

Long-term safety and efficacy of olopatadine-mometasone combination nasal spray in patients with perennial allergic rhinitis

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ABSTRACT

Background: Safety and efficacy of GSP301 nasal spray, an investigational fixed-dose combination of olopatadine hydrochloride and mometasone furoate, was established in three large, 2-week seasonal allergic rhinitis studies.

Objective: To evaluate long-term (52 weeks) safety and efficacy of GSP301 in patients with perennial allergic rhinitis (PAR).

Methods: In this randomized, double-blind, parallel-group study, 601 patients (ages ≥ 12 years) with PAR were randomized 4:1:1 to twice-daily GSP301 (olopatadine 665 μg and mometasone 25 μg [pH 3.7]) or two GSP301 vehicle formulations (placebo pH 3.7 or 7.0). Safety (primary end point) was monitored through adverse events (AE), laboratory assessments, vital signs, and physical examinations at weeks 30 and 52. The change from baseline in the average A.M. reflective Total Nasal Symptom Score (rTNSS) and instantaneous Total Nasal Symptom Score (iTNSS), Physician-assessed Nasal Symptom Scores (PNSS), and quality of life were assessed for GSP301 versus placebo pH 3.7 ($p < 0.05$ was considered statistically significant).

Results: At week 52, treatment-emergent AEs (TEAE) occurred in 51.7, 41.4, and 53.5% of patients in the GSP301, placebo pH 3.7 and placebo 7.0 groups, respectively. No clinically meaningful differences were observed in TEAE incidences or other safety assessments across treatments. At weeks 6 and 30, GSP301 provided significant and clinically meaningful improvements in average rTNSS and iTNSS versus placebo pH 3.7 ($p < 0.01$, all comparisons). Similarly, at week 52, GSP301 provided significant and clinically meaningful improvements in rTNSS (least-squares mean difference -0.91 [95% confidence interval {CI}, -1.35 to -0.47]; $p < 0.001$), and iTNSS (least-squares mean difference -0.75 [95% CI, -1.17 to -0.33]; $p < 0.001$) versus placebo pH 3.7, with significant improvements in each individual symptom ($p < 0.05$, all comparisons). PNSS and quality of life were significantly improved versus placebo pH 3.7 at weeks 6 and 30 ($p < 0.05$, all comparisons), but these greater improvements did not reach statistical significance at week 52 (PNSS, $p = 0.552$; quality of life, $p = 0.790$).

Conclusion: Twice-daily GSP301 was well tolerated and provided statistically significant and clinically meaningful improvements in PAR nasal symptoms versus placebo over 52 weeks and demonstrated a favorable safety profile and efficacy. Clinical trial NCT02709538, www.clinicaltrials.gov.

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Allergic rhinitis (AR) is an exaggerated nasal inflammatory allergen response characterized by one or more symptoms of nasal congestion, sneezing, rhinorrhea, and nasal itching.¹ One of the most com-

mon chronic diseases,² AR affects 5.6 million children³ and 19.9 million adults in the United States,⁴ with debilitating symptoms that can severely impair quality of life.^{2,5} AR can be categorized as perennial AR (PAR), which occurs year round from allergen exposure, or seasonal AR (SAR), which occurs during a specific

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allergen season. The distinction between the two is not always clear: in tropical climates, seasonal allergens can be present year round, patients with PAR can have exacerbations from seasonal allergens, and mold can be present seasonally and perennially.^{1,6} Among patients with AR, ~20% have SAR, 40% have PAR, and 40% have PAR with seasonal exacerbations.⁷

For patients with persistent allergies, avoidance measures, pharmacological treatment, and consistent medication use (adherence) are key to maintaining symptom control.^{1,8} Unfortunately, AR symptom control is often insufficient, and, as a result, many patients will use multiple prescriptions and/or over-the-counter medications.^{2,9} In addition, long-term use of some AR medications may result in tachyphylaxis (loss of efficacy) over weeks or months, even when taken as prescribed.^{9,10} A fixed-dose combination (FDC) that contains an intranasal antihistamine (azelastine hydrochloride [HCl]) and corticosteroid (fluticasone propionate) has been shown to provide greater relief of SAR nasal symptoms than placebo or either monotherapy component,¹¹ and also provided greater relief of PAR nasal symptoms than did fluticasone monotherapy.¹²

GSP301 is an investigational FDC of the antihistamine olopatadine HCl and the corticosteroid mometasone furoate developed as a single nasal spray for the treatment of SAR symptoms. In short-term (14 days) clinical studies, GSP301 was well tolerated and provided significant, sustained improvements in SAR symptoms versus placebo^{13–16} and the component monotherapies,¹⁵ with a rapid onset of action of 15 minutes.^{15,17}

The main objective of the current study was to evaluate the long-term (52 weeks) safety and tolerability of GSP301 (pH 3.7) compared with two placebo formulations of differing pH (low pH 3.7, neutral pH 7.0) in patients with PAR. In addition, the long-term efficacy of GSP301 compared with placebo pH 3.7 was evaluated (secondary objective). The U.S. Food and Drug Administration (FDA) approved intranasal formulations of olopatadine HCl and mometasone furoate monohydrate both have pHs that are lower than 7.0 (olopatadine, pH ~3.7¹⁸; mometasone, pH 4.3–4.9¹⁹). GSP301 is a combination of sponsor-formulated olopatadine and mometasone in an aqueous suspension with an approximate pH of 3.7. As such, it is possible that the incidence of adverse events (AE) and other safety parameters could be influenced by the low pH (pH 3.7). To address the potential effect of pH, a second placebo with a neutral pH of ~7.0 was also evaluated.

