; once-daily GSP301, olopatadine 665 µg and mometasone 50 µg.^bIndicates statistical significance ($P < .025$) vs placebo.

individual symptoms vs placebo ($P \leq .001$, all; Table 5). Once-daily GSP301 significantly improved all individual symptoms compared with placebo ($P < .001$), with the exception of nasal itching ($P = .081$; Table 5).

Safety

The percentage of patients reporting a treatment-emergent AE (TEAE) for each treatment is reported in Table 6. The TEAEs reported by at least 2% of patients in any treatment group were headache and dysgeusia, with headache occurring more frequently in the once-daily GSP301 group (3.8%) and dysgeusia occurring more frequently in the twice-daily olopatadine group (3.1%; Table 6). Dysgeusia was observed only in the treatment arms containing olopatadine. Most AEs were mild or moderate in severity. One patient in the once-daily GSP301 group experienced 2 serious AEs (SAE; gastritis and gastrointestinal ulcer) that were considered unrelated to treatment (Table 6). Of the 13 patients discontinuing the study because of a TEAE, only 1 discontinued because of treatment-related TEAEs (cervicogenic headache and nausea in the once-daily mometasone group); all TEAEs leading to discontinuation resolved by study end. No deaths occurred during the study. No clinically relevant treatment-related findings were seen for vital signs, laboratory evaluations, or ECGs; the number of patients who had abnormal ENT examinations was low and similar across the treatments (data not shown). No nasal septal perforations were seen.

Discussion

Food and Drug Administration–approved intranasal olopatadine (twice-daily) and mometasone (once-daily) are both efficacious and well-tolerated monotherapies for the treatment of AR.^{18,19} In this study, treatment with twice- or once-daily GSP301 FDC nasal spray containing olopatadine and mometasone provided significant and clinically meaningful²³ average morning and evening rTNSS (primary endpoint) improvements vs placebo in patients with SAR; improvements occurred on day 1 and were sustained over 14 days of treatment. However, only twice-daily GSP301 demonstrated significant and clinically meaningful improvements in rTNSS vs both component monotherapies. Because twice-daily GSP301 satisfied the regulatory threshold that an FDC should be superior to placebo as well as the individual monotherapies,²⁴ it was considered the optimally effective dosing regimen and was chosen for further evaluation in later phase 3 studies.²⁶

Table 6
Summary of Adverse Events (SAS)

n (%)	Twice-daily GSP301 (n = 157)	Twice-daily olopatadine (n = 160)	Twice-daily mometasone (n = 159)	Once-daily GSP301 (n = 158)	Once-daily olopatadine (n = 158)	Once-daily mometasone (n = 160)	Placebo (n = 159)
Patients reporting ≥ 1 TEAE	17 (10.8)	25 (15.6)	10 (6.3)	15 (9.5)	17 (10.8)	15 (9.4)	13 (8.2)
TEAEs ^a							
Headache	0 (0)	1 (0.6)	1 (0.6)	6 (3.8)	1 (0.6)	2 (1.3)	1 (0.6)
Dysgeusia	2 (1.3)	5 (3.1)	0 (0)	2 (1.3)	2 (1.3)	0 (0)	0 (0)
Patients discontinuing due to TEAEs	2 (1.3)	2 (1.3)	2 (1.3)	2 (1.3)	2 (1.3)	3 (1.9)	0 (0)
Patients with SAEs	0 (0)	0 (0)	0 (0)	1 (0.6) ^b	0 (0)	0 (0)	0 (0)
Deaths	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Abbreviations: SAE, serious adverse event; SAS, safety analysis set; TEAE, treatment-emergent adverse event.

Twice-daily GSP301, olopatadine 665 μ g, and mometasone 25 μ g; once-daily GSP301, olopatadine 665 μ g, and mometasone 50 μ g; twice- and once-daily olopatadine and, 665 μ g; twice-daily mometasone, 25 μ g; once-daily mometasone, 50 μ g.^aOccurring in $\geq 2\%$ of patients in any treatment group.^bGastritis and gastrointestinal ulcer in 1 patient; both SAEs were judged by the investigator as not related to study treatment.

