

Pharmacokinetics of intranasal olopatadine in the fixed-dose combination GSP301 versus two monotherapy intranasal olopatadine formulations

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ABSTRACT

Background: GSP301 is a fixed-dose combination of the antihistamine olopatadine hydrochloride and the corticosteroid mometasone furoate developed as a single nasal spray.

Objective: To assess the relative bioavailability of olopatadine administered as GSP301 versus two olopatadine monotherapy nasal spray formulations.

Methods: In this single-dose, open-label, crossover study, healthy adults (18–65 years old) were equally randomized to one of six treatment sequences for three 48-hour treatment periods with GSP301 (olopatadine 665 µg–mometasone 50 µg), the olopatadine monotherapy component of GSP301 (OLO-sponsor; 665 µg) and U.S. Food and Drug Administration approved olopatadine (OLO; 665 µg); each treatment was administered as a single dose (two sprays in each nostril). To assess the relative bioavailability of olopatadine in the fixed-dose nasal spray versus two monotherapies, pharmacokinetic (PK) estimates, maximum plasma concentration (C_{max}), area under the plasma concentration time curve (AUC) from time 0 to the last time point with measurable concentration (AUC_{0-t}), and AUC from time 0 to time infinity ($AUC_{0-\infty}$) were compared by analysis of variance. Safety and tolerability were also evaluated.

Results: A total of 30 healthy adults (mean age, 43.1 years) were randomized. The majority of the subjects were white men. The geometric mean ratios for natural log transformed C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ of olopatadine in GSP301 and OLO-sponsor were 86.63, 86.92, and 92.83, respectively. For GSP301 and OLO, geometric mean ratios for C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ were 84.68, 87.87, and 93.80, respectively. The percentage of subjects who reported treatment-emergent adverse events (AE) for GSP301, OLO-sponsor, and OLO were 13.8, 10.3, and 10.0%, respectively, with mild AEs reported. One subject withdrew from the study due to an AE (minor oropharyngeal pain) during OLO treatment, before receiving GSP301.

Conclusion: Olopatadine bioavailability with GSP301 was comparable with OLO-sponsor and OLO. The presence of mometasone in GSP301 did not considerably affect the PK of olopatadine. GSP301 was well tolerated, with only mild AEs reported.

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Allergic rhinitis (AR) affects ~10–30% of adults and 40% of children in the United States and is generally characterized by symptoms of nasal congestion, rhinorrhea, sneezing, and nasal itching.^{1,2} In 2005, the total expenditure on AR in the United States was estimated at \$11.2 billion, with almost 60% of costs attributed to prescription drugs.³ Although several drug options are available to treat AR

(e.g., oral or intranasal antihistamines, decongestants, mast cell inhibitors, leukotriene receptor antagonists, intranasal corticosteroids),¹ more than half of patients are nonadherent, partly due to inadequate symptom control.⁴

The American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology 2017 guidelines for AR treatment recommend combining an intranasal antihistamine with an intranasal corticosteroid for treatment of moderate-to-severe AR nasal symptoms.⁵ Both nasal spray (NS) antihistamines and NS corticosteroids are efficacious monotherapies, with notable differences in their onset of action: antihistamines have a short average onset of action (15–30 minutes) and, thus, provide immediate symptom relief, whereas the longer onset of action of corticosteroids (3–36 hours) provides more sustained symptom relief.¹ Furthermore, simplifying treatments by reducing dosing frequency or the number of treatments (i.e., one fixed-dose combination [FDC] versus

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multiple monotherapies) can improve medication adherence.^{1,6,7}

GSP301 is an FDC of the antihistamine olopatadine hydrochloride (HCl) and the corticosteroid mometasone furoate, developed as a single NS. Olopatadine HCl is a highly selective histamine H₁-receptor antagonist, with mast cell-stabilizing and other anti-inflammatory properties⁸ that effectively reduces AR symptoms of sneezing and of itchy and/or runny nose.^{9,10} Mometasone furoate reduces AR symptoms by inhibiting the release of inflammatory mediators.¹¹ As NS monotherapies, both olopatadine (approved as Patanase, Alcon Laboratories Inc., Fortworth, TX) and mometasone (approved as Nasonex, Schering Corporation, a subsidiary of Schering-Plough Corporation, Kenilworth, NJ), are safe and efficacious treatments for AR.^{9,10,12,13}

The objective of this study was to assess the relative bioavailability of olopatadine administered as GSP301 (olopatadine HCl 665 µg–mometasone furoate 50 µg FDC NS) versus two olopatadine NS monotherapies: the olopatadine monotherapy component of GSP301 (OLO-sponsor) and the U.S. Food and Drug Administration (FDA) approved olopatadine NS Patanase (OLO).¹⁴ A similarly designed study that assessed the relative bioavailability of the mometasone component of GSP301 FDC NS versus an investigational mometasone monotherapy NS (sponsor mometasone) and Nasonex is reported in a companion article in this issue of the journal (see pp 232–239, Ref. 22).

