EFFICACY AND SAFETY OF OLOPATADINE/MOMETASONE COMBINATION NASAL SPRAY IN PATIENTS WITH SEASONAL ALLERGIC RHINITIS

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ABSTRACT

Rationale

Combining an intranasal antihistamine with an intranasal corticosteroid for the treatment of allergic rhinitis (AR) may provide improved symptom relief over monotherapy treatment. GSP301 nasal spray is a fixed-dose combination of the antihistamine olopatadine hydrochloride and the corticosteroid mometasone furoate. The efficacy and safety of GSP301 were evaluated in a large, phase 3 seasonal AR (SAR) study.

Methods

In this double-blind, randomized, parallel-group study [NCT02631551], patients (≥12 years) with SAR were equally randomized to twice-daily GSP301 (olopatadine 665 µg/mometasone 25 µg BID), olopatadine HCl (665 µg BID), mometasone furoate (25 µg BID), or placebo (BID) for 14 days. The primary efficacy endpoint was the mean change from baseline in AM and PM reflective Total Nasal Symptom Scores (rTNSS), analyzed using mixed-effect model repeated measures. Adverse events (AEs) were also assessed.

Results

A total of 1,180 patients were randomized. GSP301 demonstrated significant improvement on rTNSS versus placebo (least squares mean difference [95% CI]: -0.98 [-1.38, -0.57], $P<0.001$) and versus olopatadine (-0.61 [-1.01, -0.21]; $P=0.003$). A clinically meaningful, numerical improvement in rTNSS that approached significance was observed with GSP301 versus mometasone (-0.39 [-0.79, 0.01], P=0.059). Compared with placebo, mometasone monotherapy significantly improved rTNSS (-0.59 [-1.00, -0.19]; $P=0.004$), but olopatadine monotherapy was not significant (-0.37 [-0.78, 0.04]; P=0.076). Additionally, the percentages of patients with treatment-emergent AEs were similar across treatment groups: 12.9%, 12.5%, 7.1%, and 9.4% in the GSP301, olopatadine, mometasone, and placebo groups, respectively.

Conclusion

In this study, twice-daily GSP301 treatment provided significant and clinically meaningful improvements in SAR nasal symptoms versus placebo and was well tolerated.

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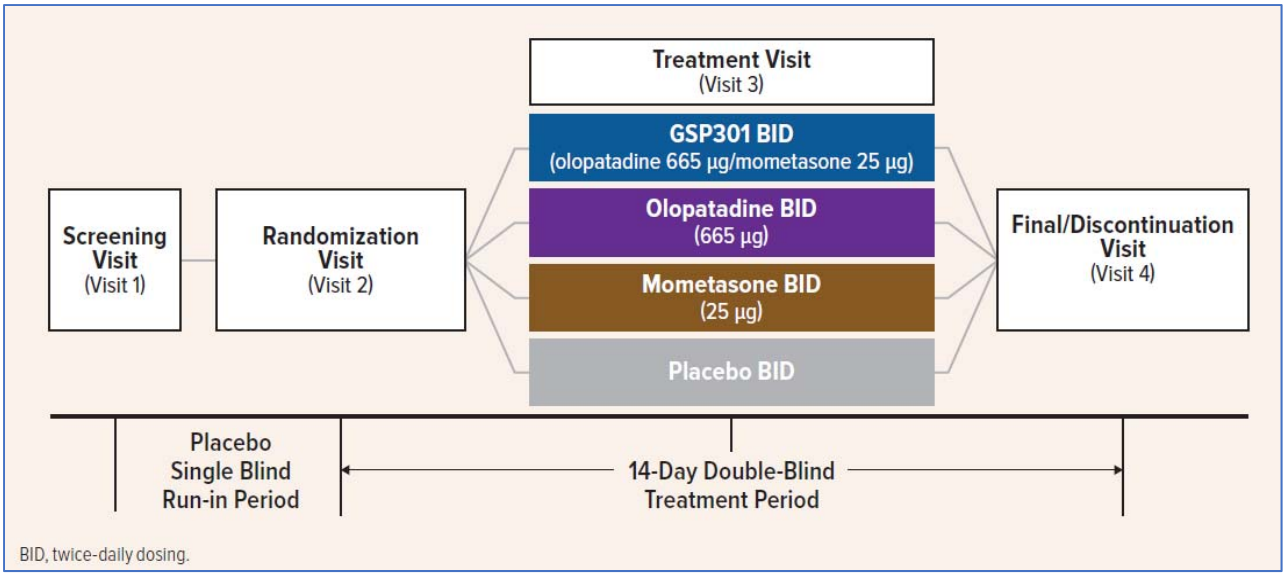
KEY FINDINGS

STUDY DESIGN

- Randomized, double-blind, parallel-group study (NCT02631551) conducted in patients ≥12 years of age with SAR (≥2 years) during the Spring pollen season (eg, tree/grass)

Figure 1. Study Design



BID, twice-daily dosing.