METHODS

This study was conducted at 33 study sites in the United States 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 the Novum Independent Institutional Review Board (Pittsburgh, PA). Adult patients provided written informed consent, and adolescent patients ages 12–17 years (inclusive) provided an assent form.

Study Design

This phase III, double-blind, randomized, parallel-group study consisted of 12 visits, with a placebo run-in period and a treatment period (Fig. 1). After completion of the placebo run-in period, patients who met randomization criteria were randomized (4:1:1) to one of three intranasal treatments: GSP301 (665 µg olopatadine HCl and 25 µg mometasone furoate [pH 3.7]), placebo pH 3.7 (GSP301 vehicle), or placebo pH 7.0 (GSP301 vehicle). All treatments were self-administered as two sprays per nostril twice daily. Use of oral loratadine (10 mg/day) as a rescue medication was permitted on an as-needed basis after week 6 (visit 4) until symptoms were controlled; additional non-nasal medications were provided if loratadine was ineffective. Details regarding prohibited medications are in the Online Supplemental Material and Supplemental Table 1.

Patients

Patients (aged ≥ 12 years) with a clinical history of PAR for ≥ 2 years before the screening visit and clinical evidence of active symptoms, with a positive skin-prick test result for at least one known PAR allergen (e.g., pet allergens and/or dander, house dust mites, indoor molds, cockroaches²⁰); and a wheal diameter at least 3 mm larger than the negative control, were eligible. Patients were expected to continue allergen exposure for the study duration. For randomization, the patients were required to have the following: a minimum average 24-hour A.M. reflective Total Nasal Symptom Score (rTNSS) of ≥5 of 12 and an A.M. reflective nasal congestion score of ≥2 during the last 4 days of the placebo run-in period (last four consecutive A.M. assessments from day –3 to the A.M. assessment on the day of randomization); adequate symptom diary compliance (no missing diary entries ≥ 2 A.M. assessment sessions) during the last 4 days of the run-in period, including the A.M. assessment on the day of randomization; and ≥80% medication compliance during the placebo run-in period. Additional enrollment criteria are provided in the Online Supplemental Material.

Assessments

Safety was monitored *via* AEs; laboratory assessments; vital signs; physical and eye, ear, nose; and

