



Efficacy and safety of olopatadine-mometasone combination nasal spray for the treatment of seasonal allergic rhinitis



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ABSTRACT

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

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

Methods: In this double-blind study, eligible patients (≥ 12 years of age) with SAR were randomized 1:1:1:1 to twice-daily GSP301 (665 μg of olopatadine and 25 μg of mometasone), olopatadine (665 μg), mometasone (25 μg), or placebo for 14 days. The primary end point—mean change from baseline in average morning and evening 12-hour reflective Total Nasal Symptom Score (rTNSS)—was analyzed via a mixed-effect model repeated measures ($P < .05$ was considered to be statistically significant). Additional assessments included average morning and evening 12-hour instantaneous TNSS (iTNSS), ocular symptoms, individual symptoms, onset of action, quality of life, and adverse events (AEs).

Results: A total of 1176 patients were randomized. GSP301 provided statistically significant and clinically meaningful rTNSS improvements vs placebo (least squares mean difference, -1.09; 95% CI, -1.49 to -0.69; $P < .001$) and vs olopatadine ($P = .03$) and mometasone ($P = .02$). Similar significant improvements in iTNSS were also observed with GSP301 ($P < .05$ for all). Furthermore, GSP301 significantly improved overall ocular symptoms, individual nasal and ocular symptoms, and quality of life vs placebo ($P \leq .001$ for all). Onset of action for GSP301 was observed within 15 minutes and was maintained at all subsequent timepoints. Treatment-emergent AEs occurred in 15.6%, 12.6%, 9.6%, and 9.5% of patients in the GSP301, olopatadine, mometasone, and placebo groups, respectively.

Conclusion: GSP301 is efficacious and well tolerated vs placebo for treating SAR-associated nasal and ocular symptoms, with a rapid onset of action of 15 minutes in adult and adolescent patients 12 years and older.

Clinical Trial Registration: ClinicalTrials.gov: NCT02870205.

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Introduction

Allergic rhinitis (AR) is a nasal inflammatory response caused by an exaggerated immunologic reaction to an allergen that is

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generally characterized by 1 or more symptoms of nasal congestion, sneezing, rhinorrhea, and nasal itching.¹ AR is one of the most common chronic diseases in both pediatric and adult patients, affecting 5.6 million children² and 19.9 million adults in the United States.³ Although AR is typically categorized as perennial (PAR; occurring year-round) or seasonal (SAR; occurring in a specific pollen season), the distinction between these can be difficult to determine because some patients can have both SAR and PAR, and SAR can occur year-round in tropical or warm climates.^{1,4}

According to the most recent estimates, AR presents a substantial economic burden, with total annual expenditures of \$11.2 billion in 2005, which was nearly double the costs estimated 5

years prior (\$6.1 billion in 2000).⁵ Prescription medications accounted for more than half of these expenditures, with \$305 per person spending of \$520 total in 2005.⁵ However, the burden of AR extends beyond its financial impact because AR symptoms negatively affect quality of life (QoL), including decreased work or school productivity, disturbed sleep, fatigue, and depression.^{6,7} Although reduced QoL can occur in all patients with AR regardless of age, a recent report suggests that uncontrolled nasal symptoms among adolescents results in poorer QoL vs adults or younger children.⁸

The use of pharmacotherapies is a convenient and effective approach that can provide immediate AR symptom relief, and most patients with AR will attempt at least 1 treatment strategy to combat their symptoms. In a survey of patients with SAR (with or without concurrent PAR), 47% of patients report increasing the number of prescription AR medications to 2 or more separate treatments.⁶ Although there are many strategies for controlling and improving AR symptoms—including environmental control, allergen immunotherapy, and pharmacologic therapy^{1,9}—each of these strategies has unique challenges: completely eliminating all environmental allergens is not practical,¹ immunotherapy requires prolonged adherence to treatment,¹⁰ and over-the-counter (OTC) or prescription medications (eg, corticosteroids, antihistamines, decongestants, anticholinergics, and leukotriene receptor antagonists)^{1,9} are not always effective in relieving symptoms, and some may lose efficacy over time.^{7,10} Combination treatments that contain an intranasal antihistamine with an intranasal corticosteroid are more effective in controlling AR symptoms than monotherapy alone.^{11,12} Using a single fixed-dose combination (FDC) nasal spray may have the added benefit of reducing health care costs¹³ and improving treatment adherence¹⁴ compared with multiple monotherapy use, although healthcare costs have only been studied in monotherapy and monotherapy combination nasal sprays, and adherence has not been studied in FDC nasal sprays.

GSP301 is an investigational FDC of the antihistamine olopatadine hydrochloride and the corticosteroid mometasone furoate developed as a single nasal spray for the treatment of SAR symptoms. Individually, olopatadine and mometasone are effective, well-tolerated intranasal treatments for SAR.^{15–20} When combined in a single device as GSP301 nasal spray, significant and clinically meaningful improvements²¹ in SAR nasal symptoms were observed compared with placebo^{22–25} and the individual monotherapies.^{22–24} The objectives of this study were to evaluate the efficacy, safety, and tolerability of GSP301 nasal spray vs placebo and the individual monotherapy formulations (olopatadine or mometasone) for 14 days of treatment in adult and adolescent patients with SAR.

Methods

This study was conducted at 43 US study sites in compliance with Good Clinical Practice and in accordance with the Declaration of Helsinki and International Conference on Harmonization guidelines. The protocol received clearance from a central institutional review board (Quorum Review, Seattle, Washington) and was performed in accordance with applicable local regulatory requirements. All patients provided written informed consent; for adolescent patients aged 12 years or older to younger than 18 years, parents, caregivers, or legal guardians provided consent and the patient provided assent.

Study Design

This was a phase 3, randomized, double-blind, parallel-group study conducted in adolescent and adult patients with SAR during the fall and mountain cedar pollen seasons. There were 2 study periods: the 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 the completion of the placebo run-in period, patients who met the randomization criteria (see [eMethods](#)) were equally randomized to 1 of 4 intranasal treatments for 14 days (2 sprays per nostril twice daily): GSP301 (665 µg of olopatadine hydrochloride and 25 µg of mometasone furoate); olopatadine hydrochloride (sponsor formulation; 665 µg); mometasone furoate (sponsor formulation; 25 µg), and placebo (GSP301 vehicle; contained the same inactive ingredients as the active treatments).

Patients

Patients 12 years or older with a clinical history of SAR for 2 years or more before screening for the relevant seasonal allergen during the fall or mountain cedar allergy seasons (eg, ragweed pollen, mountain cedar pollen) with a positive skin prick test result for relevant allergens (wheal diameter ≥5 mm greater than negative control) were eligible to enroll in the study. Patients must also have had a minimum average morning and evening 12-hour reflective Total Nasal Symptom Score (rTNSS) of 8 or higher out of 12 and a morning congestion score of 2 or more at the screening visit.

Exclusion criteria included any evidence or known history of any of the following: nasal polyps; other clinically significant respiratory tract malformations; nasal structural abnormalities; nasal trauma; acute or significant chronic sinusitis or chronic purulent postnasal drip; significant atopic dermatitis or rhinitis medicamentosa (≤60 days before screening); and active pulmonary disorder or infection (eg, bronchitis, pneumonia, or influenza) or upper respiratory tract or sinus infection 14 days or more before screening or the development of respiratory infections during the placebo run-in period. See [eMethods](#) for a list of [additional key exclusion criteria](#), [prohibited medications](#), and [randomization criteria](#).

Assessments

Assessment of efficacy was based on the patient-reported rTNSS, instantaneous Total Nasal Symptom Score (iTNSS), and reflective and instantaneous Total Ocular Symptom Score (rTOSS and iTOSS, respectively). Before self-administering study medication, patients self-reported nasal and ocular reflective and instantaneous symptoms twice daily (morning and evening) in a diary. Each symptom was rated on a 4-point severity scale, ranging from 0 (absent) to 3 (severe) ([eTable 1](#)). Both rTNSS and iTNSS were defined as the sum of 4 nasal symptom scores: rhinorrhea, nasal congestion, nasal itching, and sneezing (maximum score of 12). The rTOSS and iTOSS were defined as the sum of 3 eye-related symptom scores: itching or burning eyes, tearing or watering eyes, and redness of eyes (maximum score of 9) (see [eMethods](#) for additional details).

