

Olopatadine-mometasone combination nasal spray: Evaluation of efficacy and safety in patients with seasonal allergic rhinitis

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ABSTRACT

Background: GSP301 is an investigational fixed-dose combination nasal spray that contains the antihistamine, olopatadine hydrochloride (HCl), and the corticosteroid, mometasone furoate.

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

Methods: In this double-blind, randomized, parallel-group study, patients (≥ 12 years of age) with SAR were equally randomized to intranasal GSP301 (olopatadine 665 μg and mometasone 25 μg), olopatadine HCl (665 μg), mometasone furoate (25 μg), or placebo for 14 days of twice-daily treatment. The primary end point was the mean change from baseline in the average A.M. and P.M. 12-hour reflective Total Nasal Symptom Score (rTNSS) analyzed by using mixed-effect model repeated measures ($p < 0.05$ indicates statistical significance). Additional assessments included instantaneous TNSS (iTNSS), individual nasal symptoms, reflective Total Ocular Symptom Score (rTOSS) and instantaneous Total Ocular Symptom Score (iTOSS), onset of action, Physician-assessed Nasal Symptom Score (PNSS), quality of life, and adverse events (AE).

Results: A total of 1180 patients were randomized. Over 14 days of treatment, GSP301 significantly improved average A.M. and P.M. rTNSS versus placebo (least squares mean difference -0.98 [95% confidence interval, -1.38 to -0.57]; $p < 0.001$) and versus olopatadine ($p = 0.003$), and approached statistical significance versus mometasone ($p = 0.059$). GSP301 also significantly improved average A.M. and P.M. iTNSS versus placebo and both monotherapies ($p < 0.05$, all). Further, GSP301 significantly improved individual nasal symptoms, overall ocular symptoms (rTOSS and iTOSS), and overall quality of life versus placebo ($p < 0.01$, all). Onset of action for GSP301 was observed within 15 minutes and was maintained at all subsequent time points assessed. Results for the PNSS also were significant for GSP301 versus placebo ($p < 0.001$). The percentages of patients with treatment-emergent AEs treated with GSP301, olopatadine, mometasone, and placebo were 12.9, 12.5, 7.1, and 9.4%, respectively.

Conclusion: GSP301 was efficacious and well tolerated for the treatment of SAR symptoms compared with placebo, with a rapid onset of action of 15 minutes in patients ≥ 12 years of age.

Clinical trial NCT 02631551, www.clinicaltrials.gov.

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Allergic rhinitis (AR) is a chronic disease triggered by immunoglobulin E-mediated inflammation of the nasal mucosa after exposure to an allergen. This

inflammation causes one or more symptoms of nasal congestion, rhinorrhea, sneezing, and nasal itching.¹ AR currently affects 5.6 million children² and 19.9 million adults in the United States³, the prevalence of AR is rising.⁴ AR is typically characterized as either seasonal AR (SAR) (specific to a pollen season) or perennial AR (PAR) (year-round from mold and/or dust mites, etc.), although some patients may be allergic to

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Supplemental data available at www.IngentaConnect.com

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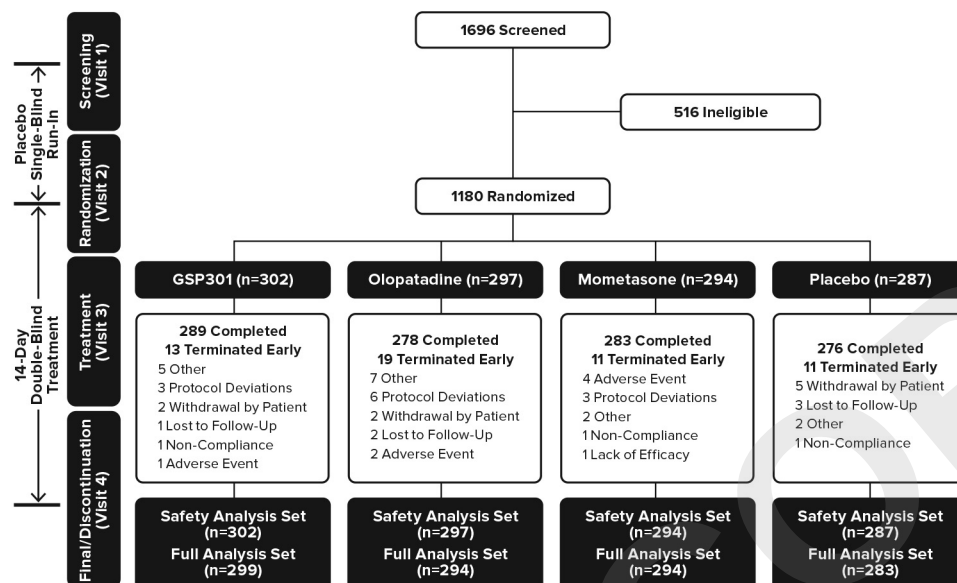


Figure 1. Patient disposition and study design. GSP301, olopatadine 665 µg and mometasone 25 µg; olopatadine, 665 µg; mometasone, 25 µg; placebo, GSP301 vehicle. The screening visit (visit 1) occurred between day –10 and day –7 before the randomization visit on day 1 (visit 2). The treatment visit (visit 3) occurred on approximately day 8, and the final or discontinuation visit (visit 4) occurred on approximately day 15. No scheduled post-treatment follow-up visit was planned for this study.

multiple allergens, which makes the distinction between SAR and PAR difficult to determine.^{1,5}

AR poses a substantial quality of life burden to patients through disturbed sleep, depression, irritability, decreased work and/or school productivity, and increased absenteeism.^{6,7} Many patients with AR also have comorbidities, such as asthma, otitis media, obstructive sleep apnea, allergic conjunctivitis, and sinusitis,^{8,9} which can be exacerbated by untreated or inadequately controlled AR.⁹ Although most patients with AR rely on pharmacologic treatments to relieve their symptoms,⁶ control with one agent may be inadequate because anywhere from 25% to almost 50% of patients surveyed reported using multiple prescription or over-the-counter medications.^{6,10} Combining treatments from two differing but complementary drug classes (e.g., an intranasal antihistamine, such as azelastine hydrochloride [HCl], and an intranasal corticosteroid, such as fluticasone propionate) provides better symptom relief than monotherapy treatment.^{11,12}