Endpoints

- Primary: mean change from baseline to end of 14-day treatment in patient-reported AM and PM 12-hour rTNSS for
  - GSP301 versus placebo
  - GSP301 versus olopatadine and mometasone monotherapies
  - Olopatadine and mometasone monotherapies versus placebo
- Additional: mean change from baseline to end of 14-day treatment in patient-reported AM and PM 12-hour iTNSS for the same treatment comparisons above; mean AM and PM individual nasal symptoms over 14-day treatment period for GSP301 versus placebo; and safety/AEs

Statistical Analyses

- Efficacy endpoints were analyzed via mixed-effect model repeated measures, with change from baseline as the dependent variable, treatment group and site as fixed effect, and adjusting for covariates (site, baseline score, and study day as the within-patient effect)
  - A difference of 0.23 units in TNSS was considered clinically meaningful (defined as the minimal clinically important difference)[1]
  - To adjust for multiplicity, a gate-keeping strategy was used in which any treatment comparisons following one that did not reach significance (statistical significance, $P<0.05$) were also considered not significant, regardless of the P value obtained

RESULTS

Patients

- Efficacy analyses were based on the full analysis set (FAS), defined as all randomized patients who received ≥1 dose of study drug and completed ≥1 post-baseline primary efficacy assessment (n=1,170)
- Safety assessments were based on the safety analysis set (SAS), which included all patients who received ≥1 dose of study drug (n=1,180)
- At baseline, patients had moderate to severe symptoms, with mean rTNSS ranging from 10.1 to 10.3 and mean iTNSS ranging from 9.2 to 9.4 (**Table 1**)

Table 1. Baseline Characteristics

	GSP301 (n=302)	Olopatadine (n=297)	Mometasone (n=294)	Placebo (n=287)
Demographics				
Age, mean ± SD, y	39.5 ± 15.4	39.6 ± 14.9	38.7 ± 16.3	39.4 ± 14.8
Sex, n (%)				
Male	101 (33.4)	116 (39.1)	96 (32.7)	105 (36.6)
Female	201 (66.6)	181 (60.9)	198 (67.3)	182 (63.4)
Race, n (%)				
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[a]	3 (1.0)	7 (2.4)	4 (1.4)	1 (0.3)
Ethnicity, n (%)				
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 Clinical Characteristics				
rTNSS, mean ± SD[b]	10.1 ± 1.2	10.3 ± 1.3	10.2 ± 1.2	10.2 ± 1.2
iTNSS, mean ± SD[b]	9.2 ± 1.7	9.4 ± 1.9	9.3 ± 1.7	9.3 ± 1.7

GSP301, olopatadine 665 µg/mometasone 25 µg BID; olopatadine, 665 µg BID; mometasone, 25 µg BID.
[a]Includes American Indian or Alaska native and native Hawaiian or other Pacific Islander.
[b]Full analysis set; GSP301 n=299; olopatadine n=294; mometasone n=294; placebo n=283.
BID, twice-daily dosing; iTNSS, instantaneous Total Nasal Symptom Score; rTNSS, reflective Total Nasal Symptom Score; SD, standard deviation.

Efficacy

rTNSS

- GSP301 treatment demonstrated significant and clinically meaningful improvements from baseline to end of 14-day treatment versus placebo ($P<0.001$) and olopatadine ($P=0.003$; **Table 2**)
- A clinically meaningful numerical improvement that approached statistical significance was observed with GSP301 versus mometasone ($P=0.059$; **Table 2**); all further comparisons were considered not statistically significant per the gate-keeping analysis strategy, even though some comparisons reached $P<0.05$ (**Table 2**)

iTNSS

- Similar to the rTNSS results, GSP301 demonstrated significant and clinically meaningful improvements from baseline to end of 14-day treatment compared with placebo ($P<0.001$; **Table 2**)
- GSP301 treatment also demonstrated significant and clinically meaningful improvements versus both monotherapy components: olopatadine, $P=0.005$; mometasone, $P=0.041$ (**Table 2**)