Onset of action for each treatment was assessed using the mean change from baseline in iTNSS vs placebo at the following time points for a total of 4 hours after the first dose of study treatment (visit 2): pre-dose (0 minutes) and at 15, 30, 45, 60, 90, 120, 150, 180, 210, and 240 minutes post-dose. Additional assessments included the Physician-assessed Nasal Symptom Scores (PNSS),²⁶ the Rhinoconjunctivitis Quality-of-Life Questionnaire—Standardized Activities (RQLQ[S]),²⁷ and the Rhinitis Control Assessment Test (RCAT)²⁸ (see [eMethods](#) for further details). Safety was monitored via adverse events (AEs); ear, nose, and throat (ENT) examinations; laboratory assessments; physical examinations; vital signs; and electrocardiograms (ECGs).

End Points

The primary end point was the mean change from baseline to the end of the 14-day treatment period in average morning and evening 12-hour rTNSS. Secondary end points were mean change from baseline to the end of 14-day treatment in average morning

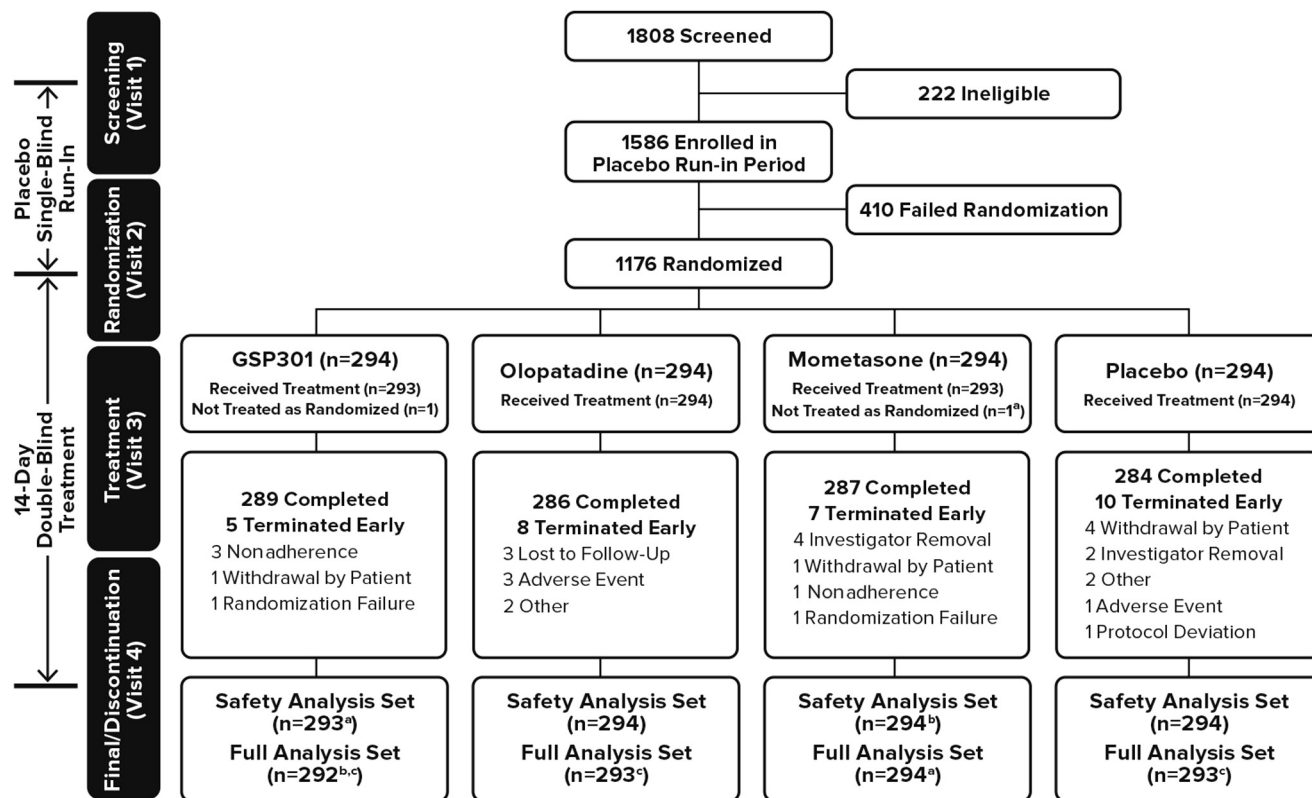


Figure 1. Study design and patient disposition. The GSP301 group received 665 μ g of olopatadine and 25 μ g of mometasone twice daily, the olopatadine group received 665 μ g twice daily, and the mometasone group received 25 μ g twice daily. The screening visit (visit 1) occurred between day –10 and day –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 post-treatment follow-up visit was planned for this study. Patients who did not meet randomization criteria were ineligible for randomization.

^aOne patient who was randomized to receive mometasone unintentionally received GSP301 (wrong drug was administered) and continued to receive GSP301 for the remainder of the 14-day treatment period. This patient was analyzed as randomized for efficacy (ie, included in the mometasone treatment group for the full analysis set) and as treated for safety (ie, included in the GSP301 treatment group for the safety analysis set).

^bExcluded 1 patient who did not receive treatment.

^cExcluded 1 patient who repeated participation at a different site.

and evening 12-hour iTNSS and average morning and evening 12-hour rTOSS; onset of action assessment; and mean change from baseline to day 15 in the overall RQLQ(S) score. Additional efficacy end points included mean change from baseline in: average morning and evening 12-hour iTNSS to the end of 14-day treatment; average morning and evening 12-hour reflective and instantaneous individual nasal symptoms during the 14-day treatment period; and the PNSS and the RCAT from baseline to day 15. Physical examinations, ECGs, and laboratory assessments were conducted at the screening and final visits, and monitoring of vital signs, ENT examinations, and AEs occurred throughout the study.

Statistical Analysis

Efficacy and RQLQ(S) analyses were based on the full analysis set (FAS) population, defined as all randomized patients who received 1 dose or more of study drug and completed 1 postbaseline primary efficacy assessment or more; safety assessments were based on the safety analysis set (SAS) population, which included all patients who received 1 dose or more of study medication. Efficacy end points were analyzed via mixed-effect model repeated measures (MMRM), adjusting for covariates (treatment, site, baseline clinical measures, and study day as the within-subject effect). To adjust for multiplicity, a gatekeeping strategy was used for rTNSS, iTNSS, and rTOSS. A difference of more than 0.23 units (direct anchor-based

regression method) on TNSS was considered clinically meaningful (defined as the minimal clinically important difference [MCID]).²¹ See eMethods for further details.

Onset of action—defined as the first postdose 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 sustained²⁹—was analyzed using the MMRM adjusted for the same covariates as the efficacy analyses. Onset baseline was defined as the predose time point at randomization (visit 2). Change from baseline in overall RQLQ(S) was analyzed using an analysis of covariance model, adjusting for study treatment, site, and baseline RQLQ(S) as the linear, continuous covariate; baseline was defined as the RQLQ(S) score at visit 2. Statistical significance was set at $P < .05$ all analyses. See eMethods for additional analysis details.

Results

Patient Demographics and Baseline Characteristics

Of 1176 patients randomized, 1147 (97.5%) completed the study: 1175 and 1172 patients were included in the SAS and the FAS populations, respectively (Fig. 1). Patients were predominantly female and white, with moderate to severe nasal and ocular symptoms at baseline; mean age ranged from 39.2 to 39.9 years (Table 1).