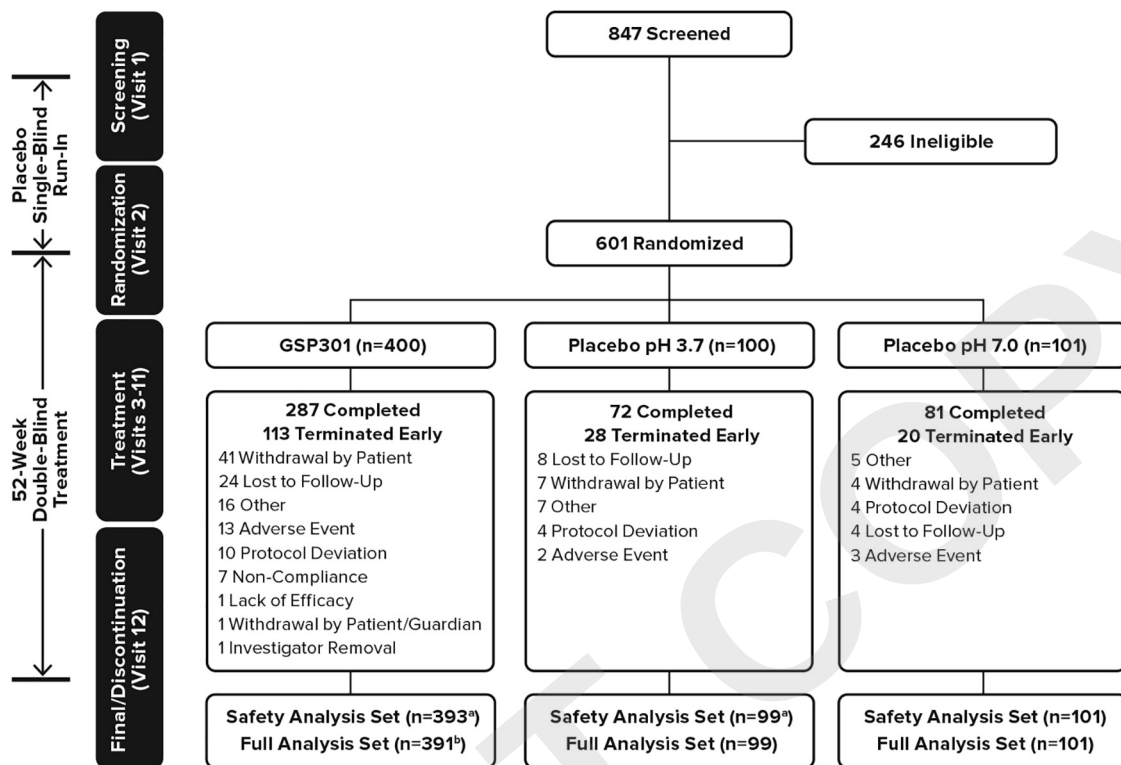


Figure 1. Study design and patient disposition. GSP301, olopatadine 665 μg and mometasone 25 μg (pH 3.7); placebo pH 3.7, GSP301 vehicle; placebo pH 7.0, GSP301 vehicle. The screening visit occurred between day -10 to day -7 before the randomization visit on day 1 (visit 2). Randomization occurred on day 1 (visit 2). Treatment visits 3–11 occurred during weeks 3, 6, 12, 18, 24, 30, 36, 42, and 48, with the final and/or discontinuation visit occurring during week 52 (visit 12). ^aSeven patients in GSP301 and one patient in placebo pH 3.7 were not randomized or did not use the study drug on one or more occasions. ^bTwo patients in GSP301 did not have a postbaseline A.M. reflective Total Nasal Symptom Score (rTNSS) assessment.

throat (ENT) examinations; and electrocardiograms. The patients self-assessed their A.M. reflective (24 hour) and instantaneous nasal symptoms in a symptom diary before self-administering the study medication. Each symptom was rated on a four-point severity scale, which ranged from 0 (absent) to 3 (severe) (Supplemental Table 2). TNSS (rTNSS and instantaneous TNSS [iTNSS]) was defined as the sum of four nasal-symptom scores: rhinorrhea, nasal congestion, nasal itching, and sneezing (maximum score of 12). Additional assessments included the Physician-assessed Nasal Symptom Scores (PNSS),²¹ the Rhinitis Control Assessment Test (RCAT),²² and the Rhinoconjunctivitis Quality-of-Life Questionnaire–Standardized Activities (RQLQ[S]).²³ See Online Supplemental Materials for further details.

End Points

The primary end point was safety assessment at weeks 30 and 52, and included the following: the proportion of patients with treatment emergent AEs (TEAE) and treatment-related TEAEs; incidence, type, and severity of TEAEs; laboratory assessments (hematology, serum biochemistry, and urinalysis); and vital

signs, physical examinations, and focused ENT and eye examinations. Secondary end points were efficacy assessments that included the mean change from baseline to weeks 6, 30, and 52 in patient-reported average A.M. rTNSS and iTNSS as well as the overall RQLQ(S) score. Additional efficacy end points comprised the mean change from baseline in patient-reported average A.M. rTNSS and iTNSS at the end of each treatment week; patient-reported average A.M. reflective and instantaneous individual nasal symptoms at weeks 6, 30, and 52, and at the end of each treatment week; PNSS at weeks 6, 30, and 52; RCAT scores at weeks 6, 30, and 52; and RQLQ(S) scores at weeks 6, 30, and 52.

Statistical Analysis

Descriptive statistics were used to summarize the primary safety results, based on the safety analysis set (SAS) population (defined in the Online Supplemental Materials). For the secondary efficacy analyses, a mixed-effect model repeated measures (MMRM) analysis was used by adjusting for the covariates of treatment, site, baseline, and week as the within-patient effect by using the full analysis set population (defined in the Online Supplemental Materials). For RQLQ(S), a

Table 1 Patient demographics (SAS) and baseline assessment scores (FAS)

Demographics	GSP301*	Placebo pH 3.7#	Placebo pH 7.0§
No. patients	393	99	101
Age, mean $\pm$ SD, y	40.4 $\pm$ 14.8	42.1 $\pm$ 15.4	41.2 $\pm$ 13.5
Sex, n (%)			
Females	269 (68.4)	68 (68.7)	68 (67.3)
Males	124 (31.6)	31 (31.3)	33 (32.7)
Race, n (%)			
White	282 (71.8)	78 (78.8)	76 (75.2)
Black	95 (24.2)	17 (17.2)	22 (21.8)
Asian	10 (2.5)	1 (1.0)	2 (2.0)
Other¶	6 (1.5)	3 (3.0)	1 (1.0)
Ethnicity, n (%)			
Non-Hispanic or Latino	279 (71.0)	73 (73.7)	73 (72.3)
Hispanic or Latino	114 (29.0)	26 (26.3)	28 (27.7)
Baseline assessment scores			
No. patients	391	99	101
Average A.M. rTNSS, mean $\pm$ SD	9.1 $\pm$ 1.9	8.9 $\pm$ 1.9	9.1 $\pm$ 1.8
Average A.M. iTNSS, mean $\pm$ SD	8.1 $\pm$ 2.6	7.7 $\pm$ 2.3	8.1 $\pm$ 2.3
PNSS, mean $\pm$ SD	8.7 $\pm$ 2.1	8.5 $\pm$ 2.2	8.5 $\pm$ 2.1
RCAT, mean $\pm$ SD	14.0 $\pm$ 4.1	14.0 $\pm$ 4.0	14.5 $\pm$ 4.3
RQLQ(S), mean $\pm$ SD	3.4 $\pm$ 1.4	3.3 $\pm$ 1.4	3.2 $\pm$ 1.4

SAS = Safety analysis set; FAS = full analysis set; SD = standard deviation; rTNSS = reflective Total Nasal Symptom Score; iTNSS = instantaneous Total Nasal Symptom Score; PNSS = Physician-assessed Nasal Symptom Score; RCAT, Rhinitis Control Assessment Test; RQLQ(S), Rhinoconjunctivitis Quality-of-Life Questionnaire—Standardized Activities.

