NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	211746
Priority or Standard	Standard
Submit Date(s)	May 21, 2018
Received Date(s)	May 21, 2018
PDUFA Goal Date	June 21, 2019
Division/Office	DPARP/ODE2
Review Completion Date	June 20, 2019
Established Name	olopatadine hydrochloride/mometasone furoate
(Proposed) Trade Name	Ryaltris
Pharmacologic Class	Antihistamine/corticosteroid
Code name	GSP 301
Applicant	Glenmark Specialty S.A.
Formulation(s)	Nasal spray suspension (delivers 665 µg of olopatadine hydrochloride and 25 µg mometasone furoate in each 0.1 ml)
Dosing Regimen	2 sprays per nostril twice daily
Applicant Proposed Indication(s)/Population(s)	Treatment of symptoms associated with seasonal allergic rhinitis in patients 12 years of age and older.
Recommendation on Regulatory Action	Complete Response (due to facilities' inspection issues)
Recommended Indication(s)/Population(s) (if applicable)	The treatment of symptoms associated with seasonal allergic rhinitis in patients 12 years of age and olde (b) (4)

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

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Glossary

AE	adverse event
ANCOVA	analysis of covariance
AR	allergic rhinitis
AUC	area under the curve
BID	twice daily
CI	confidence interval
C_{max}	peak concentration
ECG	electrocardiogram
ENT	ear, nose, and throat
FAS	full analysis set
FDC	fixed-dose combination
GM	Glenmark
HCl	hydrochloride
IND	Investigational New Drug
iTNSS	instantaneous Total Nasal System Score
IP	investigational product
J2R	jump to reference
LS	least square
MF	mometasone furoate
MMRM	mixed-effects model for repeated measures
MNAR	missing not at random
NDA	new drug application
NS	nasal spray
OLO	olopatadine hydrochloride
PAR	perennial allergic rhinitis
PK	pharmacokinetic
POC	proof of concept
PPS	per protocol set
QD	once daily
QOL	quality of life
RCAT	Rhinitis Control Assessment Test
RQLQ	Rhinoconjunctivitis Quality of Life Questionnaire
RQLQ(S)	Rhinoconjunctivitis Quality-of-Life Questionnaire – Standardized Activities
rTNSS	reflective Total Nasal System Score
rTOSS	reflective Total Ocular System Score
SAE	serious adverse event
SAP	statistical analysis plan
SAR	seasonal allergic rhinitis
SAS	safety analysis set
TBM	to-be-marketed
TNNSS	Total Non-Nasal Symptom Score

1 Executive Summary

1.1. Product Introduction

Ryaltris (hereinafter referred to as GSP 301) nasal spray (NS), is a fixed-dose combination (FDC) NS of olopatadine hydrochloride (OLO), an H_1-receptor antagonist, and mometasone furoate (MF), a corticosteroid. Each actuation delivers a volume of 0.1 ml suspension containing 665 µg of OLO and 25 µg of MF (665 µg/25 µg). The proposed indication is "the treatment of symptoms associated with seasonal allergic rhinitis (SAR) in patients 12 years of age and older." The proposed dosing regimen is 2 sprays per nostril twice daily (BID), for a total daily dose of 5,320 µg OLO and 200 µg MF.

1.2. Conclusions on the Substantial Evidence of Effectiveness

To support the efficacy and safety of GSP 301 for the proposed indication, the Applicant submitted results from two phase 3, 14-day, placebo- and active-controlled trials (GSP 301-301 and GSP 301-304) and one phase 2, 14-day, placebo- and active-controlled trial (GSP 301-201). Results from these trials demonstrated substantial evidence of efficacy as determined primarily based on statistically significant improvements in the primary endpoint, change from baseline in average AM and PM subject-reported reflective total nasal symptom score (rTNSS) over the 14-day treatment period. The reductions from baseline in rTNSS were statistically significantly greater for GSP 301 treatment than placebo and its constituent monotherapies, and the monotherapies statistically greater than placebo.[1] This was most clearly demonstrated in the results from study 304 with confirmatory evidence from studies 301 and 201. Secondary endpoints including iTNSS, rTOSS, and RQLQ also supported the primary endpoint.

From a clinical efficacy and safety standpoint, the recommended regulatory action is Approval for GSP-301 for the indication of seasonal allergic rhinitis in patients aged 12 years and older (b) (4) . However, issues arose with the facilities' inspections which preclude approval of this application in this review cycle; therefore, the application will receive a Complete Response.

[1] With the exception of the GSP 301 versus olopatadine arm, which was marginally non-significant in study 301 (p-value 0.0545 and non-significant in study 201 (p-value 0.1684).

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

GSP 301 nasal spray (NS) is a fixed-dose combination (FDC) antihistamine/corticosteroid (olopatadine, OLO; mometasone furoate, MF) proposed for the treatment of symptoms of SAR in patients 12 years of age and older. The individual components, olopatadine (OLO) and MF, are each approved for various rhinitis indications and are currently marketed in the United States.

Allergic rhinitis (AR) is a global health problem that affects children and adults and impacts quality of life (QOL). AR is characterized by the presence of nasal congestion, rhinorrhea, nasal itching and nasal obstruction. Pharmacologic agents available to treat AR include intranasal antihistamines, intranasal corticosteroids, decongestants, leukotriene modifiers, and anticholinergics. OLO and MF have different mechanisms of action and combining them may provide an additive effect on efficacy and provide better relief. Currently, there is only one combination product containing an intranasal corticosteroid and intranasal antihistamine approved and available for SAR treatment.

With this new drug application (NDA), the Applicant provided data from three 2-week studies and one long-term study that provides a clinically meaningful efficacy advantage for the combination product GSP 301 over the single ingredient products that were also efficacious in SAR. The overall safety database for GSP 301 was adequate. Serious adverse events (SAEs) were few and did not appear to be related to GSP 301 or suggest a new safety signal. The common adverse events (AEs) in patients treated with GSP 301 are typical AEs seen in SAR studies using NS products containing antihistamine or corticosteroids.

From a clinical standpoint, the Applicant has submitted adequate data to support the efficacy/safety of GSP 301 (OLO 665 µg and MF 25 µg) at a dose of 2 sprays per nostril BID for adult and adolescent patients 12 years of age and older with SAR (b) (4) . However, issues arose with the facilities' inspection that preclude approval during this review cycle; therefore, the application will receive a Complete Response pending resolution of the facilities issues.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• SAR is a common inflammatory condition affecting millions of adults and children in the United States and worldwide. • SAR adversely affects patients' QOL, sleep, cognition and school performance.[2]	SAR imposes an important disease burden on the global population. SAR imposes a significant burden on the individual patient.
Current Treatment Options	• FDA-approved treatment modalities that provide symptomatic relief for patients with SAR include intranasal and oral H_1-receptor antagonists and corticosteroids, oral leukotriene receptor antagonist, and anticholinergic NS. • In 2012, the FDA approved Dymista (azelastine HCl and fluticasone propionate), the first FDC NS for the treatment of SAR	Oral and inhaled therapies in addition to allergen avoidance are the mainstay of SAR treatment.
Benefit	• The efficacy was established in three, 2 week trials in which the combination product demonstrated efficacy compared with placebo and the respective mono-comparators with respect to the primary endpoint of reflective total nasal symptom score, Secondary endpoints also supported the primary endpoint. Sensitivity analyses confirmed the efficacy data to be robust.	The clinical development program provided substantial evidence of efficacy and safety of GSP 301 NS from a clinical standpoint.
Risk and Risk Management	• AEs occurring in ≥1% subjects receiving GSP 301 and at rates greater than placebo include dysgeusia, epistaxis, and nasal discomfort. • The surveillance facilities inspections revealed issues that could lead to deficiencies in manufacturing of the drug product.	These AEs are typical of allergic rhinitis clinical development programs and do not raise new safety concerns. Until the facilities issues are resolved, this Application cannot be approved.

[2] www.effectivehealthcare.ahrq.gov March 8, 2012

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	Sections 8.1.2, 8.1.4, 8.1.6, 8.1.8
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
□	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
□	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Seasonal allergic rhinitis is an inflammatory condition of the upper airways that occurs in response to exposure to airborne allergens (typically tree, grass, and weed pollens) in sensitized individuals. Although there is geographic variability in the seasonal emergence of allergenic pollens across the United States, tree pollens tend to emerge in the spring, grass pollens in the summer, and weed pollens in the fall. SAR is distinguished from perennial allergic rhinitis (PAR), which is caused by exposure to house dust mites, animal dander, and other allergens generally found in an indoor environment. Patients may have either SAR or PAR or both (i.e., PAR with seasonal exacerbations).[3] An estimated 14% of adults and 13% of children in the United States have been diagnosed with AR. Among diagnosed individuals, 43% of adults and 62% children reported that their nasal allergies were seasonal rather than perennial.[4,5]

SAR is often diagnosed by the history alone because it is reproducible from year to year. The four defining symptoms of AR are nasal discharge (rhinorrhea), nasal itching, sneezing, and/or nasal congestion. Many patients also have symptoms of allergic conjunctivitis, such as itchy and watery eyes. Treatment effectiveness is assessed by improvement of these symptoms and improved QOL.

The management of SAR is determined by the frequency and severity of symptoms, the age of the patient, and the presence of concurrent conditions. Management may involve allergen avoidance, pharmacotherapy, and allergen immunotherapy. For mild or episodic symptoms, patients can be treated with an oral antihistamine (e.g., cetirizine, loratadine, fexofenadine), an intranasal antihistamine (azelastine or OLO), or an intranasal glucocorticoid (MF, fluticasone furoate, or triamcinolone). For persistent or moderate-to-severe symptoms, intranasal glucocorticoids are the most effective pharmacologic therapy. Patients who do not adequately

[3] Wallace, DV, MS Dykewicz, DI Bernstein, IL Bernstein, J Blessing-Moore, L Cox, DA Khan, DM Lang, RA Nicklas, J Oppenheimer, JM Portnoy, CC Randolph, DE Schuller, SL Spector, SA Tilles, KR May, TA Miller, HM Druce, FM Baroody, JA Bernstein, TJ Craig, JW Georgitis, R Pawankar, GS Rachelefsky, RA Settipane, DP Skoner, SW Stoloff, 2008, The diagnosis and management of rhinitis: an updated practice parameter, J Allergy Clin Immunol, 122(2 Suppl):S1–S84.

[4] Nathan, RA, 2007, The burden of allergic rhinitis, Allergy Asthma Proc, 28(1):3–9.

[5] Meltzer, EO, MS Blaiss, MJ Derebery, TA Mahr, BR Gordon, KK Sheth, AL Simmons, MA Wingertzahn, JM Boyle, 2009, Burden of allergic rhinitis: Results From the Pediatric Allergies in America Survey, J Allergy Clin Immunol, 124(3 Suppl):S43–70.

respond to initial therapy with intranasal glucocorticoids may be treated with a second agent such as oral or nasal antihistamines, or combination products.[6]

Glucocorticoid nasal sprays (NS) have an onset of action of a few hours. However, maximal effect may require several days. These agents inhibit allergic inflammation in the nose and downregulate the inflammatory response by binding to intracellular glucocorticoid receptors in the cytoplasm of inflammatory cells. Potential safety concerns of corticosteroid NS include adrenal suppression, reduced bone growth and height in children, and local effects such as nosebleeds.

Antihistamines used to treat AR target the H_1 receptors. Antihistamine NS have a rapid onset of action. AEs of intranasal antihistamines may include a bitter aftertaste and drowsiness.[7]

Current treatment options are shown in Table 1.

2.2. Analysis of Current Treatment Options

Table 1. FDA Approved Nasal Sprays for Seasonal Allergic Rhinitis

Active Ingredient	Trade Name	Age Range
Fixed-dose combination product		
Azelastine hydrochloride/fluticasone propionate	Dymista	≥6 years
H_1-receptor antagonists		
Azelastine hydrochloride	Astelin	≥5years
	Astepro	≥12 years
Olopatadine	Patanase	≥ 6 years
Corticosteroids		
Beclomethasone	Beconase AQ	≥6 years
Budesonide	Rhinocort Aqua	≥6 years
Ciclesonide	Omnaris	≥12 years
Fluticasone furoate	Veramyst	≥6 years
Fluticasone propionate	Flonase and generics	≥4 years
	Xhance	≥18 years
Flunisolide	Generics	≥6 years
Mometosone furoate	Nasonex	≥2 years
Triamcinolone	Nasacort AQ and generic	≥2 years

3 Regulatory Background

[6] Seidman, MD, RK Gurgel, SY Lin, SR Schwartz, FM Baroody, JR Bonner, DE Dawson, MS Dykewicz, JM Hackell, JK Han, SL Ishman, HJ Krouse, S Malekzadeh, JW Mims, FS Omole, WD Reddy, DV Wallace, SA Walsh, BE Warren, MN Wilson, LC Nnacheta, Guideline Otolaryngology Development Group. AAO-HNSF, 2015, Clinical practice guideline: Allergic rhinitis, Otolaryngol Head Neck Surg, 152(1 Suppl):S1–S43.

[7] Hoyte, FC and RK Katial, 2011, Antihistamine therapy in allergic rhinitis, Immunol Allergy Clin North Am, 31(3):509–543.

3.1. U.S. Regulatory Actions and Marketing History

OLO and MF are available in the United States as active ingredients in multiple products. OLO is available both as a branded product (Patanase) and generic. Patanase (NDA 021861) received initial U.S. approval on April 15, 2008, for the treatment of SAR in adults and children 6 years of age and older.

MF is available both as a branded product (Nasonex) and generic. Nasonex NS (NDA 020762) received initial U.S. approval on October 1, 1997. Nasonex NS is indicated for:

- Treatment of nasal symptoms of AR in patients ≥2 years of age
- Treatment of nasal congestion associated with SAR in patients ≥2 years of age
- Prophylaxis of SAR in patients ≥12 years of age
- Treatment of nasal polyps in patients ≥18 years of age

The proposed product GSP 301 would be the second FDC NS of an H_1-receptor antagonist and a corticosteroid approved for the treatment of SAR. The first was Dymista (azelastine HCl and fluticasone propionate) (NDA 202236), approved on May 1, 2012.

3.2. Summary of Presubmission/Submission Regulatory Activity

Pre-Investigational New Drug (IND) meeting August 15, 2014:

- The Division reiterated that the contribution of each monotherapy component needs to be established and there should be no pharmaceutical difference between the combination product and the individual components.
- The Division recommended prospective local nasal safety throughout the development program.

IND 123164 submitted by GM on October 17, 2014:

- IND allowed to proceed.

End of phase 2 meeting September 10, 2015:

- The Division recommended that subjects with a history of nasal defects (nasal ulcerations and erosions) not be excluded.
- The Division stated the acceptability of the proposed plan to address the low pH of the formulation by including in the long-term safely study two placebo arms, one with a low pH and one with a normal pH.
- The Division recommended the final to-be-marketed (TBM) version of the drug and drug delivery system be used in the pivotal clinical studies.

End of phase 2 meeting November 12, 2015:

- It was noted that the drug regulatory specifications may need to include a test for leachables, depending on the data from the stability studies and the associated toxicological consideration.
- A test for MF particle size distribution in the suspension was recommended.

Pre-NDA meeting July 13, 2017:

- The Division reiterated its concern that the TBM 240-spray presentation had not been utilized in any study in the clinical development program. Comparative in vitro product performance assessment and patient misuse scenarios (e.g., failing to shake before use) would be a review issue at the time of NDA.

Type B chemistry, manufacturing, and controls meeting September 25, 2017:

- The Division recommended drug product characterization data comparing the three presentations (i.e., the 120-spray version used in clinical studies, and the 240- and 56-spray versions as the TBM drug product) and a comprehensive use-related risk analysis be performed to determine whether a human factors validation would be necessary.
- Given that changes in the manufacturing process had been made since the manufacture of the registration batches, it was recommended that comparative batch release data and the in-process data from each of the manufacturing processes be provided to demonstrate the changes pose no quality impact.
- The sponsor proposed that they would be pursuing the single indication SAR (b) (4)

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

No OSI investigations were conducted for this application.

4.2. Product Quality

The drug product, olopatadine hydrochloride, USP and mometasone furoate nasal spray, is manufactured with (b) (4).
The drug product is packaged in two presentations: a 240-spray presentation, which is the commercial product, and a 56-spray presentation, which is the professional sample. The manufacturing process risks have been satisfactorily mitigated by the demonstrated process understanding, appropriate control strategy and implementation practice confirmed during the pre-approval inspection of the drug product manufacturer, Glenmark Pharmaceuticals Ltd. on

September 17, 2018. However, recent surveillance inspections of the drug product manufacturer, Glenmark Pharmaceuticals Ltd (FEI 3005757050) and the proposed contract testing laboratory, (b) (4) revealed significant quality concerns with the facilities; therefore, this application was recommended WITHHOLD from facility perspective. Until these issues can be resolved, the Office of Process and Facilities (OPF) recommends that this application receive a Complete Response.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

No nonclinical studies were submitted under the original IND to support a proposed phase 2 clinical study of GSP 301. The Applicant conducted two in vivo primary pharmacology studies to evaluate the efficacy of a combination of OLO with MF in an allergen-induced rhinitis model in guinea pigs. Two combinations of OLO and MF (50 µg + 10 µg and 120 µg + 10 µg) were evaluated. In both studies, the combination of OLO and MF exhibited a significant inhibition of sneezing response and allergen-induced nasal inflammation as compared to the respective monotherapy arms.

A general toxicology study of GSP 301 submitted in support of, and prior to, long-term phase 3 clinical studies consisted of a 13-week, repeat dose intranasal toxicology study in Sprague Dawley rats. In the 13-week intranasal toxicity study, rats (10/ sex/group) were administered OLO at doses of 0.532 and 1.064 mg/day; MF at doses of 0.04 mg/day; and OLO/MF at doses of 0.266/0.02, 0.532/0.04, 0.532/0.02, and 1.064/0.04 mg/day. No target organs of toxicity were identified in the 13-week intranasal toxicity study in rats. The determined no- observed-adverse- effect level was the high dose of 1.064/0.04 mg/day OLO/MF. No evidence of novel, additive, or synergistic toxic effects with the proposed FDC of OLO and MF were observed.

Local safety margins (on a nasal surface area basis relative to the rat no-observed-adverse-effect levels) for the proposed maximum intranasal clinical daily dose of 4.8 mg OLO and 0.2 mg MF are shown in the table below. There is a minimum two-fold safety margin for the proposed daily doses of OLO and MF relative to the rat no-observed-adverse-effect levels in the 13-week study, which was considered adequate to support the safety of the product.