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

Variable	GSP301 (n = 293)	Olopatadine (n = 293)	Mometasone (n = 293)	Placebo (n = 293)
Age, mean (SD), y	39.9 (14.9)	39.9 (14.6)	39.2 (14.9)	39.6 (14.9)
Sex, No. (%)				
Female	202/293 (68.9)	189/293 (64.5)	170/293 (58.0)	176/293 (60.1)
Male	91/293 (31.1)	104/293 (35.5)	123/293 (42.0)	117/293 (39.9)
Race, No. (%)				
White	251/293 (85.7)	244/293 (83.3)	232/293 (79.2)	229/293 (78.2)
Black	30/293 (10.2)	41/293 (14.0)	50/293 (17.1)	60/293 (20.5)
Asian	7/293 (2.4)	4/293 (1.4)	8/293 (2.7)	3/293 (1.0)
Other ^b	5/293 (1.7)	4/293 (1.4)	3/293 (1.0)	1/293 (0.3)
Ethnicity, No. (%)				
Non-Hispanic or Latino	224 (76.5)	197 (67.2)	208 (71.0)	214 (73.0)
Hispanic or Latino	69 (23.5)	96 (32.8)	85 (29.0)	79 (27.0)
Baseline symptom and QoL scores, mean (SD)	GSP301 (n = 292)	Olopatadine (n = 293)	Mometasone (n = 294)	Placebo (n = 293)
Average morning and evening rTNSS	10.1 (1.2)	10.2 (1.3)	10.2 (1.3)	10.3 (1.2)
Average morning rTNSS	10.0 (1.3)	10.1 (1.3)	10.2 (1.4)	10.2 (1.3)
Average evening rTNSS	10.2 (1.3)	10.2 (1.3)	10.2 (1.4)	10.4 (1.3)
Average morning and evening iTNSS	9.2 (1.8)	9.4 (1.7)	9.4 (1.8)	9.6 (1.8)
Average morning iTNSS	9.2 (1.8)	9.4 (1.7)	9.5 (1.8)	9.5 (1.9)
Average evening iTNSS	9.1 (1.9)	9.3 (1.8)	9.4 (2.0)	9.6 (1.8)
Average morning and evening rTOSS	7.0 (1.5)	7.0 (1.5)	7.0 (1.5)	7.2 (1.4)
Average morning and evening iTTOSS	6.5 (1.8)	6.6 (1.7)	6.7 (1.7)	6.8 (1.6)
PNSS	9.2 (2.1)	9.4 (2.2)	9.5 (2.0)	9.6 (1.8)
RQLQ(S) score	4.0 (1.2)	4.1 (1.1)	4.0 (1.3)	4.0 (1.2)
RCAT score	11.9 (3.6)	11.7 (3.3)	11.4 (3.6)	11.7 (3.6)

Abbreviations: FAS, full analysis set; iTNSS, instantaneous Total Nasal Symptom Score; iTTOSS, instantaneous Total Ocular Symptom Score; PNSS, Physician-assessed Nasal Symptom Scores; QoL, quality of life; RCAT, Rhinitis Control Assessment Test; 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.

^aThe GSP301 group received 665 µg of olopatadine and 25 µg of mometasone twice daily, the olopatadine group received 665 µg twice daily, and the mometasone group received 25 µg twice daily.

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

Demographic characteristics and baseline symptom and QoL scores were similar between the treatment groups.

Patient-Reported Nasal Symptoms

Average Morning and Evening TNSS

GSP301 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 ($P < .001$) and vs each individual monotherapy ($P = .03$ vs olopatadine; $P = .02$ vs mometasone) (Table 2). Similarly, compared with placebo, olopatadine and mometasone monotherapies resulted in significant and clinically meaningful improvements (olopatadine: $P = .001$; mometasone: $P = .002$) (Table 2). On individual

days, significant improvements on average morning and evening rTNSS after GSP301 treatment vs placebo were observed from day 1 through day 14 (Fig. 2A), suggesting sustained daily improvement. Olopatadine demonstrated significant improvements vs placebo on days 1 to 10 ($P \leq .01$ for all), and mometasone demonstrated significant improvements vs placebo on days 1 to 14 ($P < .05$ for all) (Fig. 2A).

As seen for rTNSS results above, GSP301 demonstrated significant and clinically meaningful improvements in average morning and evening 12-hour iTNSS from baseline to the end of 14-day treatment vs placebo ($P < .001$) and both monotherapy components ($P = .035$ vs olopatadine; $P = .008$ vs mometasone) (Table 2). Similarly, olopatadine and mometasone monotherapies demonstrated significant and clinically meaningful improvements from

Table 2
Treatment Comparisons of Total Nasal Symptom Scores During 14 Days of Treatment (FAS)^a

Treatment Group (1 vs 2)	n 1, n 2	LSMD (95% CI)	P Value
Average morning and evening rTNSS (primary end point)			
GSP301 vs placebo	291, 290	−1.09 (−1.49 to −0.69)	<.001 ^b
GSP301 vs olopatadine	291, 290	−0.44 (−0.84 to −0.05)	.03 ^b
GSP301 vs mometasone	291, 293	−0.47 (−0.86 to −0.08)	.02 ^b
Olopatadine vs placebo	290, 290	−0.64 (−1.04 to −0.25)	.001 ^b
Mometasone vs placebo	293, 290	−0.62 (−1.01 to −0.22)	.002 ^b
Average morning and evening iTNSS (secondary end point)			
GSP301 vs placebo	291, 290	−0.94 (−1.32 to −0.56)	<.001 ^b
GSP301 vs olopatadine	291, 290	−0.41 (−0.78 to −0.03)	.04 ^b
GSP301 vs mometasone	291, 293	−0.51 (−0.88 to −0.13)	.008 ^b
Olopatadine vs placebo	290, 290	−0.54 (−0.92 to −0.16)	.005 ^b
Mometasone vs placebo	293, 290	−0.44 (−0.81 to −0.06)	.02 ^b

The mixed-effect repeated-measures analysis used change from baseline as the dependent variable, treatment group and site as the fixed effects, baseline as the covariate, and study day as the within-patient effect.

Abbreviations: FAS, full analysis set; iTNSS, instantaneous Total Nasal Symptom Score; LSMD, least squares mean difference; MMRM, mixed-effect model repeated measures; rTNSS, reflective Total Nasal Symptom Score.

^aThe GSP301 group received 665 µg of olopatadine and 25 µg of mometasone twice daily, the olopatadine group received 665 µg twice daily, and the mometasone group received 25 µg twice daily.

^bSignificant difference ($P < .05$) vs treatment group 2 using gatekeeping strategy.