* Olopatadine 665 μ g and mometasone 25 μ g (pH 3.7).

Placebo pH 3.7, GSP301 vehicle.

§ Placebo pH 7.0, GSP301 vehicle.

¶ Includes American Indian or Alaska native.

week-by-treatment interaction was also part of the MMRM. Only GSP301 (pH 3.7) and the matching placebo pH 3.7 were compared for efficacy analyses. A treatment difference of >0.23 units (direct anchor-based regression methodology) on the TNSS was considered clinically meaningful (defined as the minimal clinically important difference [MCID]).²⁴ For the TNSS, the subgroups of age, sex, race, and ethnicity were examined to determine if there was an effect of subgroup on efficacy. All analyses were two-sided, and statistical significance was set at $p < 0.05$. Descriptive statistics were used to summarize baseline demographic variables by treatment group (Online Supplemental Materials).

Sample Size

Based on the guidance from the International Conference on Harmonization E1 Guideline and the FDA,²⁵ which required ≥ 300 patients to be enrolled for 6 months and ≥ 100 patients to be enrolled for 1 year, and when assuming an attrition rate of 25% at 6 months and 50% at 52 weeks, a sample size of 600

patients (400 in the GSP301 group and 100 in each placebo group) was considered adequate.

RESULTS

Patients

A total of 601 patients were randomized, and 440 patients completed the study (Fig. 1). Demographics and baseline assessment scores were similar across treatment groups (Table 1). The patients were predominantly female and white, with a mean $\pm$ standard deviation age of 40.8 ± 14.7 years and had moderate-severe nasal symptoms.

Safety

The mean $\pm$ standard deviation duration of treatment exposure was 311.9 ± 111.3 , 322.6 ± 104.5 , and 339.9 ± 77.0 days for GSP301, placebo pH 3.7, and placebo pH 7.0, respectively. More than 90% of the patients in each treatment group achieved $\geq 75\%$ compliance. At week 30, there were no significant differences in the overall TEAE rates between the active and

Table 2 Summary of adverse events over 52 weeks (SAS)

	GSP301, n (%) (n = 393)*	Placebo pH 3.7, n (%) (n = 99)#	Placebo pH 7.0, n (%) (n = 101)§
Patients reported ≥ 1 TEAE	203 (51.7)	41 (41.4)	54 (53.5)
TEAEs reported in $\geq 5\%$ of patients in any treatment group			
Upper respiratory tract infection	25 (6.4)	6 (6.1)	9 (8.9)
Headache	16 (4.1)	3 (3.0)	5 (5.0)
Nasal discomfort	11 (2.8)	2 (2.0)	5 (5.0)
Nasopharyngitis	12 (3.1)	5 (5.1)	6 (5.9)
TEAE severity (patients reported ≥ 1)			
Mild	119 (30.3)	24 (24.2)	29 (28.7)
Moderate	128 (32.6)	28 (28.3)	36 (35.6)
Severe	20 (5.1)	6 (6.1)	3 (3.0)
Patients with ≥ 1 treatment-related TEAE	44 (11.2)	7 (7.1)	10 (9.9)
Treatment-related TEAEs reported in $\geq 5\%$ of patients in any treatment group			
Nasal discomfort	10 (2.5)	2 (2.0)	5 (5.0)
Patients discontinued due to a TEAE	15 (3.8)	2 (2.0)	3 (3.0)
Patients with ≥ 1 SAE	7 (1.8)¶	2 (2.0)	2 (2.0)**
Deaths	0 (0)	0 (0)	0 (0)

SAS = Safety analysis set; TEAE = treatment-emergent adverse event; SAE = serious adverse event.

* Olopatadine 665 μg and mometasone 25 μg (pH 3.7).

Placebo pH 3.7, GSP301 vehicle.

§ Placebo pH 7.0, GSP301 vehicle.

¶ One of each of the following: pneumonia, cellulitis, cholelithiasis, renal cell carcinoma, anaplastic astrocytoma, invasive ductal breast carcinoma.

|| One appendicitis, one ectopic pregnancy.