GSP301 is an investigational fixed-dose combination (FDC) that contains the antihistamine, olopatadine HCl, and the corticosteroid, mometasone furoate, developed in a single nasal spray device for the treatment of symptoms associated with SAR. Intranasal antihistamines relieve symptoms rapidly, whereas corticosteroids provide sustained relief.¹³ Individually, olopatadine and mometasone are effective and safe intranasal monotherapies for SAR.^{14–18} The combination of these treatments as GSP301 has previously been reported to be efficacious and well tolerated compared with placebo for both nasal and ocular symptoms associated

with SAR in adult and adolescent patients exposed to fall (e.g., ragweed) or winter (e.g., mountain cedar) pollens.^{19–21} The objective of this study was to evaluate the efficacy, safety, and tolerability of GSP301 FDC nasal spray compared with placebo and the component monotherapies (olopatadine and mometasone) over 14 days in adult and adolescent patients with SAR during the spring pollen season.

METHODS

This study was performed at 37 study centers 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 was reviewed and approved by a central institutional review board (Novum Independent Institutional Review Board, Pittsburgh, PA), and all patients provided written informed consent; adolescent patients ages 12 to 18 years (inclusive) provided an assent form.

Study Design

This was a phase III, double-blind, randomized, parallel-group study conducted in adult and adolescent patients with SAR during the spring pollen season. The study consisted of two 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 completion of the placebo-run in period, eligible patients were equally randomized to one of four intranasal treatments for 14 days (2 sprays/

nostril twice daily): GSP301 (665 μ g olopatadine HCl and 25 μ g mometasone furoate), olopatadine HCl (sponsor formulation; 665 μ g), mometasone furoate (sponsor formulation; 25 μ g), and placebo (GSP301 vehicle).

Patients

Eligible patients were ≥ 12 years of age with a clinical history of SAR for ≥ 2 years before the screening visit for the relevant seasonal allergen during the spring allergy season (e.g., tree and/or grass pollen) and a positive skin-prick test result for spring allergens (wheal diameter at least 5 mm greater than the negative control). Patients also needed to have a minimum 12-hour reflective Total Nasal Symptom Score (rTNSS) ≥ 8 out of 12 and a morning congestion score ≥ 2 at the screening visit.

Key exclusion criteria were any known history of nasal polyps or other clinically significant respiratory tract malformations, disorders, or infections; recent nasal biopsy; trauma or surgery; significant atopic dermatitis; acute or significant chronic sinusitis; chronic purulent postnasal drip; rhinitis medicamentosa; active pulmonary disorder or infection (e.g., bronchitis, pneumonia, or influenza); upper respiratory tract or sinus infection (within 14 days of the screening visit); or the development of respiratory infections (during the placebo run-in period). See Online Supplemental Material for additional details.

Assessments

Twice daily, patients self-assessed A.M. and P.M. reflective and instantaneous nasal symptoms (i.e., nasal congestion, rhinorrhea, itchy nose, and sneezing) and non-nasal symptoms (i.e., itching and/or burning, tearing and/or watering and redness of eyes [ocular symptoms], and itching of ears or palate), and these were recorded in a symptom diary before self-administering study medication. Symptoms were rated on a scale of 0 (absent) to 3 (severe) (Supplemental Table 1) and were reported as reflective (over the previous 12 hours) and instantaneous (over the 10 minutes before dosing). The rTNSS or instantaneous TNSS (iTNSS) were defined as the sum of four nasal-related symptom scores, with a maximum score of 12 (see Online Supplemental Material for additional details). The reflective Total Ocular Symptom Score (rTOSS) or instantaneous Total Ocular Symptom Score (iTOSS) were defined as the sum of three ocular-related non-nasal symptom scores with a maximum score of 9.

Onset of action for each treatment was evaluated for 4 hours during visit 2 (randomization visit) by using the mean change from baseline in iTNSS versus placebo at 0 minutes (pre-dose) and at the following post-dose time points: 15, 30, 45, 60, 90, 120, 150, 180, 210,

and 240 minutes. Additional assessments included the the Physician-assessed Nasal Symptom Score (PNSS),²² the Rhinoconjunctivitis Quality-of-Life Questionnaire–Standardized Activities [RQLQ(S)],²³ and the Rhinitis Control Assessment Test (RCAT)²⁴ (see Online Supplemental Material for further details). Safety was monitored *via* adverse events (AE); laboratory assessments; vital signs; electrocardiograms; physical examinations; and ear, nose, and throat examinations.

End Points

The primary efficacy end point was the mean change from baseline to the end of the 14-day treatment in average A.M. and P.M. 12-hour rTNSS for the following: GSP301 versus placebo, GSP301 versus olopatadine and mometasone monotherapies, and olopatadine and mometasone monotherapies versus placebo. Secondary efficacy end points included the following: mean change from baseline to the end of the 14-day treatment in average A.M. and P.M. 12-hour iTNSS and rTOSS for the same treatment comparisons as the rTNSS, onset of action for all active treatments, and the mean change from baseline to day 15 in the overall RQLQ(S) score for the same comparisons as the rTNSS.

Additional efficacy end points included the mean change from baseline in the following: average A.M. and P.M. 12-hour rTNSS and iTNSS for each day, average A.M. and P.M. 12-hour reflective and instantaneous individual nasal symptoms over the 14-day treatment period, average A.M. and P.M. 12-hour iTOSS over the 14-day treatment period, and mean change from baseline to day 15 in PNSS and RCAT scores. The additional efficacy end points compared the same treatments as the rTNSS (described above), with the exception of the average A.M. and P.M. 12-hour rTNSS and iTNSS for each day in which comparisons of GSP301 versus the monotherapies are not shown. Laboratory assessments, electrocardiograms, and physical examinations were conducted at the screening and final visits, and ear, nose, and throat examinations and monitoring of vital signs and AEs occurred throughout the study.