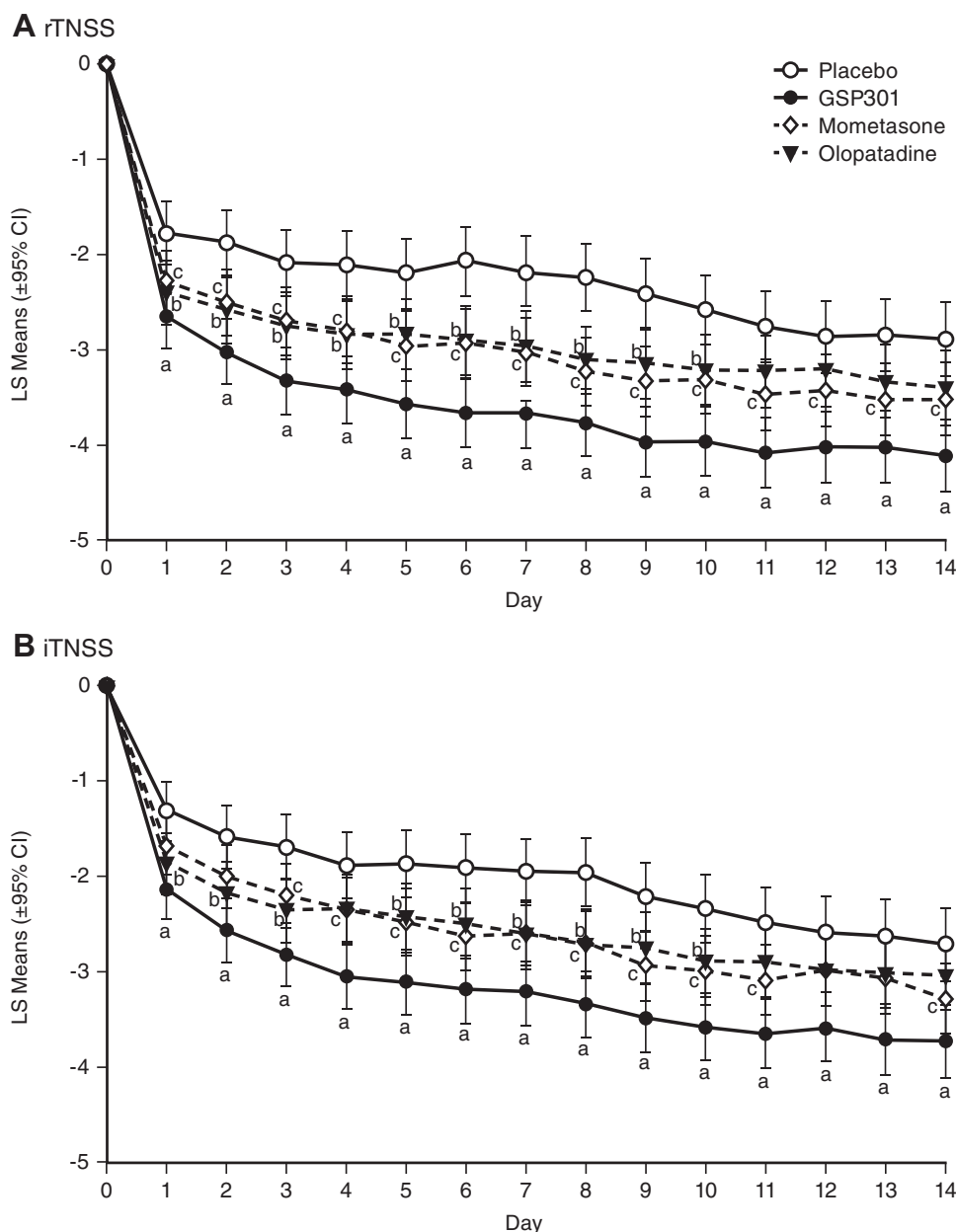


Figure 2. Treatment comparisons of average morning and evening reflective Total Nasal Symptom Score (rTNSS) (A) and instantaneous Total Nasal Symptom Score (iTNSS) (B) during 14 days of treatment (full analysis set). The GSP301 group received 665 μg of olopatadine and 25 μg of mometasone twice daily, the olopatadine group received 665 μg twice daily, and the mometasone group received 25 μg twice daily. Mixed-effect repeated-measures analysis used change from baseline as the dependent variable, treatment group and site as the fixed effects, baseline as the covariate, and study day as the within-patient effect. Abbreviations: CI, confidence interval; FAS, full analysis set; iTNSS, instantaneous Total Nasal Symptom Score; LS, least squares; MMRM, mixed-effect model repeated measures; rTNSS, reflective Total Nasal Symptom Score.

^aSignificant difference ($P < .05$) for GSP301 vs placebo.

^bSignificant difference ($P < .05$) for olopatadine vs placebo.

^cSignificant difference ($P < .05$) for mometasone vs placebo.

baseline to the end of 14-day treatment vs placebo (olopatadine: $P = .005$; mometasone: $P = .02$) (Table 2). When assessed by individual day, significant improvements with GSP301 treatment vs placebo on the average morning and evening iTNSS were demonstrated from day 1 through day 14 (Fig. 2B), suggesting sustained daily improvement. Olopatadine monotherapy treatment resulted in significant improvements compared with placebo on days 1 to 3 and 5 to 10 ($P < .05$ for all), and improvements with mometasone were significant on days 3 to 11 and 14 ($P < .05$ for all) (Fig. 2B).

Average Morning and Evening Individual Nasal Symptoms

GSP301 significantly improved all average morning and evening reflective and instantaneous individual nasal symptoms vs placebo during the 14-day treatment period ($P < .001$ for all) (Table 3). Both monotherapies provided significant improvements compared with placebo on average morning and evening individual nasal symptoms ($P \leq .05$ for all) (eTable 2), with the exception of olopatadine on instantaneous and reflective nasal congestion (instantaneous: $P = .11$; reflective: $P = .06$) and mometasone on instantaneous nasal itching ($P = .15$) (eTable 2).

Table 3Treatment Comparisons of Individual Reflective and Instantaneous Nasal Symptom Scores for GSP301 vs Placebo During 14 Days of Treatment (FAS)^a

GSP301 vs Placebo	n 1, n 2	LSMD (95% CI)	P Value
Reflective			
Rhinorrhea	291, 290	−0.30 (−0.41 to −0.19)	<.001 ^b
Nasal congestion	291, 290	−0.20 (−0.30 to −0.09)	<.001 ^b
Nasal itching	291, 290	−0.23 (−0.34 to −0.12)	<.001 ^b
Sneezing	291, 290	−0.41 (−0.53 to −0.29)	<.001 ^b
Instantaneous			
Rhinorrhea	291, 290	−0.29 (−0.39 to −0.18)	<.001 ^b
Nasal congestion	291, 290	−0.19 (−0.29 to −0.09)	<.001 ^b
Nasal itching	291, 290	−0.21 (−0.32 to −0.10)	<.001 ^b
Sneezing	291, 290	−0.29 (−0.41 to −0.18)	<.001 ^b

The mixed-effect repeated-measures analysis used change from baseline as the dependent variable, treatment group and site as the fixed effects, baseline as the covariate, and study day as the within-patient effect.

Abbreviations: FAS, full analysis set; LSMD, least squares mean difference; MMRM, mixed-effect model repeated measures.

^aThe GSP301 group received 665 µg of olopatadine and 25 µg of mometasone twice daily.

^bSignificant difference ($P < .05$) vs placebo.

Average Morning TNSS and Average Evening TNSS

When analyzed separately, GSP301 treatment resulted in significantly greater improvements vs placebo on the average morning and the evening rTNSS (morning least squares mean difference [LSMD], −1.19; 95% CI, −1.60 to −0.78; $P < .001$; evening LSMD, −1.16; 95% CI, −1.56 to −0.75; $P < .001$) and the average morning and evening iTNSS (morning LSMD, −1.10; 95% CI, −1.49 to −0.71; $P < .001$; evening LSMD, −0.95; 95% CI, −1.35 to −0.56; $P < .001$). GSP301 provided significantly greater improvements on the average morning rTNSS, evening rTNSS, and morning iTNSS vs both monotherapies ($P \leq .05$ for all) (eTable 3); the difference between GSP301 and olopatadine on the evening iTNSS was not statistically significant. ($P = .06$). Both olopatadine and mometasone treatments resulted in significant improvements compared with placebo on the average morning and evening

rTNSS and iTNSS ($P \leq .05$ for all) (eTable 3). GSP301 significantly improved each individual nasal symptom of the morning only and evening only rTNSS and iTNSS vs placebo ($P < .001$ for all; data not shown).

Onset of Action

Onset of action for GSP301 was observed at 15 minutes (first timepoint assessed: LSMD −0.34; 95% CI, −0.65 to −0.04; $P = .03$), and all subsequent time points were significant compared with placebo ($P < .05$ for all) (Fig. 3). Similar results were observed for olopatadine, which had an onset of action of 15 minutes (LSMD −0.34; 95% CI, −0.64 to −0.03; $P = .03$); all time points up to 4 hours after dosing were significantly different from placebo. Onset of action for mometasone could not be determined because there was no statistically significant difference in iTNSS vs placebo at any time point up to 4 hours (Fig. 3).

Patient-Reported Ocular Symptoms

Average Morning and Evening TOSS

GSP301 demonstrated significant improvements in average morning and evening 12-hour rTOSS from baseline to the end of 14-day treatment vs placebo ($P = .001$) (Table 4). The difference between GSP301 and olopatadine was not statistically significant ($P = .30$), and as a result, all further treatment comparisons were not considered statistically significant per the gatekeeping strategy, including the comparison between GSP301 and mometasone ($P = .03$) (Table 4).

Similar to the rTOSS results, GSP301 provided significant improvements vs placebo on the average morning and evening 12-hour iTOSS during the 14-day treatment period ($P = .001$) (Table 4). The comparison between GSP301 and olopatadine was not statistically significant ($P = .23$). GSP301 treatment resulted in significantly greater improvements compared with mometasone ($P = .02$). Olopatadine provided greater improvements vs placebo (LSMD, −0.31; $P = .04$), whereas the comparison between mometasone and placebo did not reach statistical significance ($P = .36$) (Table 4).