METHODS

This study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, and according to International Conference on Harmonization guidelines. All aspects of the protocol were reviewed and approved by the Optimum Clinical Research Inc. institutional review board (Oshawa, Ontario, Canada) and carried out according to applicable local regulatory requirements. All the subjects provided written informed consent.

Subjects

Eligible subjects were healthy men and women, 18–65 years of age, with a body mass index of 18.5–32 kg/m². Exclusion criteria included a history of perennial or seasonal allergies, nasal surgery, or nasal structural abnormalities; clinically significant or acute cardiovascular, pulmonary, hepatic, renal, gastrointestinal, hematologic, endocrine, metabolic, mental, or neurologic disease, or electrocardiogram (ECG) abnormalities; and regular use of corticosteroids (systemic or orally inhaled) or antihistamines, including olopatadine. Additional exclusion criteria consisted of any use before the first treatment period of systemic or orally inhaled cortico-

steroids for 60 days or intranasal corticosteroids for 30 days, any surgical or medical condition that could significantly alter the absorption, distribution, metabolism, or excretion of the study drugs, or exposure to cytochrome P450 3A4 inhibiting or inducing drugs (e.g., ritonavir, ketoconazole, itraconazole, erythromycin, rifampicin, St. John's wort [*Hypericum perforatum*]) 30 days before the screening visit.

Before the initial treatment, the following medications were not permitted: immunoglobulin E antagonists (120 days before), antihistamines (3 days before), or prescription drugs (≤14 days before). Medications not permitted before initial dosing or during study participation included the following: over-the-counter medications, such as herbal supplements, vitamins (multivitamins were not to be taken 14 days before to the first treatment period until study completion), and homeopathy and/or ayurvedic treatments (≤14 days before); hormone replacement therapy (180 days before); and all intranasal therapies and topical corticosteroids (except to treat small, localized lesions, from period 1 check-in), ophthalmic drops or clinical trial drugs (30 days before); radiation therapy; and initiation of injectable immunotherapy.

The subjects were not allowed to consume any food or drink that contained pomelo, grapefruit, apple, orange, any vegetables from the mustard green family, or charbroiled meat for 30 days before the study start until study completion. Caffeine-containing products or products with poppy seeds were not permitted for 48 hours before the study start or during study participation. For the 24 hours before the study start and for the duration of the study, alcohol consumption was not permitted. Vitamin water could not be consumed from the start of treatment through study completion.

Study Design

In this phase I, single-center, single-dose, open-label, three-way crossover study, the subjects were randomized (1:1:1:1:1:1) to one of six treatment sequences. Each treatment sequence comprised three inpatient, single-dose treatment periods, with a 7- to 14-day washout between doses and a postdosing safety follow-up *via* telephone 1 to 7 days after treatment period 3 (Fig. 1). The subjects received a single dose (two sprays per nostril) of each NS treatment: GSP301 (olopatadine HCl 665 µg–mometasone furoate 50 µg per spray), OLO-sponsor (olopatadine HCl monotherapy component, 665 µg/spray), and OLO (FDA-approved olopatadine HCl monotherapy, 665 µg/spray). OLO and OLO-sponsor contained the same active drug, olopatadine HCl (665 µg/spray). Doses for all the treatments were chosen based on those currently approved by the FDA for use as monotherapy in adolescents and adults, which resulted in the same daily doses as those of the

