LONG-TERM SAFETY AND EFFICACY OF OLOPATADINE/MOMETASONE COMBINATION NASAL SPRAY IN PATIENTS WITH PERENNIAL ALLERGIC RHINITIS

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ABSTRACT

Introduction

The efficacy and safety of GSP301 nasal spray, a newly developed investigational fixed-dose combination of olopatadine hydrochloride/mometasone furoate, was demonstrated in large 2-week seasonal allergic rhinitis studies. This study compared the 52-week safety (primary endpoint) and efficacy (secondary endpoint) of GSP301 in patients with perennial allergic rhinitis (PAR).

Methods

In this randomized, double-blind, parallel-group study (NCT02709538), 601 patients with PAR (≥12 years) were randomized 4:1:1 to twice-daily GSP301 (olopatadine 665 µg/mometasone 25 µg; pH 3.7) and two GSP301 vehicle formulations (placebo pH 3.7 or 7.0). Treatment-emergent adverse events (TEAEs) were analyzed using descriptive statistics. Mean change from baseline in average 24-hour AM reflective and instantaneous Total Nasal Symptom Scores (rTNSS, iTNSS) for GSP301 vs placebo pH 3.7 were analyzed using mixed-effect model repeated measures (P<0.05 = statistically significant).

Results

At week 52, TEAEs occurred in 51.7%, 41.4%, and 53.5% of patients in the GSP301, placebo pH 3.7 and 7.0 groups. The most frequently reported TEAEs (≥5% in any treatment group) included upper respiratory tract infection, headache, nasal discomfort, and nasopharyngitis. No clinically meaningful differences were observed in TEAE incidences or other safety assessments across treatments. At weeks 6 and 30, GSP301 significantly improved rTNSS and iTNSS vs placebo pH 3.7 (P<0.01, all). At week 52, GSP301 significantly improved rTNSS (least-squares mean difference [95% CI]: -0.91 [-1.35, -0.47]; P<0.001) and iTNSS (-0.75 [-1.17, -0.33]; P=0.001) vs placebo pH 3.7, with significant improvements in individual symptoms (P<0.05, all).

Conclusions

In this long-term study, GSP301 was well tolerated and provided statistically significant and clinically meaningful improvements in PAR symptoms vs placebo.

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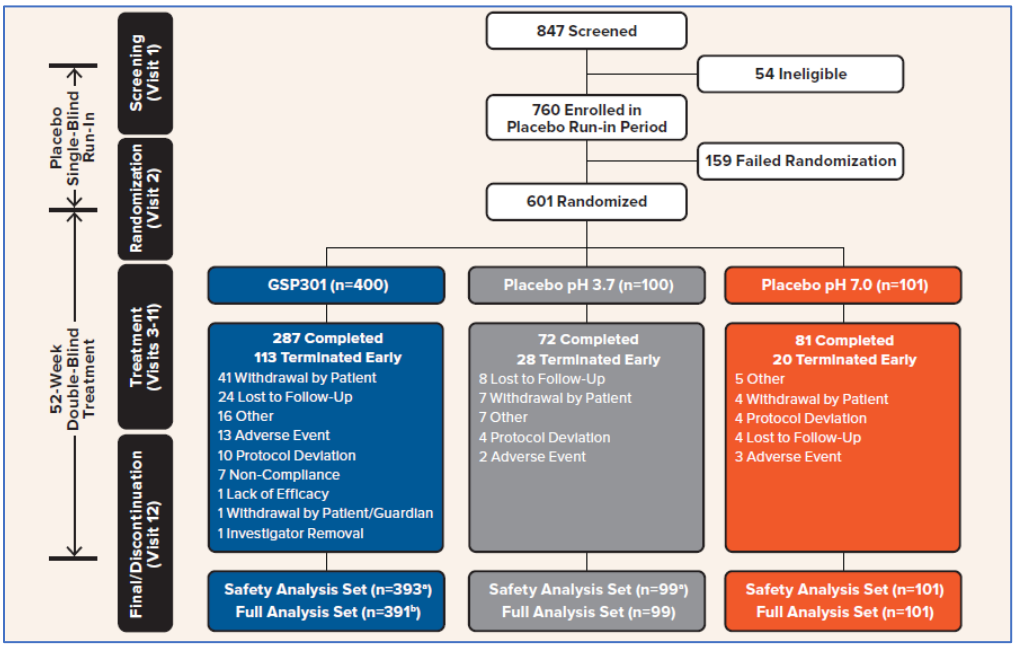
STUDY DESIGN