On each individual ocular symptom of the average morning and evening rTOSS and iTOSS, GSP301 provided significant improvements vs placebo ($P < .05$ for all) (eTable 4).

Physician-Assessed Nasal Symptoms

GSP301 significantly improved PNSS vs placebo ($P < .001$) and olopatadine ($P = .001$) from baseline to day 15 (Table 4). The difference between GSP301 and mometasone did not reach statistical significance ($P = .26$). Compared with placebo, both olopatadine ($P = .01$) and mometasone ($P < .001$) provided significant improvements (Table 4). GSP301 also significantly improved each individual PNSS symptom—rhinorrhea, nasal congestion, nasal itching, and sneezing—vs placebo ($P < .001$ for all; data not shown).

Rhinoconjunctivitis Quality-of-Life Questionnaire—Standardized Activities

Significant improvement in overall RQLQ(S) score from baseline to day 15 was observed with GSP301 vs placebo ($P < .001$) (Table 4). GSP301 treatment also resulted in significant improvement in the overall score compared with olopatadine ($P = .009$); however, improvement with GSP301 vs mometasone did not reach statistical significance ($P = .42$). Although improvement with olopatadine vs placebo was not significant ($P = .22$), mometasone provided significant improvement vs placebo ($P = .002$) (Table 4). In addition to improvement in the overall score, most individual domain scores were significantly improved with GSP301 treatment vs placebo ($P < .05$ for all aside from practical problems [$P = .46$] and emotional scores [$P = .74$]; data not shown).

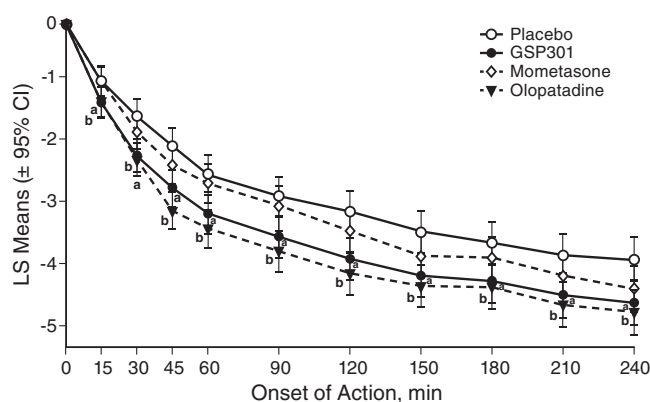


Figure 3. Onset of action for active treatments vs placebo (full analysis set). The GSP301 group received 665 µg of olopatadine and 25 µg of mometasone twice daily, the olopatadine group received 665 µg twice daily, and the mometasone group received 25 µg twice daily. Onset of action was the first postdose time point at which significant differences in iTNSS change from baseline between the active treatment and placebo were observed as long as the significant difference was sustained. Mixed-effect repeated-measures analysis used change from baseline as the dependent variable, treatment group and site as the fixed effects, baseline as the covariate, and study day as the within-patient effect. Abbreviations: FAS, full analysis set; iTNSS, instantaneous Total Nasal Symptom Score; LS, least squares; MMRM, mixed-effect model repeated measures.

^aSignificant difference ($P < .05$) for GSP301 vs placebo.

^bSignificant difference ($P < .05$) for olopatadine vs placebo.

Table 4Baseline to End of Treatment Comparisons of TOSS, PNSS, RQLQ(S), and RCAT (FAS)^a

Treatment Groups (1 versus 2)	n 1, n 2	LSMD	95% CI	P value
Average AM and PM 12-hour rTOSS				
GSP301 versus Placebo	291, 290	−0.52	−0.84, −0.20	.001 ^b
GSP301 versus Olopatadine	291, 290	−0.17	−0.48, 0.15	.297
GSP301 versus Mometasone	291, 293	−0.35	−0.66, −0.03	.030 ^c
Olopatadine versus Placebo	290, 290	−0.35	−0.67, −0.04	.029 ^c
Mometasone versus Placebo	293, 290	−0.17	−0.49, 0.14	.282
Average AM and PM 12-hour iTOSS				
GSP301 versus Placebo	291, 290	−0.50	−0.81, −0.19	.001 ^b
GSP301 versus Olopatadine	291, 290	−0.19	−0.49, 0.12	.227
GSP301 versus Mometasone	291, 293	−0.36	−0.66, −0.05	.021 ^b
Olopatadine versus Placebo	290, 290	−0.31	−0.62, −0.01	.045 ^b
Mometasone versus Placebo	293, 290	−0.14	−0.45, 0.16	.357
PNSS				
GSP301 versus Placebo	292, 290	−1.30	−1.75, −0.85	<.001 ^b
GSP301 versus Olopatadine	292, 290	−0.73	−1.17, −0.28	.001 ^b
GSP301 versus Mometasone	292, 293	−0.25	−0.70, 0.19	.263
Olopatadine versus Placebo	290, 290	−0.57	−1.02, −0.13	.012 ^b
Mometasone versus Placebo	293, 290	−1.05	−1.49, −0.60	<.001 ^b
RQLQ(S) score				
GSP301 versus Placebo	283, 280	−0.45	−0.68, −0.22	<.001 ^b
GSP301 versus Olopatadine	283, 276	−0.31	−0.54, −0.08	.009 ^b
GSP301 versus Mometasone	283, 280	−0.09	−0.32, 0.14	.424
Olopatadine versus Placebo	276, 280	−0.14	−0.38, 0.09	.222
Mometasone versus Placebo	280, 280	−0.36	−0.59, −0.13	.002 ^b
RCAT score				
GSP301 versus Placebo	290, 289	2.33	1.49, 3.17	<.001 ^b
GSP301 versus Olopatadine	290, 290	1.25	0.42, 2.09	.003 ^b
GSP301 versus Mometasone	290, 291	0.85	0.01, 1.68	.046 ^b
Olopatadine versus Placebo	290, 289	1.07	0.24, 1.91	.012 ^b
Mometasone versus Placebo	291, 289	1.48	0.65, 2.32	<.001 ^b

Abbreviations: FAS, full analysis set; LS, least squares; LSMD, least squares mean difference; iTOSS, instantaneous Total Ocular Symptom Score; PNSS, Physician-assessed Nasal Symptom Scores; RCAT, Rhinitis Control Assessment Test; RQLQ(S), Rhinoconjunctivitis Quality-of-Life Questionnaire—Standardized Activities; rTOSS, reflective Total Ocular Symptom Score.

^aThe GSP301 group received 665 µg of olopatadine and 25 µg of mometasone twice daily, the olopatadine group received 665 µg twice daily, and the mometasone group received 25 µg twice daily.

^bSignificant difference ($P < .05$) vs treatment group 2.

^cNot statistically significant per gatekeeping strategy.

Rhinitis Control Assessment Test

GSP301 significantly improved RCAT scores from baseline to day 15 vs placebo ($P < .001$) (Table 4), olopatadine ($P = .003$), and mometasone ($P = .046$). Olopatadine and mometasone treatment resulted in significant improvements compared with placebo (oloapatadine: $P = .01$; mometasone: $P < .001$) (Table 4). In addition, GSP301 significantly improved all individual question (domain) scores compared with placebo ($P < .01$ for all; data not shown).