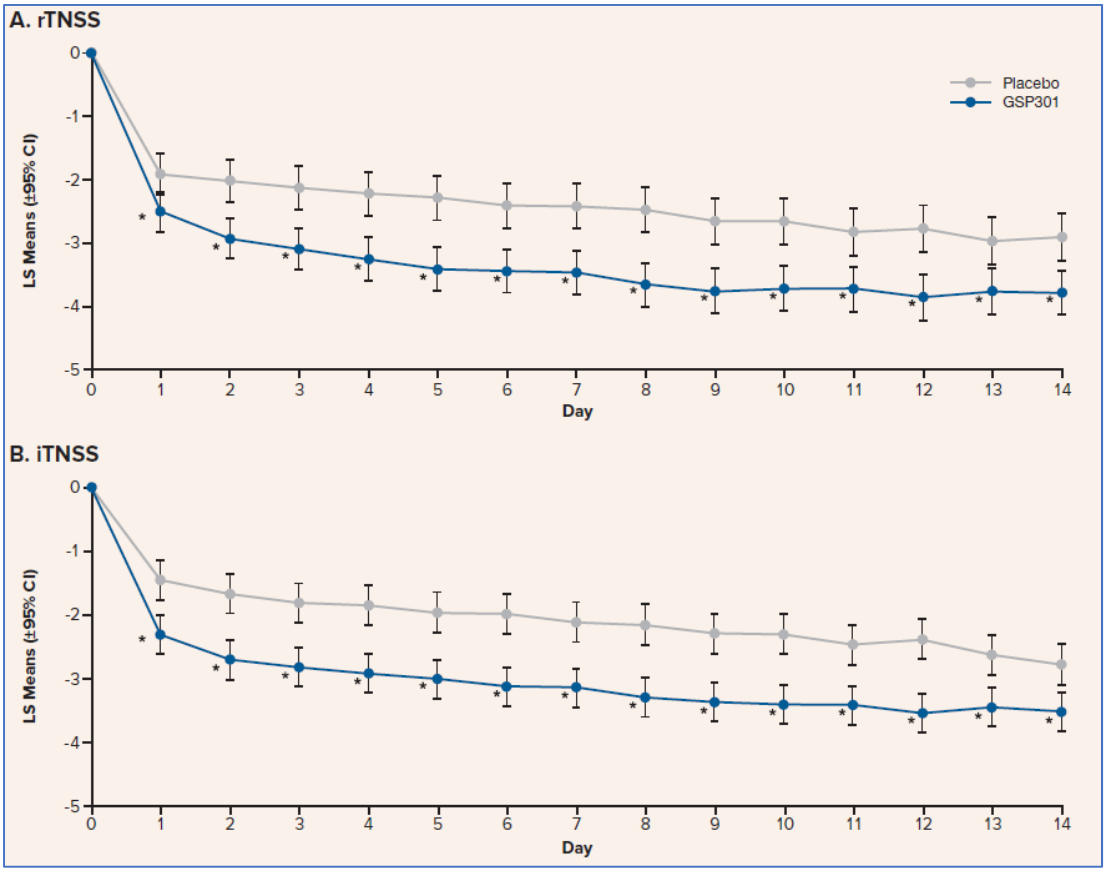
Table 2. LS Mean Difference in Average AM and PM rTNSS and iTNSS Over 14 Days of Treatment

Treatment Groups (1 vs 2)	n1, n2	LSMD	95% CI	*P* value
rTNSS				
GSP301 vs Placebo	299, 283	-0.98	-1.38, -0.57	<0.001*
GSP301 vs Olopatadine	299, 294	-0.61	-1.01, -0.21	0.003*
GSP301 vs Mometasone	299, 294	-0.39	-0.79, 0.01	0.059
Olopatadine vs Placebo	294, 283	-0.37	-0.78, 0.04	0.076
Mometasone vs Placebo	294, 283	-0.59	-1.00, -0.19	0.004†
iTNSS				
GSP301 vs Placebo	299, 283	-0.93	-1.28, -0.58	<0.001*
GSP301 vs Olopatadine	299, 294	-0.50	-0.85, -0.15	0.005*
GSP301 vs Mometasone	299, 294	-0.36	-0.71, -0.01	0.041*
Olopatadine vs Placebo	294, 283	-0.43	-0.78, -0.07	0.018*
Mometasone vs Placebo	294, 283	-0.57	-0.92, -0.21	0.002*

GSP301, olopatadine 665 µg/mometasone 25 µg BID; Olopatadine, 665 µg BID; Mometasone, 25 µg BID.
*Indicates significance (*P*<0.05) vs treatment group 2.
†Not significant per gate-keeping strategy, even though *P*<0.05.
BID, twice-daily dosing; CI, confidence interval; LS, least squares; LSMD, least squares mean difference; iTNSS, instantaneous Total Nasal Symptom Score; rTNSS, reflective Total Nasal Symptom Score.