Some treatment comparisons such as twice-daily GSP301 vs twice-daily olopatadine for iTNSS, once-daily GSP301 vs once-daily mometasone for rTNSS and iTNSS, and several exploratory comparisons did not reach statistical significance. This could be a result of the potentially confounding factors inherent in SAR studies, such as patient-reported symptom assessments (requiring patients to optimally assess and report symptom severity and onset) and differences in pollen level exposures and pollen seasons. Results from 2 large, phase 3 SAR studies, however, demonstrated that twice-daily GSP301 treatment provided significant improvements in average morning and evening rTNSS and iTNSS vs placebo^{27,28} and vs mometasone and olopatadine.²⁸ Although not all comparisons of GSP301 with the monotherapies on TNSS were statistically significant in the current study, they were clinically meaningful as indicated by the LSMDs, which were greater than the established MCID of 0.23 units (direct anchor-based regression methodology).²³

In the current study, onset of action could not be determined for any of the active treatment groups. However, in 2 similarly designed phase 3 natural-allergen SAR studies, twice-daily GSP301 demonstrated a rapid onset of action of 15 minutes.^{27,28} Similarly, in an environmental exposure chamber (EEC) study, a significant difference in change from baseline in iTNSS for twice-daily GSP301 vs placebo was observed at 10 minutes, and significance was maintained at 11 of the 12 time points assessed.²⁹ Although the reason why onset could not be determined in this study was not clear, it may be partly because of differences in study design. The potentially confounding factors found in SAR studies noted above make it difficult to directly compare study results. Additionally, studies can vary by sample size and inclusion/exclusion criteria. For example, in the current study, patients were not required to be actively symptomatic immediately before their onset of action evaluation (although they met overall symptom requirements for study inclusion), whereas the patients in the EEC and phase 3 studies were required to be symptomatic just before their onset evaluation. Because SAR clinical studies are conducted under varying conditions and designs, knowing why onset could not be determined in this study is not possible. However, replicate evidence indicates that twice-daily GSP301 has a rapid onset of action of 15 minutes.^{27,28}

That inadequate AR symptom control can negatively impact patients' quality of life has been well established.^{7,8} In this study, both twice- and once-daily GSP301 treatments provided significant and clinically meaningful (treatment difference, ≥ 0.50 units)²⁵ improvements in RQLQ(S) scores vs placebo, indicating improvement in patients' quality of life. Additionally, many patients with AR experience ocular symptoms that can negatively impact quality of life.^{8,30} In the current study, twice-daily and once-daily GSP301

demonstrated improvements vs placebo on both rTOSS and iTOSS, with $P < .05$; however, for twice-daily GSP301 these improvements did not reach statistical significance per the a priori significance level of $P < .025$. In later phase 3 clinical studies, twice-daily GSP301 provided significant ($P < .05$) improvements in ocular symptoms vs placebo,^{27,28} indicating that twice-daily GSP301 is effective in improving both nasal and ocular SAR symptoms.

Both twice- and once-daily GSP301 were well tolerated, with rates of TEAEs that were similar to those of the other treatment groups. The most commonly reported TEAEs were headache and dysgeusia. Headache was reported more frequently in the once-daily GSP301 compared with once-daily monotherapies, twice-daily treatments, or placebo. Dysgeusia was reported more frequently in the olopatadine-containing treatments (once- and twice-daily GSP301 and olopatadine monotherapy) compared with mometasone or placebo treatments. Headache is a common adverse event for both olopatadine and mometasone nasal sprays^{18,19} and dysgeusia is reported with olopatadine nasal spray use.¹⁸ In the current study, these events occurred in fewer than 5% of patients in the GSP301 treatment groups. Two SAEs were reported by 1 patient receiving once-daily GSP301 (gastritis and gastrointestinal ulcer reported in 1 admission) and were considered by the investigator not related to treatment; the patient was withdrawn from the study and both SAEs resolved. In 2 pharmacokinetic studies of GSP301 in healthy patients,^{31,32} good tolerability and safety profiles were observed with low systemic exposure. Further, twice-daily GSP301 also demonstrated good tolerability and safety profiles in an EEC study (dosed twice- or once-daily),²⁹ in 2 replicate phase 3 natural-allergen studies in patients with SAR,^{27,28} and in a 52-week study in patients with perennial allergic rhinitis,³³ supporting its favorable safety and tolerability profile.