Safety

Of the 1175 patients in the SAS population, 139 (11.8%) experienced 1 or more treatment-emergent AE (TEAE). Most TEAEs were mild or moderate in severity and were not considered related to treatment (Table 5). The percentage of patients reporting TEAEs was generally similar among treatments, with a greater percentage in GSP301 and olopatadine treatments than in placebo or

Table 5Summary of Adverse Events (SAS)^a

Adverse Event	No. (%) of Adverse Events			
	GSP301 (n = 294)	Olopatadine (n = 294)	Mometasone (n = 293)	Placebo (n = 294)
Patients reporting ≥ 1 TEAE	46 (15.6)	37 (12.6)	28 (9.6)	28 (9.5)
TEAEs ^b				
Nasal discomfort	3 (1.0)	3 (1.0)	4 (1.4)	5 (1.7)
Dysgeusia	11 (3.7)	2 (0.7)	0 (0)	0 (0)
Epistaxis	2 (0.7)	3 (1.0)	3 (1.0)	3 (1.0)
Upper respiratory tract infection	1 (0.3)	3 (1.0)	1 (0.3)	1 (0.3)
Nasal dryness	0 (0)	3 (1.0)	0 (0)	0 (0)
Urinary tract infection	3 (1.0)	0 (0)	0 (0)	0 (0)
Patients with SAEs ^c	0 (0)	2 (0.7) ^d	1 (0.3) ^e	1 (0.3) ^f
Deaths	0 (0)	0 (0)	0 (0)	0 (0)

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

^aThe GSP301 group received 665 µg of olopatadine and 25 µg of mometasone twice daily, the olopatadine group received 665 µg twice daily, and the mometasone group received 25 µg twice daily.

^bOccurring in 1% or more of patients in any treatment group.

^cAll SAEs were judged by the investigator as not related to study treatment.

^dDiverticulitis, large intestinal obstruction, and large intestinal perforation in 1 patient and ischemic stroke in 1 patient.

^ePeritonsillar abscess.

^fFoot fracture, syncope, and osteomyelitis; foot fracture led to study withdrawal.

mometasone treatments. The most frequently reported TEAEs were nasal discomfort ($n = 15$), dysgeusia ($n = 13$; reported as a bad/bitter taste in mouth/throat), and epistaxis ($n = 11$); only dysgeusia occurred in 2% or more of patients in any treatment group (GSP301). Four patients experienced 8 serious AEs (SAEs); none were considered related to study treatment (Table 5). One SAE (foot fracture) led to study withdrawal (placebo group); 3 additional patients were withdrawn because of a TEAE, all in the olopatadine group: bronchitis ($n = 1$; considered unrelated to treatment), upper respiratory tract infection ($n = 1$; considered unrelated), and seizure ($n = 1$; considered related). All 4 AEs that led to discontinuation were not clinically significant and recovered or resolved with sequelae. No deaths occurred in the study. No clinically significant findings were observed for vital signs or ECGs. None of the clinically significant results on ENT examinations, laboratory assessments, or physical examinations led to study discontinuation.

Discussion

For many patients with AR, nasal symptom control is inadequate, with almost half reporting somewhat or poor symptom control with pharmacologic treatment.¹⁰ Because patients desire treatments that provide fast, long-lasting effectiveness,^{6,10} the ideal therapeutic agent would effectively address the pathophysiologic mechanisms of both acute- and late-phase allergic reactions.³⁰

In this study, twice-daily treatment with GSP301 FDC nasal spray resulted in statistically significant and clinically meaningful²¹ improvements in SAR nasal symptoms compared with placebo and the individual component monotherapies olopatadine and mometasone. Symptom improvement with GSP301 was rapid (15 minutes) and sustained for 14 days of treatment. Although both monotherapies were efficacious in relieving the average morning and evening 12-hour instantaneous and reflective nasal symptoms, GSP301 provided greater improvements than either monotherapy alone. Improvements in each of the individual nasal symptoms support the efficacy of GSP301 for treating all nasal symptom components of SAR. When morning and evening nasal symptoms (rTNSS/iTNSS) were analyzed separately, GSP301 resulted in greater improvements than placebo and monotherapies, both in the morning and in the evening, on nearly all comparisons. The significant nasal symptom improvements seen with GSP301 vs placebo in the predose morning and predose evening iTNSS indicate that efficacy was maintained during the entire 12-hour dosing interval.

The improvements in nasal symptoms with GSP301 twice-daily were not only statistically significant but are considered clinically meaningful. MCIDs are widely used thresholds for patient-reported outcomes that reflect the changes in measures at which patients perceive improvements with a particular intervention.³¹ The concept of MCIDs has emerged in clinical studies because statistical differences (or lack thereof) between treatments are sometimes found to be at odds with clinical experience. For the TNSS (0- to 12-point scale), the MCID of 0.23 units was derived using a direct anchor-based regression method as the lower threshold.²¹ In the present study, the statistically significant improvements in nasal symptoms with GSP301 vs placebo or individual monotherapies were considered clinically meaningful in that the LSMDs exceeded the specified MCID of 0.23 for both rTNSS and iTNSS. The LSMDs for both monotherapies vs placebo were also greater than the MCID of 0.23 units.²¹

GSP301 had a rapid onset of action of 15 minutes in this study and in another similarly designed phase 3 clinical study,³² which is shorter than the 30-minute onset observed in a natural allergen study of another intranasal FDC that contained the antihistamine azelastine and the corticosteroid fluticasone (AzeFlu).³³ When tested in a more highly controlled environmental exposure chamber study, significant iTNSS improvements with azelastine-

fluticasone were seen at 5 minutes.³⁴ In an environmental exposure chamber study of GSP301, the first of 2 consecutive time points on the iTNSS where GSP301 significantly differed from placebo occurred at 10 minutes, and this significant difference was maintained at 11 of 12 subsequent timepoints.²² Future adequately designed comparative studies are needed to compare the overall efficacy and onset of action of azelastine-fluticasone and GSP301. The rapid onset of GSP301 in the present study may be attributed primarily to the olopatadine monotherapy component, which relieved symptoms within 15 minutes, whereas the onset of mometasone monotherapy could not be determined. The onset of action for olopatadine in this study was shorter than that observed in studies of the marketed olopatadine monotherapy (30 minutes).^{35,36} Previous studies of mometasone have found an onset ranging from 150 minutes³⁶ to 11 hours³⁷; with such a large range, it is possible that if the evaluation period in the current study had been longer than 4 hours that the mometasone onset could have been determined. Despite this, mometasone significantly improved rTNSS on all 14 days and significantly improved iTNSS on 10 of 14 days, suggesting sustained relief. The reasons for the differences in onset of the constituent monotherapies between this study and others is unclear. Overall, the results of the current study indicate that nasal symptom improvement with GSP301 FDC was rapid and sustained during the entire 14-day treatment period, demonstrating its efficacy for both acute- and late-phase allergic reactions.

In addition to improvements in nasal symptoms, treatment with GSP301 also resulted in significant ocular symptom relief compared with placebo. This finding is important because many patients with SAR have both nasal and ocular symptoms,^{10,38} which can impair QoL.^{7,38} Indeed, the relief of nasal and ocular SAR symptoms with GSP301 vs placebo in the present study may have helped improve QoL because RQLQ(S) scores were significantly improved with GSP301 vs placebo (treatment difference of -0.45 ; $P < .001$), although the difference from placebo was slightly below the established MCID of 0.50 units for this measure.³⁹

Results from this study are consistent with those from other clinical studies of GSP301 in patients with SAR.^{22,23,40} The current data indicate that the FDC GSP301 effectively relieves SAR nasal symptoms vs placebo and the component monotherapies. These results are also similar to those from study of the FDC azelastine-fluticasone, which provided greater improvements in nasal SAR symptoms than placebo and the constituent monotherapies.³³ Cross-study comparisons between azelastine-fluticasone and GSP301 are not currently possible because these clinical studies were conducted under widely varying conditions and designs. For example, in the pivotal phase 3 studies of azelastine-fluticasone,⁴¹ symptoms were assessed twice daily (morning and evening), and TNSS was calculated using a 12-point scale that summed the morning and evening values (total maximum score of 24 per day), whereas TNSS in the current study was calculated using a 12-point scale that averaged the morning and evening values (total maximum daily score of 12). Thus, caution should be exercised when comparing the efficacy results of different treatments across different clinical studies without normalization of scores when possible.

GSP301 was safe and well tolerated and had similar incidences of AEs compared with placebo or individual monotherapies. The most commonly reported TEAE was dysgeusia, which occurred more frequently in the GSP301 group. Of the 4 SAEs that occurred during study treatment, none were considered related to treatment. These results are similar to those observed in several early clinical studies of GSP301 in patients with^{22,23} and without SAR,^{42,43} in another short-term phase 3 clinical study of patients with SAR,²⁴ and in a long-term phase 3 study of patients with PAR,²⁵ confirming that GSP301 has a favorable safety and tolerability profile.