Statistical Analyses

Efficacy analyses were based on the full analysis set (FAS), defined as all randomized patients who received one or more doses of the study drug and completed one or more postbaseline primary efficacy assessments. Safety assessments were based on the safety analysis set (SAS), which included all randomized patients who received one or more doses of the study drug. Efficacy end points were analyzed *via* mixed-effect model repeated measures (MMRM) adjusting for the covariates treatment, site, and baseline score, with study day as the within-patient effect. To adjust for

multiplicity, a gatekeeping strategy was used for rTNSS, iTNSS, and rTOSS (see Online Supplemental Material for more details). A treatment difference of at least 0.23 units (direct anchor-based regression methodology) on TNSS was considered clinically meaningful (defined as the minimal clinically important difference [MCID]).²⁵

Onset of action was defined as the first post-dose time point at which statistically significant differences in iTNSS change from baseline between the active treatments and placebo were observed and sustained,²⁶ and were analyzed by using an MMRM adjusting for the covariates of treatment, site, and baseline iTNSS, with the time point as the within-patient effect. Baseline for onset was defined as the pre-dose time point at randomization (visit 2). Overall RQLQ(S) scores were analyzed by using an analysis of covariance (ANCOVA) adjusting for treatment and site (fixed effect), with the baseline score as the linear, continuous covariate. Baseline RQLQ(S) was the score on day 1 (visit 2). Statistical significance was set at $p < 0.05$ for efficacy and quality of life analyses, unless otherwise noted. See Online Supplemental Material for additional analysis information.

RESULTS

Patient Disposition and Demographics

A total of 1180 patients were randomized, and 1126 patients completed the study; 1170 were included in the FAS and 1180 were included in the SAS (Fig. 1). The majority of patients were female and white, with a mean $\pm$ standard deviation age of 39.3 ± 15.3 years and had moderate-severe baseline nasal and ocular symptoms. Baseline assessment scores and demographics were similar among the treatment groups (Table 1).

Patient-Reported Nasal Symptoms

Average A.M. and P.M. 12-Hour TNSS. GSP301 treatment resulted in significant and clinically meaningful (MCID) (>0.23 units²⁵) improvements in average 12-hour A.M. and P.M. rTNSS (primary end point) from baseline to the end of 14-day treatment versus placebo ($p < 0.001$) and olopatadine ($p = 0.003$) (Table 2). A greater clinically meaningful improvement that approached statistical significance was observed with GSP301 compared with mometasone ($p = 0.059$); as a result, the comparisons of olopatadine and mometasone versus placebo were not considered statistically significant per the gatekeeping analysis strategy, although the treatment comparison resulted in $p < 0.05$ for mometasone versus placebo ($p = 0.004$). When assessed by individual day, GSP301 significantly improved the average

A.M. and P.M. rTNSS versus placebo on days 1 through 14 ($p < 0.01$, all), which suggests sustained daily improvement of symptoms (Fig. 2). Compared with placebo, olopatadine showed greater improvements on each day, with significantly greater improvements on days 1, 3, and 8 ($p < 0.05$, all; data not shown). For mometasone versus placebo, greater improvements were observed on each day and significantly greater improvements occurred on days 3–14 ($p < 0.05$, all; data not shown).

GSP301 also demonstrated significant and clinically meaningful improvements in average A.M. and P.M. 12-hour iTNSS from baseline to the end of the 14-day treatment compared with placebo ($p < 0.001$) (Table 2) as well as compared with each individual monotherapy ($p = 0.005$ versus olopatadine; $p = 0.041$ versus mometasone). Similarly, olopatadine and mometasone monotherapies resulted in significant and clinically meaningful average A.M. and P.M. iTNSS improvements compared with placebo (olopatadine, $p = 0.018$; mometasone, $p = 0.002$). On individual days, GSP301 significantly improved iTNSS versus placebo on days 1–14 ($p \leq 0.001$, all), which demonstrated sustained daily symptom improvement (Fig. 2). Greater improvements were observed with olopatadine versus placebo on all 14 days; these improvements were significant on days 1 and 3 ($p < 0.05$, both; data not shown). With mometasone, greater improvements were shown on all 14 days, with significant improvements on days 1 through 14 versus placebo ($p < 0.05$, all; data not shown).

Average A.M. and P.M. 12-Hour Individual Nasal Symptoms. Treatment with GSP301 resulted in significant improvements in all average A.M. and P.M. 12-hour individual nasal symptoms versus placebo over the 14-day treatment period ($p < 0.01$, all) (Table 3). GSP301 also provided greater improvements on all reflective and instantaneous individual nasal symptoms compared with the monotherapies (data not shown), but not all comparisons reached statistical significance. When compared with olopatadine, GSP301 significantly improved all symptoms ($p < 0.05$, all) except reflective rhinorrhea, in which the improvement over olopatadine approached statistical significance ($p = 0.053$). Compared with mometasone, GSP301 significantly improved reflective and instantaneous sneezing ($p < 0.01$, both) and instantaneous nasal itching ($p = 0.03$). Olopatadine monotherapy resulted in greater improvements on all individual nasal symptoms versus placebo, with only reflective and instantaneous sneezing ($p < 0.01$, both) and instantaneous nasal itching reaching significance ($p = 0.02$; data not shown). Mometasone monotherapy provided significantly greater improvements in all individual nasal symptoms compared with placebo ($p < 0.05$, all; data not shown).

Table 1 Demographics (SAS) and baseline assessment scores (FAS)

