PHARMACOKINETICS OF OLOPATADINE ADMINISTERED AS GSP301 NASAL SPRAY VERSUS OLOPATADINE MONOTHERAPY

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ABSTRACT

Introduction

GSP301 is a fixed-dose combination of the antihistamine olopatadine hydrochloride and the corticosteroid mometasone furoate developed by Glenmark Specialty SA as a single nasal spray (NS). The objective of this study was to assess the relative bioavailability of olopatadine administered as GSP301 versus olopatadine in GSP301 vehicle (Glenmark olopatadine) and marketed olopatadine (Patanase®) in healthy adults.

Methods

In this single-dose, open-label, crossover study, 30 healthy adults (18–65 years) were randomized equally to 1 of 6 treatment sequences for three 48-hour treatment periods with GSP301 (olopatadine 665µg/mometasone 50µg), olopatadine 665µg (Glenmark), and olopatadine 665µg (Patanase); all administered as 2 sprays in each nostril. To assess relative bioavailability of olopatadine, pharmacokinetic (PK) estimates, maximum plasma concentration (C_{max}), area under the plasma concentration time curve (AUC) from time 0 to 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. Adverse events (AEs) were also evaluated.

Results

The relative bioavailability of olopatadine in GSP301 was approximately 85–94% of olopatadine (Patanase) and 87–93% of olopatadine (Glenmark). The percentage of participants reporting treatment-emergent AEs (TEAEs) for GSP301, olopatadine (Glenmark), and olopatadine (Patanase) were 13.8%, 10.3%, and 10.0%, respectively, with only mild AEs reported. No participants discontinued GSP301 or olopatadine (Glenmark) due to AEs.

Conclusions

Olopatadine PK with GSP301 was comparable to olopatadine (Glenmark or Patanase). Mometasone in GSP301 did not significantly influence PK of olopatadine. GSP301 was well tolerated, with only mild AEs reported.

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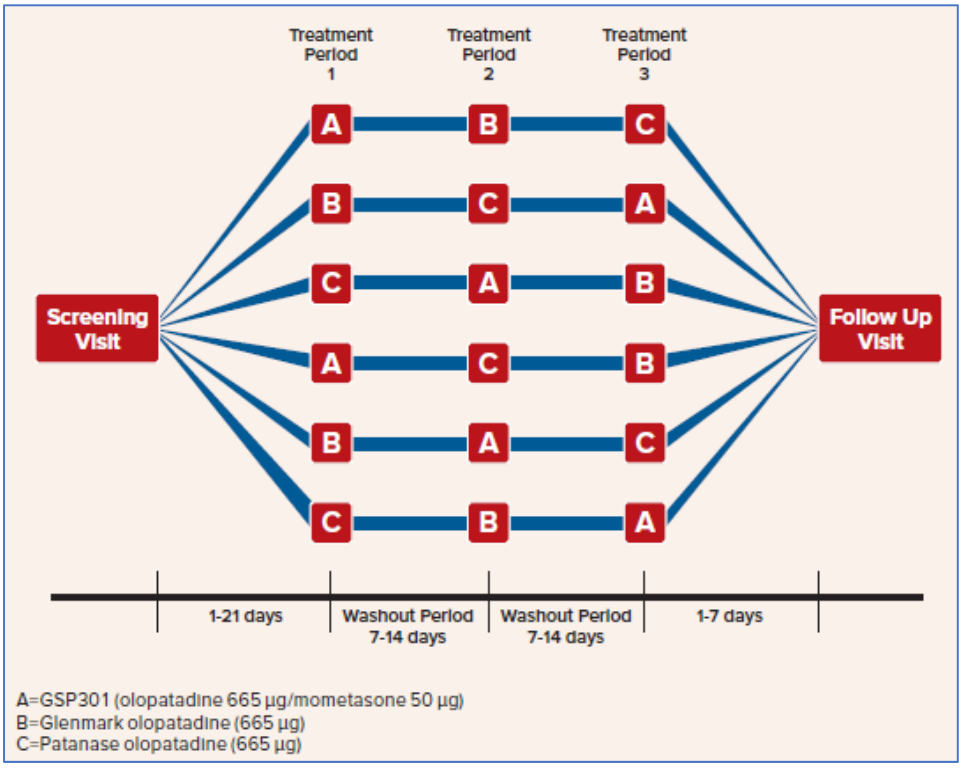
KEY FINDINGS