** One nephrolithiasis, one cholelithiasis.

placebo treatment groups, and most TEAEs were of mild-moderate severity (week 30 data not shown). The overall TEAE rates at week 52 were numerically greater in the placebo pH 7.0 group than in the other two treatment groups (Table 2). Overall TEAE rates were generally comparable between weeks 30 and 52. The most frequently reported TEAEs ($\geq 5\%$) in any treatment group at week 52 were upper respiratory tract infection, nasopharyngitis, nasal discomfort, and headache, all of which occurred more frequently in the placebo pH 7.0 group. Dysgeusia was reported in 0, 1.0, and 2.0% of patients treated with placebo pH 3.7, placebo pH 7.0, and GSP301, respectively. Three patients in the placebo pH 7.0 group experienced foot fractures compared with no patients in each of the other two groups at week 52, although these events were considered unrelated to the study treatment.

Most TEAEs were mild to moderate in severity at week 52 (Table 2). A total of 61 patients experienced TEAEs of special interest. One patient (in the GSP301 group) experienced an asymptomatic nasal septal perforation that was of severe intensity but was determined to be preexisting and considered unrelated to

treatment (Supplemental Table 3). All severe intensity AEs were resolved except for triple-negative breast cancer (negative receptor tests for estrogen, progesterone, and the HER-2 gene; one patient in the GSP301 group). The rate of treatment-related TEAEs was numerically greater in the GSP301 group compared with either placebo group at week 52. The most frequently reported treatment-related TEAE in any treatment group was nasal discomfort (Table 2).

Over 52 weeks, serious AEs (SAE) were experienced by 11 patients, although none of the SAEs were related to treatment: 7 in the GSP301 group, 2 in the placebo pH 3.7 group, and 2 in the placebo pH 7.0 group (Table 2). A total of 18 patients withdrew from the study as a result of a TEAE (Table 2); 3 of the 18 patients experienced SAEs (one ectopic pregnancy in the placebo pH 3.7 group, and one renal cell carcinoma and one anaplastic astrocytoma in the GSP301 group). All TEAEs that led to withdrawal resolved with the exception of two (one patient with herpes zoster and one patient with a liver function test result abnormality), and neither unre-

Table 3 Treatment comparisons of Total Nasal Symptom Scores for GSP301 vs placebo pH 3.7 from baseline to weeks 6, 30, and 52 (FAS)*#

Treatment Groups	Wk	n1, n2	LSMD	95% CI	p
Average A.M. rTNSS: GSP301 vs placebo pH 3.7	6	391, 99	−0.81	−1.29 to −0.32	0.001§
	30¶	391, 99	−0.96	−1.41 to −0.50	<0.001§
	52¶	391, 99	−0.91	−1.35 to −0.47	<0.001§
Average A.M. iTNSS: GSP301 vs placebo pH 3.7	6	391, 99	−0.66	−1.12 to −0.20	0.005§
	30¶	391, 99	−0.83	−1.26 to −0.39	<0.001§
	52¶	391, 99	−0.75	−1.17 to −0.33	0.001§

FAS = full analysis set; n1 = GSP301; n2 = placebo pH 3.7; LSMD = least squares mean difference; CI = confidence interval; rTNSS = reflective Total Nasal Symptom Score; iTNSS = instantaneous Total Nasal Symptom Score; MMRM = mixed-effect model repeated measures.

* MMRM analysis with the change from baseline as the dependent variable, treatment group and site as the fixed effect, baseline as the covariate, and study week as the within-patient effect.

#GSP301, olopatadine 665 µg and mometasone 25 µg (pH 3.7); placebo pH 3.7, GSP301 vehicle.

§ Indicates significance ($p < 0.05$) vs placebo pH 3.7.

¶ Oral rescue medication use was permitted on an as-needed basis after wk 6 (visit 4) until symptoms were controlled.

solved event was related to treatment. No deaths occurred during the study (Table 2).

The majority of the patients had laboratory values, vital signs, and physical examination findings within normal ranges at week 52. The rate of abnormal, clinically significant findings on ENT examinations was low and generally similar across treatment groups (data not shown). There were no abnormal, clinically significant findings on eye examinations in any treatment group (data not shown). Open-angle glaucoma of moderate severity occurred in one patient in the GSP301 group, and intraocular pressure increase of mild severity occurred in one patient in the placebo pH 3.7 group (Supplement Table 3); neither of these events were considered related to treatment.

Efficacy and Quality of Life

Rescue medication (allowed as needed only after week 6) was used by fewer patients in the GSP301 group (35.6%) compared with either the placebo pH 3.7 (46.5%) or placebo pH 7.0 (50.5%) groups. Over the first 6 weeks, during which no rescue medication for AR was allowed, GSP301 treatment resulted in significant and clinically meaningful improvements in patient-reported average A.M. rTNSS and iTNSS compared with placebo ($p < 0.01$, all comparisons) (Table 3). GSP301 also provided significant and clinically meaningful sustained improvements in rTNSS and iTNSS versus placebo over weeks 30 and 52 ($p \leq 0.001$, all comparisons) (Table 3). Greater improvements in rTNSS and iTNSS were reported from week 1 onward (Fig. 2), and the treatment difference remained clinically meaningful (MCID > 0.23 units²⁴) from weeks 1 through 52 and statistically significant at 45 of 52 weekly time points for rTNSS and 40 of 52 for