	GSP301	Olopatadine	Mometasone	Placebo
Demographics				
No. subjects	302	297	294	287
Age, mean $\pm$ SD, y	39.5 $\pm$ 15.4	39.6 $\pm$ 14.9	38.7 $\pm$ 16.3	39.4 $\pm$ 14.8
Sex, <i>n</i> (%)				
Female	201 (66.6)	181 (60.9)	198 (67.3)	182 (63.4)
Male	101 (33.4)	116 (39.1)	96 (32.7)	105 (36.6)
Race, <i>n</i> (%)				
White	241 (79.8)	219 (73.7)	224 (76.2)	231 (80.5)
Black	56 (18.5)	67 (22.6)	59 (20.1)	48 (16.7)
Asian	2 (0.7)	4 (1.3)	7 (2.4)	7 (2.4)
Other*	3 (1.0)	7 (2.4)	4 (1.4)	1 (0.3)
Ethnicity, <i>n</i> (%)				
Non-Hispanic or Latino	230 (76.2)	229 (77.1)	221 (75.2)	221 (77.0)
Hispanic or Latino	72 (23.8)	68 (22.9)	73 (24.8)	66 (23.0)
Baseline assessment scores				
No. subjects	299	294	294	283
Average A.M. and P.M. rTNSS, mean $\pm$ SD	10.1 $\pm$ 1.2	10.3 $\pm$ 1.3	10.2 $\pm$ 1.2	10.2 $\pm$ 1.2
Average A.M. rTNSS, mean $\pm$ SD	10.1 $\pm$ 1.3	10.3 $\pm$ 1.4	10.1 $\pm$ 1.3	10.1 $\pm$ 1.2
Average P.M. rTNSS, mean $\pm$ SD	10.2 $\pm$ 1.3	10.4 $\pm$ 1.4	10.2 $\pm$ 1.3	10.2 $\pm$ 1.2
Average A.M. and P.M. iTNSS, mean $\pm$ SD	9.2 $\pm$ 1.7	9.4 $\pm$ 1.9	9.3 $\pm$ 1.7	9.3 $\pm$ 1.7
Average A.M. iTNSS, mean $\pm$ SD	9.2 $\pm$ 1.8	9.4 $\pm$ 2.0	9.3 $\pm$ 1.8	9.3 $\pm$ 1.8
Average P.M. iTNSS, mean $\pm$ SD	9.2 $\pm$ 1.8	9.5 $\pm$ 2.0	9.3 $\pm$ 1.9	9.3 $\pm$ 1.7
Average A.M. and P.M. rTOSS, mean $\pm$ SD	7.1 $\pm$ 1.4	7.3 $\pm$ 1.3	7.0 $\pm$ 1.5	7.2 $\pm$ 1.3
Average A.M. and P.M. iTOSS, mean $\pm$ SD	6.6 $\pm$ 1.7	6.9 $\pm$ 1.6	6.6 $\pm$ 1.8	6.8 $\pm$ 1.6
PNSS, mean $\pm$ SD	9.6 $\pm$ 2.1	9.7 $\pm$ 2.9	9.7 $\pm$ 1.8	9.6 $\pm$ 1.9
RQLQ(S) score, mean $\pm$ SD	4.0 $\pm$ 1.1	4.0 $\pm$ 1.3	3.9 $\pm$ 1.2	3.9 $\pm$ 1.2
RCAT score, mean $\pm$ SD	12.0 $\pm$ 3.2	11.7 $\pm$ 3.5	12.1 $\pm$ 3.6	12.2 $\pm$ 3.4

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

Treatments: GSP301, olopatadine 665 μ g and mometasone 25 μ g; olopatadine, 665 μ g; mometasone, 25 μ g; placebo, GSP301 vehicle.

* Includes American Indian or Alaska native and native Hawaiian or other Pacific Islander.

Average A.M. and Average P.M. TNSS. When average A.M. and average P.M. TNSS were analyzed separately, the results were comparable with the average A.M. and P.M. 12-hour TNSS results presented above. GSP301 treatment provided greater nasal symptom improvements versus placebo in the average A.M. and average P.M. rTNSS (A.M. least squares mean difference [LSMD] -0.90 [95% confidence interval [CI], -1.22 to -0.59], $p < 0.001$; P.M.: -0.75 [95% CI, -1.14 to -0.36], $p < 0.001$), and average A.M. and average P.M. iTNSS (A.M.: -1.07 [95% CI, -1.19 to -0.95], $p < 0.001$; P.M.: -0.97 [95% CI, -1.09 to -0.84], $p < 0.001$) (Supplemental Table 2). GSP301 treatment resulted in significantly greater improvements on the average A.M. rTNSS, A.M. iTNSS, and P.M. iTNSS versus both monotherapies ($p \leq 0.05$, all) (Supplemental Table 2);

the greater improvement provided by GSP301 versus mometasone on the P.M. rTNSS was not statistically significant ($p = 0.206$). Both olopatadine and mometasone treatments resulted in significant improvements compared with placebo on the average A.M. rTNSS and on the average A.M. and average P.M. iTNSS ($p < 0.05$, all); on the average P.M. rTNSS, the greater improvements that resulted from mometasone treatment versus placebo were also significant ($p = 0.011$) and those from olopatadine versus placebo approached statistical significance ($p = 0.067$) (Supplement Table 2).

Onset of Action

A rapid onset of action with GSP301 treatment was demonstrated at 15 minutes (first time point assessed)

Table 2 Treatment comparisons of average A.M. and P.M. rTNSS and iTNSS over 14 days of treatment (FAS)

Treatment Group (1 vs 2)	n1, n2	LSMD	95% CI	p
Average A.M. and P.M. rTNSS (primary end point)				
GSP301 vs placebo	299, 283	−0.98	−1.38 to −0.57	<0.001*
GSP301 vs olopatadine	299, 294	−0.61	−1.01 to −0.21	0.003*
GSP301 vs mometasone	299, 294	−0.39	−0.79 to 0.01	0.059
Olopatadine vs placebo	294, 283	−0.37	−0.78 to 0.04	0.076
Mometasone vs placebo	294, 283	−0.59	−1.00 to −0.19	0.004#
Average A.M. and P.M. iTNSS (secondary end point)				
GSP301 vs placebo	299, 283	−0.93	−1.28 to −0.58	<0.001*
GSP301 vs olopatadine	299, 294	−0.50	−0.85 to −0.15	0.005*
GSP301 vs mometasone	299, 294	−0.36	−0.71 to −0.01	0.041*
Olopatadine vs placebo	294, 283	−0.43	−0.78 to −0.07	0.018*
Mometasone vs placebo	294, 283	−0.57	−0.92 to −0.21	0.002*

rTNSS = reflective Total Nasal Symptom Score; iTNSS = instantaneous Total Nasal Symptom Score; FAS = full analysis set; n1 = treatment group 1; n2 = treatment group 2; LSMD = least squares mean difference; CI = confidence interval; MMRM = mixed-effect model repeated measures.