STUDY DESIGN

- Phase 1, open-label, 3-way crossover study with 30 healthy participants were randomized to receive single doses (2 sprays/nostril) of GSP301 fixed-dose combination (olopatadine 665 µg/mometasone 50 µg), Glenmark olopatadine (665 µg), or Patanase olopatadine (665 µg) (**Figure 1**)
- Included healthy adults (18 – 65 years) with a body mass index 18.5 – 32 kg/m^2

Figure 1. Treatment Schedule



Endpoints

- Primary: PK estimates of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of olopatadine
- Secondary: Apparent clearance (CL/F), terminal elimination rate constant (λ_z), T_{max}, and $t_{1/2}$ of olopatadine; and AEs

RESULTS

Participants

- The majority of participants were non-obese, white males approximately 43 years of age (**Table 1**)
  - One in the Patanase group withdrew due to AE; 1 in the GSP301 group withdrew due to protocol violation

KEY FINDINGS

Table 1. Baseline Characteristics

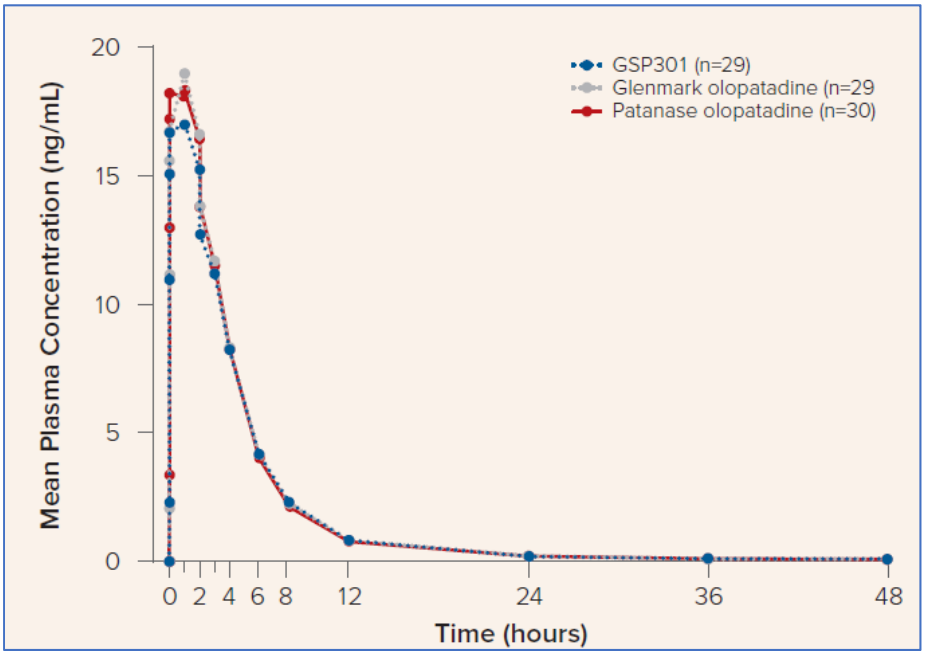
	All Participants (N=30)
Age, mean ± SD, y	43.1 ± 11.1
Gender, n (%)	
Male	18 (60.0)
Female	12 (40.0)
Race, n (%)	
White	22 (73.3)
Black or African American	5 (16.7)
Asian	3 (10.0)
Ethnicity, n (%)	
Non-Hispanic/Latino	25 (83.3)
Hispanic or Latino	5 (16.7)
BMI, mean ± SD, kg/m²	25.7 ± 2.8

BMI, body mass index; SD, standard deviation.