Table 2. Local Safety Margins for GSP 301 Based on Nasal Cavity Surface Area at the NOAEL in Rats Relative to the Proposed Human Clinical Dose (13-Week Duration)[1]

			Local (Nasal) Safety Margins	
Proposed Clinical Dose (mg)	**Nasal Surface Area (cm^2)**	**Nasal Dose (mg/cm^2)**	**Rat NOAEL (1.064 mg/day Olopatadine HCl) Nasal dose=0.08 mg/cm^2**	**Rat NOAEL (0.04 mg/day Mometasone furoate) Nasal dose=0.003 mg/cm^2**
Olopatadine HCl 4.8	160	0.03	2.7	-
Mometasone furoate 0.2	160	0.0013	-	2.3

[1]Gizurarson S. 1990. Animal models for intranasal drug delivery studies. Acta Pharmaceutica Nordica. 2(2):105-122.
Abbreviations: NOAEL=no-observed-adverse-effect level; HCl=hydrochloride

No additional general toxicology data was required prior to an NDA filing for IND 123164. In addition, no further developmental/reproductive toxicity or carcinogenicity studies with OLO or MF were required. Extensive nonclinical programs with OLO and MF were conducted and reviewed in support of the approved products described under Regulatory Background.

During the course of the IND and NDA reviews, the nonclinical reviewer has also assessed the safety of excipients, impurities / degradants, and extractables / leachables for the proposed product. In particular, an extensive evaluation of data and justification related to potential (b) (4) leachables was conducted. No safety concerns were identified for the proposed dose, duration, and patient population (refer to the Nonclinical Review dated May 17, 2019).

Overall, the application is recommended for Approval from the pharmacology-toxicology perspective.

6 Clinical Pharmacology

6.1. Executive Summary

On May 21, 2018, Glenmark submitted NDA 211746 seeking marketing approval for a FDC NS containing OLO and MF. The Applicant references Patanase NS (NDA 021861) and Nasonex NS (NDA 020762) as the listed drugs for OLO and MF, respectively. The Office of Clinical Pharmacology has reviewed the clinical pharmacology information provided within NDA 211746 and recommends Approval.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Pharmacology

GSP 301 contains both OLO and MF; therefore, the mechanism of action described below for the individual components would apply to GSP 301. These drugs represent two different classes of medications, histamine H_1-receptor antagonist and synthetic corticosteroid.

Olopatadine Hydrochloride

OLO is a histamine H_1-receptor antagonist. The antihistaminic activity of OLO has been documented in isolated tissues, animal models, and humans.

Mometasone Furoate

MF is a corticosteroid demonstrating potent anti-inflammatory properties. The precise mechanism of corticosteroid action on AR is not known. Corticosteroids have been shown to have a wide range of effects on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation.

Clinical Pharmacokinetics

The clinical pharmacology program in this NDA consists of two phase 1 studies to assess the relative bioavailability of OLO and MF from GSP 301 against the listed drugs, and to identify any potential drug interaction between OLO and MF. The Applicant also conducted a population pharmacokinetic (PK) analysis to address the effect of age, sex, and race on the PK profile of OLO and MF following intranasal administration of GSP 301 in patients with SAR. The following are the major clinical pharmacology findings:

1. Following single dose administration of GSP 301-1[8] (containing 50 µg MF and 665 µg OLO per spray, 2 sprays per nostril) in healthy subjects, the mean peak concentration (C_{max}) and area under the curve ($AUC_{0-\infty}$) of MF were 10.81 pg/mL and 103.77 pg·h/mL, respectively. In the same study, the C_{max} and $AUC_{0-\infty}$ of MF following single dose administration of 200 µg of Nasonex NS (containing 50 µg of MF per spray, 2 sprays per nostril) in healthy subjects were 7.62 pg/mL and 90.12 pg·h/mL, respectively (study GSP 301-102). Following single dose administration of the TBM GSP 301 (containing 25 µg MF and 665 µg OLO, 2 sprays per nostril) in patients with SAR, the C_{max} of MF was 6.27 pg/mL (study GSP 301-301), which is comparable to C_{max} of 7.62 pg/mL for Nasonex NS in study GSP 301-102 (cross-study comparison). Following repeat (BID) dosing of GSP 301 in study GSP 301-301 for 8 days, the $AUC_{ss\ (0-12h)}$ for MF was 52.67 pg·h/mL, which was comparable to the $AUC_{0-\infty}$ of 45.06 pg·h/mL (adjusted to 100 µg MF) for Nasonex NS in study GSP 301-102 (cross-study comparison). Therefore, some relevant information for MF, including

[8] Formulation GSP 301-1 is different from the TBM formulation in the pivotal phase 3 clinical trials. This formulation is different from the TBM formulation only in the content of MF per spray (50 µg per spray in GSP 301-1 vs. 25 µg per spray in GSP 301), and only used in the early phase clinical trials (studies 101, 102, and 201).

PK, drug interaction, PK in special populations, systemic safety and others, could rely on the approved U.S. labeling for Nasonex NS.

2. Following single dose administration of GSP 301-1OLO in healthy subjects, the C_{max} and $AUC_{0-\infty}$ of OLO were 17.27 ng/mL and 83.26 ng·h/mL, respectively. In the same study, the C_{max} and $AUC_{0-\infty}$ of OLO following single dose administration of 2660 µg of Patanase NS (containing 665 µg OLO per spray, 2 sprays per nostril) in healthy subjects were 20.39 ng/mL and 88.76 ng·h/mL, respectively (study GSP 301-101). Following single dose administration of the TBM formulation of GSP 301 in patients with SAR, the C_{max} of MF was 18.77 ng/mL (study GSP 301-301), which is comparable to C_{max} of 20.39 ng/mL for Patanase NS in study GSP 301-101 (cross-study comparison). Following repeat (BID) dosing of GSP 301 in study GSP 301-301 for 8 days, the $AUC_{ss\ (0-12h)}$ for OLO was 85.74 ng·h/mL, which was comparable to $AUC_{0-\infty}$ of 88.76 ng·h/mL for Patanase NS in study GSP 301-101 (cross-study comparison). Therefore, some relevant information for OLO, including PK, drug interaction, PK in special populations, systemic safety and others, could rely on the approved U.S. labeling for Patanase NS.

3. The dose and dosing regimen for GSP 301 has been adequately explored in the pivotal phase 2 dose-ranging study (GSP301-201). Regardless of the dosing intervals, each monotherapy showed a statistically significant difference in the change from baseline in average AM and PM reflective Total Nasal Symptom Score (rTNSS) compared to placebo. However, only the BID dosing regimen (665 µg OLO/25 µg MF, two sprays per nostril BID) showed statistically significant difference in the change from baseline in average AM and PM rTNSS compared to its corresponding monotherapy arms (i.e., 665 µg OLO two sprays per nostril BID and 25 µg MF two sprays per nostril BID). The once daily (QD) dosing regimen (665 µg OLO/50 µg MF, two sprays per nostril QD) failed to show a statistically significant difference to its corresponding MF monotherapy arm (50 µg MF, two sprays per nostril QD).

4. Population PK model was developed to describe the systemic exposure of OLO and MF in subjects with SAR and determine if any intrinsic factors influence the systemic exposure. Age, sex, and race had no relevant effect on the systemic exposure of OLO and MF following administration of GSP 301.

Studies will hereafter be referred to by their last 3 numbers (e.g., Study GSP 301-201 will be Study 201).

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

GSP 301 is to be administered intranasally at the proposed dose of two sprays per nostril BID in patients 12 years and older. Each spray (0.1 mL suspension) contains 665 µg of OLO (600 µg OLO equivalent) and 25 µg of MF.

Therapeutic Individualization

Not applicable.

Outstanding Issues

Not applicable

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Olopatadine Disposition[9]

Distribution

The protein binding of OLO was moderate at approximately 55% in human serum, and independent of drug concentration over the range of 0.1 to 1000 ng/mL. OLO was bound predominately to human serum albumin.

Metabolism

OLO is not extensively metabolized. Based on plasma metabolite profiles following oral administration of [^{14}C] OLO, at least six minor metabolites circulate in human plasma. OLO accounts for 77% of peak plasma total radioactivity and all metabolites amounted to <6% combined. Two of these have been identified as the OLO N-oxide and N-Desmethyl OLO. In in vitro studies with cDNA-expressed human cytochrome P450 (CYP) isoenzymes and flavin-containing monooxygenases, N-Desmethyl OLO formation was catalyzed mainly by CYP3A4, while OLO N-oxide was primarily catalyzed by flavin-containing monooxygenases 1 and 3. OLO at concentrations up to 33,900 ng/mL did not inhibit the in vitro metabolism of specific substrates for CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. The potential for OLO and its metabolites to act as inducers of CYP enzymes has not been evaluated.

Elimination

The plasma elimination half-life of OLO is 8 to 12 hours. OLO is mainly eliminated through urinary excretion. Approximately 70% of a [^{14}C] OLO oral dose was recovered in urine with 17% in the feces. Of the drug-related material recovered within the first 24 hours in the urine, 86% was unchanged OLO with the balance comprised of OLO N-oxide and N-Desmethyl OLO.

Olopatadine Special Population

Hepatic Impairment

[9] Patanase package insert. Alcon Laboratories, Inc.

No specific PK study examining the effect of hepatic impairment was conducted. Since metabolism of OLO is a minor route of elimination, no adjustment of the dosing regimen of Patanase NS is warranted in patients with hepatic impairment.

Renal Impairment

The mean C_{max} values for OLO following single intranasal doses were not markedly different between healthy subjects (18.1 ng/mL) and patients with mild, moderate, and severe renal impairment (range 15.5 to 21.6 ng/mL). Mean plasma AUC_{0-12} was two-fold higher in patients with severe impairment (creatinine clearance <30 mL/min/1.73 m^2). In these patients, peak steady-state plasma concentrations of OLO are approximately ten-fold lower than those observed after higher 20 mg oral doses BID, which were well tolerated. These findings indicate that no adjustment of the dosing regimen of Patanase NS is warranted in patients with renal impairment.

Olopatadine Drug Interaction Studies

Drug interactions with inhibitors of liver enzymes are not anticipated because OLO is eliminated predominantly by renal excretion. OLO did not inhibit the in vitro metabolism of specific substrates for CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. Based on these data, drug interactions involving P450 inhibition are not expected. Due to the modest protein binding of OLO (55%), drug interactions through displacement from plasma proteins are also not expected.

Mometasone Furoate Disposition[10]

Distribution

The in vitro protein binding for MF was reported to be 98% to 99% in concentration range of 5 to 500 ng/mL.

Metabolism

Studies have shown that any portion of a MF dose which is swallowed and absorbed undergoes extensive metabolism to multiple metabolites. There are no major metabolites detectable in plasma. Upon in vitro incubation, one of the minor metabolites formed is 6β-hydroxy-mometasone furoate. In human liver microsomes, the formation of the metabolite is regulated by CYP3A4.

Elimination

Following intravenous administration, the effective plasma elimination half-life of MF is 5.8 hours. Any absorbed drug is excreted as metabolites mostly via the bile, and to a limited extent, into the urine.

[10] Nasonex package insert. Schering Corporation

Mometasone Furoate Specific Populations

Hepatic Impairment

Administration of a single inhaled dose of 400 µg MF to subjects with mild (n=4), moderate (n=4), and severe (n=4) hepatic impairment resulted in only 1 or 2 subjects in each group having detectable peak plasma concentrations of MF (ranging from 50 to 105 pg/mL). The observed plasma C_{max} appear to increase with severity of hepatic impairment, however, the numbers of detectable levels were few.

Renal Impairment

The effects of renal impairment on MF PK have not been adequately investigated.

Mometasone Furoate Drug Interactions

Inhibitors of CYP3A4: In a drug interaction study, an inhaled dose of MF 400 µg was given to 24 healthy subjects BID for 9 days and ketoconazole 200 mg (as well as placebo) were given BID concomitantly on days 4 to 9. MF plasma concentrations were <150 pg/mL on day 3 prior to coadministration of ketoconazole or placebo. Following concomitant administration of ketoconazole, 4 out of 12 subjects in the ketoconazole group (n=12) had plasma C_{max} of MF >200 pg/mL on day 9 (211–324 pg/mL).

6.3.2. Clinical Pharmacology Questions

6.3.2.1. What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

The clinical pharmacology studies are summarized in Table 3 below.

Table 3. Overview of Clinical Pharmacology Studies

Study ID	Phase	Treatments	Comment
GSP301-101	1	GSP 301-1 NS (665 µg / 50 µg) Olopatadine HCl NS 665 µg Patanase NS 665 µg	Not to-be-marketed[#]
GSP301-102	1	GSP 301-1 NS (665 µg / 50 µg) Mometasone furoate NS 50 µg Nasonex NS 50 µg	Not to-be-marketed[#]
GSP301-301	3	GSP 301 NS (665 µg / 25 µg) Olopatadine HCl NS 665 µg Mometasone furoate NS 25 µg Placebo	To-be-marketed formulation[#]
GSP301POPPK		GSP 301-1 NS (665 µg / 50 µg) GSP 301 NS (665 µg / 25 µg)	

[#]The only difference between the to-be-marketed and not to-be-marketed formulation is the amount of mometasone furoate (25 µg vs. 50 µg per spray).
Source: adapted from NDA 211746 Module 2.5 Table 2 in Clinical Overview

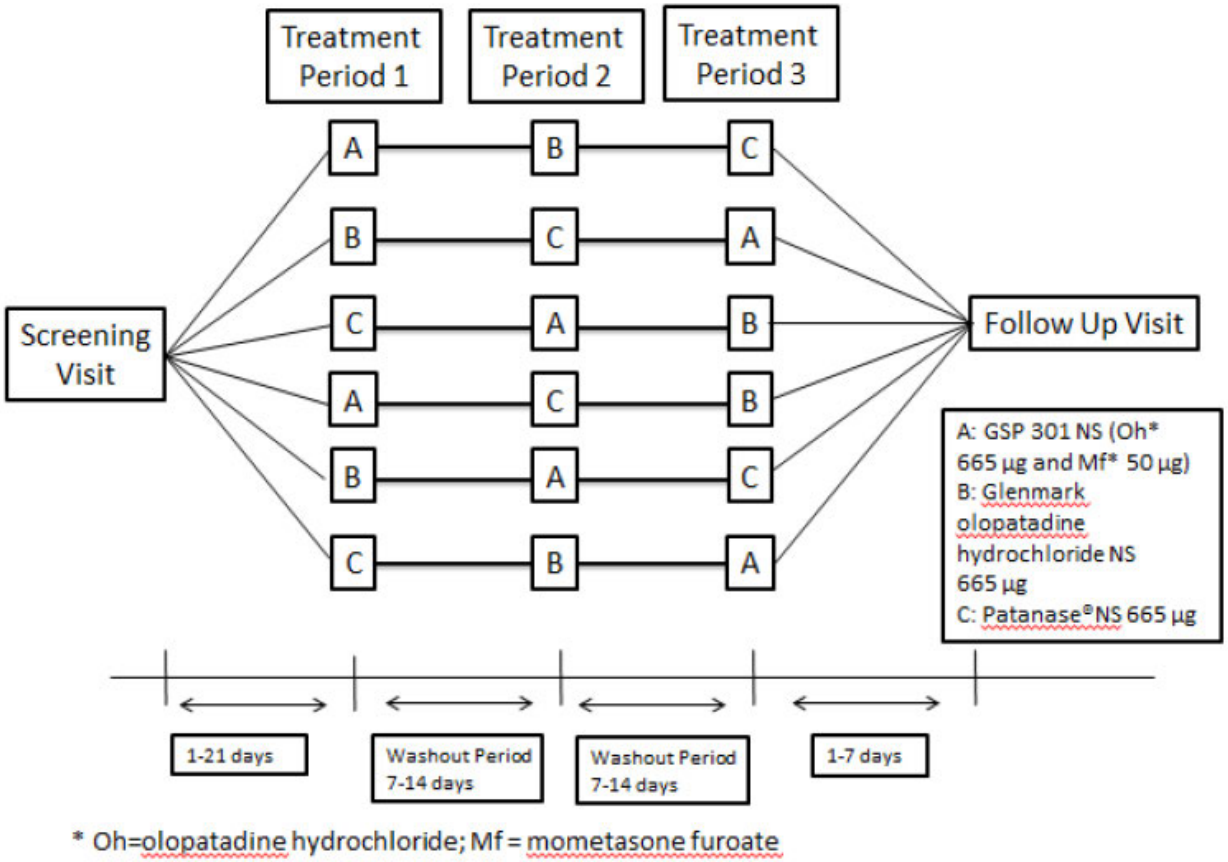
Abbreviations: NS=nasal spray; HCl=hydrochloride; POPPK=Population Pharmacokinetics

Two phase 1 studies were conducted to assess the relative systemic exposure of OLO and MF from the proposed combination product GSP 301 versus monotherapy comparators in GSP 301 vehicle versus listed drug(s).

Study 101 was a single-center, single-dose, randomized, open-label, crossover study conducted in 30 healthy subjects. The study population included healthy male and nonpregnant female subjects 18 to 64 years of age whose body mass index at screening ranged from 18.5 to 32 kg/m^2.

Subjects were randomized to one of the six treatment sequences in a 1:1:1:1:1:1 ratio; all subjects received GSP 301-1 NS, GM OLO NS, and Patanase NS.