- This phase 3, double-blind, randomized, parallel-group study was conducted over 52 weeks in patients with PAR (**Figure 1**)
- Patients self-assessed 24-hour AM reflective and instantaneous nasal symptoms (once daily) in a symptom diary after self-administering study medication (twice daily)
- Use of non-nasal formulations of loratadine (10 mg/day) as a rescue medication (on an as-needed-basis) was permitted after week 6 (visit 4) until symptoms were controlled; additional non-nasal rescue medications were provided if loratadine was not effective in treating the AR
- A treatment difference of >0.23 units in TNSS was considered clinically meaningful (defined as the minimal clinically important difference)[1]

Figure 1. Study Design



GSP 301, olopatadine 665 µg/mometasone 25 µg BID (pH 3.7); placebo pH 3.7, GSP301 vehicle; placebo pH 7.0, GSP301 vehicle.
Screening occurred on days -7 to -10. Randomization occurred on day 1. Treatment visits occurred during weeks 3, 6, 12, 18, 24, 30, 36, 42, and 48 with the final visit occurring during week 52.
[a] Seven patients in GSP301 and 1 patient in placebo pH 3.7 were not randomized or did not use the study drug on ≥1 occasion.
[b] Two patients in GSP301 did not have a post-baseline AM rTNSS assessment.
BID, twice-daily; rTNSS, reflective Total Nasal Symptom Score.

Endpoints

- The primary safety endpoints were treatment emergent AEs (TEAEs), treatment-related TEAEs, laboratory assessments, vital signs, and physical examinations at weeks 30 and 52 for:
  - GSP301 versus placebo pH 3.7
  - GSP301 versus placebo pH 7.0
- Secondary/additional efficacy endpoints included mean change from baseline in:
  - Patient-reported average 24-hour AM reflective and instantaneous TNSS at weeks 6, 30, and 52
  - Patient-reported average 24-hour AM rTNSS and iTNSS by week
  - Patient-reported average 24-hour AM individual reflective and instantaneous nasal symptoms at weeks 6, 30, 52
    - Treatment comparisons for efficacy endpoints presented here are for GSP301 versus the matching placebo formulation (pH 3.7) only

RESULTS

Patients

- A total of 601 patients were randomized and 440 completed the study (**Figure 1**)
- Demographics and baseline nasal symptom scores were similar across the treatment groups (**Table 1**)
- Patients were predominantly female and white, with a mean (standard deviation [SD]) age of 40.8 (14.7) years; they had moderate-severe nasal symptoms (**Table 1**)

Table 1. Baseline Characteristics

Demographics	GSP301 (n=393)	Placebo pH 3.7 (n=99)	Placebo pH 7.0 (n=101)
Age, mean ± SD, y	40.4 ± 14.8	42.1 ± 15.4	41.2 ± 13.5
Sex, n (%)			
Female	269 (68.4)	68 (68.7)	68 (67.3)
Male	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[a]	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 nasal symptom scores, mean ± SD	GSP301 (n=391)	Placebo pH 3.7 (n=99)	Placebo pH 7.0 (n=101)
Average AM rTNSS	9.1 ± 1.9	8.9 ± 1.9	9.1 ± 1.8
Average AM iTNSS	8.1 ± 2.6	7.7 ± 2.3	8.1 ± 2.3

GSP301, olopatadine 665 µg/mometasone 25 µg BID (pH 3.7); placebo pH 3.7, GSP301 vehicle; placebo pH 7.0, GSP301 vehicle.
[a] Includes American Indian or Alaska native.
BID, twice-daily; iTNSS, instantaneous Total Nasal Symptom Score; rTNSS, reflective Total Nasal Symptom Score; SD, standard deviation.

Safety

- Mean (SD) 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 treatments, respectively
- Over 90% of patients achieved ≥75% medication compliance
- Rescue medication use was 35.6%, 46.5%, and 50.5% in the GSP301, placebo pH 3.7 and placebo pH 7.0 groups, respectively
- Differences in overall TEAE rates were comparable across treatment groups at week 52 (**Table 2**)
- The most frequently reported TEAEs in any treatment group (≥5%) at week 52 were upper respiratory tract infection, headache, nasal discomfort, and nasopharyngitis (**Table 2**)
- Most TEAEs were mild-moderate in severity, serious AEs occurred in ≤2% of patients in any treatment group, <4% of patients in any treatment group discontinued due to an AE, and no deaths occurred (**Table 2**)
- There were no clinically meaningful differences between GSP301 and either placebo treatment (pH 3.7 and 7.0) in the incidence of AEs or on any other safety assessments