PK Parameters

- Mean plasma concentration-time profiles were similar for olopatadine across treatments (**Figure 2**)
- With all treatments, plasma concentrations of olopatadine were detectable at the first post-dose time point of 5 minutes, and peak concentrations were attained at ~1 hr post-dose (median T_{max})

Figure 2. Mean Linear Plasma-time Concentration Curve for Olopatadine Formulations



GSP301, olopatadine 665 µg/mometasone 50 µg; Glenmark olopatadine, 665 µg; Patanase olopatadine, 665 µg.

KEY FINDINGS

- All mean PK values for GSP301 were within 15% of the corresponding values for Glenmark and Patanase olopatadine formulations (**Table 2**)

Table 2. Relative Bioavailability of Olopatadine Administered as GSP301, Glenmark, or Patanase Formulations

PK Parameter, unit	n[a]	Geometric Mean[b]		Relative Bioavailability[c]		ISV (%)
		GSP301	Glenmark Olopatadine	GMR (%)	90% CI	
C_{max}, ng/mL	28	17.42	20.10	86.63	75.70, 99.15	30.18
$AUC_{(0-t)}$, ng•h/mL	28	70.78	81.43	86.92	75.21, 100.47	32.49
$AUC_{(0-\infty)}$, ng•h/mL	24[d]	83.39	89.82	92.83	81.23, 106.09	27.32
PK Parameter, unit	n[a]	Geometric Mean[b]		Relative Bioavailability[c]		ISV (%)
		GSP301	Patanase Olopatadine	GMR (%)	90% CI	
C_{max}, ng/mL	29	17.27	20.39	84.68	69.96, 102.49	44.58
$AUC_{(0-t)}$, ng•h/mL	29	70.95	80.74	87.87	72.94, 105.84	43.36
$AUC_{(0-\infty)}$, ng•h/mL	24[d]	83.26	88.76	93.80	78.89, 111.53	35.73

GSP301, olopatadine 665µg/mometasone 50 µg; Glenmark olopatadine, 665 µg; Patanase olopatadine, 665 µg.
[a]Number of paired subjects using ANOVA for each parameter.
[b]Geometric means were based on the exponential of least square means of natural-log transformed values.
[c]Relative bioavailability was based on GMR expressed as a percentage.
[d]In the estimation of λz, R^2 must be ≥0.80 for the regression. If R^2 was <0.80, λz and the parameters that utilize λz for determination ($AUC_{0-\infty}$) were not reported for an individual participant.
ANOVA, analysis of variance; $AUC_{(0-\infty)}$, area under the plasma concentration versus time curve from time 0 to infinity; $AUC_{(0-t)}$, area under the plasma concentration versus time curve from time 0 to the last measurable concentration; CI, confidence interval; C_{max}, maximum measured plasma concentration; GMR, geometric mean ratio of GSP301:Patanase; λz, terminal elimination rate constant; ISV, intrasubject variability.

- All TEAEs were mild and similar across treatment groups; no deaths occurred (**Table 3**)

Table 3. Adverse Events

	GSP301 (n=29)	Glenmark Olopatadine (n=29)	Patanase Olopatadine (n=30)
Participants reporting at least 1 TEAE, n (%)	4 (13.8)	3 (10.3)	3 (10.0)
TEAEs (≥3%), n (%)	0	0	0
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, n (%)	2 (6.9)	1 (3.4)	2 (6.7)
TEAEs leading to withdrawal, n (%)	0	0	1 (3.3)
SAEs, n (%)	0	0	0
Deaths, n (%)	0	0	0

GSP301, olopatadine 665µg/mometasone 50 µg; Glenmark olopatadine, 665 µg; Patanase olopatadine, 665 µg.
SAE, severe adverse event; TEAE, treatment -emergent adverse event.

CONCLUSIONS

- PK parameters of the olopatadine component in GSP301 were comparable to Patanase and Glenmark olopatadine formulations in healthy adults
- The addition of mometasone furoate to olopatadine in GSP301 did not considerably affect olopatadine PK
- GSP301 was well tolerated, with only mild AEs reported