Figure 1. Study GSP 301-101 Study Design Schematic



Source: NDA 211746, Module 5.3.1.2, Figure 1 in Study GSP-301-101 Clinical Study Report Version 01_07 Aug 2015
Abbreviations: NS=nasal spray

Subjects received the following three treatments:

Treatment A: GSP 301-1 NS; 665 µg OLO/50 µg MF per spray (2 sprays per nostril)

Treatment B: OLO in GSP 301 NS vehicle; 665 µg OLO per spray (2 sprays per nostril)

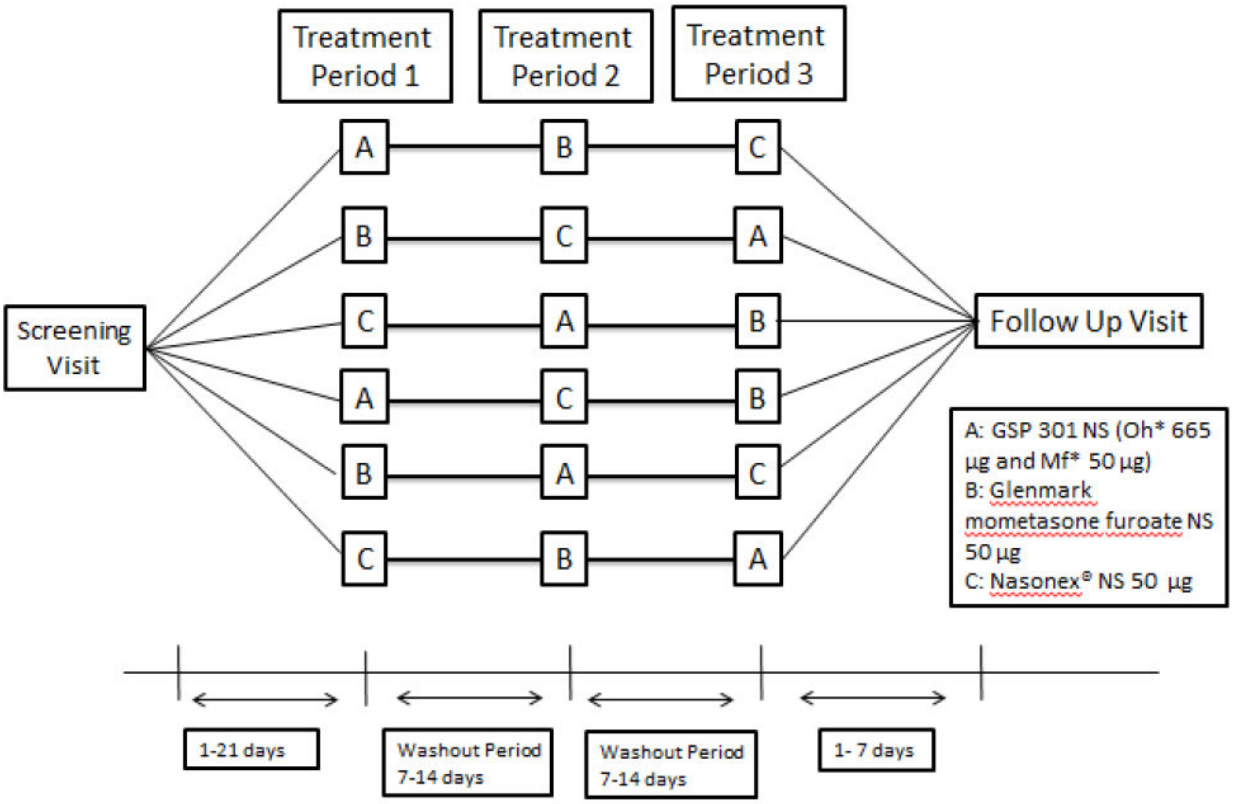
Treatment C: Patanase NS; 665 µg OLO per spray (2 sprays per nostril)

For each treatment period, blood samples were collected immediately prior to dosing and at 5, 15, 30, and 45 mins, and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, and 72 hours post-dose.

Study 102 was a single-center, single-dose, randomized, open-label, crossover study conducted in 30 healthy subjects. The study population included healthy male and nonpregnant female subjects 18 to 64 years of age whose body mass index at screening ranged from 18.5 to 32 kg/m^2.

Subjects were randomized to one of six treatment sequences in a 1:1:1:1:1:1 ratio; all subjects received GSP 301-1 NS, GM MF NS, and Nasonex NS in each sequence.

Figure 2. Study GSP 301-102 Study Design Schematic



* Oh = olapatadine hydrochloride; Mf = mometasone furoate

Source: NDA 211746, Module 5.3.1.2, Figure 1 in Study GSP-301-102 Clinical Study Report Version 01_07 Aug 2015
Abbreviations: NS=nasal spray

Subjects received the following three treatments:

Treatment A: GSP 301-1 NS; 665 µg OLO/50 µg MF per spray (2 sprays per nostril)

Treatment B: MF in GSP 301 NS vehicle; 50 µg MF per spray (2 sprays per nostril)

Treatment C: Nasonex NS; 50 µg MF per spray (2 sprays per nostril)

For each treatment period, blood samples were collected immediately prior to dosing and at 5, 15, 30, and 45 mins, and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, and 72 hours post-dose.

In one pivotal phase 3 study (Study 301), plasma samples were collected for the evaluation of PK of OLO and MF. Rich PK samples were collected for both OLO and MF in 26 patients on day 1 and day 8 following intranasal administration of GSP 301. The rich PK sampling time points were: Day 1: predose (before the morning dose), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours after the morning dose; day 8: 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 (before the evening dose) hours after the morning dose. Also, sparse PK samples (mainly trough samples) were collected in 272 patients following intranasal administration of GSP 301.

6.3.2.2. What are the PK characteristics of OLO and MF following BID administration of the to-be-marketed formulation GSP 301 in patients with SAR?

The PK of OLO and MF following BID administration of GSP 301 at the proposed dose level in patients with SAR were characterized in Study 301. Rich PK samples were collected in 26 patients taking GSP 301. These rich PK samples were collected at predose (before the AM dose) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 (before the PM dose) hours after the morning dose on day 1 and day 8. The corresponding summary of PK parameters are given in Table 4.

Table 4. Mean Pharmacokinetic Parameters of Olopatadine and Mometasone Furoate Following Intranasal Administration of GSP 301 NS to Subjects with Seasonal Allergic Rhinitis (PK Analysis Set)

PK parameter	Olopatadine		PK parameter	Mometasone furoate	
	Day 1	Day 8		Day 1	Day 8
C_{max} (ng/mL)	**n = 26**	**n= 25**	**C_{max} (pg/mL)**	**n = 26**	**n = 26**
Mean (SD)	19.82 (6.36)	19.80 (7.01)	Mean (SD)	6.78 (2.71)	9.92 (3.74)
CV%	32.12	35.39	CV%	39.96	37.69
Min-Max	8.70 - 31.60	9.67 - 37.30	Min-Max	2.67 - 12.80	3.58 - 16.10
Geo Mean (Geo CV%)	18.77 (35.61)	18.70 (35.34)	Geo Mean (Geo CV%)	6.27 (42.80)	9.17 (43.88)
AUC_{tau} (ng*hr/mL)	**n = 26**	**n = 24**	**AUC_{tau} (pg*hr/mL)**	**n= 26**	**n = 25**
Mean (SD)	75.48 (20.02)	88.77 (23.87)	Mean (SD)	28.56 (13.33)	58.40 (27.00)
CV%	26.53	26.89	CV%	46.67	46.23
Min-Max	39.33 - 116.80	53.35 – 138.34	Min-Max	12.11 - 72.54	25.68 - 124.05
Geo Mean (Geo CV%)	72.90 (27.67)	85.74 (27.54)	Geo Mean (Geo CV%)	26.16 (43.51)	52.67 (49.48)
T_{max} (hour)	**n = 26**	**n = 26**	**T_{max} (hour)**	**n= 26**	**n= 26**
Median (range)	1.00 (0.25 – 3)	1.00 (0.25 – 2)	Median (range)	1.00 (0.25 – 2)	1.00 (0.25 – 2)

AUC_{tau} = area under the plasma concentration-time curve over the dosing interval; C_{max} = maximum plasma concentration; CV=coefficient of variation; Geo= geometric; Min=minimum; Max=maximum; SD = standard; PK=pharmacokinetic; deviation; $T_{max=}$ time to attain C_{max}

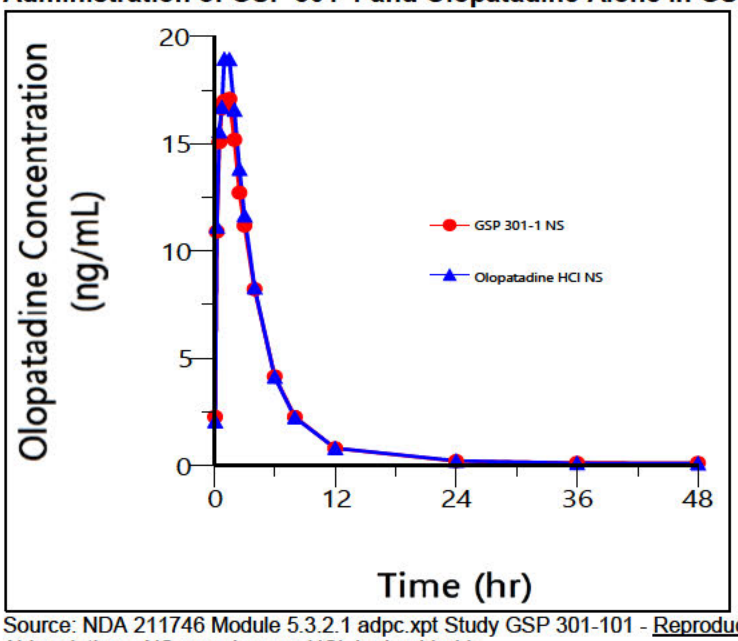
Source: NDA 211746, Module 5.3.5.1, Table 27 in Study GSP-301-301 Clinical Study Report (Final_26-Oct-2017)

6.3.2.3. Do the drug interaction studies suggest any potential change in systemic exposures of OLO and MF for GSP 301 vs. monotherapy products (i.e., investigational and monotherapy comparators and commercial monotherapy products)?

Olopatadine

No. The mean concentration-time profiles of OLO following intranasal administration of GSP 301-1 and OLO as a monotherapy in GSP 301 vehicle are shown in Figure 3. The corresponding relative bioavailability results are summarized in Table 5. Following intranasal administration of GSP 301-1, the C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, were 13.37%, 13.08%, and 7.17% lower than OLO alone, respectively. These differences in systemic exposure are not considered clinically meaningful.

Figure 3. Mean Concentration-Time Profile of Olopatadine Following Single Dose Intranasal Administration of GSP 301-1 and Olopatadine Alone in GSP 301 Vehicle (Study 101)



Source: NDA 211746 Module 5.3.2.1 adpc.xpt Study GSP 301-101 - Reproduced by Reviewer
Abbreviations: NS=nasal spray; HCl=hydrochloride

Table 5. Relative Bioavailability of Olopatadine Following Single Dose Intranasal Administration of GSP 301 NS and Olopatadine HCl in GSP 301 Vehicle in PK Analysis Set (Study GSP 301-101)

PK Parameter	Number of Subjects[a]	Geometric Mean[b]		Relative Bioavailability[c]		Intrasubject Variability (%CV)
		GSP 301 NS	Glenmark Olopatadine HCl NS	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

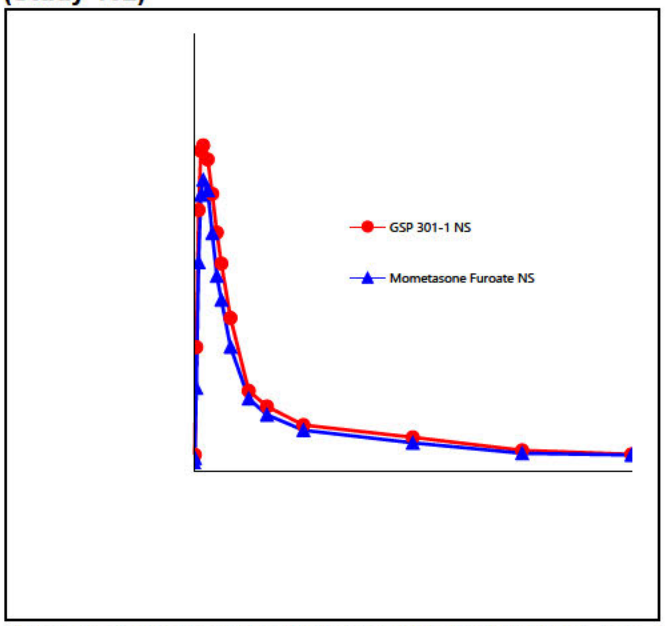
a: Number of paired subjects used in the ANOVA for each parameter.
b: Geometric means were based on the exponential of LSMs of ln-transformed values.
c: Relative bioavailability is based on GMR expressed as a percentage.
d: In the estimation of λz, R^2 must be ≥0.80 for the regression. If R^2 was <0.80, λz and the parameters that utilize λz for determination ($t_{1/2}$, AUC_∞, and CL/F) were not reported for an individual subject.
Source: NDA 211746, Module 5.3.1.2, Table 8 in Study GSP-301-101 Clinical Study Report_Version 01_07 Aug 2015
Abbreviations: 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; C_{max}=maximum measured plasma concentration; CI=confidence interval; %CV=percent coefficient of variation; Glenmark Olo=Glenmark olopatadine HCl NS; GMR (geometric mean ratio [GSP 301 NS:Glenmark Olo]); HCl=hydrochloride; ln=natural log; LSM=least squares means; NS=nasal spray.

Mometasone Furoate

The average concentration-time profiles of MF following intranasal administration of GSP 301-1 and MF as a monotherapy in GSP 301 vehicle are shown in Figure 4. The corresponding relative bioavailability results are summarized in Table 6. Following intranasal administration of GSP

301-1, the C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, were 13.83%, 18.36%, and 18.50% higher than MF alone. These differences in systemic exposure are not considered clinically meaningful.

Figure 4. Mean Concentration-Time Profile of Mometasone Furoate Following Single Dose Intranasal Administration of GSP 301 Versus Mometasone Furoate Alone in GSP 301 Vehicle (Study 102)



Source: NDA 211746 Module 5.3.2.1 adpc.xpt Study GSP 301-102 - Reproduced by Reviewer
Abbreviations: NS=nasal spray

Table 6. Relative Bioavailability of Mometasone Furoate Following Single-Dose Intranasal Administration of GSP 301 and Glenmark Mometasone Furoate NS in PK Analysis Set (Study 102)

PK Parameter	Number of Subjects[a]	Geometric Mean[b]		Relative Bioavailability[c]		Intrasubject Variability (%CV)
		GSP 301 NS	Glenmark Mometasone Furoate NS	GMR (%)	90% CI	
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

a: Number of paired subjects used in the ANOVA for each parameter.
b: Geometric means were based on the exponential of LSMs of ln-transformed values.
c: Relative bioavailability is 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 ($t_{1/2}$, $AUC_{0-\infty}$, and CL/F) were not reported for an individual subject.
Source: NDA 211746, Module 5.3.1.2, Table 9 in Study GSP-301-102 Clinical Study Report_Version 01_07 Aug 2015
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; C_{max}=maximum measured plasma concentration; CI=confidence interval; %CV=percent coefficient of variation; Glenmark MF=Glenmark mometasone furoate NS; GMR (geometric mean ratio [GSP 301 NS: Glenmark MF]); ln=natural log; LSM=least squares means; NS=nasal spray.

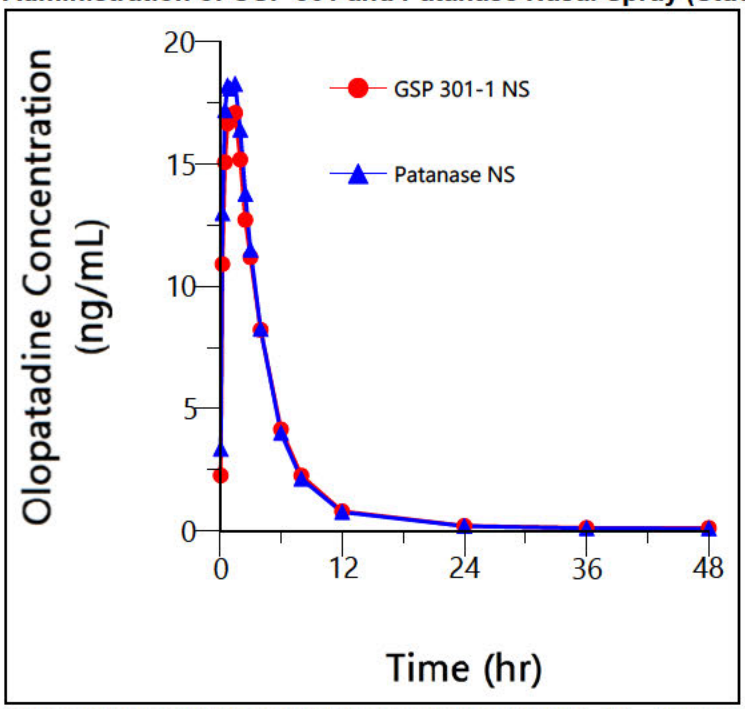
6.3.2.4. Is systemic exposure for olopatadine and mometasone furoate equal to or less than the corresponding listed drug?

Olopatadine

Yes. The average concentration-time profiles of OLO following intranasal administration of GSP 301-1 (containing 50 µg MF and 665 µg OLO per spray, 2 sprays per nostril) and Patanase NS (containing 665 µg OLO per spray, 2 sprays per nostril) are presented in Figure 5. The corresponding relative bioavailability results are shown in Table 7. Following intranasal administration of GSP 301-1, the systemic exposure of OLO in terms of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, was 15.32%, 12.13%, and 7.20% lower than Patanase NS, respectively.

The proposed dosing regimen for OLO in the TBM GSP 301 is two sprays per nostril BID at 665 µg OLO per spray. The PK of OLO in the TBM formulation was evaluated in the phase 3 Study 301 in patients with SAR. The C_{max} of OLO following single dose administration of the TBM GSP 301 was 18.77 ng/mL, which is comparable to C_{max} of 20.39 ng/mL for Patanase NS in study 101 (cross-study comparison). The $AUC_{ss\ (0\text{-}12h)}$ for OLO on day 8 was 85.74 ng·h/mL, which is comparable to $AUC_{0-\infty}$ of 88.76 ng·h/mL for Patanase NS in study 101 (cross-study comparison). The cross-study (cross-population, cross-formulation) comparison for OLO PK profile was further evaluated using a population PK approach. No formulation effect was identified (see Section 6.3.2.5 for further details).