Table 2. Adverse Events at Week 52

n, (%)	52 Weeks		
	GSP301 (n=393)	Placebo pH 3.7 (n=99)	Placebo pH 7.0 (n=101)
Patients reporting ≥1 TEAE	203 (51.7)	41 (41.4)	54 (53.5)
TEAEs reported in ≥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 reporting ≥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 ≥5% of patients			
Nasal discomfort	10 (2.5)	2 (2.0)	5 (5.0)
Patients discontinuing due to a TEAE	15 (3.8)	2 (2.0)	3 (3.0)
Patients with ≥1 SAE	7 (1.8)[a]	2 (2.0)[b]	2 (2.0)[c]
Deaths	0 (0)	0 (0)	0 (0)

GSP301, olopatadine 665 µg/mometasone 25 µg BID (pH 3.7); placebo pH 3.7, GSP301 vehicle; placebo pH 7.0, GSP301 vehicle.

[a] 1 prostate cancer; 1 pneumonia; 1 cellulitis; 1 cholelithiasis; 1 renal cell carcinoma; 1 anaplastic astrocytoma; 1 invasive ductal breast carcinoma.

[b] 1 appendicitis; 1 ectopic pregnancy.

[c] 1 nephrolithiasis; 1 cholelithiasis.

BID, twice-daily; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Efficacy

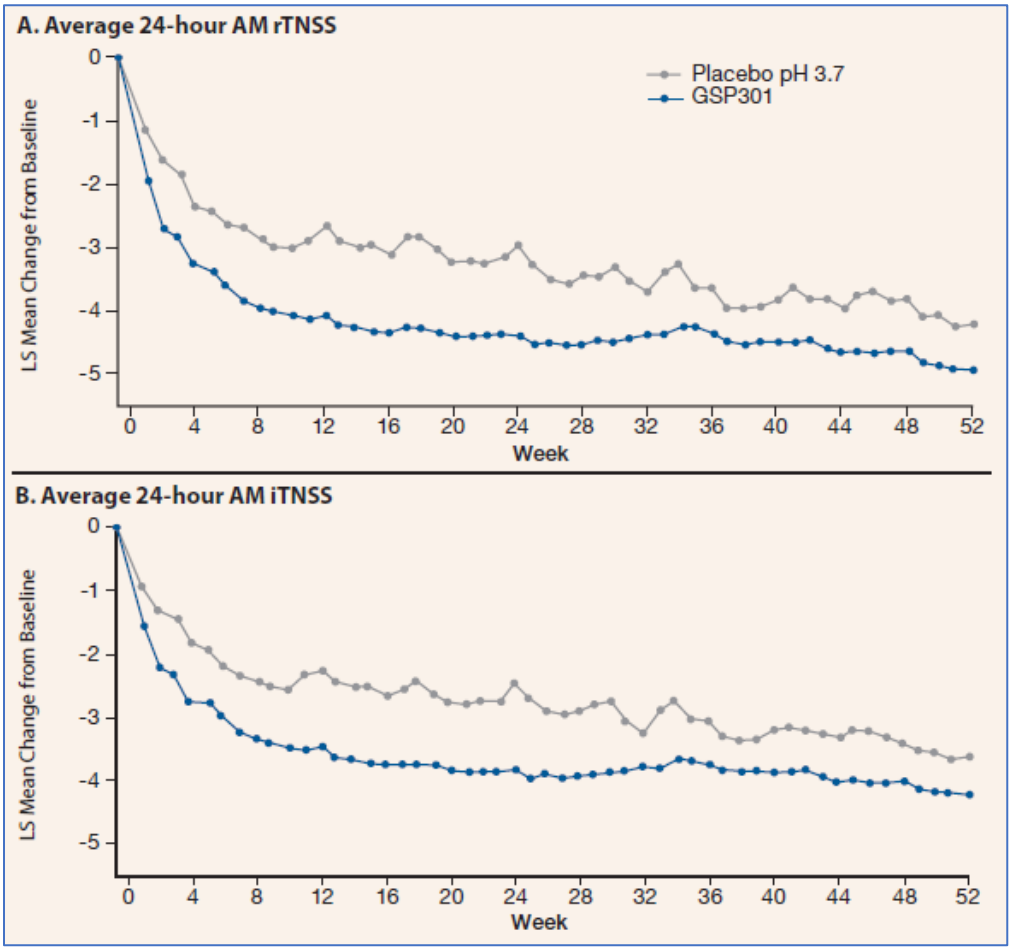
- Over the first 6 weeks, GSP301 treatment resulted in statistically significant and clinically meaningful improvements in both rTNSS and iTNSS compared with placebo pH 3.7 ($P<0.01$, all; **Table 3**)
- Over weeks 30 and 52, GSP301 also resulted in significant and clinically meaningful improvements in both rTNSS and iTNSS versus placebo pH 3.7 ($P<0.01$, all; **Table 3**)
- GSP301 provided clinically meaningful improvements in rTNSS and iTNSS versus placebo from baseline to the end of 52-week treatment (**Figure 2**); 45 out of 52 weekly time points were statistically significant for rTNSS and 39 out of 52 for iTNSS
- Similar to the overall nasal symptoms, GSP301 significantly improved all average 24-hour AM reflective and instantaneous individual nasal symptoms versus placebo over the first 6 weeks and over 30 and 52 weeks ($P<0.05$, all; **Table 4**)