In conclusion, these results demonstrate that GSP301 is efficacious and well tolerated vs placebo for the treatment of nasal and ocular symptoms associated with SAR in adult and adolescent patients 12 years and older.

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Supplementary Data

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Supplementary Data

Additional Key Exclusion Criteria

Patients were not allowed to travel outside the known pollen area for the investigative site for (1) 24 hours or more during the last 7 days of the run-in period or (2) 2 or more consecutive days OR 3 or more days total between randomization (visit 2) and final treatment (visit 4). Patients could not have impaired hepatic function; gastrointestinal disease; subcapsular cataracts, glaucoma, or other ocular disturbances; a systemic infection; malignant tumor (excluding basal cell carcinoma); current neuropsychological condition with or without drug therapy; cardiovascular disease (eg, uncontrolled hypertension); hepatic, hematologic, renal, or endocrine disorder (except for postmenopausal symptoms or hypothyroidism); known failure to show allergic rhinitis symptom improvement with any approved monotherapy component of GSP301; or respiratory disease other than mild asthma.

Prohibited Medications

Use of the following was not permitted during the study or for a specified number of days before screening: vasoconstrictors or major tranquilizers (3 days prior); short-acting antihistamines (5 days prior); over-the-counter products that contained antihistamines, topical, oral, or nasal decongestants, food supplements or diet to reduce leukotrienes, leukotriene antagonists (7 days prior); long-acting antihistamines (10 days prior); cromolyn, nedocromil, lodoxamide, systemic antibiotics, ocular mast cell stabilizers, monoamine oxidase inhibitors, tricyclic antidepressants (14 days prior); nonstudy intranasal, topical, ocular, or inhaled corticosteroids, investigational nonbiological drugs, cytochrome P450 inducers or inhibitors (30 days prior); systemic corticosteroids, immunotherapy injections, immunosuppressive/immunomodulating medications (60 days prior); IgE antagonist, investigational biological drugs, anti-interleukin-5 treatment (120 days); or sublingual immunotherapy (180 days). Patients with mild asthma were eligible if treatment was limited to only inhaled short-acting β -agonists (up to 8 puffs per day).

Key Randomization Criteria

Only patients who met the following symptom 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) were eligible for randomization: an average morning and evening 12-hour reflective Total Nasal Symptom Score (rTNSS) score of 8 or more out of 12, with an average congestion score of 2 or higher, and an average morning and evening 12-hour reflective Total Ocular Symptom Score (rTOSS) of 4 or more out of 9. In addition, patients were required to have an average morning and evening 12-hour instantaneous TNSS (iTNSS) of 8 or more out of 12 with an average congestion score of 2 or higher at the start of the onset of action assessment.

Additional Assessment Details

Each TNSS and TOSS symptom was rated on a 4-point severity scale with scores of 0 (absent), 1 (mild), 2 (moderate), or 3 (severe) (eTable 1). Symptoms were reported as reflective (occurring during the previous 12 hours) and instantaneous (occurring during the 10 minutes before dosing). The daily TNSS can be calculated as either a 12-point (averaging the morning and evening values) or a 24-point scale (summing the morning and evening values); for this study, the daily TNSS were calculated as a 12-point scale.

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])² was self-administered during visits 2 and 4. It consists of 28 questions in 7 domains: activities, sleep, non-nose or eye symptoms, practical problems, nasal symptoms, eye problems, and emotional. The Rhinitis Control Assessment Test (RCAT) is a self-administered questionnaire that contains 6 questions (domains) about allergic rhinitis symptom control during the prior week. A total score ranging from 6 to 30 is calculated by adding the ratings for all questions, with higher scores indicating better control.³

Additional Statistical Analysis Information

Baseline for TNSS and TOSS was defined as the average of the last 8 scores obtained during the last 4 days of the placebo run-in period, including the morning assessment at visit 2. Average morning and evening 12-hour TNSS and TOSS were assessed as the change from baseline for each day and then averaged during the 14-day treatment period. To adjust for multiplicity, treatment comparisons for rTNSS, iTNSS, and rTOSS were made using a gate-keeping strategy. No further treatment comparisons were conducted if GSP301 vs placebo did not reach statistical significance ($P < .05$). If statistically significant, then the following comparisons were performed in order until one was $P > .05$ using the following comparison hierarchy: (1) GSP301 vs placebo, (2) GSP301 vs olopatadine, (3) GSP301 vs mometasone, (4) olopatadine vs placebo, and (5) mometasone vs placebo.

For all efficacy end points, the interactions of site by treatment and baseline by treatment were investigated separately in the model and were only included if they reached statistical significance (defined as $\alpha = .05$). Unless otherwise noted, all analyses were 2-sided, and statistical significance was set at $P < .05$. Descriptive statistics were used to summarize baseline demographic variables and safety evaluations by treatment group. All statistical analyses were conducted using SAS statistical software, version 9.3 or higher (SAS Institute Inc, Cary, North Carolina).

Sample Size

To assess the superiority of GSP301 compared with placebo, a sample size of 279 patients per treatment group would have a 94% power to detect a between-treatment group difference of 0.9 units (assuming a standard deviation [SD] of 3.0) in the absolute change from baseline in average morning and evening 12-hour rTNSS during the 14-day treatment period. This sample size would also provide 94% power to detect a between-treatment group difference of 0.6 units (assuming an SD of 2.0) in the absolute change from baseline in average morning and evening 12-hour rTNSS during the 14-day treatment period between GSP301 and each monotherapy. Finally, 279 patients per treatment would provide 90% power to detect a treatment difference of 0.55 units (assuming an SD of 2.0) in the absolute change from baseline in average morning and evening 12-hour rTNSS during the 14-day treatment period between each monotherapy and placebo. Thus, a total of approximately 1176 patients (294 per treatment group) were to be randomized, assuming a dropout rate of 5%.

Average Morning and Evening TNSS: Individual Nasal Symptom Results

The differences in average morning and evening reflective and instantaneous individual nasal symptoms for all active treatments vs placebo and GSP301 vs olopatadine and mometasone are presented in eTable 2.

Average Morning TNSS and Average Evening TNSS Results

The differences in the average morning TNSS and average evening TNSS for all active treatments vs placebo and for GSP301 vs each monotherapy are given in eTable 3.

Average Morning and Evening 12-Hour TOSS: Individual Ocular Symptom Results

Differences between the GSP301 and placebo treatments on each individual ocular symptom of the average morning and evening rTOSS and iTOSS are presented in eTable 4. In addition to ocular symptom improvement vs placebo, GSP301 significantly improved the non-nasal symptom itching of ears or palate vs placebo (average morning and evening instantaneous and reflective; $P < .001$ for both; data not shown).

eTable 1

Description of Severity Rating Scores for Nasal and Ocular Symptom Scales^a

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

^aData are from the US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research.⁴

eTable 2

Treatment Comparisons of Average Morning and Evening Reflective and Instantaneous Individual Nasal Symptom Scores During 14 Days of Treatment (FAS)^a