Figure 5. Mean Concentration-Time Profile of Olopatadine Following Single Dose Intranasal Administration of GSP 301 and Patanase Nasal Spray (Study 101)



Source: NDA 211746 Module 5.3.2.1 adpc.xpt Study GSP 301-101 - Reproduced by Reviewer
Abbreviations: NS=nasal spray

Table 7. Relative Bioavailability of Olopatadine Following Single Dose Intranasal Administration of GSP 301 NS and Patanase Nasal Spray in PK Analysis Set (Study 101)

PK Parameter	Number of Subjects[a]	Geometric Mean[b]		Relative Bioavailability[c]		Intrasubject Variability
		GSP 301 NS	Patanase NS	GMR (%)	90% CI	(%CV)
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

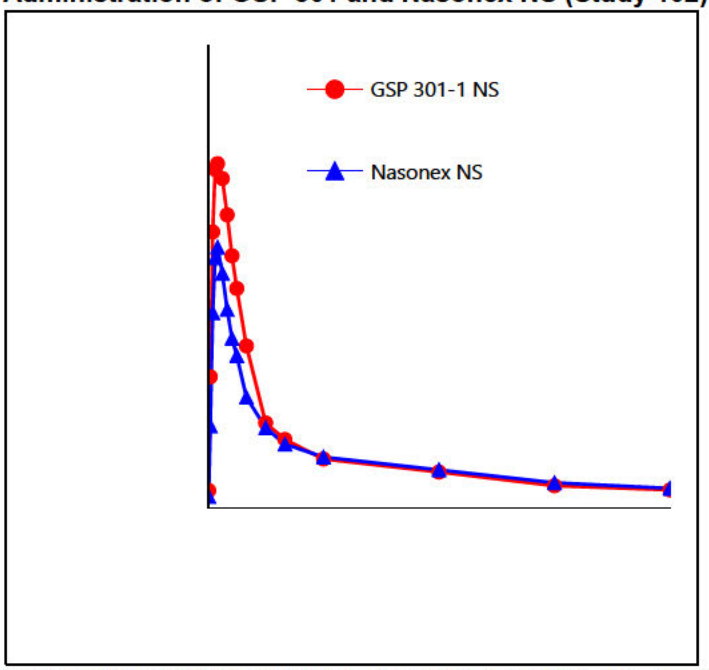
a: Number of paired subjects used in the ANOVA for each parameter.
b: Geometric means were based on the exponential of LSMs of ln-transformed values.
c: Relative bioavailability is based on GMR expressed as a percentage.
d: In the estimation of λz, R^2 must be ≥0.80 for the regression. If R^2 was <0.80, λz and the parameters that utilize λz for determination ($t_{1/2}$, $AUC_{0-\infty}$, and CL/F) were not reported for an individual subject.
Source: NDA 211746, Module 5.3.1.2, Table 7 Study GSP-301-101 Clinical Study Report_Version 01_07 Aug 2015
Abbreviations: 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; C_{max}=maximum measured plasma concentration; CI=confidence interval; %CV=percent coefficient of variation; GMR (geometric mean ratio [GSP 301 NS:Patanase NS]); ln=natural log; LSM=least squares means; NS=nasal spray; PK=pharmacokinetics

Mometasone Furoate

The average concentration-time profiles of MF following intranasal administration of GSP 301-1 and Nasonex NS are shown in Figure 6. The corresponding relative bioavailability results are summarized in Table 8. Following intranasal administration of GSP 301, the systemic exposure of MF in terms of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ was 41.84%, 9.92%, and 15.14% higher than Nasonex NS, respectively. The highest approved dose of Nasonex NS is 2 sprays per nostril BID for treatment of nasal polyps in adults.

The proposed dosing regimen for MF in the TBM GSP 301 is two sprays per nostril BID at 25 µg MF per spray. The PK of MF in the TBM formulation was evaluated in the Phase 3 study 301 in patients with SAR. The C_{max} of MF following single dose administration of the TBM GSP 301 was 6.27 pg/mL, which is comparable to C_{max} of 7.62 pg/mL for Nasonex NS in Study 102 (cross-study comparison). The $AUC_{ss\ (0-12h)}$ for MF on day 8 was 52.67 pg·h/mL, which is comparable to the $AUC_{0-\infty}$ of 45.06 pg·h/mL (adjusted to 100 µg MF) for Nasonex NS in Study 102 (cross-study comparison). The cross-study (cross-population, cross-formulation) comparison for MF PK profile was further evaluated using a population PK approach. No formulation effect was identified (see Section 6.3.2.5 for further details).

Figure 6. Average Concentration Time Profiles of Mometasone Furoate after Intranasal Administration of GSP 301 and Nasonex NS (Study 102)



Source: NDA 211746 Module 5.3.2.1 adpc.xpt Study GSP 301-102 - Reproduced by Reviewer
Abbreviations: NS=nasal spray

Table 8. Relative Bioavailability of Mometasone Furoate After Single Doses of GSP 301-1 NS and Nasonex NS in Pharmacokinetic Analysis Set (Study 102)

PK Parameter	Number of Subjects[a]	Geometric Mean[b]		Relative Bioavailability[c]		Intrasubject Variability (%CV)
		GSP 301 NS	Nasonex NS	GMR (%)	90% CI	
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

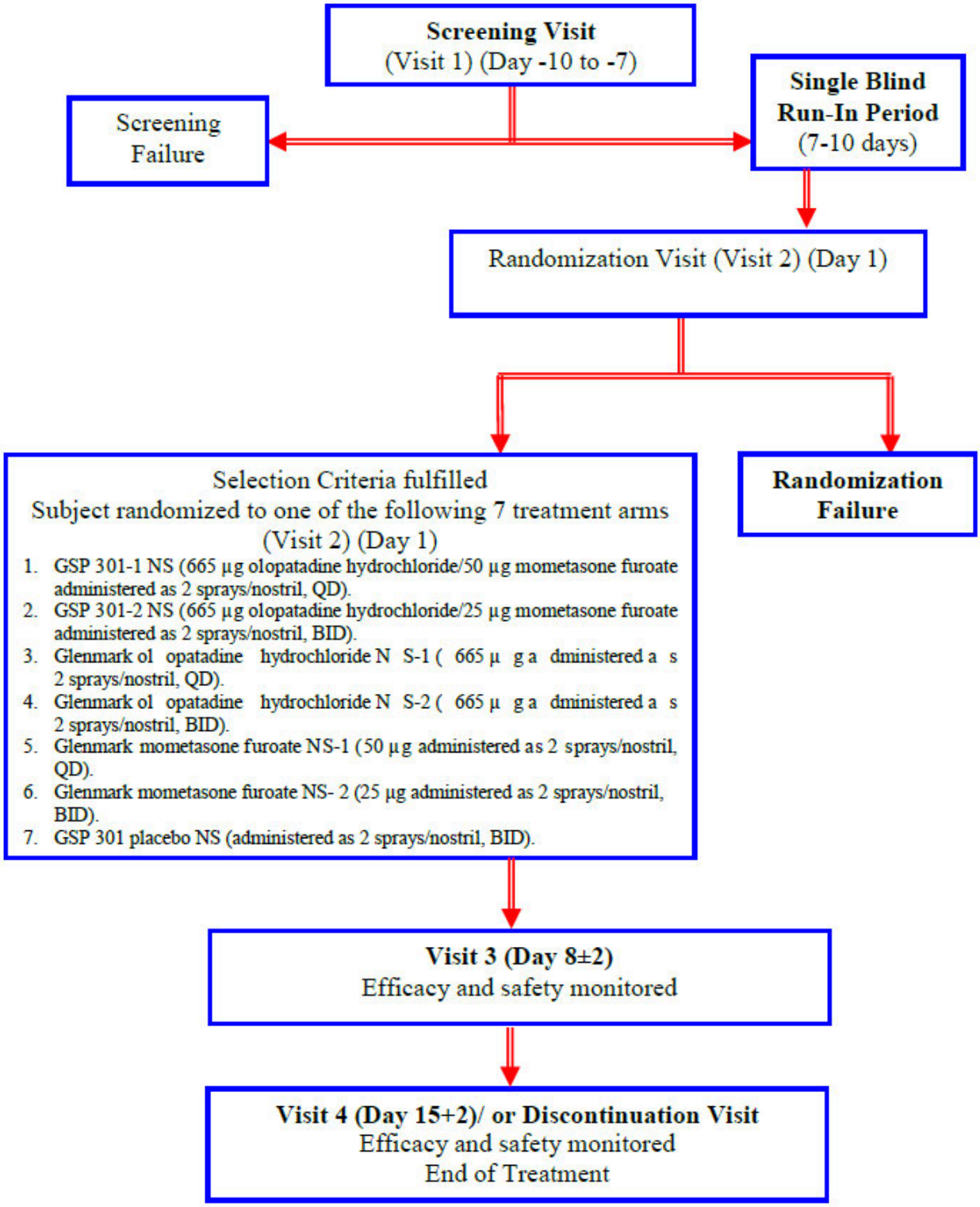
a: Number of paired subjects used in the ANOVA for each parameter.
b: Geometric means were based on the exponential of LSMs of ln-transformed values.
c: Relative bioavailability is based on GMR expressed as a percentage.
d: In the estimation of λz, R^2 must be ≥0.80 for the regression. If R^2 was <0.80, λz and the parameters that utilize λz for determination ($t_{1/2}$, $AUC_{0-\infty}$, and CL/F) were not reported for an individual subject.
Source: NDA 211746, Module 5.3.1.2, Table 8 in Study GSP-301-102 Clinical Study Report_Version 01_07 Aug 2015
Abbreviations: 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; C_{max}=maximum measured plasma concentration; CI=confidence interval; %CV=percent coefficient of variation; Glenmark MF=Glenmark mometasone furoate NS; GMR (geometric mean ratio [GSP 301 NS:Glenmark MF]); ln=natural log; LSM=least squares means; NS=nasal spray; PK=pharmacokinetic

6.3.2.5. Is the dose selection for olopatadine and mometasone furoate reasonable?

Yes. OLO (Patanase NS) is approved for the relief of the symptoms of SAR in adults and children 6 years of age and older at 2 sprays per nostril BID (665 µg per spray). MF (Nasonex NS) is approved for the treatment of nasal congestion associated with SAR at 2 sprays in each nostril QD (50 µg per spray).

In the pivotal phase 2 study (Study 201), two dosing regimens of the OLO/MF combination (GSP 301-1 NS and GSP 301-2 NS) were evaluated with their corresponding monotherapies and placebo. Study 201 was a phase 2, double-blind, double-dummy, randomized, parallel-group, placebo- and active-controlled study to evaluate the efficacy, safety and tolerability of two FDCs of OLO and MF (GSP 301-1 NS and GSP 301-2 NS) as compared with the individual monotherapy constituents (OLO 665 µg NS QD, OLO 665 µg NS BID, MF 50 µg NS QD, and MF 25 µg NS BID) and GSP 301 placebo NS (placebo) in adult and adolescent subjects with SAR who were allergic to mountain cedar pollen. The phase 2 study design is depicted in Figure 7.

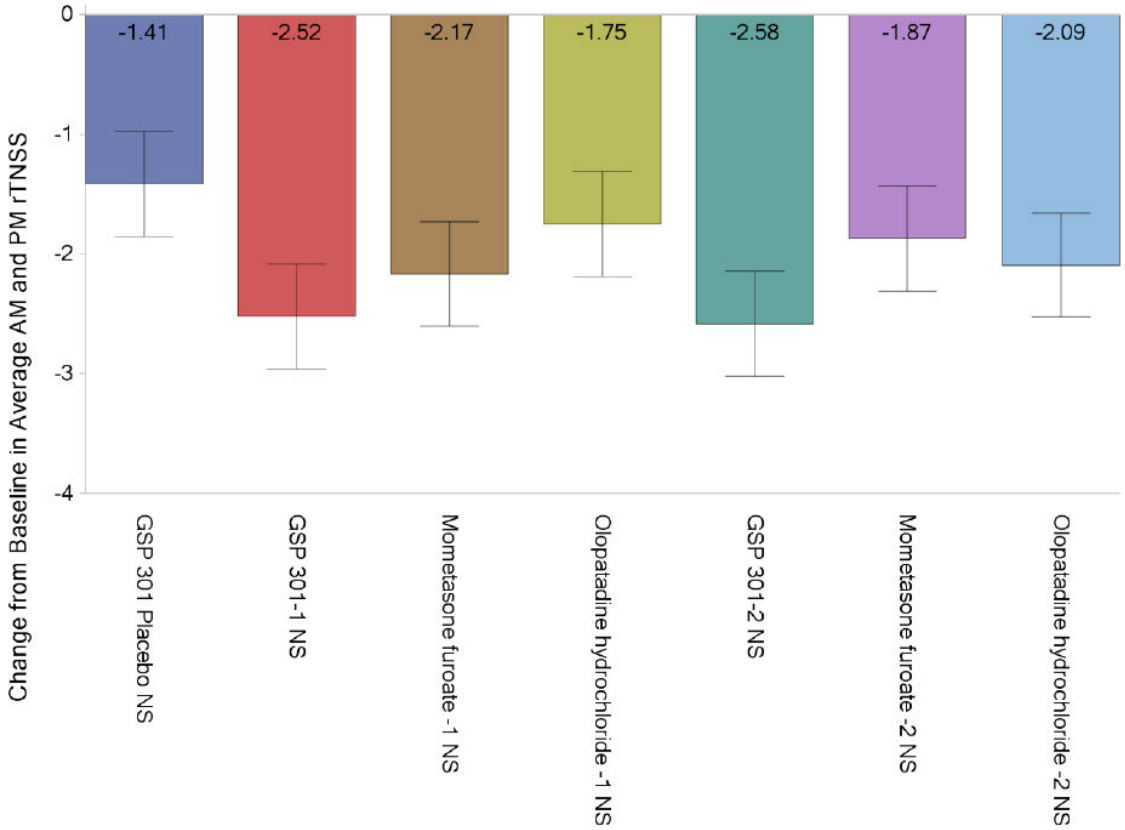
Figure 7. Study GSP 301-201 Study Design



Abbreviations: NS=nasal spray; QD=once daily; BID=twice daily

The efficacy results for the primary endpoint, rTNSS, are depicted in Figure 8.

Figure 8. Least Squares Mean Change From Baseline in Average AM and PM rTNSS Over the 14-day Treatment Period (Full Analysis Set)



AM = morning; NS = nasal spray; PM = evening; rTNSS = reflective Total Nasal Symptom Score. Graph shows least squares mean changes from baseline and associated 95% confidence intervals. Monotherapy formulations used are Glenmark Formulations.
Source: NDA 211746 Module 5.3.5.1, Figure 3 in GSP301-201 Study Report

Regardless of the dosing interval, each monotherapy showed a statistically significant difference in the change from baseline in average AM and PM rTNSS compared to placebo. However, only the GSP 301-2 NS BID dosing regimen showed statistically significant difference in this endpoint compared to each monotherapy. The GSP 301-1 NS QD dosing regimen failed to show a statistically significant difference when compared to MF-1 NS. Therefore, the dosing regimen for GSP 301-2 NS was further evaluated in two phase 3 efficacy studies (Studies 301 and 304). The total daily dose of OLO and MF in GSP 301-2 NS is the same as the approved total daily dose for each listed drug. Considering GSP 301-2 NS showed numerically better efficacy in the change from baseline in average AM and PM rTNSS, the proposed dosing regimen is acceptable, and the dose and dosing regimen selection for GSP 301 are reasonable.

6.3.2.6. Which formulations and doses are used in the clinical pharmacology studies and efficacy studies?

Phase 1 development (Studies 101 and 102) relied on once-daily dosing of 665 µg OLO and 50 µg MF. However, based on results from the phase 2 dose-ranging study (Study 201, see Section 6.3.2.5), BID dosing of 665 µg OLO and 25 µg MF per spray was selected for the phase 3 efficacy and safety studies. As shown in Table 9, the GSP 301-1 and GSP 301 formulations differ only in the amount of MF per spray.

Table 9. Composition of GSP 301 Nasal Spray

Component and Quality Standard	Function	GSP 301 Nasal Spray			
		665/25 µg/spray[1]		665/50 µg/spray[2]	
		mg/g	%	mg/g	%
Mometasone furoate monohydrate (in-house)	Active				(b) (4)
Olopatadine hydrochloride, USP	Active				
Microcrystalline cellulose (b) (4) (b) (4)	(b) (4)				
Carboxymethylcellulose sodium, USP (b) (4) (b) (4)					
Sodium chloride, USP					
Edetate disodium, USP					
Dibasic sodium phosphate heptahydrate, USP					
Polysorbate 80, NF					
Benzalkonium chloride (b) (4)					
Hydrochloric acid, NF					
Sodium hydroxide, NF					
Water for Injection, USP					
Total[3]					(b) (4)

Abbreviations: USP=United States Pharmacopeia

No bridging study was conducted for the two formulations. However, reviewer's assessment of the population PK analysis found no obvious differences between the formulations with regard to PK parameters such as clearance and absorption rate constant.

6.3.2.7. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

As summarized in Table 10, the Applicant's population PK analysis concluded that age, sex, and race were not significant covariates of population PK of OLO and MF.

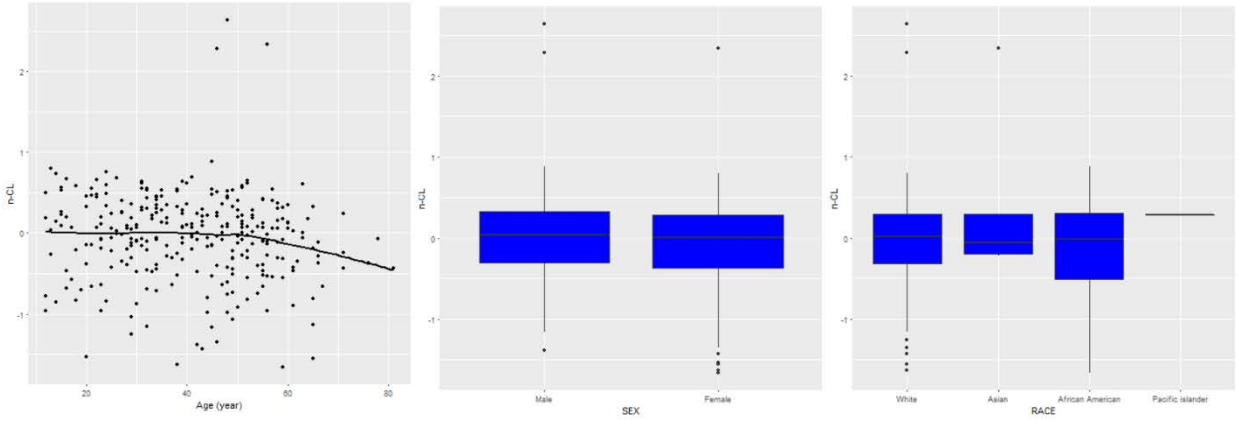
Table 10. Subject Characteristic for Data Used in Population Pharmacokinetic Analysis.