In conclusion, twice-daily GSP301 was efficacious and well tolerated, providing statistically significant and clinically meaningful improvements in rTNSS (primary endpoint) vs placebo and both monotherapies.

Acknowledgments

Assistance in medical writing, editing, and formatting of the manuscript for submission was provided by Lynn M. Anderson, PhD, and Kristen A. Andersen, PhD, of Prescott Medical Communications Group (Chicago, IL) and funded by Glenmark Pharmaceuticals SA. All authors met the ICMJE authorship criteria. Neither honoraria nor payments were made for authorship. Charles P. Andrews, MD and Dale Mohar, MD were compensated by Glenmark Specialty SA as site principal investigators on this study.

References

- Galli SJ, Tsai M, Piliponsky AM. The development of allergic inflammation. *Nature*. 2008;454(7203):445–454.
- Blackwell DL, Villarreal MA. Tables of summary health statistics for US adults: 2017 National Health Interview Survey. 2018. Available at: https://ftp.cdc.gov/pub/Health_Statistics/NCHS/NHIS/SHS/2017_SHS_Table_A-2.pdf. Accessed August 15, 2019.
- Black LI, Benson V. Tables of summary health statistics for US children: 2017 National Health Interview Survey. 2018. Available at: https://ftp.cdc.gov/pub/Health_Statistics/NCHS/NHIS/SHS/2017_SHS_Table_C-2.pdf. Accessed August 15, 2019.
- Dykewicz MS, Wallace DV, Baroody F, et al. Treatment of seasonal allergic rhinitis: an evidence-based focused 2017 guideline update. *Ann Allergy Asthma Immunol*. 2017;119(6):489–511.
- Dalal AA, Stanford R, Henry H, Borah B. Economic burden of rhinitis in managed care: a retrospective claims data analysis. *Ann Allergy Asthma Immunol*. 2008;101(1):23–29.
- Hadley JA, Derebery MJ, Marple BF. Comorbidities and allergic rhinitis: not just a runny nose. *J Fam Pract*. 2012;61(2 Suppl):S11–S15.
- Marple BF, Fornadley JA, Patel AA, et al. Keys to successful management of patients with allergic rhinitis: focus on patient confidence, compliance, and satisfaction. *Otolaryngol Head Neck Surg*. 2007;136(6 Suppl):S107–S124.
- Meltzer EO, Blaiss MS, Naclerio RM, et al. Burden of allergic rhinitis: allergies in America, Latin America, and Asia-Pacific adult surveys. *Allergy Asthma Proc*. 2012;33(Suppl 1):S113–S141.
- Meltzer EO. Allergic rhinitis: burden of illness, quality of life, comorbidities, and control. *Immunol Allergy Clin North Am*. 2016;36(2):235–248.
- Blaiss MS. Allergic rhinitis: direct and indirect costs. *Allergy Asthma Proc*. 2010;31(5):375–380.
- Pawankar R, Mori S, Ozu C, Kimura S. Overview on the pathomechanisms of allergic rhinitis. *Asia Pacific Allergy*. 2011;1(3):157–167.
- Prenner BM. A review of the clinical efficacy and safety of MP-AzeFlu, a novel intranasal formulation of azelastine hydrochloride and fluticasone propionate, in clinical studies conducted during different allergy seasons in the US. *J Asthma Allergy*. 2016;9:135–143.
- Feng S, Fan Y, Liang Z, Ma R, Cao W. Concomitant corticosteroid nasal spray plus antihistamine (oral or local spray) for the symptomatic management of allergic rhinitis. *Eur Arch Otorhinolaryngol*. 2016;273(11):3477–3486.
- Meltzer EO, Hampel FC, Ratner PH, et al. Safety and efficacy of olopatadine hydrochloride nasal spray for the treatment of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. 2005;95(6):600–606.
- Fairchild CJ, Meltzer EO, Roland PS, Wells D, Drake M, Wall GM. Comprehensive report of the efficacy, safety, quality of life, and work impact of olopatadine 0.6% and olopatadine 0.4% treatment in patients with seasonal allergic rhinitis. *Allergy Asthma Proc*. 2007;28(6):716–723.
