PHARMACOKINETICS OF MOMETASONE FUROATE ADMINISTERED AS GSP301 NASAL SPRAY VERSUS MOMETASONE MONOTHERAPY

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ABSTRACT

Introduction

GSP301 is a fixed-dose combination of antihistamine olopatadine hydrochloride and corticosteroid mometasone furoate developed by Glenmark Specialty SA as a single nasal spray (NS). The study objective was to assess relative bioavailability of mometasone administered as GSP301 versus mometasone in GSP301 vehicle (Glenmark mometasone) and marketed mometasone (Nasonex®) 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 72 hour treatment periods with GSP301 (olopatadine 665µg/mometasone 50µg), mometasone 50µg (Glenmark), or mometasone 50µg (Nasonex); all administered as 2 sprays per nostril. To assess relative bioavailability of mometasone, pharmacokinetics (PK) estimates, maximum plasma concentration (C_{max}), area under the plasma concentration time curve from time zero to last time point with measurable concentration (AUC_{0-t}), and AUC from time zero to infinity ($AUC_{0-\infty}$) were compared by analysis of variance. Adverse events (AEs) were recorded.

Results

The relative bioavailability of mometasone with GSP301 was approximately 110–142% of mometasone (Nasonex) and 114–119% of mometasone (Glenmark). The percentages of participants reporting treatment-emergent AEs (TEAEs) were 10.0%, 13.3%, and 10.3% for GSP301, mometasone (Glenmark), and mometasone (Nasonex), respectively. All TEAEs were mild and none resulted in discontinuation.

Conclusions

Mometasone PK with GSP301 was comparable to mometasone (Glenmark or Nasonex). A slightly higher mean C_{max} was observed with GSP301 over mometasone (Nasonex). Olopatadine in GSP301 did not significantly influence PK of mometasone. GSP301 was well tolerated, with only mild AEs reported.

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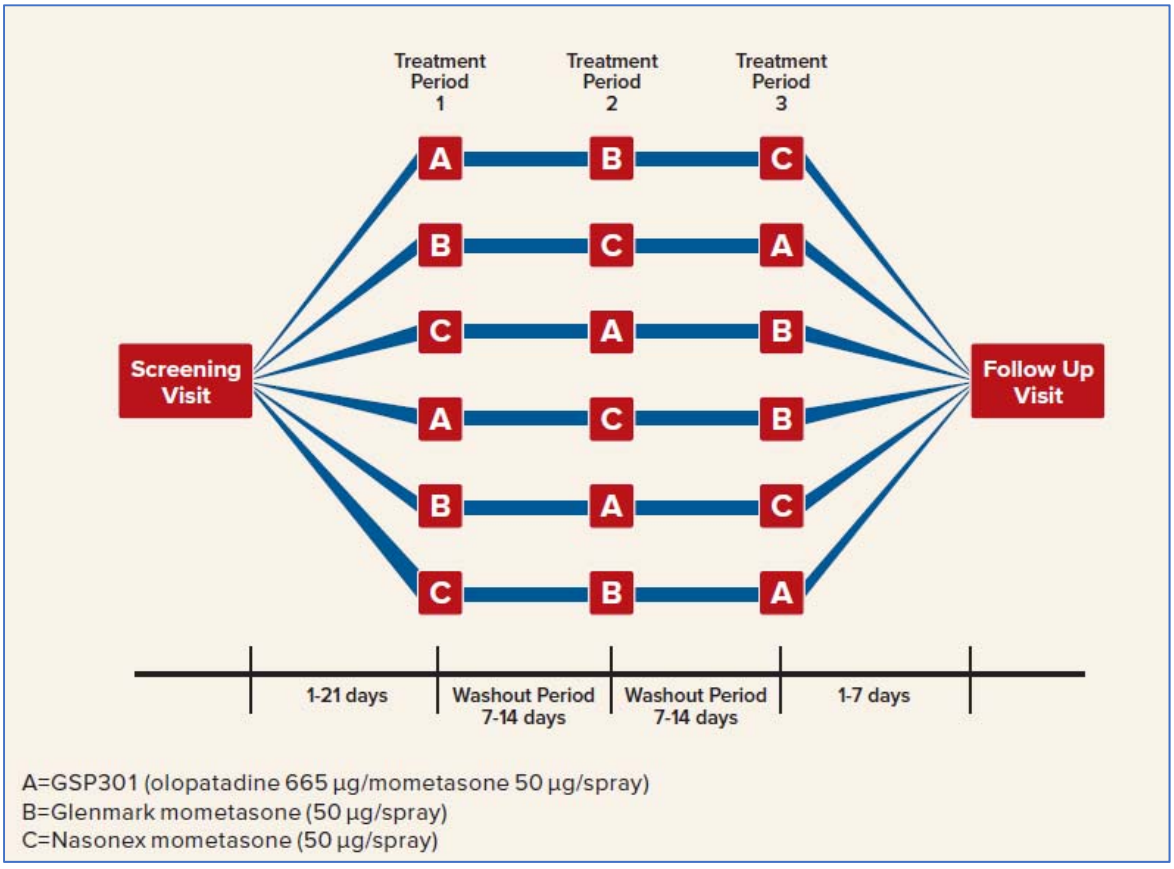
KEY FINDINGS