Characteristic	Level	GSP301-101	GSP301-102	GSP301-301
N		29	30	298
Age	Mean (Range)	43.4 (23, 60)	42.6 (21, 63)	39.6 (12, 81)
Sex	Male	18	18	100
	Female	11	12	198
Race	White	22	16	238
	Black or African American	4	5	55
	Asian	3	9	2
	Native Hawaiian or other Pacific Islander	0	0	1
	Other	0	0	2

Source: NDA 211746, Module 5.3.3.5, Table 2 and Table 3 in GSP 301 NS – POPULATION PK Report

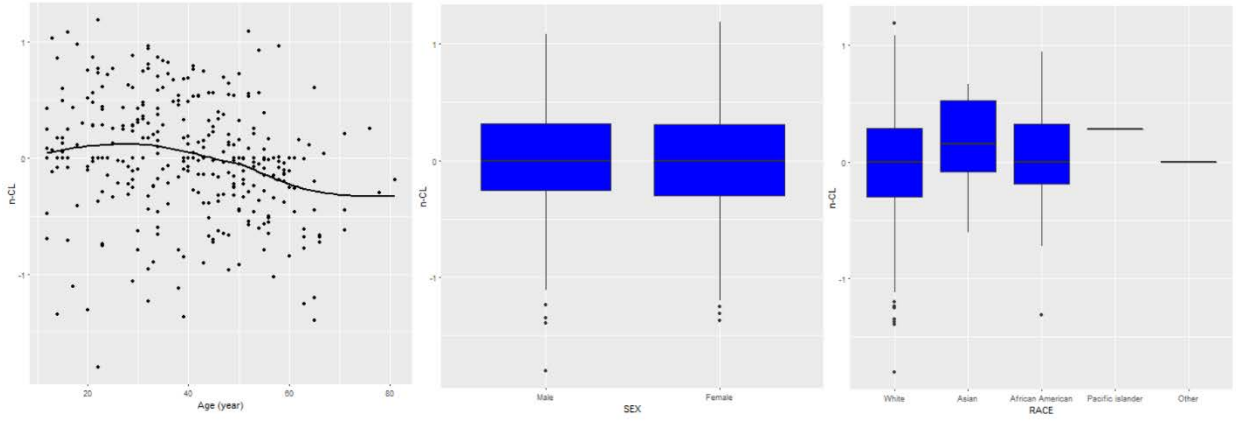
Figure 9 and Figure 10 illustrate that there were no obvious effects of age, sex, and race on clearance of OLO and MF, respectively. This was also the case for other PK parameters.

Figure 9. Effect of Age (Left), Sex (Middle), and Race (Right) on Clearance of Olopatadine



Source: NDA 211746 Module 5.3.3.5, Figure 37, Figure 20, and Figure 19 in GSP 301 NS – POPULATION PK Report

Figure 10 Effect of Age (left), Sex (middle), and Race (right) on Clearance of Mometasone Furoate



Source: NDA 211746 Module 5.3.3.5, Figure 34, Figure 17, and Figure 16 in GSP 301 NS – POPULATION PK Report

After reviewing the Applicant's population PK analysis, the reviewer finds the modeling methods reasonable and the results acceptable.

6.3.2.8. What bioanalytical methods are used to assess concentrations of the measured moieties?

Table 11 lists the moieties measured and validation report numbers for studies submitted to this NDA.

Table 11. List of Analytical Methods

Moiety Measured	Matrix	Method Description	Validation Report
Olopatadine	Human plasma	HPLC-MS/MS	LCMSC 697
Mometasone furoate	Human plasma	HPLC-MS/MS	LCMSD 345.1 version 3

Abbreviations: HPLC-MS/MS=high-performance liquid chromatography with tandem mass spectrometry

6.3.2.9. What are the details of the bioanalytical method and validation parameters for olopatadine?

The bioanalytical method for OLO in human plasma is summarized in Table 12. Based on reported validation parameters, this method is considered adequate for quantitation of OLO.

Table 12. Summary of Bioanalytical Method LCMSC 697 and Its Validation Parameters Used in Clinical Studies 101 and 301

Parameter	Description
Method description	Olopatadine and internal standard (Olopatadine-d6) were extracted from a 50-µL sample aliquot by protein precipitation. The final extract is analyzed via HPLC with MS/MS detection
Instrument	API 4000 mass spectrometer
LLOQ	0.05 ng/mL
Standard curve concentration range	0.05 to 60 ng/mL
Regression model and weighing factor	Linear Y=mX+C ; $1/conc^2$
QC levels	0.05, 0.15, 0.45, 1.80, 7.50, 30.0 and 45.0 ng/mL
Accuracy (% Bias) Intra-run Inter-run	 -9.55% to 2.77% -3.33% to 1.89%
Precision (at LLOQ) Intra-run Inter-run Precision (excluding LLOQ) Intra-run Inter-run	 ≤6.21% ≤7.31% ≤7.23% ≤4.82%
Selectivity	No significant interfering peaks noted in blank plasma samples from 6 lots
Average recovery of drug (%)	72.7%
Dilution factor	1.80 ng/mL diluted two-fold 300 ng/mL diluted ten-fold
Hemolysis	No effect of hemolysis on quantification of olopatadine
Lipemia	No effect of lipemia on quantification of olopatadine
Whole blood stability	2 hours at room temperature and on ice
Freeze thaw stability in matrix	5 freeze-thaw cycles at -20°C and -70°C alone and in the presence of mometasone furoate
Thawed matrix stability	25 hours at room temperature
Long-term stability	• Olopatadine alone: At least 447 days at -20°C & 128 days at -70°C • Olopatadine in presence of mometasone furoate: At least 1106 days at -20°C & -70°C

LLOQ=Lower limit of quantification; QC=quality control

Source: NDA 211746, Module 2.7.1, Table 1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

6.3.2.10. What are the details of the bioanalytical method and validation parameters for mometasone furoate?

The method used for quantitation of MF in human plasma is summarized in Table 13. Based on the validation report, this method is adequate for quantitation of MF.

Table 13. Summary of Bioanalytical Method LCMSC 345.1 and its Validation Parameters Used in Clinical Studies 102 and 301

Parameter	Description
Method description	Mometasone furoate and internal standard (Mometasone furoate-^{13}C, d6) were extracted from 1 mL sample aliquot by liquid-liquid extraction. The final extract was analyzed via HPLC with MS/MS detection.
Instrument	API 5000 mass spectrometer
LLOQ	0.25 pg/mL
Standard curve concentration range	0.25 to 25 pg/mL
Regression model and weighing factor	Linear Y=mX+C; ; 1/conc^2
QC levels	0.25, 0.5, 1.0, 2.5, 6.0, 19.0 pg/mL
Accuracy (% Bias) Intra-run Inter-run	 -11.9% to 7.10% -2.51% to 0.178%
Precision (at LLOQ) Intra-run Inter-run Precision (excluding LLOQ) Intra-run Inter-run	 ≤16.2% ≤16.8% ≤10.7% ≤14.1%
Selectivity	No significant interfering peaks noted in blank plasma samples from 6 lots
Average recovery of drug (%)	89%
Dilution factor	2.50 pg/mL diluted two-fold 80.0 pg/mL diluted 10-fold 300 pg/mL diluted 20-fold
Hemolysis	No effect of hemolysis on quantification of mometasone furoate
Lipemia	No effect of lipemia on quantification of mometasone furoate
While blood stability	1 hour at room temperature and on ice
Freeze thaw stability in matrix	5 freeze-thaw cycles at -70°C and -20°C alone and also in presence of olopatadine.
Thawed matrix stability	22 hours at room temperature
Processed extract stability	At least 525 hours at room temperature
Long-term stability	• Mometasone furoate alone: At least 1050 days at -20°C and 439 days at -70 °C • Mometasone furoate in presence of olopatadine: at least 152 days at -20°C and 128 days at -70°C

LLOQ=Lower limit of quantification; QC=quality control
Source: NDA 211746, Module 2.7.1, Table 2 Summary of Biopharmaceutic Studies and Associated Analytical Methods

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 14. Pivotal Clinical Efficacy and Safety Studies GSP 301

Study ID Study Dates	Design/ Population/ Duration	Treatment Groups[a]	N	Primary Endpoint	No. of Centers/ Countries
GSP 301 Proof-of-concept Jan 2014 – Feb 2014	R, DB, DD, PG Adults with SAR for at least two years 14 days	GSP 301 665/50 µg QD GSP 301 662/25 µg BID DYMISTA 1 spray BID Patanase 2 sprays BID GSP 301 placebo BID	36 36 36 36 36	rTNSS	1 site Ontario
GSP301-201 Dec 2014 – Feb 2015	R, DB, DD, PG, PC, AC Adults with SAR for at least 2 years 14 days	GSP 301 665/50 µg QD GSP 301 665/25 µg BID GM MF 50 µg QD GM MF 25 µg BID GM OLO 665 µg BID GM OLO 665 µg QD GSP 301 placebo BID	158 159 160 159 160 158 159	rTNSS	10 sites U.S.
GSP301-301 Mar 2016 – Jul 2016	R, DB, PG, PC, AC Adults with SAR for at least 2 years 14 days	GSP 301 665/25 µg BID GM OLO 665 µg BID GM MF 25 µg BID GSP 301 placebo BID	302 297 294 287	rTNSS	37 sites U.S.
GSP301-304 Aug 2016 – Jan 2017	R, DB, PG, PC, AC Adults with SAR for at least 2 years 14 days	GSP 301 665/25 µg BID GM OLO 665 µg BID GM MF 25 µg BID GSP301 placebo BID	294 294 294 294	rTNSS	43 sites U.S.
GSP301-303 Apr 2016 – Jul 2017	R, DB, PG, PC Adults with PAR for at least 2 years 52 weeks	GSP 301 665/25 µg BID GSP 301 placebo pH 3.7 GSP 301 placebo pH 7.0	400 100 100	Safety	33 sites U.S.

a. All treatment groups received 2 sprays/nostril
Source: GSP 301 NS CSR Module 5.2 p. 1
Abbreviations: R: randomized; DB: double-blind; AC: active control; PG: parallel group; PC: placebo-controlled; DD: double dummy; SAR: seasonal allergic rhinitis; PAR: perennial allergic rhinitis; QD: once daily; BID: twice daily; GSP 301: olopatadine/mometasone fixed dose combination nasal spray; GM: Glenmark; OLO: olopatadine; MF: mometasone furoate, POC: proof-of concept; rTNSS: reflective Total Nasal Symptom Score

7.2. Review Strategy

Five clinical studies to support the efficacy/safety of GSP 301 were included in this NDA submission as shown in the table above.

The clinical development program for GSP 301 was comprised of three, 2-week efficacy and safety trials (GSP 301-201, GSP 301-301, GSP 301-304) in adults with SAR, and a year-long safety trial (GSP 301-303) in adults with PAR. In addition, two phase 1 PK trials were conducted (GSP 301-101 and GSP 301-102). The Applicant proposed that phase 2 study, GSP 301-201, established GSP 301 BID as the optimally safe and efficacious dose and regimen, and that the efficacy of this regimen was confirmed in the phase 3 studies, GSP 301-301 and GSP 301-304.

With regards to the organization of this review, Section 8.1 includes a discussion of the design employed in the three 2-week efficacy and safety trials and the year-long safety trial.

The pivotal studies to support efficacy were: GSP 301-201, GSP 301-301, and GSP 301-304) studies providing key data to support the efficacy/safety of GSP 301 BID in patients aged 12 years and older with SAR. The efficacy review is located in Section 8.1 by individual study. The review of efficacy focused first on the analysis of the primary endpoint, the change from baseline in average AM and PM rTNSS over the entire 14-day treatment period, using data from the three relevant 2-week efficacy and safety trials (201, 301, and 304). Also reviewed were secondary endpoints such as the instantaneous Total Nasal Symptom Score (iTNSS), onset of action, Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), and reflective Total Ocular Symptom Score (rTOSS).

Data from these studies were also integrated to demonstrate robust efficacy from a larger group of subjects. The efficacy review focused on individual studies, with some comparisons to integrated analysis where there was evidence of lack of power in the individual studies.

The review of safety was based primarily upon results from the three 2-week efficacy and safety trials (studies 201, 301, and 304), the GSP 301 BID group of the proof of concept (POC) study, and the year-long safety trial (study 303). Pooling across studies 201, 301, 304, and the GSP 301 BID group of the POC study to examine the emergence of any safety signals was deemed acceptable as these trials were similar in design. The safety population included all randomized subjects who received at least one dose of study treatment. This safety population was the primary safety analysis population. Safety analyses and discussion are provided in Section 8.2.

Data Sources

The Applicant submitted clinical trial tabulation and analysis datasets conforming to the Study Data Tabulation Model and Analysis Data Model data standards, respectively, to the CDER electronic document room in SAS transport format. Clinical trial protocols, reporting and analysis plans, clinical study reports, correspondence, and datasets were accessed under the electronic document room link : \\CDSESUB1\evsprod\NDA211746\211746.enx

Data and Analysis Quality

The electronic submission was appropriately indexed and complete to allow for review. The NDA included complete study reports, appropriate case report forms, and proposed labeling changes. There were no issues with the submission quality or data integrity.

The studies were conducted in accordance with good clinical practice as required by the International Council on Harmonization guidelines and in accordance with country-specific laws and regulations governing clinical studies of investigational products (IPs) and data protection. Compliance with these requirements also constitute conformity with the ethical principles of the Declaration of Helsinki:

- The protection of human subjects (21 CFR part 50)
- Institutional review boards (21 CFR part 56)
- The obligation of clinical investigators

The application states that none of the clinical investigators disclosed a proprietary interest in the proposed product or significant equity related to the Applicant.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study GSP 301-301

- Study dates: March 18, 2016–July 22, 2016
- Study sites: 37 U.S. sites
- Study report date: October 26, 2017

Objectives

Primary

- To compare the efficacy of GSP 301 with placebo and individual constituent monotherapies at the same dose in the same vehicle as well as the efficacy of these individual constituent monotherapies versus placebo over 14 days of study treatment

Secondary

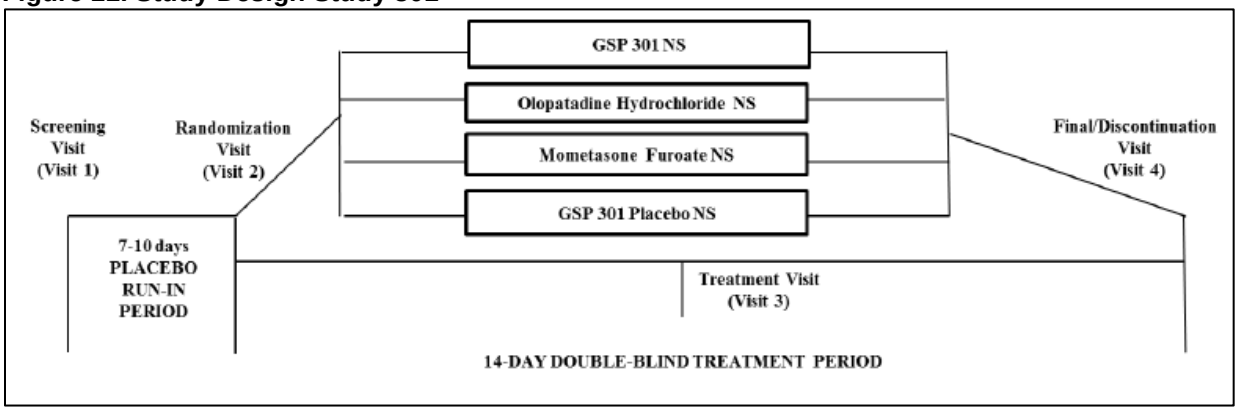
- To assess the safety and tolerability of each treatment
- To investigate the PK of MF and OLO

Trial Design

Study 301 was a phase 3, randomized, double-blind study to establish the safety and efficacy of GSP 301 NS compared with placebo and monotherapy formulations. The study enrolled adult and adolescent patients with clinically evident symptoms of SAR during the spring allergy season. There were two study periods: a placebo run-in period of 7 to 10 days, and a treatment period of 14 days. Only those patients who completed the single-blind placebo run-in period and met randomization criteria were randomized to treatment.

A total of 1,696 subjects were screened and 1,180 were randomized 1:1:1:1 to four treatment groups as shown in Figure 11.

Figure 11. Study Design Study 301



Source: Clinical Study Report 301-301, Figure 1

The schedule of assessments and procedures (Table 15) is shown below:

Table 15. Schedule of Procedures and Assessments

Activity/Observation	Screening Visit (Visit 1)	Randomization Visit (Visit 2)	Treatment Visit (Visit 3)	Final Visit (Visit 4)
	Day -7 to -10	Day 1	Day 8±2[a]	Day 15+2[a]
Written informed consent (assent, if applicable) and HIPAA authorization	X			
Inclusion/exclusion criteria review	X			
Demographic data	X			
Medical and treatment history	X			
Concomitant medication evaluation	X	X	X	X
Physical examination	X			X
Vital signs	X	X	X	X
Height and weight measurements	X			X
Laboratory assessments (hematology biochemistry and urine analysis)	X			X
Focused ENT examination	X	X	X	X
Allergy testing (skin prick test for relevant allergen, if required)	X			
12-lead ECG	X			X
Urine pregnancy test (if applicable)	X	X		X
Review instructions and train on proper use of nasal spray using the GSP301 placebo NS device	X			
Review instructions and train on proper use of nasal spray		X	X	
Prime and dispensation and administration of single-blind placebo nasal spray at the clinic	X			
Distribution of symptom assessment diary	X	X	X	
Collection/review of symptom assessment subject diary		X	X	X
Subject assessment of AR symptoms and recording at the clinical site	X			
Subject assessment of AR symptoms and recording	X	———	———	———
Physician assessment of nasal symptom severity		X		X
Review randomization criteria		X		
Randomization/treatment Assignment		X		
Prime and dispensing of double-blind study medication		X		
Administration of first dose of double-blind study medication		X		
Onset of action efficacy Assessment		X		
Administration of double-blind study medication			X	

Activity/Observation	Screening Visit (Visit 1)	Randomization Visit (Visit 2)	Treatment Visit (Visit 3)	Final Visit (Visit 4)
Sparse-PK sampling and assessments[a]			X	X
Rich-PK sampling and assessments[a]		X	X	
Distribution of RQLQ, review instructions with the subject and subject completion of RQLQ		X		X
Rhinitis Control Assessment Test		X		X
Adverse event monitoring	X	X	X	X
Return of study medication		X		X
Return of subject diary				X
Subject compliance check (study procedures, diary and study medication)		X	X	X
Concomitant medication evaluation	X	X	X	X

Source: Study GSP 301-304 CSR Table 4 page 27
a: Rich-PK sampling was only done for subjects aged ≥18 years who had consented for the rich-PK procedures at a few selected clinical sites (PK sites). Blood samples for the rich-PK group (approximately 25 subjects per each active treatment group and approximately 10 subjects in the placebo group) was collected on Days 1 (Visit 2) and 8 (Visit 3) at predose (before the AM dose) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 (before the PM dose) hours after the morning dose. For day 8, the predose sample was collected as part of sparse PK sampling. The sampling times were calculated from the end of the second spray into the second nostril. For sparse-PK sampling, blood samples were collected at predose (before the morning dose) on Day 8 (Visit 3) and Day 15 (Visit 4) from all randomized subjects at all study sites.
Abbreviations: AR = allergic rhinitis; ECG = Electrocardiogram; ENT = Ear, Nose and Throat; HIPPA = Health Insurance Portability and Accountability Act; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire.