Table 3. Change in Average 24-hour AM rTNSS and iTNSS Over Weeks 6, 30, and 52

Treatment Groups	Week	n1, n2	LSMD	95% CI	*P* value
Average 24-hour AM rTNSS					
GSP301 versus Placebo pH 3.7	6	391, 99	-0.81	-1.29, -0.32	0.001*
	30	391, 99	-0.96	-1.41, -0.50	<0.001*
	52	391, 99	-0.91	-1.35, -0.47	<0.001*
Average 24-hour AM iTNSS					
GSP301 versus Placebo pH 3.7	6	391, 99	-0.66	-1.12, -0.20	0.005*
	30	391, 99	-0.83	-1.26, -0.39	<0.001*
	52	391, 99	-0.75	-1.17, -0.33	0.001*

GSP301, olopatadine 665 µg/mometasone 25 µg BID (pH 3.7); placebo pH 3.7, GSP301 vehicle.
* Indicates significance ($P<0.05$) versus placebo pH 3.7.
BID, twice-daily; CI, confidence interval; iTNSS, instantaneous Total Nasal Symptom Score; LSMD, least squares mean difference; rTNSS, reflective Total Nasal Symptom Score.

Figure 2. Average 24-hour AM rTNSS (A) and iTNSS (B) for GSP301 Versus Placebo pH 3.7 by Week



GSP301, olopatadine 665 µg/mometasone 25 µg BID (pH 3.7); placebo pH 3.7, GSP301 vehicle.
For GSP301 vs placebo, 45 out of 52 weekly time points were statistically significant for rTNSS and 39 out of 52 for iTNSS.
BID, twice-daily; iTNSS, instantaneous Total Nasal Symptom Score; LS, least squares; rTNSS, reflective Total Nasal Symptom Score.

Table 4. Average 24-hour AM Reflective and Instantaneous Individual Nasal Symptom Scores with GSP301 Versus Placebo pH 3.7 at Weeks 6, 30, and 52

	First 6 Weeks		30 Weeks		52 Weeks	
	Reflective	Instantaneous	Reflective	Instantaneous	Reflective	Instantaneous
Rhinorrhea						
LSMD	-0.18	-0.16	-0.24	-0.22	-0.21	-0.19
95% CI	-0.32, -0.04	-0.29, -0.02	-0.37, -0.12	-0.35, -0.09	-0.33, -0.09	-0.31, -0.07
***P* value**	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, -0.07	-0.34, -0.08	-0.32, -0.08	-0.33, -0.10	-0.29, -0.04	-0.31, -0.08
***P* value**	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, -0.01	-0.31, -0.04	-0.31, -0.05	-0.33, -0.08	-0.29, -0.04	-0.31, -0.07
***P* value**	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, -0.16	-0.30, -0.03	-0.44, -0.18	-0.33, -0.08	-0.42, -0.17	-0.33, -0.09
***P* value**	<0.001*	0.018*	<0.001*	0.002*	<0.001*	0.001*

GSP301, olopatadine 665 µg/mometasone 25 µg BID (pH 3.7); placebo pH 3.7, GSP301 vehicle.
* Indicates significance ($P<0.05$) versus placebo pH 3.7.
BID, twice-daily; CI, confidence interval; LSMD, least squares mean difference.

CONCLUSIONS

- In this study, long-term (52-week) treatment with twice-daily GSP301 FDC nasal spray was well tolerated in PAR patients, with similar incidences of AEs compared with either placebo formulation (pH 3.7 and pH 7.0)
- This study also confirmed no reported safety concerns as a result of the lower pH (3.7) used in the GSP301 active and matching placebo formulations
- GSP301 treatment resulted in statistically significant and clinically meaningful improvements[1] in PAR nasal symptoms versus placebo (pH 3.7) over 52 weeks
- Overall, GSP301 was well tolerated and provided statistically significant and clinically meaningful improvements[1] in PAR nasal symptoms versus placebo, demonstrating long-term safety and efficacy without tachyphylaxis over 52 weeks

REFERENCE

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