- Penagos M, Compalati E, Tarantini F, Baena-Cagnani CE, Passalacqua G, Canonica GW. Efficacy of mometasone furoate nasal spray in the treatment of allergic rhinitis: meta-analysis of randomized, double-blind, placebo-controlled, clinical trials. *Allergy*. 2008;63(10):1280–1291.
- Hochhaus G. Pharmacokinetic/pharmacodynamic profile of mometasone furoate nasal spray: potential effects on clinical safety and efficacy. *Clin Ther*. 2008;30(1):1–13.
- Patanase (olopatadine hydrochloride nasal spray). *US prescribing information*. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2015.
- Nasonex (mometasone furoate monohydrate nasal spray). *US prescribing information*. Whitehouse Station, NJ: Merck & Co, Inc; 2018.
- Andrews CP, Ratner PH, Ehler BR, et al. The mountain cedar model in clinical trials of seasonal allergic rhinoconjunctivitis. *Ann Allergy Asthma Immunol*. 2013;111(1):9–13.
- Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. *Clin Exp Allergy*. 1991;21(1):77–83.
- Kim K, Weiswasser M, Nave R, et al. Safety of once-daily ciclesonide nasal spray in children 2 to 5 years of age with perennial allergic rhinitis. *Pediatr Asthma Allergy Immunol*. 2007;20(4):229–242.
- Barnes ML, Vaidyanathan S, Williamson PA, Lipworth BJ. The minimal clinically important difference in allergic rhinitis. *Clin Exp Allergy*. 2010;40(2):242–250.
- Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Allergic rhinitis: developing drug products for treatment guidance for industry. Draft guidance, 2018. Available at: <https://www.fda.gov/downloads/drugs/guidances/ucm071293.pdf>. Accessed August 15, 2019.
- Juniper EF, Guyatt GH, Griffith LE, Ferrie PJ. Interpretation of rhinoconjunctivitis quality of life questionnaire data. *J Allergy Clin Immunol*. 1996;98(4):843–845.
- U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for industry: development of two or more new investigational drugs for use in combination. 2013. Available at: <https://www.fda.gov/media/80100/download>. Accessed August 15, 2019.
- Hampel F, Pedinoff A, Jacobs R, Caracta C, Tantry S. Olopatadine/mometasone combination nasal spray: evaluation of efficacy and safety in patients with seasonal allergic rhinitis. *Allergy Asthma Proc*. 2019;40(4):261–272.
- Gross GN, Berman G, Amar NJ, Caracta CF, Tantry SK. Efficacy and safety of olopatadine/mometasone combination nasal spray for the treatment of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. 2019;122(6):630–638.
- Patel P, Salapatek AM, Tantry SK. Effect of olopatadine-mometasone combination nasal spray on seasonal allergic rhinitis symptoms in an environmental exposure chamber study. *Ann Allergy Asthma Immunol*. 2019;122(2):160–166.
- Baroody FM, Naclerio RM. Nasal-ocular reflexes and their role in the management of allergic rhinoconjunctivitis with intranasal steroids. *World Allergy Organ J*. 2011;4(1 Suppl):S1–S5.
- Patel P, Salapatek AM, Talluri RS, Tantry SK. Pharmacokinetics of intranasal mometasone in the fixed-dose combination GSP301 versus two monotherapy intranasal mometasone formulations. *Allergy Asthma Proc*. 2018;39(3):232–239.
- Patel P, Salapatek AM, Talluri RS, Tantry SK. Pharmacokinetics of intranasal olopatadine in the fixed-dose combination GSP301 versus two monotherapy intranasal olopatadine formulations. *Allergy Asthma Proc*. 2018;39(3):224–231.
- Segall N, Prenner B, Lumry W, Caracta CF, Tantry SK. Long-term safety and efficacy of olopatadine-mometasone combination nasal spray in patients with perennial allergic rhinitis. *Allergy Asthma Proc*. 2019;40(5):301–310.