Investigators from 37 study sites in the United States participated in this study. The first subject was recruited on March 18, 2016, and the last subject completed the last visit on July 22, 2016.

For inclusion into the study, subjects were required to fulfill all the following criteria:

1. Males and nonpregnant females aged ≥12 years.
2. Signed informed consent/assent form (subject and/or parent/caregiver/legal guardian) that met all criteria of the current U.S. FDA/local regulations.
3. Documented clinical history of SAR (for at least 2 years preceding the screening visit (visit 1)) with exacerbations (clinical evidence of active symptoms) for the relevant seasonal allergen during the spring allergy season (tree/grass pollen) and exhibiting a documented positive skin prick test (wheal diameter at least 5 mm greater than negative diluent control wheal) to spring allergens. Documentation of a positive result within 12 months prior to the screening visit (visit 1) was acceptable.
4. A 12-hour rTNSS ≥8 out of a possible 12 and a congestion score ≥2 for the morning (AM) assessment at the screening visit (visit 1).
5. General good health and free of any disease or concomitant treatment that could interfere with the interpretation of study results as determined by the investigator.
6. Subjects must have been able to demonstrate the correct NS application technique at the screening visit (visit 1).

7. Subjects must have been willing and able to comply with all aspects of the protocol.

Any of the following was regarded as a criterion for exclusion from the study:

1. Had a positive pregnancy test or established pregnancy, breast-feeding or planned to become pregnant during the study.
2. Female subjects of child-bearing potential (as judged by the investigator) who did not agree to remain abstinent or use medically acceptable methods of contraception (e.g., implants, injectables, combined oral contraceptives, intrauterine devices, double barrier protection) during the study. Male participants who did not agree to use a condom with spermicide during intercourse (if not surgically sterilized) during the study.
3. Plans to travel outside the known pollen area for the investigational site for 24 hours or longer during the last 7 days of the run-in period.
4. Plans to travel outside the known pollen area for the investigational site for two or more consecutive days OR three or more days in total between the randomization visit (visit 2) and the final visit (visit 4).
5. History of significant atopic dermatitis or rhinitis medicamentosa (within 60 days prior to the screening visit (visit 1)).
6. Treatment with any known potent CYP3A4 inducers (carbamazepine, dexamethasone, phenytoin, rifabutin, rifampin, pioglitazone, etc.) or potent inhibitors (e.g., azole antifungals, macrolide antibiotics) within 30 days prior to or during the study.
7. Non-vaccinated exposure to or active infection with chickenpox or measles within the 21 days preceding the screening visit (visit 1).
8. Known hypersensitivity to any corticosteroids or antihistamines or to the study drug or its excipients.
9. History of anaphylaxis and/or other severe local reaction(s) to skin testing.
10. History of alcohol or drug dependence within 2 years preceding the screening visit (visit 1).
11. History of a positive test for human immunodeficiency virus, Hepatitis B, or Hepatitis C infection.
12. Evidence of acute or significant chronic sinusitis or chronic purulent postnasal drip.
13. Any of the following conditions (including but not limited to the following) that were judged by the investigator to be clinically significant and/or to affect the subject's ability to participate in this study:
    - Impaired hepatic function including alcohol-related liver disease or cirrhosis
    - Any systemic infection

- Hematological, hepatic, renal, endocrine disorder (except for postmenopausal symptoms or hypothyroidism)
- Gastrointestinal disease
- Malignancy (excluding basal cell carcinoma)
- Current neuropsychological condition with or without drug therapy
- Cardiovascular disease (e.g., uncontrolled hypertension)
- Respiratory disease other than mild asthma

14. Any major surgery (as assessed by investigator) within 4 weeks of the screening visit (visit 1).
15. Requirement for the chronic use of tricyclic antidepressants.
16. Dependence (in the opinion of the investigator) on nasal, oral, or ocular decongestants, nasal topical antihistamines, or nasal steroids.
17. Active pulmonary disorder or infection (including but not limited to bronchitis, pneumonia, or influenza) or upper respiratory tract or sinus infection within the 14 days prior to the screening visit (visit 1) or the development of respiratory infections during the run-in period. Subjects with mild asthma were allowable on the condition that treatment was limited to inhaled short-acting beta-agonists only (up to eight puffs per day).
18. Use of antibiotic therapy for acute conditions within 14 days prior to the screening visit (visit 1). Low doses of antibiotics taken for prophylaxis were allowed if the therapy was started prior to the screening visit (visit 1) and was expected to continue at the same stable dose throughout the clinical study duration.
19. Had posterior subcapsular cataracts or glaucoma, or any other ocular disturbances, or other listed related conditions including:
    - History of increased intraocular pressure
    - History of retinal detachment or surgery
    - History of incisional eye surgery (other than cataract extraction or laser-assisted in situ keratomileusis)

Concomitant medication exclusions are shown in Table 16.

Table 16. Concomitant Medication Exclusions

Type of Medication	Days Prohibited Prior to the Screening Visit
Vasoconstrictors (e.g., epinephrine, sumatriptan).	3 days
Major tranquilizers (e.g., antipsychotics such as chlorpromazine, haloperidol, risperidone, clonazepam)	3 days
Short-acting antihistamines (oral, ocular or intranasal antihistaminic, (e.g., azelastine))	5 days
OTC cough and cold preparations or sleep aids containing antihistamines	7 days
Topical/oral/nasal decongestants (e.g., oxymetazoline, pseudoephedrine, tetrahydrozoline)	7 days
OTC food supplement/diet to reduce leukotrienes (Airozin)	7 days
Leukotriene antagonists or arachidonate 5-lipoxygenase Inhibitors	7 days
Inhaled/oral/intranasal anticholinergics	7 days
Long-acting antihistamines (e.g., cetirizine, fexofenadine)	10 days
Cromolyn (all forms), nedocromil or lodoxamide (intranasal, ocular, or oral)	14 days
Systemic antibiotics	14 days
Ocular mast cell stabilizers	14 days
Monoamine oxidase inhibitors	14 days
Tricyclic antidepressants	14 days
All intranasal/topical/ocular corticosteroids (except study medication)	30 days
Inhaled corticosteroids	30 days
Any other investigational nonbiological drug	30 days
Treatment with any known potent CYP3A4 inducers (carbamazepine, dexamethasone, phenytoin, rifabutin, rifampin, pioglitazone, etc.)	30 days
Treatment with any known potent CYP3A4 inhibitors (azole antifungals, macrolide antibiotics, etc.)	30 days
Systemic corticosteroids (intermittent or chronic including intra-articular)	60 days
Immunotherapy injections and immunosuppressive/immune-modulator medications (except topical pimecrolimus cream or tacrolimus ointment if initiated at least 30 days prior to screening and maintained on stable dose)	60 days
IgE antagonist or any other anti IgE therapy	120 days
Any other investigational biological drug	120 days
Anti-interleukin-5 therapy (reslizumab, mepolizumab, etc.)	120 days
Sublingual immunotherapy (investigational or other)	180 days

Abbreviations: OTC=over-the-counter

Study Endpoints

Primary and Secondary Efficacy Endpoints

Total Nasal Symptom Score (TNSS)

The primary efficacy endpoint Study 301-301 was the subject-reported TNSS. TNSS was defined as the sum of the subject-reported symptom scores for four nasal symptoms: rhinorrhea (runny

nose), nasal congestion, nasal itching, and sneezing. The subject assessed and reported his/her nasal symptoms twice (AM and PM assessments) on each day of placebo run-in and double-blind treatment periods prior to administering the study treatment. Subjects recorded the symptom scores on a paper AR assessment diary. The AM assessment was to be performed prior to bathing, consumption of food or beverages, or strenuous activities. The PM assessment was to be performed approximately 12 hours after the AM assessment. Study medication was administered immediately after completion of the AR assessment diary.

The subject was asked to assess both rTNSS (i.e., an evaluation of symptom severity over the past 12 hours prior to the recording of the score) and iTNSS (i.e., an evaluation of the symptom severity just before taking study medication (within 10 minutes)) nasal symptoms.

The primary efficacy analysis is based on the results of the rTNSS.

Each of the symptoms (rhinorrhea, nasal congestion, nasal itching, and sneezing) were rated on a four-point severity scale as follows:

- 0 = Absent (no sign/symptom evident)
- 1 = Mild (sign/symptom clearly present, but minimal awareness; easily tolerated)
- 2 = Moderate (definite awareness of sign/symptom that is bothersome but tolerable)
- 3 = Severe (sign/symptom that is hard to tolerate (i.e., caused interference with activities of daily living and/or sleeping))

Total Ocular Symptom Score (TOSS)
TOSS was calculated using three ocular symptoms (itching/burning, tearing/watering, and redness) on a scale of 0 to 3. The grading scale for itchy eyes and watery eyes is the same as that for the TNSS. The grading scale for eye redness is as follows:

- 0 = None (no redness present)
- 1 = Mild (slightly dilated blood vessels and pinkish color compared to subject's normal color)
- 2 = Moderate (more dilation of blood vessels and red color compared to subject's normal color)
- 3 = Severe (large, numerous dilated blood vessels and deep red color compared to subject's normal color)

Onset of Action

The onset of action was assessed and based on the iTNSS score taken at the clinic following the first dose of study drug administration at the randomization visit (visit 2) for 4 hours. The iTNSS was measured at the following time points: predose, 15±3 minutes, 30±3 minutes, 45±3 minutes, 60±5 minutes, 90±5 minutes, 120±10 minutes, 150±10 minutes, 180±10 minutes,

210±10 minutes, and 240±10 minutes after the first study treatment.

Rhinoconjunctivitis Quality-of-Life Questionnaire - Standardized Activities

The Rhinoconjunctivitis Quality-of-Life Questionnaire - Standardized Activities (RQLQ(S)) is a disease-specific, validated, QOL questionnaire developed to measure the functional problems (physical, emotional, and social) troublesome to adults and adolescents (aged ≥12 years) with allergies. The RQLQ(S) measures both atopic and non-atopic experiences because of subjects' nasal and ocular symptoms.

The RQLQ(S) has 28 questions in 7 domains (activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional). Subjects were asked to recall their experiences during the previous week and to give their responses on a 7-point scale (0=not troubled to 6=extremely troubled) for the domains of activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, and eye symptoms. The domain "emotional" utilized a seven-point scale (0=none of the time to 6=all of the time). When required at a particular visit, this questionnaire was completed as the first activity of the visit.

The self-administered version of the RQLQ(S) was completed by the subjects at the investigational site at the randomization visit (visit 2) and the final visit/discontinuation visit (visit 4). The RQLQ(S) administration was to be the first procedure conducted at these study visits.

Safety Assessments

Monitored safety parameters included the following:

- Spontaneous and elicited AEs, SAEs, discontinuations due to AEs
- Focused ENT examination
- Physical examination
- Clinical laboratory evaluation
- Vital signs
- ECG
- Urine pregnancy testing

Statistical Analysis Plan

The statistical analysis plan (SAP) for this study was signed off on August 10, 2016. The Applicant stated the SAP was approved prior to database lock and unblinding of the study. The database was locked and approved on August 29, 2016.

Populations used in the analyses included safety analysis set (SAS), full analysis set (FAS), per protocol set (PPS), and RQLQ(S) analysis set. The Applicant defined these as follows:

The SAS consisted of all subjects who took at least one dose of study medication following randomization and was used for all safety analyses.

The FAS consisted of all subjects who were randomized and received at least one dose of IP and had at least one postbaseline primary efficacy assessment. This was the primary analysis set for efficacy analyses.

The PPS consisted of the subset of the FAS who did not meet criteria for PPS exclusion. These criteria were to capture relevant nonadherence to the protocol (especially those that affected interpretation of the primary endpoint). The PPS was a secondary analysis set for the primary efficacy endpoint and selected secondary endpoints.

The RQLQ(S) analysis set consisted of all English-speaking subjects ≥18 years old with impaired QOL at baseline as defined by RQLQ(S) score at the Randomization Visit (Visit 2; baseline) of 3.0 or greater. This analysis set was defined, but the FAS was used to analyze RQLQ. We note the inconsistency of defining a population specific to the analysis of RQLQ and use of FAS population. The Applicant's use of FAS population for this analysis was reasonable.

The primary endpoint was the change from baseline in average AM and PM rTNSS during the 14-day treatment period. The change from baseline was analyzed using a mixed-effects models for repeated measures (MMRM). The model included study treatment, site, baseline 12-hour rTNSS and study day as the within-subject effect, with the assumption that any missing data is missing at random.[11]

Sensitivity analysis of the primary endpoint assuming data is missing not at random (MNAR) was performed to assess the impact of missing data with a tipping point analysis.[12]

The interactions of site-by-treatment and baseline-by-treatment were investigated separately using two independent models and were only included in the final model if they were statistically significant at the 5% alpha level. To determine the interaction(s) to be included in the final model, the main-effects model containing study treatment, site, baseline 12-hour rTNSS, and study day were fitted first with an unstructured covariance. If the model did not converge using the unstructured covariance structure, the autoregressive (order 1) structure was used. If the autoregressive (order 1) structure also did not converge, other covariance structures deemed appropriate to fit the data were used. Two independent models were fitted using the covariance structure of the model that converged in step 1: one model containing the

[11] If an AM or PM measurement was missing, then the non-missing AM or PM measurement was used as the mean response for that day. If both the AM and PM measurements were missing, then the mean response for that day was set to missing.

[12] This approach assesses the possibility that subjects on active drug with missing values have worse outcomes than subjects on placebo in which you search for the tipping point that reverses the study conclusion.

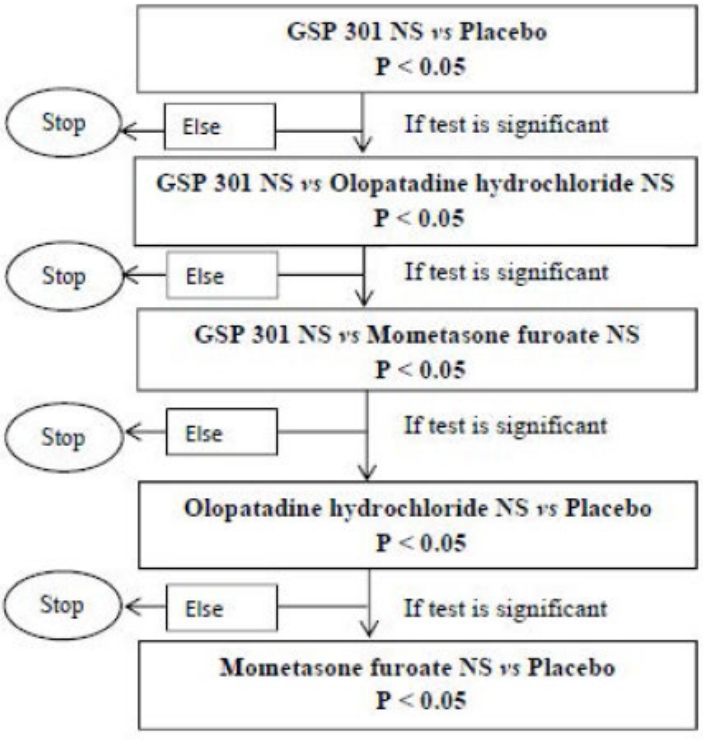
site-by-treatment interaction and the other model containing the baseline-by-treatment interaction. If the interaction term was significant, it was included in the final model.

The same methodology and handling of missing data were applied to secondary endpoints change from baseline in average AM and PM 12-hour iTNSS and rTOSS and tertiary endpoints change from baseline in average AM and PM iTOSS, and iTNSS. If either baseline or postbaseline results were missing, change from baseline and percent change were also set to missing.

Significance testing for rTNSS was performed to assess the superiority of GSP 301 over placebo NS and its constituent monotherapies as well as that of the constituent monotherapies over placebo. Demonstration of superiority for this treatment comparison will be based on a hypothesis testing approach, whereby the null hypothesis states that there is no difference between treatment groups and the alternative hypothesis states that there is a difference between the treatment groups. A two-sided 5% risk associated with incorrectly rejecting the null hypothesis (significance level) was noted for this study.

To adjust for multiplicity, the treatment comparisons for the primary endpoint were made using a gate-keeping strategy, as shown in Figure 12.

Figure 12. Gatekeeping Strategy for Primary Endpoint Analysis



Source: Clinical Study Report 301-301, Figure 2
Abbreviations: NS=nasal spray

This gate-keeping strategy was also used for the secondary endpoints iTNSS and rTOSS. However, there was no strategy in place to evaluate rTNSS, iTNSS, and rTOSS with respect to each other in a multiplicity adjustment plan, which was a fundamental aspect of multiplicity adjustment and maintaining the overall type 1 error to 0.05 for the study as a whole.

No description was provided by the Applicant for handling of missing data for this study.[13]

Subgroup analyses by age group (12–17, 18–64, 65 and above), sex, race and ethnicity were conducted for rTNSS, iTNSS, and rTOSS.

The Applicant's focus in their submission was on the pooled analysis of studies 201, 301, and 304, with a proposed label describing the results of study 304 only. This is discussed in Section 8.1.4.

Protocol Amendments

Version 1.0 of this study protocol was put on hold on December 22, 2016, postponing the start of the study. The postponement occurred after the shipping of the IP to the sites and prior to subject consent and screening. When the Applicant became aware of a manufacturing oversight, it was determined that this study would be postponed until all IP could be replaced.