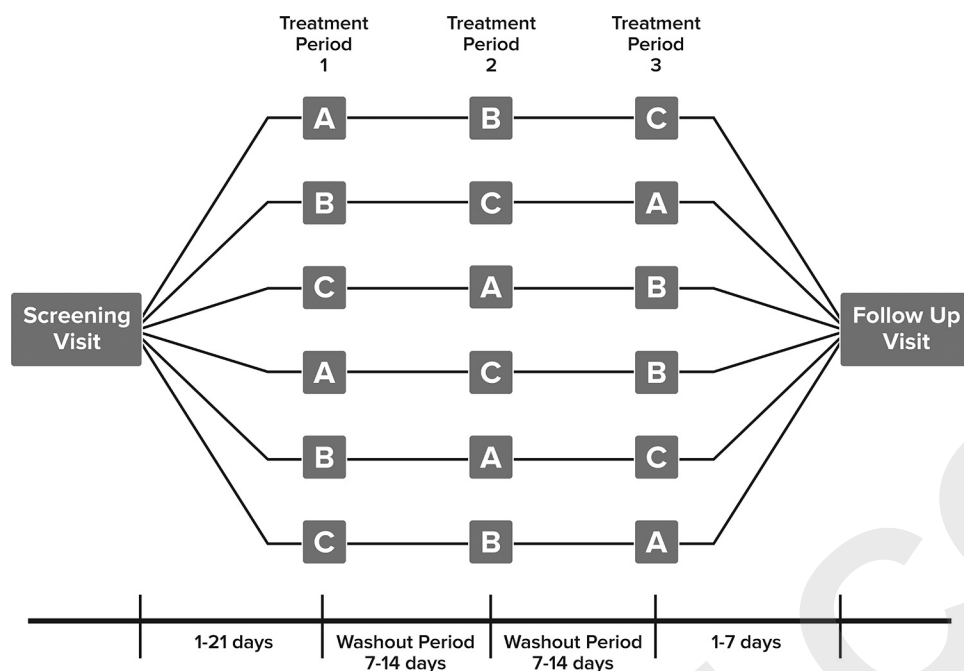


Figure 1. Treatment schedule. (A) GSP301 (olopatadine 665 µg-mometasone 50 µg fixed-dose combination); (B) OLO-sponsor (olopatadine monotherapy component, 665 µg); and (C) OLO (U.S. Food and Drug Administration approved olopatadine, 665 µg).

FDA-approved monotherapies.^{14,15} After adequate training in the use of the NS device, the subjects self-administered treatments (two sprays per nostril) under supervision (after 10 hours of overnight fasting).

Pharmacokinetic Assessments

In each treatment period, serial blood samples (5 mL at each time point) were collected before dosing and at 5, 15, 30, and 45 minutes, and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, and 48 hours after dosing. Plasma concentrations of olopatadine were determined *via* fully validated,¹⁶ highly sensitive high performance liquid chromatography–tandem mass spectrometry (Sciex API 4000, Sciex, Framingham, MA [triple quadrupole LC/MS/MS mass spectrometer]) method, with column-switching, and tandem mass spectrometry (MS/MS) detection by using a positive ion electrospray. The analyte was isolated through protein precipitation and phospholipid removal by using Captiva nondrip lipid 96-well plates (Agilent Technologies, Santa Clara, CA). The lower limit of quantitation (LLQ) for olopatadine was 0.05 ng/mL, with a calibration range of 0.05 to 60.0 ng/mL. Interassay coefficients of variation (precision) ranged from 2.08 to 7.31% and accuracy ranged from 96.67 to 101.89%, with mean values within 15% of the actual value. Precision did not exceed 15% of the coefficient of variation at any concentration level.

Pharmacokinetic (PK) estimates of maximum plasma concentration (C_{max}), area under the plasma concentration time curve (AUC) from time 0 to the last time point with measurable concentration (AUC_{0-t}), AUC from time 0 to time infinity ($AUC_{0-\infty}$), apparent clearance, terminal elimination rate constant (λ_z), time (after

drug administration) when the maximum plasma concentration was reached (T_{max}), and the elimination half-life ($t_{1/2}$) of olopatadine were calculated by using standard noncompartmental approaches *via* SAS Statistical Analysis Software (SAS Institute, Inc., Cary, NC).

Safety Assessments

Safety was evaluated throughout the study *via* adverse event (AE) reporting; standard 12-lead ECG recordings; and monitoring of hematology, urinalysis, blood chemistry evaluations, and vital signs. All safety assessments were based on the safety analysis set population, which consisted of all the subjects who received one or more doses of the study drug.