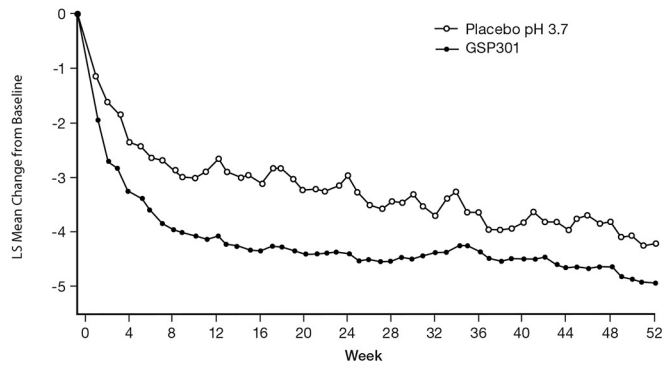
iTNSS ($p < 0.05$, all relevant comparisons). Similar to the overall TNSS, GSP301 significantly improved all average A.M. reflective and instantaneous individual nasal symptoms versus placebo over weeks 6, 30, and 52 ($p < 0.05$, all comparisons) (Table 4). There were no obvious effects on efficacy due to age, sex, or ethnicity. For race, there was no effect observed for the white or black groups; the “other race” group had too few patients to determine if there was an effect.

Statistically significant greater improvements in PNSS were observed with GSP301 versus placebo from baseline to weeks 6 ($p = 0.003$) and 30 ($p = 0.027$); numerically greater improvements were observed over 52 weeks that were not statistically significant ($p = 0.552$) (Table 5). RCAT scores were significantly improved by GSP301 over weeks 6 ($p = 0.003$) and 30 ($p = 0.024$) versus placebo; although the scores over 52 weeks showed numerical improvements in the GSP301 group, they were not statistically significant ($p = 0.151$) (Table 5). Treatment with GSP301 significantly improved RQLQ(S) scores compared with placebo over weeks 6 ($p = 0.004$) and 30 ($p = 0.019$), but improvements over 52 weeks did not reach statistical significance ($p = 0.790$) (Table 5).

DISCUSSION

Over 52 weeks of treatment in patients with PAR, the safety and tolerability profile of twice-daily GSP301 was similar to that of the two placebo formulations. GSP301 also provided statistically significant and clinically meaningful improvements²⁴ in nasal symptoms, with no evidence of tachyphylaxis. These results, when combined with those of short-term phase II and phase III SAR studies,^{13–16} confirmed that GSP301 was a well-tolerated and effective treatment.

A. Average AM rTNSS



B. Average AM iTNSS

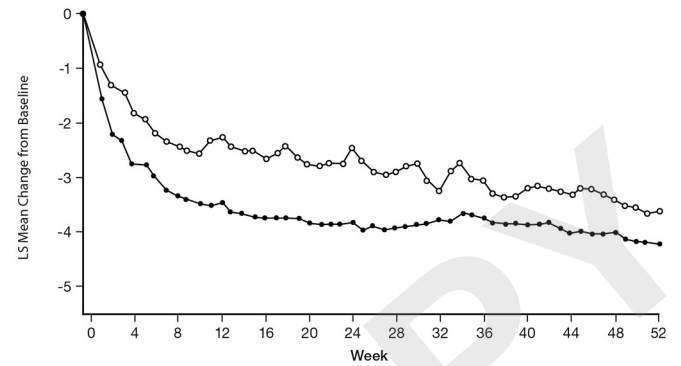


Figure 2. Improvements in (A) average A.M. rTNSS and (B) average A.M. iTNSS with GSP301 versus placebo pH 3.7 over 52 weeks of treatment (FAS) GSP301, olopatadine 665 µg and mometasone 25 µg (pH 3.7); placebo pH 3.7, GSP301 vehicle. MMRM analysis with the change from baseline as the dependent variable, treatment group and site as the fixed effect, baseline as the covariate, and study week as the within-patient effect and week-by-treatment interaction. Improvements with GSP301 versus placebo were significant at (A) 45 of 52 time points for rTNSS and (B) 40 of 52 for iTNSS ($p < 0.05$, all relevant comparisons). Note: Oral rescue medication use was permitted on an as-needed basis after week 6 (visit 4) until symptoms were controlled. rTNSS = reflective Total Nasal Symptom Score; iTNSS = instantaneous Total Nasal Symptom Score; FAS = full analysis set; MMRM = mixed-effect model repeated measures; LS = least squares.