- GSP301 demonstrated significant improvements on rTNSS and iTNSS vs placebo on day 1 and each subsequent day up to day 14 (*P*<0.05, all) suggesting sustained symptom improvement (**Figure 2**; data for olopatadine and mometasone not shown)

Figure 2. LS Mean (95% CI) Change from Baseline in Average AM and PM rTNSS (A) and iTNSS (B) With GSP301 vs Placebo Over 14 Days of Treatment



GSP301, olopatadine 665 µg/mometasone 25 µg BID.
**P*<0.05 vs placebo.
BID, twice-daily dosing; CI, confidence interval; LS, least squares; iTNSS, instantaneous Total Nasal Symptom Score; rTNSS, reflective Total Nasal Symptom Score.

KEY FINDINGS

- GSP301 demonstrated significant improvements on all individual nasal symptoms versus placebo over the 14-day treatment period (P<0.01, all; **Table 3**; data for olopatadine and mometasone not shown)

Table 3. LS Mean Difference in Individual Reflective and Instantaneous Nasal Symptom Scores with GSP301 vs Placebo

Reflective	LSMD (95% CI)	*P* value
Rhinorrhea	-0.16 (-0.27, -0.06)	0.002*
Nasal congestion	-0.16 (-0.25, -0.08)	<0.001*
Nasal itching	-0.22 (-0.33, -0.11)	<0.001*
Sneezing	-0.32 (-0.40, -0.23)	<0.001*
Instantaneous	**LSMD (95% CI)**	***P* value**
Rhinorrhea	-0.22 (-0.33, -0.12)	<0.001*
Nasal congestion	-0.18 (-0.27, -0.08)	<0.001*
Nasal itching	-0.26 (-0.36, -0.16)	<0.001*
Sneezing	-0.29 (-0.39, -0.18)	<0.001*

GSP301, olopatadine 665 µg/mometasone 25 µg BID.
* Significant *P* values vs placebo.
BID, twice-daily dosing; CI, confidence interval; LS, least squares; LSMD, least squares mean difference.

Safety

- Only 2 TEAEs (dysgeusia and headache) occurred in ≥2% of patients in any treatment group (**Table 4**); the majority of TEAEs were mild or moderate in severity and were not considered related to treatment
- One serious AE (spontaneous abortion in the GSP301 group) was judged to be unrelated to study treatment, and no deaths occurred (**Table 4**)

Table 4. Adverse Events During 14-Day Treatment Period

n, (%)	GSP301 (n=302)	Olopatadine (n=297)	Mometasone (n=294)	Placebo (n=287)
Patients reporting ≥1 TEAE	39 (12.9)	37 (12.5)	21 (7.1)	27 (9.4)
TEAEs[a]				
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 with a TEAE leading to withdrawal	0 (0)	2 (0.7)	4 (1.4)	1 (0.3)
Patients with an SAE	1 (0.3)	0 (0)	0 (0)	0 (0)
Deaths	0 (0)	0 (0)	0 (0)	0 (0)

GSP301, olopatadine 665 µg/mometasone 25 µg BID; olopatadine, 665 µg BID; mometasone, 25 µg BID.
[a]Occurring in ≥2% of patients in any treatment group.
BID, twice-daily dosing; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- In this study, twice-daily (BID) treatment with GSP301 fixed-dose combination nasal spray demonstrated significant, sustained, and clinically meaningful[1] improvements in SAR nasal symptoms compared with placebo
- GSP301 was well tolerated with similar incidences of AEs as either placebo or component monotherapies
- These results demonstrate that GSP301 BID is efficacious and well tolerated for the treatment of nasal symptoms associated with SAR in adolescent and adult patients 12 years of age and older

REFERENCE

1. Barnes ML, et al. *Clin Exp Allergy*. 2010;40(2):242-250.