* Indicates a significant difference ($p < 0.05$) vs treatment group 2 by using the gatekeeping strategy.

Indicates the difference was not significant per the gatekeeping strategy, even if $p < 0.05$.

Treatments: GSP301, olopatadine 665 μg and mometasone 25 μg ; olopatadine, 665 μg ; mometasone, 25 μg ; placebo, GSP301 vehicle.

rTNSS and iTNSS were analyzed using an MMRM analysis with change from baseline as dependent variable, treatment group and site as fixed effect, baseline as covariate, and study day as the within-patient effect.

after the first dose versus placebo (LSMD −0.35 [95% CI, −0.63 to −0.07]; $p = 0.014$), and this significant improvement was maintained at all later time points (Fig. 3). For olopatadine, the first time point at which iTNSS significantly differed from placebo was at 45 minutes post-dose (−0.45 [−0.82 to −0.09], $p = 0.015$), and only two other nonconsecutive time points were significantly different from placebo: 90 minutes (−0.45 [−0.88 to −0.03], $p = 0.038$) and 180 minutes (−0.48 [−0.95 to −0.02], $p = 0.043$). Thus, per the *a priori* onset of action definition,²⁶ onset for olopatadine could not be determined. For mometasone, there were no statistically significant differences from placebo on iTNSS at any time point up to 240 minutes post-dose and, as such, no onset of action could be determined (data not shown).

Patient-Reported Ocular Symptoms

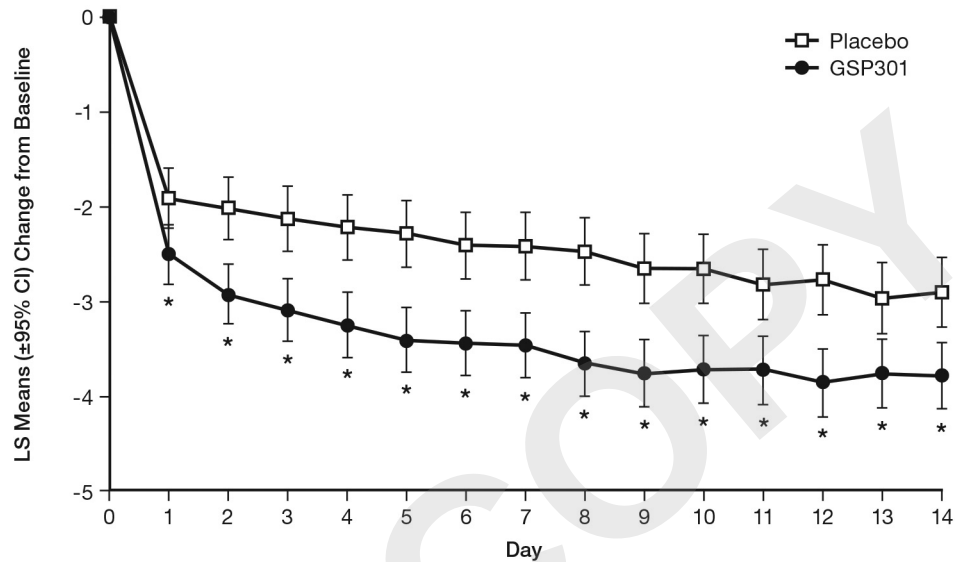
Average A.M. and P.M. 12-Hour TOSS. Treatment with GSP301 provided significant improvements in average A.M. and P.M. 12-hour rTOSS compared with placebo ($p = 0.001$) (Table 4). GSP301 also improved rTOSS compared with olopatadine ($p = 0.542$) and mometasone ($p = 0.211$) monotherapies, but these comparisons did not reach statistical significance (data not shown). Improvements in rTOSS with olopatadine versus placebo were not considered statistically significant per the gatekeeping

strategy, although $p = 0.01$ (data not shown). The comparison of mometasone with placebo was also not statistically significant per the gatekeeping strategy ($p = 0.051$; data not shown). Similar to the rTOSS results, treatment with GSP301 significantly improved average A.M. and P.M. 12-hour iTOSS compared with placebo ($p < 0.001$) (Table 4). GSP301 improved iTOSS versus olopatadine ($p = 0.300$) and mometasone ($p = 0.164$), but these comparisons did not reach statistical significance (data not shown). Both monotherapies provided significant iTOSS improvements compared with placebo (olopatadine, $p = 0.014$; mometasone, $p = 0.034$; data not shown). GSP301 provided significant improvements versus placebo in each individual ocular symptom of the average A.M. and P.M. 12-hour rTOSS and iTOSS ($p < 0.01$, all) (Supplement Table 3).

Physician-Assessed Nasal Symptoms

From baseline to day 15, GSP301 provided significant improvements in overall PNSS versus placebo ($p < 0.001$) (Table 4) and olopatadine ($p < 0.001$; data not shown). The greater treatment effect with GSP301 versus mometasone did not reach statistical significance ($p = 0.153$; data not shown). Mometasone provided significantly greater improvements versus placebo ($p = 0.024$; data not shown). Improvements with olopatadine versus placebo were not statistically sig-