Statistical Analyses

PK analyses were based on the PK analysis set population, which consisted of all the subjects in the safety analysis set without major protocol violations, who had plasma drug concentration levels above the LLQ to estimate C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$. Baseline demographic and clinical characteristics, plasma concentrations and PK of olopatadine, and safety measures were summarized by treatment with descriptive statistics. Analysis of variance was performed on the natural log transformed primary PK parameters to assess the relative bioavailability and associated 90% confidence intervals. The analysis of variance included sequence, treatment, and period as fixed effects and subject within the treatment sequence as a random effect. Confidence intervals were expressed as percentages rela-

Table 1 Baseline demographic characteristics (safety analysis set) (N = 30)

Characteristics	
Age, mean $\pm$ SD, y	43.1 $\pm$ 11.1
Gender, no. (%)	
Men	18 (60.0)
Women	12 (40.0)
Race, no. (%)	
White	22 (73.3)
Black/African American	5 (16.7)
Asian	3 (10.0)
Ethnicity, no. (%)	
Non-Hispanic/Latino	25 (83.3)
Hispanic/Latino	5 (16.7)
Body mass index, mean $\pm$ SD, kg/m ²	25.7 $\pm$ 2.8

SD = Standard deviation.

tive to the least squares mean of the reference drug (OLO-sponsor or OLO). This analysis was performed *via* PROC MIXED SAS procedure (SAS Institute Inc.). All analyses were conducted by using SAS version 9.2 (SAS Institute Inc.).

A sample size of 30 was considered adequate based on experience from previous studies of a similar design. A 20% dropout rate was assumed to ensure a final sample of 24 subjects. The study was primarily designed to assess the effect of the presence of mometasone on olopatadine PK when administered as GSP301 and to assess the relative bioavailability of olopatadine administered as GSP301 and the FDA-approved NS (OLO).

RESULTS

A total of 30 healthy adults were randomized. The subjects had a mean $\pm$ standard deviation age of 43.1 $\pm$ 11.1 years, and 60% were white men (Table 1). Two subjects did not complete the study: one withdrew during OLO treatment (period 2) due to an adverse event (minor oropharyngeal pain) before receiving GSP301, and one was withdrawn during treatment with GSP301 (period 2) due to a protocol violation.

PK Analysis

The mean plasma concentration-time profiles for olopatadine were similar across treatments (Fig. 2). With all the treatments, quantifiable plasma concentrations of olopatadine appeared rapidly in systemic circulation; the median T_{max} occurred at 1 hour. The mean terminal elimination half-life for all treatments ranged from 7 to 8 hours (Table 2). The terminal disposition of olopatadine was well characterized, and the extrapolated fraction of the $AUC_{0-\infty}$ values were within 20% of the total AUC in all the subjects and treatments. Pre-

dose plasma concentrations of olopatadine were below the LLQ, which indicated that the washout period between treatments was sufficient. Consistent with the mean PK estimates, olopatadine exposure with GSP301 was comparable with OLO-sponsor and OLO; for olopatadine with GSP301 and OLO-sponsor, the geometric mean ratios of natural log transformed C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ were 86.63, 86.92, and 92.83, respectively. For GSP301 and OLO, geometric mean ratios for C_{max} , AUC_{0-t} and AUC_{0-8} were 84.68, 87.87, and 93.80, respectively (Table 3).

Safety

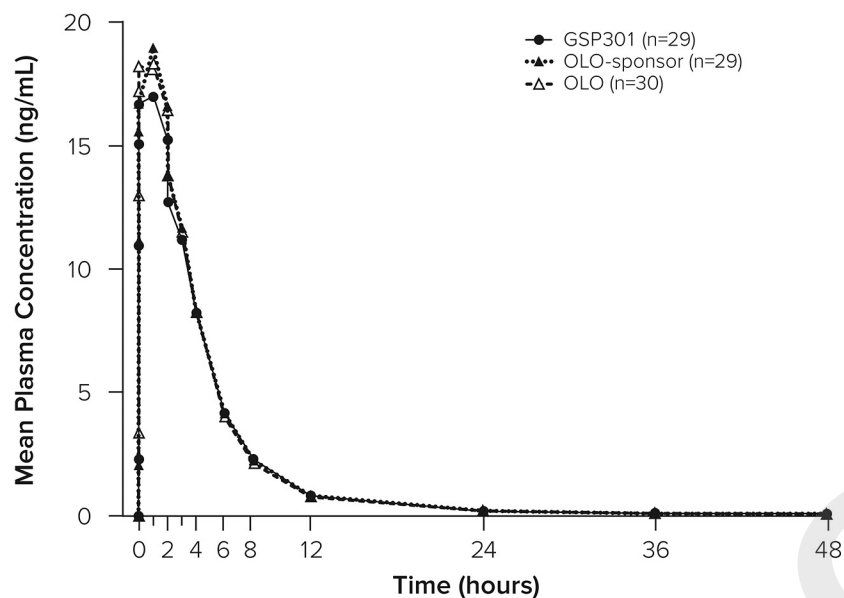
A total of 10 subjects reported treatment-emergent AEs (TEAE), with a similar percentage of TEAEs reported with each treatment (Table 4). Five of these reports were considered at least possibly related to the study drug: conjunctivitis, hypotension, nasal edema, somnolence, and oropharyngeal pain. One subject withdrew from the study due to an AE (minor oropharyngeal pain) during OLO treatment before receiving GSP301. No subjects discontinued during the GSP301 or OLO-sponsor treatment period due to AEs. All TEAEs were mild, and no deaths occurred. No clinically significant changes in vital signs, ECG assessments, or laboratory values were observed (data not shown).