eMethods

Prohibited Concomitant Medications

Use of the following medications was not permitted for the specified number of days before screening or during the study: vasoconstrictors or major tranquilizers (3 days before); ocular, oral, or intranasal short-acting antihistamines (5 days before); over-the-counter cough/cold treatments or sleep aids containing antihistamines, topical, oral, or inhaled decongestants or anticholinergics, or over-the-counter food supplements or diets to reduce leukotrienes, leukotriene antagonists, or 5-lipoxygenase inhibitors (7 days earlier); long-acting antihistamines (10 days before); cromolyn, nedocromil, lodoxamide, systemic antibiotics, ocular mast cell stabilizers, or tricyclic antidepressants (14 days before); intranasal, topical, ocular, or inhaled corticosteroids or other investigational drug (30 days earlier); cytochrome P450 3A4 inhibitors or inducers (30 days before); systemic corticosteroids, immune suppressors/modulators (unless dosage is stable for the past 90 days), or immunoglobulin E antagonists (60 days earlier).

For the duration of the study, use of the following medications was also not permitted: radiation therapy; herbal, ayurvedic or homeopathic allergic rhinitis (AR) treatments; topical/dermatologic corticosteroids (except to treat small, localized lesions); intranasal therapies (including saline); ophthalmic drops; clinical trial drugs; AR or asthma medications except for inhaled short-acting β -agonists for asthma (≤ 8 puffs/day); initiation of injectable immunotherapy (continuation of therapy was permitted if initiated ≥ 90 days before the screening visit, and a stable maintenance dose was maintained 30 days or more before the screening visit, as well as during the entire study); St. John's Wort; pimecrolimus cream $\geq 1\%$ or tacrolimus ointment $\geq 0.03\%$ unless initiated ≥ 30 days before screening with a stable maintenance dose.

Additional Key Exclusion Criteria

Use of topical $\geq 1\%$ hydrocortisone or equivalent ≤ 30 days before screening or in any concentration covering more than 20% of body surface was not permitted. Any history of the following was also exclusionary: anaphylaxis; human immunodeficiency virus or hepatitis B or C infection; impaired hepatic function; gastrointestinal disease; subcapsular cataracts, glaucoma, or other ocular disturbances; a systemic infection; malignancy (excluding basal cell carcinoma); current neuropsychological condition with or without drug therapy; cardiovascular disease (eg, uncontrolled hypertension); hepatic, hematological, renal or endocrine disorder (except for postmenopausal symptoms or hypothyroidism); known history of hypothalamic-pituitary-adrenal axis impairment; or respiratory disease other than mild asthma. Patients could not travel outside of the known pollen area for the investigative site for: ≥ 24 hours during the last 7 days of the run-in period; for ≥ 2 consecutive days; OR ≥ 3 days total between the randomization visit (visit 2) and the final treatment visit (visit 4).

Key Randomization Criteria

During the last 4 days of the placebo run-in period (last 8 consecutive morning and evening assessments from the evening assessment on day -4 to the morning assessment on the day of randomization), patients had to have a minimum average 12-hour reflective Total Nasal Symptom Score (rTNSS) of 8 or more out of 12, with an average congestion score 2 or greater and a minimum 12-hour reflective Total Ocular Symptom Score (rTOSS) of 4 or more out of 9. Patients needed to have adequate symptom diary compliance (no missing diary entries on 2 or more morning or evening assessment sessions) during the last 4 days of the run-in period, including the morning assessment on the day of randomization.