A. rTNSS



B. iTNSS

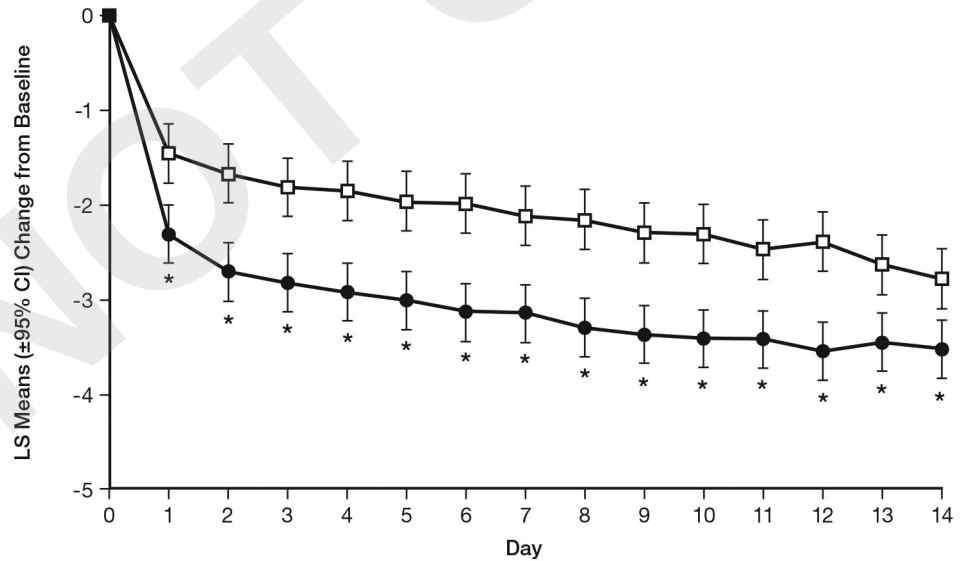


Figure 2. (A) Average A.M. and P.M. rTNSS and (B) iTNSS with GSP301 versus placebo over 14 days of treatment (FAS). Treatments: GSP301, olopatadine 665 μ g and mometasone 25 μ g; placebo, GSP301 vehicle. MMRM analysis with change from baseline as the dependent variable, treatment group and site as fixed effect, baseline as covariate, and study day as the within-patient effect. *Indicates a significant difference ($p < 0.05$) versus placebo. rTNSS = reflective Total Nasal Symptom Score; iTNSS = instantaneous Total Nasal Symptom Score; FAS = full analysis set; MMRM = mixed-effect model repeated measures; CI = confidence interval; LS = least squares.

nificant ($p = 0.850$; data not shown). GSP301 significantly improved each individual PNSS symptom (rhinorrhea, nasal congestion, nasal itching, sneezing) compared with placebo ($p < 0.05$, all) (Supplemental Table 4).

Quality of Life

Treatment with GSP301 resulted in significant improvements in overall RQLQ(S) scores from baseline to day 15 versus placebo ($p < 0.001$) (Table 4). GSP301 also significantly improved all seven individual domain scores compared with placebo (*i.e.*, activities, sleep, non-nose/eye symptoms, nasal symptoms, eye problems, practical problems, and emotional; $p < 0.05$, all) (Supplemental Table 5). GSP301 significantly im-

proved overall RQLQ(S) scores versus olopatadine ($p = 0.011$; data not shown). The greater RQLQ(S) improvement that resulted from GSP301 treatment versus mometasone approached statistical significance ($p = 0.069$; data not shown). Mometasone provided significant improvements in overall scores versus placebo ($p = 0.035$; data not shown), whereas improvements with olopatadine versus placebo did not reach statistical significance ($p = 0.166$; data not shown).

Rhinitis Control Assessment Test

Treatment with GSP301 significantly improved RCAT scores from baseline to day 15 compared with placebo ($p < 0.001$) (Table 4), olopatadine ($p = 0.002$; data not shown), and mometasone ($p = 0.016$; data not

Table 3 Treatment comparisons of average A.M. and P.M. individual reflective and instantaneous nasal symptom scores with GSP301 vs placebo over 14 days of treatment (FAS)

GSP301 vs Placebo	LSMD (95% CI)	<i>p</i>
Reflective		
Rhinorrhea	−0.16 (−0.27 to −0.06)	0.002*
Nasal congestion	−0.16 (−0.25 to −0.08)	<0.001*
Nasal itching	−0.22 (−0.33 to −0.11)	<0.001*
Sneezing	−0.32 (−0.40 to −0.23)	<0.001*
Instantaneous		
Rhinorrhea	−0.22 (−0.33 to −0.12)	<0.001*
Nasal congestion	−0.18 (−0.27 to −0.08)	<0.001*
Nasal itching	−0.26 (−0.36 to −0.16)	<0.001*
Sneezing	−0.29 (−0.39 to −0.18)	<0.001*

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

* Indicates a significant difference ($p < 0.05$) vs placebo.

Treatments: GSP301, olopatadine 665 µg and mometasone 25 µg; placebo, GSP301 vehicle.

Treatment group *n*'s: GSP301, *n* = 299; placebo, *n* = 283. Individual nasal symptom scores were analyzed using an MMRM analysis with change from baseline as dependent variable, treatment group and site as fixed effect, baseline as covariate, and study day as the within-patient effect.

shown). GSP301 also significantly improved all six individual RCAT nasal symptom scores (*i.e.*, nasal congestion, sneezing, watery eyes, interference with sleep, nasal and/or other allergy symptom control, avoiding activities because of allergy) compared with placebo ($p < 0.05$, all; data not shown). Mometasone provided significant improvements in RCAT scores compared with placebo ($p = 0.037$; data not shown). Olopatadine treatment provided improvements versus placebo that did not reach statistical significance ($p = 0.167$; data not shown).

Safety

The percentage of patients who reported treatment-emergent AEs (TEAE) was generally similar among treatments, with a greater percentage in the GSP301 and olopatadine treatment groups than the mometasone or placebo treatment groups (Table 5). Only two TEAEs, dysgeusia and headache, occurred in $\geq 2\%$ of patients in any treatment group. The majority of TEAEs were mild or moderate in severity. A total of seven patients withdrew due to TEAEs, none of which was considered to be of severe intensity or a serious AE (SAE). The one SAE that occurred (spontaneous abortion in the GSP301 group) was judged to be unrelated to study treatment. No deaths occurred (Table 5).

DISCUSSION

In this study, twice-daily treatment with GSP301 nasal spray (FDC that contained olopatadine and mometasone) resulted in statistically significant and clinically meaningful²⁵ improvements in SAR nasal symptoms (rTNSS and iTNSS) compared with placebo; improvements were rapid (within 15 minutes) and sustained over 14 days of treatment.