Treatment Groups (1 vs 2)	n 1, n 2	LSMD (95% CI)	P Value
Reflective			
Rhinorrhea			
GSP301 vs placebo	291, 290	−0.30 (−0.41 to −0.19)	<.001 ^b
GSP301 vs olopatadine	291, 290	−0.16 (−0.27 to −0.06)	.003 ^b
GSP301 vs mometasone	291, 293	−0.14 (−0.24 to −0.03)	.01 ^b
Olopatadine vs placebo	290, 290	−0.13 (−0.24 to −0.02)	.02 ^b
Mometasone vs placebo	293, 290	−0.16 (−0.27 to −0.05)	.003 ^b
Nasal congestion			
GSP301 vs placebo	291, 290	−0.20 (−0.30 to −0.09)	<.001 ^b
GSP301 vs olopatadine	291, 290	−0.09 (−0.20 to 0.01)	.07
GSP301 vs mometasone	291, 293	−0.04 (−0.14 to 0.07)	.51
Olopatadine vs placebo	290, 290	−0.10 (−0.21 to 0.00)	.06
Mometasone vs placebo	293, 290	−0.16 (−0.27 to −0.06)	.002 ^b
Nasal itching			
GSP301 vs placebo	291, 290	−0.23 (−0.34 to −0.12)	<.001 ^b
GSP301 vs olopatadine	291, 290	−0.06 (−0.17 to 0.05)	.28
GSP301 vs mometasone	291, 293	−0.12 (−0.23 to −0.01)	.04 ^b
Olopatadine vs placebo	290, 290	−0.17 (−0.28 to −0.06)	.003 ^b
Mometasone vs placebo	293, 290	−0.11 (−0.22, 0.00)	.047 ^b
Sneezing			
GSP301 vs placebo	291, 290	−0.41 (−0.53 to −0.29)	<.001 ^b
GSP301 vs olopatadine	291, 290	−0.16 (−0.28 to −0.05)	.006 ^b
GSP301 vs mometasone	291, 293	−0.21 (−0.33 to −0.10)	<.001 ^b
Olopatadine vs placebo	290, 290	−0.25 (−0.37 to −0.13)	<.001 ^b
Mometasone vs placebo	293, 290	−0.20 (−0.31 to −0.08)	<.001 ^b
Instantaneous			
Rhinorrhea			
GSP301 vs placebo	291, 290	−0.29 (−0.39 to −0.18)	<.001 ^b
GSP301 vs olopatadine	291, 290	−0.17 (−0.27 to −0.07)	.001 ^b
GSP301 vs mometasone	291, 293	−0.16 (−0.26 to −0.05)	.003 ^b
Olopatadine vs placebo	290, 290	−0.12 (−0.22 to −0.01)	.03 ^b
Mometasone vs placebo	293, 290	−0.13 (−0.23 to −0.02)	.02 ^b
Nasal congestion			
GSP301 vs placebo	291, 290	−0.19 (−0.29 to −0.09)	<.001 ^b
GSP301 vs olopatadine	291, 290	−0.11 (−0.21 to −0.02)	.02 ^b
GSP301 vs mometasone	291, 293	−0.07 (−0.17 to 0.02)	.13
Olopatadine vs placebo	290, 290	−0.08 (−0.18 to 0.02)	.11
Mometasone vs placebo	293, 290	−0.12 (−0.21 to −0.02)	.02 ^b
Nasal itching			
GSP301 vs placebo	291, 290	−0.21 (−0.32 to −0.10)	<.001 ^b
GSP301 vs olopatadine	291, 290	−0.07 (−0.18 to 0.04)	.22
GSP301 vs mometasone	291, 293	−0.13 (−0.24 to −0.02)	.02 ^b
Olopatadine vs placebo	290, 290	−0.14 (−0.25 to −0.03)	.01 ^b
Mometasone vs placebo	293, 290	−0.08 (−0.19 to 0.03)	.15
Sneezing			
GSP301 vs placebo	291, 290	−0.29 (−0.41 to −0.18)	<.001 ^b
GSP301 vs olopatadine	291, 290	−0.09 (−0.21 to 0.02)	.10
GSP301 vs mometasone	291, 293	−0.17 (−0.28 to −0.06)	.004 ^b
Olopatadine vs placebo	290, 290	−0.20 (−0.31 to −0.09)	<.001 ^b
Mometasone vs placebo	293, 290	−0.13 (−0.24 to −0.01)	.03 ^b

Abbreviations: CI, confidence interval; FAS, full analysis set; LSMD, least squares mean difference; MMRM, mixed-effect model repeated measures.

^aThe GSP301 group received 665 μg of olopatadine and 25 μg of mometasone twice daily, the olopatadine group received 665 μg twice daily, and the mometasone group received 25 μg twice daily. MMRM analysis used change from baseline as the dependent variable, treatment group and site as the fixed effects, baseline as the covariate, and study day as the within-patient effect.

^bSignificant difference ($P < .05$) vs placebo.

eTable 3

Treatment Comparisons of Average Morning and Average Evening rTNSS and iTNSS During 14 Days of Treatment (FAS)^a

Treatment Groups (1 vs 2)	n 1, n 2	LSMD (95% CI)	P Value
Morning rTNSS			
GSP301 vs placebo	291, 290	−1.19 (−1.60 to −0.78)	<.001 ^b
GSP301 vs olopatadine	291, 290	−0.53 (−0.94 to −0.13)	.01 ^b
GSP301 vs mometasone	291, 293	−0.49 (−0.89 to −0.88)	.02 ^b
Olopatadine vs placebo	290, 290	−0.65 (−1.06 to −0.25)	.002 ^b
Mometasone vs placebo	293, 290	−0.70 (−1.11 to −0.29)	<.001 ^b
Evening rTNSS			
GSP301 vs placebo	291, 291	−1.16 (−1.56 to −0.75)	<.001 ^b
GSP301 vs olopatadine	291, 290	−0.48 (−0.88 to −0.08)	.02 ^b
GSP301 vs mometasone	291, 293	−0.55 (−0.95 to −0.15)	.007 ^b
Olopatadine vs placebo	290, 291	−0.68 (−1.08 to −0.28)	<.001 ^b
Mometasone vs placebo	293, 291	−0.60 (−1.00 to −0.20)	.003 ^b
Morning iTNSS			
GSP301 vs placebo	291, 290	−1.10 (−1.49 to −0.71)	<.001 ^b
GSP301 vs olopatadine	291, 290	−0.52 (−0.91 to −0.14)	.008 ^b
GSP301 vs mometasone	291, 293	−0.58 (−0.96 to −0.19)	.003 ^b
Olopatadine vs placebo	290, 290	−0.58 (−0.96 to −0.19)	.003 ^b
Mometasone vs placebo	293, 290	−0.52 (−0.91 to −0.14)	.008 ^b
Evening iTNSS			
GSP301 vs placebo	291, 291	−0.95 (−1.35 to −0.56)	<.001 ^b
GSP301 vs olopatadine	291, 290	−0.38 (−0.77 to 0.02)	.06
GSP301 vs mometasone	291, 293	−0.51 (−0.90 to −0.12)	.01 ^b
Olopatadine vs placebo	290, 291	−0.58 (−0.97 to −0.18)	.004 ^b
Mometasone vs placebo	293, 291	−0.44 (−0.83 to −0.05)	.03 ^b

Abbreviations: CI, confidence interval; FAS, full analysis set; iTNSS, instantaneous Total Nasal Symptom Score; LSMD, least squares mean difference; MMRM, mixed-effect model repeated measures; rTNSS, reflective Total Nasal Symptom Score.

^aThe GSP301 group received 665 µg of olopatadine and 25 µg of mometasone twice daily, the olopatadine group received 665 µg twice daily, and the mometasone group received 25 µg twice daily. MMRM analysis used change from baseline as the dependent variable, treatment group and site as the fixed effects, baseline as the covariate, and study day as the within-patient effect.

^bSignificant difference ($P < .05$) vs treatment group 2.

eTable 4

Treatment Comparisons of Average Morning and Evening Reflective and Instantaneous Individual Ocular Symptom Scores with GSP301 vs Placebo During 14 Days of Treatment (FAS)^a

Individual Symptoms	LSMD (95% CI)	P Value
Reflective		
Itching or burning eyes	−0.21 (−0.32 to −0.10)	<.001 ^b
Tearing or watering of eyes	−0.20 (−0.31 to −0.08)	<.001 ^b
Redness of eyes	−0.13 (−0.24 to −0.02)	.02 ^b
Instantaneous		
Itching or burning eyes	−0.17 (−0.28 to −0.06)	.002 ^b
Tearing or watering of eyes	−0.18 (−0.29 to −0.07)	.001 ^b
Redness of eyes	−0.17 (−0.28 to −0.06)	.002 ^b

Abbreviations: CI, confidence interval; FAS, full analysis set; LSMD, least squares mean difference; MMRM, mixed-effect model repeated measures.

^aThe GSP301 received 665 µg of olopatadine and 25 µg of mometasone twice daily. Sample sizes were $n = 291$ in the GSP301 and $n = 290$ in the placebo group. MMRM analysis used change from baseline as the dependent variable, treatment group and site as the fixed effects, baseline as the covariate, and study day as the within-patient effect.

^bStatistical significance ($P < .05$) vs placebo.

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