Additional Assessment Details

Patients self-reported nasal (TNSS) and ocular (TOSS) symptoms twice daily (morning and evening) in a diary before treatment; symptoms were rated on a 4-point severity scale with scores ranging from 0 (absent) to 3 (severe; eTable 1). Symptoms were reported as instantaneous (occurring over the 10 minutes before dosing) and reflective (occurring over the previous 12 hours). The reflective and instantaneous TNSS were defined as the sum of 4 nasal-symptom scores (rhinorrhea, nasal congestion, nasal itching, and sneezing), with a maximum score of 12. The daily TNSS can be calculated as either a 12-point (averaging the morning and evening values) or a 24-point scale (summing morning and evening values); scores were calculated on a 12-point scale for the current study. The reflective and instantaneous TOSS were defined as the sum of 3 eye-related symptom scores (itching/burning eyes, tearing/watering eyes, and redness of eyes), with a maximum score of 9.

Nasal symptoms of nasal congestion, rhinorrhea, nasal itching, and sneezing were assessed by physicians using the Physician-assessed Nasal Symptom Score (PNSS)¹; ear, nose, and throat examinations were performed, and patients were queried about symptom severity. The validated Rhinoconjunctivitis Quality-of-Life Questionnaire—Standardized Activities (RQLQ[S]) was self-administered by adult patients who had an adequate understanding of the English language (≥ 18 years only) during visits 2 and 4. It consists of 28 questions in 7 domains: activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye problems, and emotional.² A treatment difference of 0.50 units on the overall RQLQ(S) was considered clinically meaningful (defined as the MCID).³

Additional Statistical Analysis Information

Baseline for TNSS and TOSS was defined as the mean of the last 8 TNSS or TOSS obtained during the last 4 days of the placebo run-in period before randomization, including the morning assessment on the day of randomization. Baseline for onset of action was defined as the pre-dose time point at randomization (visit 2). For the RQLQ(S) and PNSS, baseline was defined as the score at randomization (visit 2).

A gate-keeping, pairwise analysis strategy was used for all efficacy endpoints in which no further treatment comparisons were conducted if the comparisons of GSP301 with placebo did not reach statistical significance ($P < .025$). If significant, then comparisons for GSP301 vs olopatadine ($P < .05$) and GSP301 vs mometasone ($P < .05$) were conducted. Twice- and once-daily GSP301 vs placebo comparisons were tested in parallel, and a Bonferroni correction was used to divide the alpha equally between the twice- and once-daily comparisons. Comparisons between olopatadine or mometasone vs placebo were exploratory.

For rTNSS, iTNSS, rTOSS, iTOSS, and RQLQ(S), the interactions of center by treatment group and baseline score by treatment group were analyzed separately in the ANCOVA and removed from the final model if they were not statistically significant at $\alpha = 0.05$. Descriptive statistics were used to summarize baseline demographic variables and AEs by treatment group. All analyses were conducted using SAS statistical software (v 9.4 or higher; Cary, NC).

eTable 1

Description of Severity Rating Scores for Nasal and Ocular Symptom Scales

Score	Severity rating	Description
0	Absent	No signs/symptoms evident.
1	Mild	Signs/symptoms are clearly present but minimal awareness; easily tolerated.
2	Moderate	Definite awareness of signs/symptoms; bothersome but tolerable.
3	Severe	Signs/symptoms that are hard to tolerate; interference with activities of daily living or sleeping.

Source: US Food and Drug Administration Allergic Rhinitis Guidance for Industry, 2018. Available at: <https://www.fda.gov/downloads/drugs/guidances/ucm071293.pdf>⁴.

References

1. Kim K, Weiswasser M, Nave R, et al. Safety of once-daily ciclesonide nasal spray in children 2 to 5 years of age with perennial allergic rhinitis. *Pediatr Asthma Allergy Immunol*. 2007;20(4):229–242.
2. Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. *Clin Exp Allergy*. 1991;21(1):77–83.
3. Juniper EF, Guyatt GH, Griffith LE, Ferrie PJ. Interpretation of rhinoconjunctivitis quality of life questionnaire data. *J Allergy Clin Immunol*. 1996;98(4):843–845.
4. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Allergic rhinitis: developing drug products for treatment guidance for industry. Draft guidance. 2018. Available at: <https://www.fda.gov/downloads/drugs/guidances/ucm071293.pdf>. Accessed August 15, 2019.