Table 4 Treatment comparisons of average A.M. reflective and instantaneous individual nasal symptom scores with GSP301 ($n = 391$) vs placebo pH 3.7 ($n = 99$) from baseline to weeks 6, 30, and 52 (FAS)*#

	First 6 Wks		30 Wks§		52 Wks§	
	Reflective	Instantaneous	Reflective	Instantaneous	Reflective	Instantaneous
Rhinorrhea						
LSMD	-0.18	-0.16	-0.24	-0.22	-0.21	-0.19
95% CI	-0.32 to -0.04	-0.29 to -0.02	-0.37 to -0.12	-0.35 to -0.09	-0.33 to -0.09	-0.31 to -0.07
p	0.012¶	0.025¶	<0.001¶	0.001¶	0.001¶	0.003¶
Nasal congestion						
LSMD	-0.20	-0.21	-0.20	-0.22	-0.17	-0.20
95% CI	-0.33 to -0.07	-0.34 to -0.08	-0.32 to -0.08	-0.33 to -0.10	-0.29 to -0.04	-0.31 to -0.08
p	0.003¶	0.001¶	0.001¶	<0.001¶	0.008¶	0.001¶
Nasal itching						
LSMD	-0.15	-0.18	-0.18	-0.20	-0.16	-0.19
95% CI	-0.29 to -0.01	-0.31 to -0.04	-0.31 to -0.05	-0.33 to -0.08	-0.29 to -0.04	-0.31 to -0.07
p	0.032¶	0.011¶	0.008¶	0.002¶	0.012¶	0.002¶
Sneezing						
LSMD	-0.31	-0.17	-0.31	-0.20	-0.29	-0.21
95% CI	-0.45 to -0.16	-0.30 to -0.03	-0.44 to -0.18	-0.33 to -0.08	-0.42 to -0.17	-0.33 to -0.09
p	<0.001¶	0.018¶	<0.001¶	0.002¶	<0.001¶	0.001¶

FAS = Full analysis set; LSMD = least squares mean difference; CI = confidence interval; MMRM = mixed-effect model repeated measures.

* MMRM analysis with a change from baseline as the dependent variable, treatment group and site as the fixed effect, baseline as the covariate, and study week as the within-patient effect.

GSP301, olopatadine 665 µg and mometasone 25 µg (pH 3.7); placebo pH 3.7, GSP301 vehicle.

§ Oral rescue medication use was permitted on an as-needed basis after week 6 (visit 4) until symptoms were controlled.

¶ Indicates significance ($p < 0.05$) versus placebo pH 3.7.

Although there is some potential concern that the use of multiple treatments in combination (either in a single-delivery device or as separate monotherapies used concurrently) could possibly increase the number of

adverse effects,¹ the overall incidence of TEAEs reported in the current study for GSP301 treatment at 30 and 52 weeks was low, and there was no evidence of accumulation over time. Further, adverse effects that

Table 5 Treatment comparisons of overall PNSS, RCAT, and RQLQ(S) scores for GSP301 vs placebo from baseline to weeks 6, 30, and 52 (FAS)*#

Assessment	First 6 Wks	30 Wks§	52 Wks§
PNSS			
LSMD	−0.87	−0.69	−0.20
95% CI	−1.44 to −0.29	−1.31 to −0.08	−0.87 to 0.46
<i>p</i>	0.003¶	0.027¶	0.552
RCAT score			
LSMD	1.57	1.24	0.85
95% CI	0.54 to 2.61	0.17 to 2.32	−0.31 to 2.01
<i>p</i>	0.003¶	0.024¶	0.151
RQLQ(S) score			
LSMD	−0.42	−0.33	−0.04
95% CI	−0.70 to −0.14	−0.60 to −0.05	−0.34 to 0.26
<i>p</i>	0.004¶	0.019¶	0.790

PNSS = Physician-assessed Nasal Symptom Score; RCAT = Rhinitis Control Assessment Test; RQLQ(S), Rhinoconjunctivitis Quality-of-Life Questionnaire—Standardized Activities; FAS = full analysis set; LSMD = least squares mean difference; CI = confidence interval; MMRM = mixed-effect model repeated measures.

* MMRM analysis with the change from baseline as the dependent variable, the treatment group and site as the fixed effect, baseline as the covariate, study week as the within-patient effect, and week-by-treatment interaction for PNSS and RCAT; a week-by-treatment interaction was included for RQLQ(S).

GSP301, olopatadine 665 µg and mometasone 25 µg (pH 3.7); placebo pH 3.7, GSP301 vehicle.

§ Oral rescue medication use was permitted on an as-needed basis after wk 6 (visit 4) until symptoms were controlled.

¶ Indicates significance (*p* < 0.05) vs placebo pH 3.7.

are commonly associated with intranasal corticosteroids (e.g., epistaxis, nasal irritation) and with intranasal antihistamines (e.g., headache, bitter aftertaste, epistaxis, sedation),²⁶ were reported at lower rates with long-term GSP301 treatment (epistaxis, 4.6%; headache, 4.1%; nasal discomfort, 2.5%; dysgeusia [bad taste], 2.0%; and somnolence, 0.8%).

The pH of nasal spray formulations is often adjusted to prevent tissue irritation, ensure efficient drug absorption, prevent bacterial growth, and maintain drug stability.²⁷ The FDA-approved intranasal olopatadine HCl and intranasal mometasone furoate both have pHs that are lower than neutral (olopatadine, pH ~3.7¹⁸; mometasone, pH 4.3–4.9¹⁹). Because GSP301 is a combination of similar sponsor-formulated versions of olopatadine and mometasone, the pH of GSP301 is also < 7.0. Because the incidence of TEAEs could be influenced by the low pH of GSP301 (pH 3.7), a neutral pH placebo formulation (pH 7.0) was included in the current study to compare AEs and other safety parameters between low and neutral pH formulations. There were no clinically relevant differences between GSP301 and placebo pH 3.7 or placebo pH 7.0 in the incidence of AEs or on any other safety assessments, which suggested no potential influence of low pH (pH 3.7). The overall TEAE rates at week 52 were numerically greater in the placebo pH 7.0 group than in the other two low pH treatment groups, although the reasons for this were unclear.