STUDY DESIGN

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

Figure 1. Treatment Schedule



A=GSP301 (olopatadine 665 µg/mometasone 50 µg/spray)
B=Glenmark mometasone (50 µg/spray)
C=Nasonex mometasone (50 µg/spray)

Endpoints

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

RESULTS

Participants

- The majority of participants were non-obese, white males approximately 43 years of age (**Table 1**)
- Two participants in the Glenmark mometasone group withdrew consent; 1 in the GSP301 group withdrew due for “other” reasons

KEY FINDINGS

Table 1. Baseline Characteristics

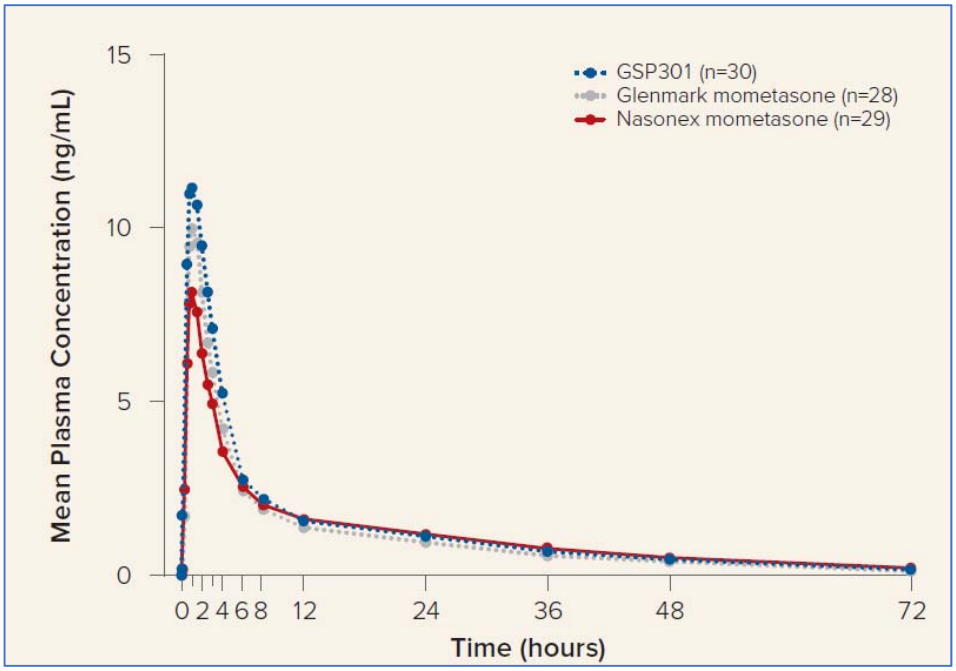
	All Participants (N=30)
Age, mean ± SD, y	42.6 ± 11.5
Gender, n (%)	
Male	18 (60.0)
Female	12 (40.0)
Race, n (%)	
White	16 (53.3)
Asian	9 (30.0)
Black or African American	5 (16.7)
Ethnicity, n (%)	
Non-Hispanic/Latino	23 (76.7)
Hispanic or Latino	7 (23.3)
BMI, mean ± SD, kg/m²	25.0 ± 2.8

BMI, body mass index; SD, standard deviation.