DISCUSSION

The olopatadine mean plasma concentration versus time profiles were nearly identical with all the treatments, GSP301, OLO-sponsor (GSP301 olopatadine monotherapy component), and OLO (FDA-approved olopatadine, Patanase), in healthy adults, which indicated a similar *in vivo* performance in terms of olopatadine bioavailability (*i.e.*, C_{max} , AUC_{0-t} , $AUC_{0-\infty}$). Although the olopatadine C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ achieved with GSP301 were slightly lower than those achieved with OLO, these differences were not considered clinically meaningful because these results were comparable with those previously reported for Patanase.¹⁴ The geometric mean C_{max} for all olopatadine formulations in this study ranged from 17.19 to 20.32 ng/mL compared with the reported value of 16.0 $\pm$ 8.99 ng/mL for Patanase in healthy adults.¹⁴ In addition, the $t_{1/2}$ was comparable with that reported for Patanase with a geometric mean range of 7 to 8 hours for all olopatadine treatments in this study versus 8 to 12 hours previously reported for Patanase.¹⁴

In addition, the data from the current study indicated that the excipients in the GSP301 formulation did not alter olopatadine bioavailability because comparable PK values were obtained with GSP301 and both OLO formulations. Olopatadine and mometasone are eliminated through two different pathways: olopatadine undergoes renal excretion,¹⁴ whereas mometa-

A.



B.

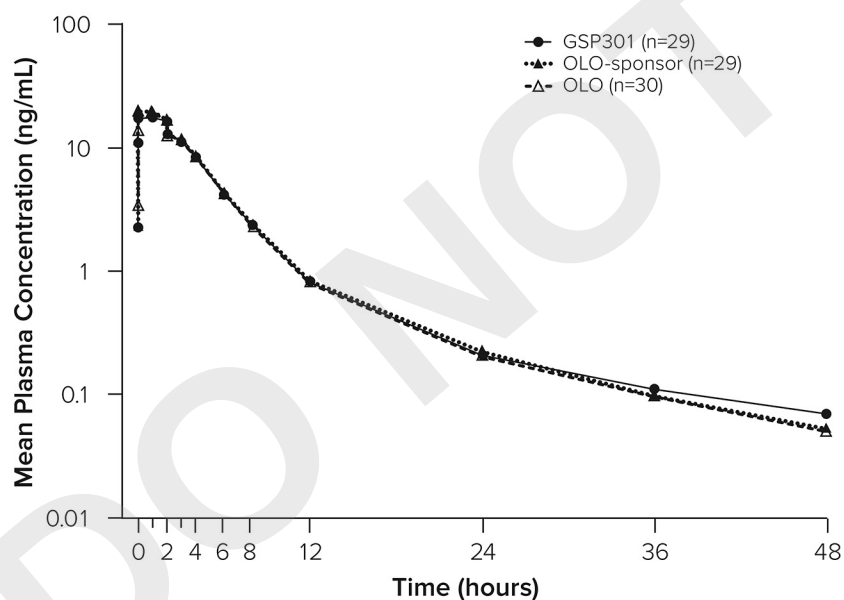


Figure 2. Mean (A) linear and (B) semilog plasma concentration-time curves for olopatadine formulations (PK analysis set). GSP301 = Olopatadine 665 μ g–mometasone 50 μ g fixed-dose combination; OLO-sponsor = olopatadine monotherapy component, 665 μ g; OLO = U.S. Food and Drug Administration approved olopatadine, 665 μ g; PK = pharmacokinetic.

sone is primarily eliminated *via* hepatic metabolism.¹⁵ Hence, concurrent administration of mometasone and olopatadine is unlikely to alter the PK of olopatadine. In agreement with this, data from the present study also indicated that the mometasone component of GSP301 did not have any considerable effect on the rate or extent of olopatadine absorption and did not seem to significantly alter the subsequent *in vivo* distribution, metabolism, or clearance, which ruled out potential PK drug interactions.