When compared with the individual monotherapies, GSP301 provided statistically significant improvements in average A.M. and P.M. iTNSS versus each component monotherapy. GSP301 also resulted in statistically significant and clinically meaningful²⁵ improvements in the average A.M. and P.M. rTNSS compared with olopatadine, but the comparison between GSP301 and mometasone approached statistical significance, with $p = 0.059$. The comparison of olopatadine versus placebo was not statistically significant, and the comparison of mometasone versus placebo on average A.M. and P.M. rTNSS was not considered statistically significant according to the *a priori* gatekeeping strategy, even though $p = 0.004$. The reason some of these comparisons did not reach statistical significance was unclear, but results from two similarly designed SAR studies showed that average A.M. and P.M. rTNSS and iTNSS were statistically significant for GSP301 versus mometasone and olopatadine versus placebo.^{19,20} Similarly, mometasone and olopatadine monotherapies provided significantly greater improvements than placebo (per the gatekeeping strategy) in the replicate SAR study conducted during the fall or mountain cedar allergy seasons.²⁰

In addition to improvements in average A.M. and P.M. rTNSS and iTNSS, GSP301 significantly improved all individual nasal symptoms compared with placebo for both measures, which provided further support for its efficacy in treating SAR nasal symptoms. When reflective and instantaneous TNSS nasal symptoms were analyzed separately as A.M. and P.M. assessments, the significant nasal symptom improvements with GSP301 versus placebo in the pre-dose A.M. and pre-dose P.M. iTNSS indicated that efficacy was maintained over the entire 12-hour dosing interval.

Clinically meaningful changes, indicated by minimal thresholds (*i.e.*, MCID),²⁷ reflect the changes in assessments at which patients perceive improvements with a treatment. The accepted MCIDs for the 12-point TNSS are 0.23 and 0.55 units,^{25,28} with the MCID of 0.23 units generally considered a more robust value as a result of its derivation from a direct anchor-based regression methodology.^{25,28} All treatment differences on TNSS for GSP301 versus placebo and monotherapies in the current study were thus considered clinically meaningful (>0.23 units). Differences for both monotherapies

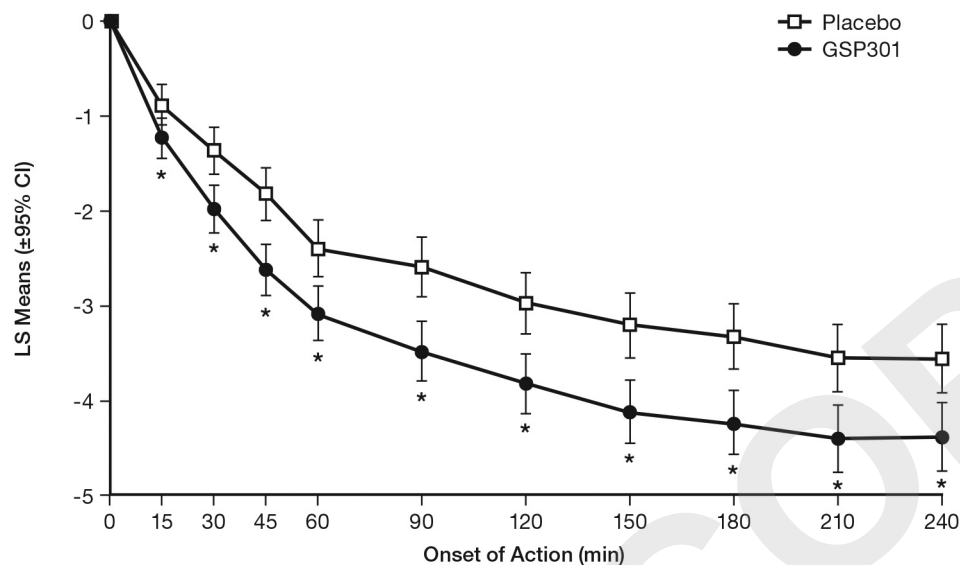


Figure 3. Onset of action for GSP301 versus placebo (FAS). Treatments: GSP301, olopatadine 665 µg and mometasone 25 µg; placebo, GSP301 vehicle. Onset of action was defined as the first post-dose time point at which significant differences in iTNSS change from baseline between the active treatment and placebo were observed as long as the significant difference was sustained. MMRM analysis with change from baseline as dependent variable, treatment group, site, and interaction treatment by time point as fixed effect, baseline as covariate, and time point as the within-patient effect. *Indicates a significant difference ($p < 0.05$) versus placebo. FAS = full analysis set; iTNSS = instantaneous Total Nasal Symptom Score; MMRM = mixed-effect model repeated measures; CI = confidence interval; LS = least squares.

Table 4 Treatment comparisons of TOSS, PNSS, RQLQ(S), and RCAT for GSP301 vs placebo from baseline to end of treatment (FAS)

GSP301 vs Placebo	n1, n2	LSMD	95% CI	p
Average A.M. and P.M. rTOSS	299, 283	-0.49	-0.79 to -0.19	0.001*
Average A.M. and P.M. iTOSS	299, 283	-0.50	-0.78 to -0.22	<0.001*
PNSS	299, 279	-0.82	-1.26 to -0.38	<0.001*
RQLQ(S) score	298, 279	-0.43	-0.64 to -0.21	<0.001*
RCAT score	292, 276	1.81	1.01 to 2.60	<0.001*

TOSS = Total Ocular Symptom Score; PNSS = Physician-assessed Nasal Symptom Score; RQLQ(S) = Rhinoconjunctivitis Quality-of-Life Questionnaire– Standardized Activities; RCAT = Rhinitis Control Assessment Test; FAS = full analysis set; n1 = GSP301; n2 = placebo; LSMD = least squares mean difference; CI = confidence interval.

* Indicates significance ($p < 0.05$) vs placebo.

Treatments: GSP301, olopatadine 665 µg and mometasone 25 µg; placebo, GSP301 vehicle.

versus placebo were also greater than the MCID of 0.23 units.

Patients with AR desire treatments that are not only effective but that also provide rapid and long-lasting relief.^{6,10} Such a pharmacologic agent would need to be effective against both acute and late-phase allergic reactions²⁹ and have both rapid and long-lasting effectiveness. In the present study, the onset of action for GSP301 occurred at 15 minutes (first time point assessed) and was sustained over the entire 14-day treatment period. An onset of action of 15 minutes was also observed in another large, phase III natural allergen exposure study of GSP301,³⁰ which thus provided rep-

licate evidence of a rapid onset of action. The onset of action results as well as the results over the entire 14-day treatment period suggest that GSP301 provides relief of acute- and late-phase allergic symptoms.