The protocol was amended (Version 2.0, Amendment 1) during this time, but this version was never submitted to the institutional review board because it was apparent that the mountain cedar allergen would be missed, and the protocol would require another more extensive amendment targeting seasonal allergies. There was no value in submitting this version since both targeted the mountain cedar allergen.

Because all patients were enrolled under the same and final version, no amendments are noted here.

8.1.2. Study Results

Compliance with Good Clinical Practices

The submission included complete study reports of the clinical trials, proposed labeling, and appropriate case report forms. The clinical section was appropriately indexed and organized to allow review. The submission included raw datasets for the major clinical trials. The application stated that none of the clinical investigators disclosed a proprietary interest in the proposed product or significant equity.

[13] There was a description of missing data handling included in study 201 CSR

The application includes a statement of good clinical practice, indicating that all clinical trials were conducted under the supervision of an institutional review board and with adequate informed consent procedures.

Patient Disposition

A summary of study populations is presented in Table 17.

Table 17. Study Populations

Subjects	GSP 301 placebo NS (N=287) n (%)	GSP 301 NS (N=302) n (%)	Olopatadine HCl NS (N=297) n (%)	Mometasone furoate NS (N=294) n (%)	Overall (N=1180) n (%)
Randomized	287 (100.0)	302 (100.0)	297 (100.0)	294 (100.0)	1180 (100.0)
Safety analysis set	287 (100.0)	302 (100.0)	297 (100.0)	294 (100.0)	1180 (100.0)
Did not take any study medication	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Full analysis set	283 (98.6)	299 (99.0)	294 (99.0)	294 (100.0)	1170 (99.2)
Did not have at least one post-baseline primary efficacy assessment	4 (1.4)	3 (1.0)	3 (1.0)	0 (0.0)	10 (0.8)
Per protocol set	278 (96.9)	292 (96.7)	288 (97.0)	287 (97.6)	1145 (97.0)
Subjects with Major protocol violation	5 (1.7)	7 (2.3)	6 (2.0)	7 (2.4)	25 (2.1)
RQLQ(S) analysis set	202 (70.4)	231 (76.5)	218 (73.4)	201 (68.4)	852 (72.2)

These are the populations as defined by the Applicant.
Source: Study GSP 301-301 Clinical Study Report, Table 10; checked against ADSL dataset.
Abbreviations: NS=nasal spray; HCl=hydrochloride; RQLQ(S)=Rhinoconjunctivitis Quality of Life Questionnaire (Standardized Activities)

Patient disposition is presented Table 18.

Table 18. Summary of Subject Disposition (Safety Analysis Set)

Disposition	GSP 301 Placebo N=287 n (%)	GSP 301 N=302 n (%)	Olopatadine N=297 n (%)	Mometasone N=294 n (%)
Randomized	287 (100.0)	302 (100.0)	297 (100.0)	294 (100.0)
Terminated early	11 (3.8)	13 (4.3)	19 (6.4)	11 (3.7)
Completed study	276 (96.2)	289 (95.7)	278 (93.6)	283 (96.3)
Early termination reason				
Adverse event	0	1 (0.3)	2 (0.7)	4 (1.4)
Lack of efficacy	0	0	0	1 (0.3)
Lost to follow up	3 (1.0)	1 (0.3)	2 (0.7)	0
Non-compliance with study drug	0	1 (0.3)	0	0
Non-compliance with study procedure	1 (0.3)	0	0	1 (0.3)
Protocol deviation	0	3 (1.0)	6 (2.0)	3 (1.0)
Withdrawal by subject	5 (1.7)	2 (0.7)	2 (0.7)	0
Other	2 (0.7)	5 (1.7)	7 (2.4)	2 (0.7)

Source: Study GSP 301-301 Table 14.1.9.1

Protocol Violations/Deviations

During the randomized treatment period, protocol deviations occurred in a small number (ranging from 44 (15.3%) to 51 (17.3%)) of subjects per group across all treatment groups. The most commonly reported deviation was “outside visit window” and were similar across all treatment arms. The most common deviations are listed in Table 19.

Table 19. Protocol Violations/Deviations (Safety Analysis Set)

Violation/Deviation	GSP 301 Placebo N=287 n (%)	GSP 301 N=302 n (%)	Olopatadine N=297 n (%)	Mometasone N=294 n (%)
Subjects with protocol deviations	44 (15.3)	48 (15.9)	48 (16.2)	51 (17.3)
Total deviations	57	62	60	65
Restricted medication	2	1	2	0
Lost to follow-up	3	1	2	0
Randomized in error	2	4	2	2
Noncompliance with study drug	1	2	0	0
Noncompliance with study procedure	5	4	5	5
Outside visit window	12	17	19	19
Procedure not completed per protocol	5	6	5	9
Dosing noncompliance	7	12	6	4
Dosed prior to blood collection	8	7	7	11
Other	12	8	12	15

Source: Study GSP 301-301 CSR Table 14.1.9.2.1

Table of Demographic Characteristics

The demographic and baseline characteristics were generally well balanced across treatment arms. As presented in Table 20, subjects were predominantly female, white and not Hispanic or Latino.

Table 20. Summary of Demographic Data (Full Analysis Set)

Demographics	GSP 301 Placebo N=283	GSP 301 N=299	Olopatadine N=294	Mometasone N=294
Age (years)				
Mean (SD)	39.4 (14.9)	39.6 (15.4)	39.7 (14.9)	38.7 (16.3)
Median	41.0	40.0	40.0	38.0
Min, max	12, 83	12, 81	12, 87	12, 84
Sex, n (%)				
Male	103 (36.4)	100 (33.4)	114 (38.8)	96 (32.7)
Female	180 (63.6)	199 (66.6)	180 (61.2)	198 (67.3)
Race, n (%)				
American Indian or Alaska Native	0	0	2 (0.7)	1 (0.3)
Asian	7 (2.5)	2 (0.7)	3 (1.0)	3 (1.0)
White	228 (80.6)	239 (79.9)	217 (73.8)	224 (76.2)
Black/African American	47 (16.6)	54 (18.4)	66 (22.4)	59 (20.1)
Native Hawaiian or Pacific Islander	1 (0.4)	1 (0.3)	2 (0.7)	0
Other	0	2 (0.7)	3 (1.0)	8 (0.7)
Ethnicity, n (%)				
Hispanic or Latino	65 (23.0)	70 (23.4)	68 (23.1)	73 (24.8)
Not Hispanic or Latino	218 (77.0)	229 (76.6)	226 (76.9)	221 (75.2)

Source: Study 301-301 CSR Table 14.1.9.4.2
Abbreviations: SD=standard deviation

Efficacy Results – Primary Endpoint

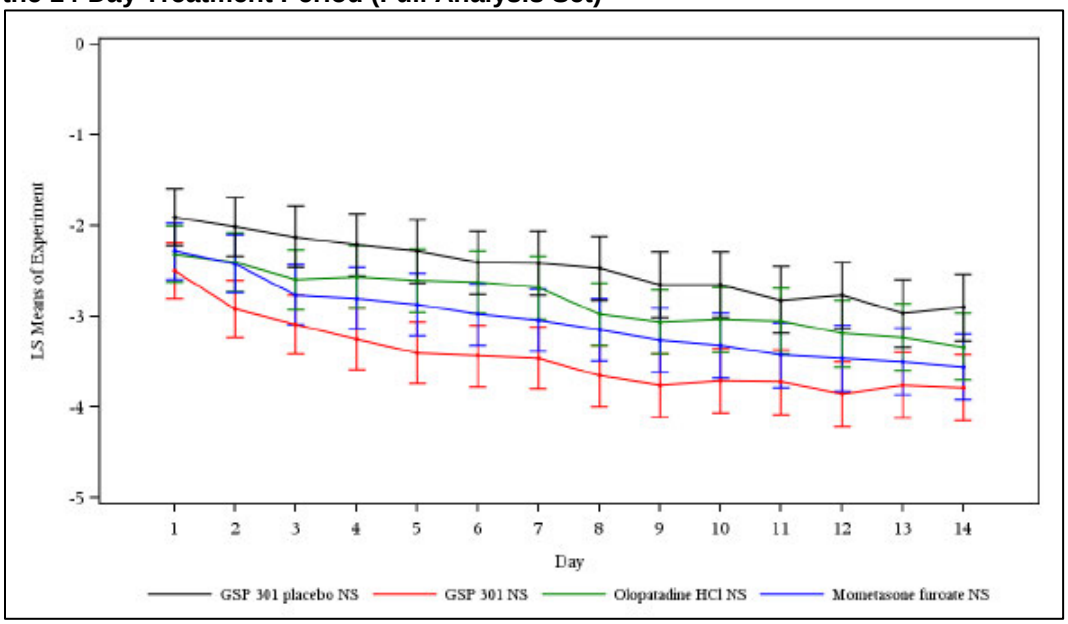
In an MMRM analysis based on the FAS population for rTNSS adjusted for investigational site and patients' baseline values, GSP 301 showed statistically significantly greater improvements in reflective total symptom scores than placebo during the 14-day treatment period (least square (LS) mean difference: -0.78) (Table 21). Point estimates for the GSP 301 combination versus single components were -0.37 and -0.30 for OLO and MF, respectively, with the former being statistically significant and the latter being marginally insignificant. The mean differences for single components versus placebo were 0.41 and 0.48-unit reductions for OLO and MF, respectively. The statistical reviewer's analysis did not match the results of the Applicant, which assumed compound symmetry covariance structure, whereas the reviewer assumed unstructured covariance. In Section 0, a similar model using unstructured variance was used across pooled studies, a more reasonable and conservative option for this analysis.

Table 21. Results of Primary Efficacy Analysis, Repeated Measures on AM and PM rTNSS Over 14-Day Treatment (Full Analysis Set)

Treatment Group (Trt 1 vs. Trt 2)	N (Trt 1 vs. Trt 2)	Least Square Mean Difference	Standard Error	95% CI	P-Value
GSP 301 NS vs. placebo	299, 283	-0.78	0.19	-1.15, -0.40	<0.001*
GSP 301 NS vs. olopatadine HCl	299, 294	-0.37	0.19	-0.74, 0.01	0.054[ns]
GSP 301 NS vs. mometasone furoate	299, 294	-0.30	0.20	-0.67, 0.01	0.116[ns]
Olopatadine HCl vs. placebo	294, 283	-0.41	0.19	-0.86, -0.10	0.013[ns]
Mometasone furoate vs. placebo	294, 283	-0.48	0.21	-1.00, -0.19	0.004[ns]

Source: Statistical reviewer
Note: Our results matched Applicant's GSP 301-301 Clinical Study Report, Table 13, except unstructured covariance matrix was assumed in our model, instead of applicant's choice of compound symmetry.
* Statistically significant, using Applicant's gatekeeping multiplicity plan
[ns] Not statistically significant, using Applicant's gatekeeping multiplicity plan
Abbreviations: NS=nasal spray; HCl=hydrochloride; CI=confidence interval; Trt=treatment; rTNSS=reflective total nasal symptom score

Figure 13. Least Square Means With 95% Confidence Intervals of Average AM and PM rTNSS Over the 14-Day Treatment Period (Full Analysis Set)



Source: GSP 301-301 Clinical Study Report, Figure F15.1.13
Least square means and 95% confidence intervals for each of the four treatments over time are displayed. Statistical Analysis model: MMRM model with change from baseline as the dependent variable and treatment group and site as fixed effects, baseline score as covariate and study day as the within-subject effect.
Abbreviations: rTNSS=reflective total nasal symptom score; NS=nasal spray; HCl=hydrochloride

The Applicant analyzed the same data using ANCOVA with study completers and got results similar to those obtained via MMRM. Our re-analysis of ANCOVA using the modelling information provided in the SAP, study report, and data definitions yielded the results in Table 22.

Table 22. Results of Supplementary Efficacy Analysis, ANCOVA on AM and PM rTNSS Over 14-Day Treatment (Full Analysis Set)

Treatment Group (Trt 1 vs. Trt 2)	N (Trt 1 vs. Trt 2)	Least Square Mean Difference	Standard Error	95% CI	P-Value
GSP 301 NS vs. placebo	299, 283	-0.89	0.25	-1.37, -0.40	<0.001*
GSP 301 NS vs. olopatadine HCl	299, 294	-0.44	0.24	-0.92, 0.04	0.074[ns]
GSP 301 NS vs. mometasone furoate	299, 294	-0.25	0.24	-0.72, 0.23	0.315[ns]
Olopatadine HCl vs. placebo	294, 283	-0.45	0.25	-0.93, 0.04	0.070[ns]
Mometasone furoate vs. placebo	294, 283	-0.64	0.215	-1.13, -0.15	0.010[ns]

Source: Statistical reviewer.
Note: Results *do not match* Applicant's GSP 301-301 Clinical Study Report, Table T14.1.9.5.5
* Statistically significant, using Applicant's gatekeeping multiplicity plan
[ns] Not statistically significant, using Applicant's gatekeeping multiplicity plan
Abbreviations: NS=nasal spray; ANCOVA=analysis of covariance; rTNSS=reflective total nasal symptom score; Trt=treatment; CI=confidence interval

The Applicant's exploration on the effects of missing data included additional analyses on the primary endpoint using J2R and tipping point analyses. Out of the 1,180 patients randomized to the study, 3.7% to 6.4% terminated early, with the MF arm having the lowest termination rate and OLO the highest (Table 18).[14] According to the Applicant, the J2R analysis could not be performed due to statistical model convergence issues, so results are not available. The tipping point analysis completed by the Applicant shifted the results by 12 units on either side of the point estimate from GSP 301 group (Table 23). All p-values remained highly statistically significant within a clinically plausible range of a shift there is no tipping point, indicating that the data is highly robust.

[14] The amount of missing data from patients who remained in the study was not quantified by the Applicant.

Table 23. Tipping Point Analysis in Average AM and PM rTNSS Over the 14-Day Treatment Period (Full Analysis Set)

Treatment Group (TRT1 vs. TRT2)	Shift	Number of Subjects (n) (TRT1, TRT2)	LSMeans (TRT1, TRT2)	LSMeans Difference	Std Err LSMeans Difference	95% CI	P-value
GSP 301 NS vs. GSP 301 placebo NS	-12	299, 283	-3.54, -2.49	-1.05	0.21	-1.46, -0.64	<.0001
	-10	299, 283	-3.53, -2.49	-1.04	0.21	-1.44, -0.63	<.0001
	-9	299, 283	-3.52, -2.50	-1.03	0.21	-1.43, -0.62	<.0001
	-7	299, 283	-3.51, -2.50	-1.01	0.21	-1.42, -0.61	<.0001
	-6	299, 283	-3.50, -2.50	-1.01	0.21	-1.41, -0.60	<.0001
	-5	299, 283	-3.50, -2.50	-1.00	0.21	-1.40, -0.59	<.0001
	-4	299, 283	-3.49, -2.50	-0.99	0.21	-1.40, -0.59	<.0001
	-3	299, 283	-3.48, -2.50	-0.99	0.21	-1.39, -0.58	<.0001
	-2	299, 283	-3.48, -2.50	-0.98	0.21	-1.38, -0.57	<.0001
	-1	299, 283	-3.47, -2.50	-0.97	0.21	-1.38, -0.57	<.0001
	1	299, 283	-3.46, -2.50	-0.96	0.21	-1.36, -0.55	<.0001
	3	299, 283	-3.44, -2.50	-0.94	0.21	-1.35, -0.54	<.0001
	4	299, 283	-3.44, -2.50	-0.93	0.21	-1.34, -0.53	<.0001
	8	299, 283	-3.41, -2.50	-0.91	0.21	-1.31, -0.50	<.0001
	9	299, 283	-3.40, -2.50	-0.90	0.21	-1.31, -0.49	<.0001
	11	299, 283	-3.39, -2.50	-0.88	0.21	-1.29, -0.47	<.0001

Results displayed for GSP 301 to placebo comparison only.
Source: GSP 301-301 Clinical Study Report, Table T14.1.9.5.7
Abbreviations: rTNSS=reflective total nasal symptom score; TRT=treatment; NS=nasal spray; CI=confidence interval; LSMeans=least square means

Lack of statistical significance can be due to lack of effectiveness of the treatment. It can also be due to underpowering the study and having a lower sample size than needed to demonstrate significance. This will be discussed further with the results of the other two studies submitted for substantial evidence below.

Results of the primary endpoint by age, sex, and race are described in Section 0.

Data Quality and Integrity

No site inspections were performed by the Office of Scientific Investigations as part of this NDA.

Efficacy Results – Secondary and Other Relevant Endpoints

Results for iTNSS were similar to the same analysis on rTNSS (Table 24, Figure 14). Point estimates and confidence intervals (CIs) were similar to rTNSS. With iTNSS, all the comparisons were statistically significant, whereas with rTNSS, two of the comparisons were marginally insignificant.