Results of our study were comparable with those reported previously in similarly designed studies.^{17,18} In a randomized PK study of two NS formulations of

another antihistamine, azelastine HCl, no significant differences in PK parameters were observed between the newly formulated and marketed versions.¹⁷ The results from the current study were also similar to those reported from another study of an approved FDC NS that contained an antihistamine and a corticosteroid (MP29-02, azelastine HCl and fluticasone propionate) in which the FDC was comparable with the monotherapy components and the individual marketed monotherapies in terms of PK profiles and systemic exposure.¹⁸ Overall, results of the current study indicate that olopatadine PK and the systemic exposure of GSP301 compared with OLO were not

Table 2 Olopatadine PK parameters (PK analysis set)

	GSP301 (n = 29)	OLO-sponsor (n = 29)	OLO (n = 30)
C_{max} , GM (%CV), ng/mL	17.19 (90.74)	20.10 (57.86)	20.32 (55.38)
T_{max} , median (minimum, maximum), hr	1.00 (0.25, 2.00)	1.00 (0.50, 2.00)	1.00 (0.25, 2.50)
AUC_{0-t} , GM (%CV), ng·hr/mL	70.65 (89.17)	81.49 (47.07)	80.86 (31.87)
$AUC_{0-\infty}$, GM (%CV), ng·hr/mL*	82.65 (61.09)	83.62 (48.14)	82.40 (48.96)
CL/F, GM (%CV), L/hr*	32.18 (61.09)	31.81 (48.14)	32.28 (48.96)
$t_{1/2}$, GM (%CV), hr*	7.12 (67.74)	7.95 (52.82)	7.24 (58.34)

PK = Pharmacokinetic; GSP301 = olopatadine 665 µg–mometasone 50 µg fixed-dose combination; OLO-sponsor = olopatadine monotherapy component, 665 µg; OLO = U.S. Food and Drug Administration approved olopatadine, 665 µg; C_{max} = maximum measured plasma concentration; T_{max} = time after administration of a drug when the maximum plasma concentration was reached; AUC_{0-t} = area under the plasma concentration vs time curve from time 0 to the last measurable concentration; $AUC_{0-\infty}$ = area under the plasma concentration versus time curve from time 0 to infinity; CL/F = apparent clearance; $t_{1/2}$, elimination half-life; GM = geometric mean; CV = coefficient of variance.

*GSP301, n = 26; OLO-sponsor, n = 27; OLO, n = 27.

Table 3 Relative bioavailability of olopatadine administered as GSP301 or monotherapy formulations (PK analysis set)

PK Parameter	No.*	Geometric Mean#			Relative Bioavailability§		ISCV, %
		GSP301	OLO-sponsor	OLO	GMR	90% CI	
Olopatadine exposure with GSP301 or OLO-sponsor							
C _{max} , ng/mL	28	17.42	20.10		86.63	75.70–99.15	30.18
AUC _{0–t} , ng·hr/mL	28	70.78	81.43		86.92	75.21–100.47	32.49
AUC _{0–∞} , ng·hr/mL	24¶	83.39	89.82		92.83	81.23–106.09	27.32
Olopatadine exposure with GSP301 or OLO							
C _{max} , ng/mL	29	17.27		20.39	84.68	69.96–102.49	44.58
AUC _{0–t} , ng·hr/mL	29	70.95		80.74	87.87	72.94–105.84	43.36
AUC _{0–∞} , ng·hr/mL	24¶	83.26		88.76	93.80	78.89–111.53	35.73

GSP301 = Olopatadine 665 µg/mometasone 50 µg fixed-dose combination; PK = pharmacokinetic; ISCV = intrasubject coefficient of variation; OLO-sponsor = olopatadine monotherapy component, 665 µg; OLO = U.S. Food and Drug Administration approved olopatadine, 665 µg; GMR = geometric mean ratio of GSP301-to-OLO-sponsor or OLO; CI = confidence interval; C_{max} = maximum measured plasma concentration; AUC_{0-t} = area under the plasma concentration versus time curve from time 0 to the last measurable concentration; $AUC_{0-\infty}$ = area under the plasma concentration versus time curve from time 0 to infinity; λ_z = terminal elimination rate constant.

*No. paired subjects by using analysis of variance for each parameter.

#Based on the exponential of least squares mean of natural log transformed values.

§Based on GMR expressed as a percentage.