PK Parameters

- Mometasone PK values for GSP301 were comparable (mean estimates within 20%) to Glenmark and Nasonex mometasone formulations, except for a slightly higher C_{max} with GSP301 compared to Nasonex (**Figure 2**)
- Mometasone was eliminated with a mean $t_{1/2}$ of approximately 18-20 hr across treatments
- With all treatments, plasma concentrations of mometasone were detectable at the first post-dose time point (5 min), and peak concentrations were attained at ~1.0–1.25 hr post-dose (median T_{max})

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



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

- The relative bioavailability of mometasone in GSP301 was approximately 114-119% of Glenmark mometasone and 110-114% of Nasonex (**Table 2**)

KEY FINDINGS

Table 2. Relative Bioavailability of Mometasone Administered as GSP301, Glenmark, or Nasonex Formulations

PK Parameter, unit	n[a]	Geometric Mean[b]		Relative Bioavailability[c]		
		GSP301	Glenmark Mometasone	GMR (%)	90% CI	ISV (%)
C_{max}, pg/mL	28	10.93	9.61	113.83	96.97, 133.61	36.22
$AUC_{(0-t)}$, pg•h/mL	22	92.85	78.45	118.36	103.73, 135.05	25.66
$AUC_{(0-\infty)}$, pg•h/mL	17[d]	98.96	83.50	118.50	104.79, 134.01	20.57
PK Parameter, unit	n[a]	Geometric Mean[b]		Relative Bioavailability[c]		
		GSP301	Nasonex Mometasone	GMR (%)	90% CI	ISV (%)
C_{max}, pg/mL	29	10.81	7.62	141.84	121.68, 165.34	35.21
$AUC_{(0-t)}$, pg•h/mL	26	84.97	77.30	109.92	95.49, 126.53	30.22
$AUC_{(0-\infty)}$, pg•h/mL	19[d]	103.77	90.12	115.14	101.77, 130.28	21.62

GSP301, olopatadine 665µg/mometasone 50 µg/spray; Glenmark mometasone, 50 µg/spray; Nasonex mometasone, 50 µg/ spray.
[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:Nasonex mometasone or Glenmark mometasone; 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=30)	Glenmark Mometasone (n=30)	Nasonex Mometasone (n=29)
Participants reporting at least 1 TEAE, n (%)	3 (10.0)	4 (13.3)	3 (10.3)
TEAEs (≥3%), n (%)			
Hypotension	2 (6.7)	1 (3.3)	1 (3.4)
Back pain	1 (3.3)	0	0
Headache	1 (3.3)	1 (3.3)	0
Tachycardia	1 (3.3)	1 (3.3)	0
Cough	0	0	1 (3.4)
Red blood cell sedimentation rate increased	0	0	1 (3.4)
Pain at venipuncture site	0	1 (3.3)	0
Drug-related TEAEs, n (%)	1 (3.3)	0	1 (3.4)
TEAEs leading to withdrawal, n (%)	0	0	0
SAEs, n (%)	0	0	0
Deaths, n (%)	0	0	0

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

CONCLUSIONS

- PK parameters of the mometasone component in GSP301 were comparable to Nasonex and Glenmark mometasone formulations in healthy adults; C_{max} was slightly higher for GSP301 compared with Nasonex
- The addition of olopatadine to mometasone in GSP301 does not appear to have a considerable effect on mometasone PK parameters
- GSP301 was well tolerated, with only mild AEs reported