Comparable results that indicated a lack of pH influence on adverse effects were previously reported for the FDA-approved olopatadine monotherapy. In a 52-week randomized safety study of olopatadine (pH 3.7) and two placebo formulations (pH 3.7 and pH 7.0), similar overall AE rates were observed across the treatment groups (52, 51, and 51%, respectively).²⁸ In addition, similar epistaxis rates (olopatadine, 22%; vehicle pH 3.7, 18%; vehicle pH 7.0, 20%) and nasal ulceration rates (7, 6, 8%) were reported across treatments, which suggested that the lower pH olopatadine formulation did not increase AE rates.²⁸ In the current study, nasal epistaxis rates were low across treatments and there were no reports of nasal ulcerations.

In the olopatadine study, nasal septal perforation was reported for one patient treated with the pH 3.7 vehicle nasal spray²⁸; however, no such event was reported with the placebo pH 3.7 treatment in the present study. One patient in the GSP301 group experienced an asymptomatic nasal septal perforation that was of severe intensity (noted as a TEAE of special interest) but was determined to be preexisting and considered unrelated to the study treatment. It should be noted that, because clinical trials are conducted under widely varying conditions, adverse reaction rates cannot be directly compared between trials and may not reflect the rates observed in practice.

Overall, the safety results of the current study indicated that combining olopatadine and mometasone in

a single device for long-term PAR treatment did not seem to influence the adverse effects profile. The results also indicated that there was no potential influence of the low pH of the formulation on adverse effects. These results, as well as those of two pharmacokinetic studies in patients without SAR^{29,30} and several phase II and III studies in patients with SAR¹³⁻¹⁶ indicated that GSP301 had a favorable safety profile for short- or long-term use.

GSP301 provided significant and clinically meaningful improvements (MCID treatment difference of >0.23 units)²⁴ in overall and individual nasal symptoms versus placebo (pH 3.7) from baseline to weeks 6, 30, and 52. These improvements were clinically meaningful from weeks 1 through 52, which indicated a lack of tachyphylaxis and demonstrated a durable response, although statistical significance was not achieved for every time point. These results were comparable with those of short-term (14-day) phase II and III studies in patients with SAR that showed significant, sustained, and clinical meaningful²⁴ improvements in nasal symptoms with GSP301 versus placebo.¹⁴⁻¹⁶ GSP301 also significantly improved patients' overall PNSS, RCAT, and RQLQ(S) scores from baseline to weeks 6 and 30, although the RQLQ(S) improvements were slightly below the established MCID (treatment difference > 0.50 units³¹; week 6: least squares mean difference, -0.42; week 30, -0.33). At week 52, improvements in the PNSS, RCAT, and RQLQ(S) with GSP301 did not reach statistical significance and the reasons for this were unclear.

To our knowledge, the present study was the only clinical study reported for GSP301 in patients with PAR. The first 6 weeks were designed as a strict efficacy study (secondary end point), similar to the 14-day SAR studies,¹⁴⁻¹⁶ which did not allow any rescue medications. Indeed, improvements in TNSS were statistically significant and clinically meaningful in the first 6 weeks, which suggested that the PAR efficacy results were consistent with the overall efficacy of GSP301 demonstrated in the short-term SAR studies.¹⁴⁻¹⁶ These results, combined with those that showed a rapid onset of action of 15 minutes in patients with SAR,^{15,17} demonstrated the short- and long-term efficacy of GSP301 treatment.

Results from this study were also similar to those observed in a 52-week study of the combination nasal spray that contained the antihistamine azelastine and the corticosteroid fluticasone (FDA-approved AzeFlu) in patients with PAR or nonallergic rhinitis.^{12,32} The combination was shown to be effective and safe for long-term use in comparison with fluticasone monotherapy, with similar rates of TEAEs between treatments.³² These results, however, could not be directly compared with those of the present study due to the differing study designs and conditions.^{12,32} In the AzeFlu study, for example, patients with either PAR or

nonallergic rhinitis were enrolled, monotherapy fluticasone was the comparator, and the efficacy assessment was the P.M. rTNSS once daily. In the current GSP301 study, only patients with PAR were enrolled, placebo was the comparator, and the efficacy assessment was the A.M. rTNSS once daily. Thus, future adequately designed studies are needed to provide head-to-head comparisons of AzeFlu and GSP301 FDCs.

CONCLUSION

GSP301 treatment was well tolerated and provided significant and clinically meaningful improvements in PAR symptoms versus placebo and demonstrated favorable long-term safety, tolerability, and efficacy over 52 weeks without tachyphylaxis in patients ≥ 12 years of age.

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