¶In the estimation of λ_z , R^2 must be ≥ 0.80 for the regression; if R^2 was < 0.80 , then λ_z and the parameters that used λ_z for determination ($AUC_{0-\infty}$) were not reported for an individual subject (from Ref. 16).

influenced by formulation effects or the presence of mometasone in the GSP301 combination NS, which demonstrated a lack of a formulation or drug interaction.

GSP301 was well tolerated in healthy volunteers, with only mild AEs reported. The percentages of subjects who discontinued the study due to AEs were small (3.3% with OLO versus 0% with OLO-sponsor or GSP301) and were similar to those of

OLO (Patanase) in multiple-dose AR trials (4.7%¹⁴ and 2.4%¹⁰). Furthermore, two recent phase III, multiple-dose AR trials that evaluated GSP301 olopatadine and mometasone monotherapy formulations found that the percentages of subjects who discontinued treatment due to AEs were $< 2\%$ in all the treatment groups versus placebo.^{19,20} Although it should be noted that the current study was conducted in healthy volunteers who only took a single dose of the study

Table 4 Adverse events (safety analysis set)

	GSP301 (n = 29)	OLO-sponsor (n = 29)	OLO (n = 30)
Subjects who reported at least 1 TEAE, no. (%) [*]	4 (13.8)	3 (10.3)	3 (10.0)
TEAEs ($\geq 3\%$), no. events (%)			
Hypotension	1 (3.4)	0	1 (3.3)
Pain at venipuncture site	0	1 (3.4)	1 (3.3)
Tachycardia	1 (3.4)	0	0
Conjunctivitis	1 (3.4)	0	0
Hypertension	1 (3.4)	0	0
Hypoesthesia	0	1 (3.4)	0
Nasal edema	0	1 (3.4)	0
Diarrhea	0	0	1 (3.3)
Somnolence	0	0	1 (3.3)
Oropharyngeal pain	0	0	1 (3.3)
Drug-related TEAEs, no. (%)	2 (6.9)	1 (3.4)	2 (6.7)
TEAEs that led to withdrawal, no. (%)	0	0	1 (3.3)
SAEs, no. (%)	0	0	0
Deaths, no. (%)	0	0	0

GSP301 = Olopatadine 665 μg /mometasone 50 μg fixed-dose combination; OLO-sponsor = olopatadine monotherapy component, 665 μg ; OLO = U.S. Food and Drug Administration approved olopatadine, 665 μg ; TEAE = treatment-emergent adverse event; SAE = severe adverse event.

^{*}Those subjects who reported one or more TEAEs during a particular treatment were counted only once for that treatment; the subjects who reported the same event during multiple treatments were counted only once for the overall safety analysis set.

drug, overall, the formulation differences did not seem to affect the tolerability of the treatments.

As previously reported, there are studies that showed that combination NS treatments are more efficacious than monotherapies in treating AR symptoms.^{19–21} The results of this PK study, taken together with the results of a similarly designed PK study to assess the relative bioavailability of mometasone administered as GSP301 FDC NS to mometasone component monotherapy NS (sponsor mometasone) and an FDA-approved mometasone monotherapy NS (Nasonex; see companion article in this issue of the journal, pp 232–239, Ref. 22), indicate no apparent drug interactions between either FDC component that could potentially impact the efficacy or the safety of the FDC. In addition, phase III studies in subjects with AR demonstrated the efficacy and safety of GSP301 twice-daily (olopatadine HCl 665 μg –mometasone furoate 25 μg)^{19,20} and once-daily (olopatadine HCl 665 μg –mometasone furoate 50 μg)¹⁹ dosing.

CONCLUSION

The bioavailability of olopatadine was comparable between GSP301 and two monotherapy formulations of olopatadine nasal spray (OLO, FDA-approved olopatadine, Patanase; and OLO-sponsor, GSP301 olopatadine monotherapy component). The addition of mometasone furoate to olopatadine in GSP301 had no

clinically meaningful influence on the overall olopatadine PK compared with olopatadine monotherapy OLO-sponsor. GSP301 was well tolerated in healthy adults with only mild AEs reported.