Further, when GSP301 was tested in a controlled environmental exposure chamber (EEC), the first of two consecutive time points on the iTNSS in which GSP301 significantly differed from placebo occurred at 10 minutes, with significant differences maintained at 11 of the 12 time points assessed.²¹ These results were supportive of the short onset observed in the present study. It is important to note that a shorter onset of action as measured in an EEC study versus a natural

Table 5 Summary of adverse events (SAS)

	GSP301, n (%) (n = 302)	Olopatadine, n (%) (n = 297)	Mometasone, n (%) (n = 294)	Placebo, n (%) (n = 287)
Patients reporting ≥ 1 TEAE	39 (12.9)	37 (12.5)	21 (7.1)	27 (9.4)
TEAEs*				
Dysgeusia	10 (3.3)	9 (3.0)	0 (0)	2 (0.7)
Headache	2 (0.7)	6 (2.0)	2 (0.7)	8 (2.8)
Patients discontinuing due to a TEAE	0 (0)	2 (0.7)	4 (1.4)	1 (0.3)
Patients with SAEs	1 (0.3)#	0 (0)	0 (0)	0 (0)
Deaths	0 (0)	0 (0)	0 (0)	0 (0)

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

* Occurring in $\geq 2\%$ of patients in any treatment group.

Spontaneous abortion; judged by the investigator as not related to study treatment.

Treatments: GSP301, olopatadine 665 μg and mometasone 25 μg ; olopatadine, 665 μg ; mometasone, 25 μg ; placebo, GSP301 vehicle.

allergen study is likely due to the difference in study designs and the time points assessed. It should be noted that the 15-minute onset of action in the natural allergen study of GSP301 occurred at the first time point being measured (at 15 minutes) and that the study design did not include any earlier time points of assessment.³⁰ In a natural allergen study of another intranasal FDC (U.S. Food and Drug Administration approved AzeFlu) that contained an antihistamine (azelastine HCl) and a corticosteroid (fluticasone propionate), the onset of action was 30 minutes when the first time point was measured at 15 minutes post-dose,³¹ whereas onset was 5 minutes when the first time point was measured at 5 minutes when tested in an EEC study.³² Based on the differences in study designs and timepoints assessed as noted above, these EEC and natural allergen study results should not be directly compared. Future comparative studies with similar designs are required to further assess the onset of action of different combination nasal sprays.

The onset of action for olopatadine and mometasone monotherapies could not be determined in the current study because the significant differences in iTNSS for olopatadine versus placebo were not sustained, and the differences between mometasone and placebo were not statistically significant at any time point. However, in another GSP301 SAR study, the same formulation of olopatadine had an onset of 15 minutes, which was sustained across the entire 4-hour assessment period.³⁰ The reason for the difference in olopatadine outcomes between the two studies was unclear. Also, whereas mometasone onset in other studies ranged from 150 minutes¹⁶ to 11 hours,³³ the onset of the sponsor mometasone formulation could not be determined in the current study or in another similarly designed phase III GSP301 study.³⁰ Due to the large range observed in various studies, it is possible that mometasone onset

could have been determined in the present study if the evaluation period had been >4 hours. Despite this, mometasone significantly improved symptoms on multiple days during the 14-day treatment period in the current study (rTNSS, 12 of 14 days; iTNSS, all 14 days), which indicated daily sustained relief.

For many patients, both nasal and ocular AR symptoms can negatively affect quality of life^{7,34} and, as such, effectively treating both types of symptoms may improve patients' overall health and well-being. Although effectively improving nasal symptoms versus placebo in the present study, GSP301 also significantly improved ocular symptoms compared with placebo. Further, GSP301 treatment significantly improved RQLQ(S) versus placebo. Although the treatment difference (0.43 units) was just below the established RQLQ(S) MCID of 0.50 units,³⁵ these results provided additional evidence that adequate relief of nasal and ocular symptoms may lead to improved quality of life in patients with SAR.

Overall, results from this study were consistent with those from several other clinical studies of GSP301 in patients with SAR,^{19–21} which demonstrated effective nasal and ocular symptom relief compared with placebo. These results were also similar to those observed with AzeFlu, in which combination treatment improved nasal and ocular AR symptoms better than placebo or the constituent monotherapies.³¹ Those results combined with the results reported in the clinical studies of GSP301 offer further evidence that antihistamine and corticosteroid FDCs may provide more effective symptom control than monotherapy treatment. However, because the SAR studies of AzeFlu and GSP301 were performed under different designs and conditions, a direct comparison of results between these two FDCs was not straightforward. For example, the daily TNSS in the current study was calculated by

using a 12-point scale that averaged the A.M. and P.M. values (total maximum daily score of 12). In the pivotal phase III studies of AzeFlu,³⁶ the symptoms were assessed twice daily (A.M. and P.M.) by using a 12-point scale and the daily TNSS was calculated by summing the A.M. and P.M. values (total maximum score of 24 per day). Therefore, without normalizing scores (when possible), caution should be exercised when comparing efficacy results across different clinical studies. Although future studies are needed to provide head-to-head comparisons of the FDC treatments AzeFlu and GSP301, the results from the separate studies of these FDCs support the role of combination treatment with intranasal corticosteroids and antihistamines over monotherapy treatment.

Combination therapies often result in greater efficacy than either treatment alone, but there is always a concern that safety may be compromised by simultaneously increasing the number of AEs.¹ In the present study, GSP301 was safe and well tolerated with similar incidences of AEs compared with placebo or individual monotherapies. Dysgeusia was the most commonly reported TEAE, which occurred slightly more frequently in the GSP301 and olopatadine groups. Only one SAE (spontaneous abortion) occurred in the GSP301 treatment group, but it was not considered related to study treatment. The safety outcomes reported here are similar to those observed in several early clinical studies of GSP301 in patients with SAR^{19,21} and without SAR,^{37,38} in a replicate phase III study of patients with SAR,²⁰ and in a 52-week study of patients with PAR,³⁹ which confirmed the favorable safety and tolerability profile of GSP301.

CONCLUSION

GSP301 is efficacious and well tolerated for the treatment SAR symptoms compared with placebo, with a rapid onset of action of 15 minutes in patients ≥ 12 years of age.

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