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REFERENCES

- Seidman MD, Gurgel RK, Lin SY, et al. Clinical practice guideline: Allergic rhinitis. *Otolaryngol Head Neck Surg*. 2015; 152(suppl):S1–S43.
- Dykewicz MS, Fineman S, Skoner DP, et al. Diagnosis and management of rhinitis: complete guidelines of the Joint Task Force on Practice Parameters in Allergy. *Asthma and Immunology American Academy of Allergy, Asthma, and Immunology. Ann Allergy Asthma Immunol*. 1998; 81:478–518.
- Blaiss MS. Allergic rhinitis: Direct and indirect costs. *Allergy Asthma Proc*. 2010; 31:375–380.
- Marple BF, Fornadley JA, Patel AA, et al. Keys to successful management of patients with allergic rhinitis: focus on patient confidence, compliance, and satisfaction. *Otolaryngol Head Neck Surg*. 2007; 136:S107–S124.
- Dykewicz MS, Wallace DV, Baroody F, et al. Treatment of seasonal allergic rhinitis: An evidence-based focused 2017 guideline update. *Ann Allergy Asthma Immunol*. 2017;119:489–511.e41.

6. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005; 353:487–497.
7. Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: a meta-analysis. *Am J Med*. 2007; 120:713–719.
8. Kaliner MA, Oppenheimer J, Farrar JR. Comprehensive review of olopatadine: the molecule and its clinical entities. *Allergy Asthma Proc*. 2010; 31:112–119.
9. Fairchild CJ, Meltzer EO, Roland PS, Wells D, Drake M, Wall GM. Comprehensive report of the efficacy, safety, quality of life, and work impact of Olopatadine 0.6% and Olopatadine 0.4% treatment in patients with seasonal allergic rhinitis. *Allergy Asthma Proc*. 2007; 28:716–723.
10. Meltzer EO, Hampel FC, Ratner PH, et al. Safety and efficacy of olopatadine hydrochloride nasal spray for the treatment of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. 2005; 95:600–606.
11. Hochhaus G. Pharmacokinetic/pharmacodynamic profile of mometasone furoate nasal spray: potential effects on clinical safety and efficacy. *Clin Ther*. 2008; 30:1–13.
12. Hebert JR, Nolop K, Lutsky BN. Once-daily mometasone furoate aqueous nasal spray (Nasonex) in seasonal allergic rhinitis: an active- and placebo-controlled study. *Allergy*. 1996; 51:569–576.
13. Davies RJ, Nelson HS. Once-daily mometasone furoate nasal spray: efficacy and safety of a new intranasal glucocorticoid for allergic rhinitis. *Clin Ther*. 1997; 19:27–38; discussion 2–3.
14. Patanase (olopatadine hydrochloride nasal spray). US prescribing information. Novartis Pharmaceuticals Corporation, East Hanover, NJ; 2012.
15. Nasonex (mometasone furoate monohydrate nasal spray). US prescribing information. Schering-Plough Corporation, Kenilworth, NJ; 2013.
16. US Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research, Center for Veterinary Medicine. Guidance for Industry, Bioanalytical Method Validation. Published May 2001. [updated September 2013; cited 2017 Mar 9]. Available from: <https://www.fda.gov/downloads/Drugs/Guidance/ucm070107.pdf>.
17. Du D, Targett D, Stolberg E, Canali A. A clinical pharmacokinetic study comparing two azelastine hydrochloride nasal formulations in a single-dose design. *Eur J Drug Metab Pharmacokinet*. 2014; 39:69–75.
18. Derendorf H, Munzel U, Petzold U, et al. Bioavailability and disposition of azelastine and fluticasone propionate when delivered by MP29–02, a novel aqueous nasal spray. *Br J Clin Pharmacol*. 2012; 74:125–133.
19. Andrews CP, Mohar D, Agarwal P, et al. Efficacy and safety of once-daily and twice-daily olopatadine/mometasone nasal spray treatment in seasonal allergic rhinitis. Poster presented at: 75th annual meeting of the American College of Allergy, Asthma, and Immunology; October 26–30, 2017; Boston, MA.
20. Ratner P, Hampel F, Breazna A, et al. Efficacy and safety of olopatadine/mometasone combination nasal spray for the treatment of seasonal allergic rhinitis. Poster presented at: 75th annual meeting of the American College of Allergy, Asthma, and Immunology; October 26–30, 2017; Boston, MA.
21. Carr W, Bernstein J, Lieberman P, et al. A novel intranasal therapy of azelastine with fluticasone for the treatment of allergic rhinitis. *J Allergy Clin Immunol*. 2012; 129:1282–1289.e10.
22. Patel P, Salapatek AM, Talluri RS, et al. Pharmacokinetics of intranasal mometasone in the fixed dose combination GSP301 versus two monotherapy intranasal mometasone formulations. *Allergy Asthma Proc*. 2018; 39:232–239. □

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