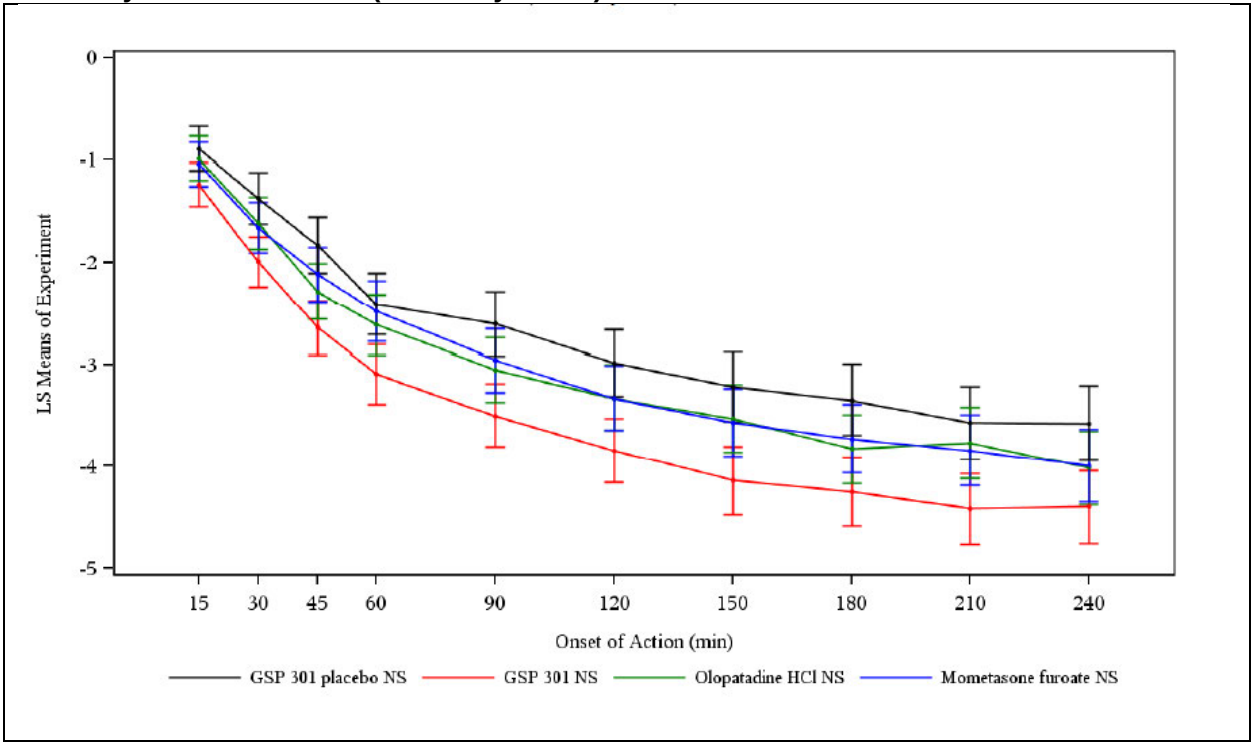
Table 24. Repeated Measures Results for Average AM and PM iTNSS Over the 14-Day Period (Full Analysis Set)

Treatment Group (TRT1 vs. TRT2)	Number of Subjects (n) (TRT1, TRT2)	LS Means Difference	95% CI	P-value
GSP 301 NS vs. GSP 301 placebo NS	299, 283	-0.93	-1.28, -0.58	<0.0001*
GSP 301 NS vs. Olopatadine HCl NS	299, 294	-0.50	-0.85, -0.15	0.0050*
GSP 301 NS vs. Mometasone furoate NS	299, 294	-0.36	-0.71, -0.01	0.0413*
Olopatadine HCl NS vs. GSP 301 placebo NS	294, 283	-0.43	-0.78, -0.07	0.0177*
Mometasone furoate NS vs. GSP 301 placebo NS	294, 283	-0.57	-0.92, -0.21	0.0017*

CI=confidence interval; HCl=hydrochloride; LS=least square; NS=nasal spray; TRT1=treatment 1; TRT2=treatment 2; vs=versus
* Statistically significant difference ($p<0.05$) using gatekeeping strategy.
Baseline score was derived as the mean of the last 8 reading scores including the AM assessment on the day of randomization.
LS Means, 95% confidence intervals and p-values are based on MMRM model with change from baseline as dependent variable, treatment group and site as fixed effect, baseline as covariate, and study day as the within-subject effect (with covariance structure of Unstructured).

Source: GSP 301-301 Clinical Study Report, Table 14
Abbreviations: iTNSS=instantaneous Total Nasal Symptom Score

Figure 14. Least Square Means With 95% Confidence Intervals of Average AM and PM iTNSS Over the 14-Day Treatment Period (Full Analysis Set)



Source: GSP 301-301 Clinical Study Report, Figure 15.1.7
Abbreviations: iTNSS=instantaneous Total Nasal Symptom Score; NS=nasal spray; HCl=hydrochloride; LS=least square

Results for rTOSS are presented in Table 25 and Figure 15. The comparison between GSP 301 and placebo was statistically significant. However, the single components were not statistically

different from GSP 301, and by the Applicant's gatekeeping rules, they were not statistically different from placebo either. As with rTNSS and iTNSS, the patients treated with GSP 301 demonstrated a consistently better point estimate over time compared to those treated with the single components. These point estimates for both single components consistently exhibited a similar pattern compared to those for placebo.

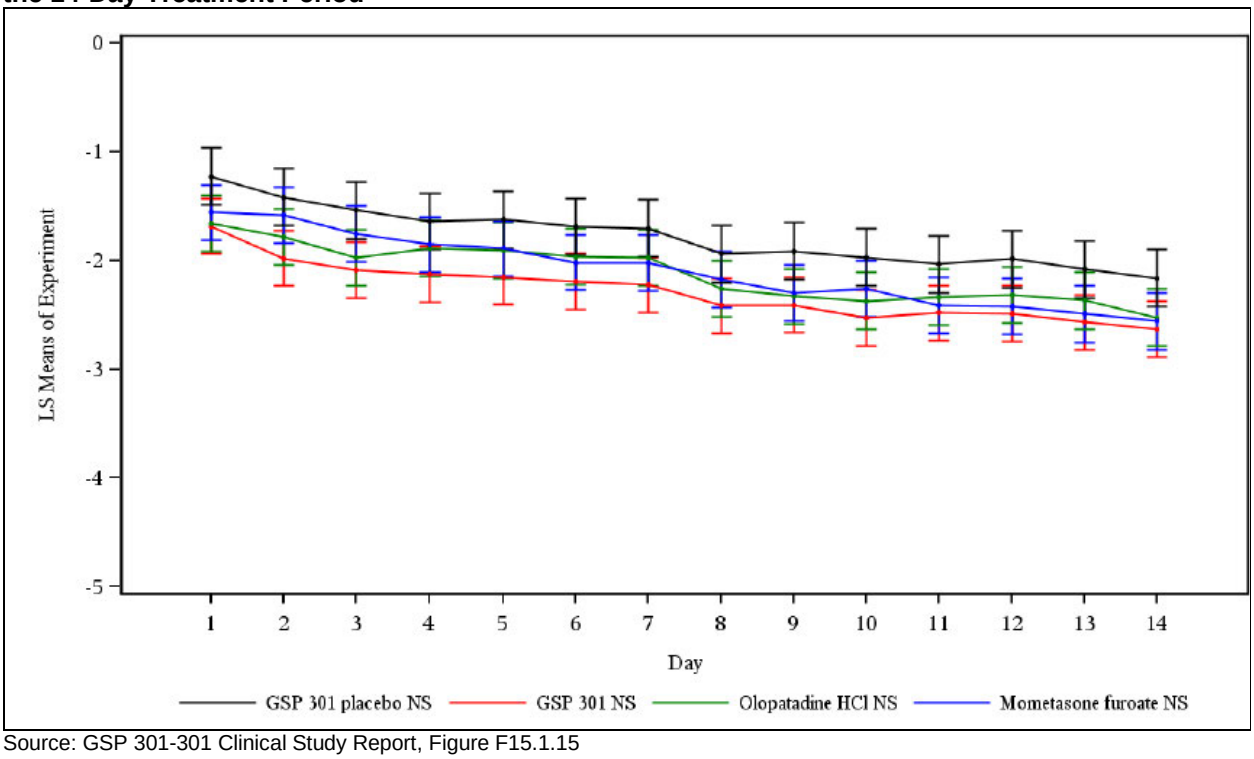
Table 25. Summary of Repeated Measures Analysis Results of Average AM and PM rTOSS Over the 14-Day Treatment Period (Full Analysis Set)

Treatment Group (TRT1 vs. TRT2)	Number of Subjects (n) (TRT1, TRT2)	LS Means Difference	95% CI	P-value
GSP 301 NS vs. GSP 301 placebo NS	299, 283	-0.49	-0.79, -0.19	0.0014*
GSP 301 NS vs. Olopatadine HCl NS	299, 294	-0.09	-0.39, 0.21	0.5423
GSP 301 NS vs. Mometasone furoate NS	299, 294	-0.19	-0.49, 0.11	0.2113
Olopatadine HCl NS vs. GSP 301 placebo NS	294, 283	-0.40	-0.70, -0.10	0.0100
Mometasone furoate NS vs. GSP 301 placebo NS	294, 283	-0.30	-0.60, 0.00	0.0510

CI=confidence interval; HCl=hydrochloride; LS=least square; NS=nasal spray; TRT1=treatment 1; TRT2=treatment 2; vs=versus
* Statistically significant difference ($p<0.05$) using gatekeeping strategy.
Baseline score was derived as the mean of the last 8 reading scores including the AM assessment on the day of randomization.
LS Means, 95% confidence intervals and p-values were based on MMRM model with change from baseline as dependent variable, treatment group and site as fixed effect, baseline as covariate, and study day as the within-subject effect (with covariance structure of Unstructured).

Source: GSP 301-301 Clinical Study Report, Table 15
Abbreviations: TRT=treatment; rTOSS=reflective Total Ocular Symptom Score; CI=confidence interval; NS=nasal spray; HCl=hydrochloride; LS=least square

Figure 15. Least Square Means With 95% Confidence Intervals of Average AM and PM rTOSS for the 14-Day Treatment Period



Source: GSP 301-301 Clinical Study Report, Figure F15.1.15
Abbreviations: rTOSS=reflective Total Ocular Symptom Score; LS=least square; NS=nasal spray; HCl=hydrochloride

iTOSS was described in the study report as a tertiary endpoint. It is noted in this section because it is included in the Applicant's proposed label. The iTOSS treatment differences and p-values (Table 26) were similar to those noted in Table 25 for rTOSS.

Table 26. Summary of Repeated Measures Analysis for AM and PM iTOSS Over the 14-Day Treatment Period (Full Analysis Set)

Treatment Group (Trt 1 vs. Trt 2)	N (Trt 1 vs. Trt 2)	Least Square Mean Difference	Standard Error	95% CI	P-Value
GSP 301 NS vs. placebo	299, 283	-0.50	0.14	-0.78, -0.22	<0.001*
GSP 301 NS vs. olopatadine HCl	299, 294	-0.15	0.14	-0.42, 0.13	0.300[ns]
GSP 301 NS vs. mometasone furoate	299, 294	-0.20	0.14	-0.47, 0.08	0.164[ns]
Olopatadine HCl vs. placebo	294, 283	-0.35	0.14	-0.64, -0.07	0.014[ns]
Mometasone furoate vs. placebo	294, 283	-0.30	0.14	-0.59, -0.02	0.034[ns]

Source: GSP 301-301 study report, Table T14.1.9.14.2
* Statistically significant, using Applicant's gatekeeping multiplicity plan
[ns] Not statistically significant, using Applicant's gatekeeping multiplicity plan
Abbreviations: iTOSS=instantaneous Total Ocular Symptom Score; Trt=treatment; CI=confidence interval; NS=nasal spray;

Results for onset of action, as measured by iTNSS, are displayed in Table 27 and Figure 16. There was a statistically significant difference between GSP 301 and placebo within 15 minutes,

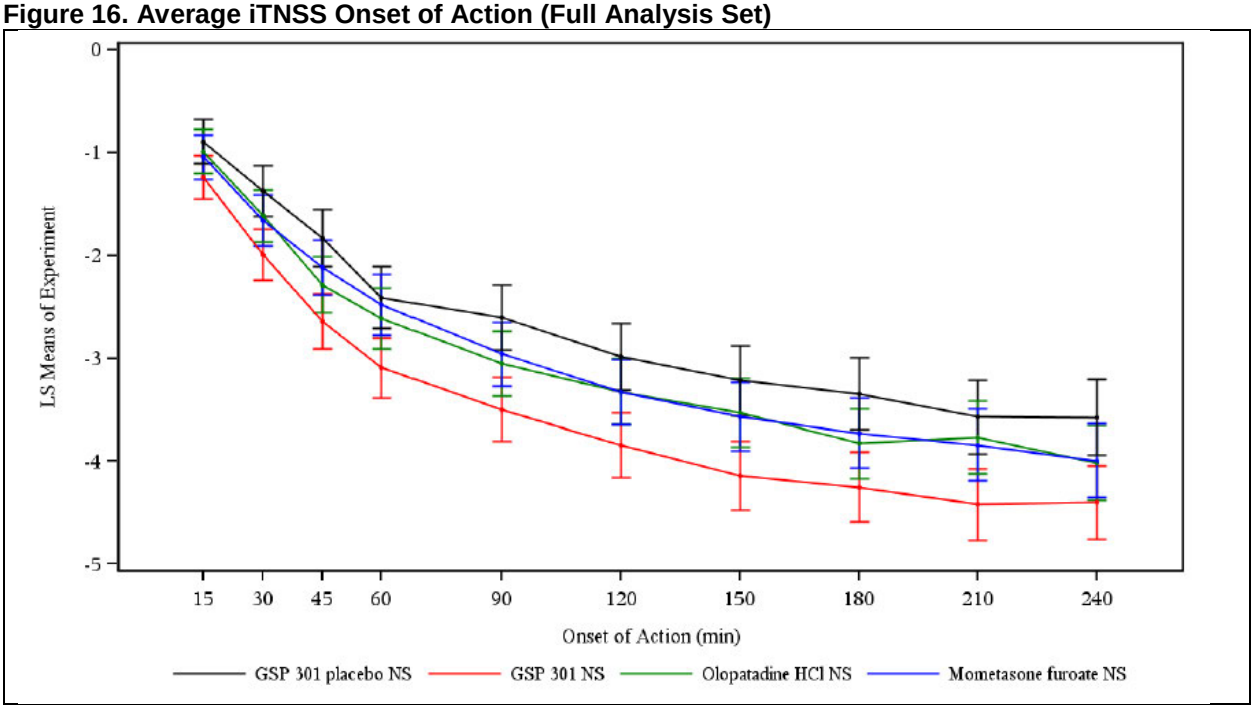
which was maintained throughout the 4 hours this endpoint was monitored. OLO did achieve a significant difference relative to placebo at 45 minutes as described by the Applicant, but statistical significance was inconsistent throughout the time course. MF did not achieve statistical significance from placebo at any timepoint.

Table 27. Summary of Repeated Measures Analysis Results of iTNSS Onset of Action (Full Analysis Set)

Treatment Group	Time Point	n Active	n Placebo	LSMeans Active	LSMeans Placebo	LSMeans Difference	95% CI	P-value Active vs. Placebo
GSP 301 NS	15 minutes	293	282	-1.24	-0.89	-0.35	-0.63, -0.07	0.0140
	30 minutes	293	281	-1.99	-1.37	-0.62	-0.95, -0.29	0.0002
	45 minutes	293	282	-2.64	-1.83	-0.81	-1.18, -0.45	<.0001
	60 minutes	293	282	-3.09	-2.41	-0.68	-1.08, -0.28	0.0008
	90 minutes	292	281	-3.50	-2.60	-0.90	-1.32, -0.47	<.0001
	120 minutes	292	282	-3.84	-2.98	-0.86	-1.30, -0.42	0.0001
	150 minutes	291	281	-4.14	-3.22	-0.92	-1.38, -0.47	<.0001
	180 minutes	292	281	-4.25	-3.34	-0.91	-1.38, -0.44	0.0001
	210 minutes	292	280	-4.42	-3.57	-0.85	-1.33, -0.36	0.0006
	240 minutes	292	282	-4.40	-3.57	-0.83	-1.32, -0.33	0.0011
Olopatadine HCl NS	15 minutes	290	282	-0.99	-0.89	-0.10	-0.37, 0.18	0.5024
	30 minutes	288	281	-1.62	-1.37	-0.24	-0.57, 0.09	0.1477
	45 minutes	288	282	-2.29	-1.83	-0.45	-0.82, -0.09	0.0150
	60 minutes	288	282	-2.62	-2.41	-0.21	-0.61, 0.19	0.3116
	90 minutes	289	281	-3.05	-2.60	-0.45	-0.88, -0.03	0.0376
	120 minutes	289	282	-3.33	-2.98	-0.34	-0.78, 0.10	0.1256
	150 minutes	290	281	-3.53	-3.22	-0.31	-0.77, 0.15	0.1825
	180 minutes	289	281	-3.83	-3.34	-0.48	-0.95, -0.02	0.0428
	210 minutes	290	280	-3.77	-3.57	-0.20	-0.69, 0.29	0.4190
	240 minutes	290	282	-4.02	-3.57	-0.44	-0.94, 0.05	0.0812
Mometasone furoate NS	15 minutes	290	282	-1.04	-0.89	-0.15	-0.43, 0.13	0.2900
	30 minutes	290	281	-1.66	-1.37	-0.28	-0.61, 0.04	0.0905
	45 minutes	290	282	-2.12	-1.83	-0.28	-0.65, 0.08	0.1273
	60 minutes	290	282	-2.48	-2.41	-0.07	-0.47, 0.33	0.7267
	90 minutes	289	281	-2.96	-2.60	-0.36	-0.78, 0.07	0.0999
	120 minutes	290	282	-3.33	-2.98	-0.35	-0.78, 0.09	0.1212
	150 minutes	290	281	-3.57	-3.22	-0.35	-0.81, 0.10	0.1304
	180 minutes	288	281	-3.73	-3.34	-0.38	-0.85, 0.08	0.1077
	210 minutes	289	280	-3.84	-3.57	-0.27	-0.76, 0.22	0.2772
	240 minutes	289	282	-3.99	-3.57	-0.42	-0.92, 0.08	0.0971

Baseline is defined as the predose time point at the Randomization Visit (Visit 2)
n: Number of subjects available at each timepoint in the specific treatment group
LSMeans, 95% confidence intervals and p-values are based on mixed-effect for repeated measures (MMRM) model with change from baseline as dependent variable, treatment group, site and the interaction treatment*time-point as fixed effect, baseline as covariate, and time-point as the within-subject effect (with covariance structure of Unstructured).
Source: GSP 301-301 study report, Table T14.1.9.8.2
Note: this endpoint was not included in the applicant's multiplicity planning
Abbreviations: iTNSS=instantaneous Total Nasal Symptom Score; NS=nasal spray; LSMeans=least square means

Figure 16. Average iTNSS Onset of Action (Full Analysis Set)



Source: GSP 301-301 study report, Figure F15.1.7
Abbreviations: iTNSS=instantaneous Total Nasal Symptom Score; LS=least square; NS=nasal spray; HCl=hydrochloride

Efficacy Results – Secondary or Exploratory Clinical Outcome Assessment (Patient Reported Outcome) Endpoints

QOL, as assessed by the secondary endpoint RQLQ scores (Table 28 and Figure 17), was statistically significantly improved for patients on GSP 301 compared to that of patients on placebo, with a mean difference of -0.43. RQLQ scores of patients treated with GSP 301 were also compared to those of patients treated with individual components: scores from GSP 301 were statistically higher compared to scores from OLO treatment (mean difference=-0.28), but they were not higher than scores from MF treatment (mean difference of -0.20). Furthermore, the responses of patients on OLO treatment were not statistically improved compared to those of patients on placebo (mean difference=-0.15), while those of patients on MF treatment were statistically improved compared to those of patients on placebo (mean difference=-0.23).

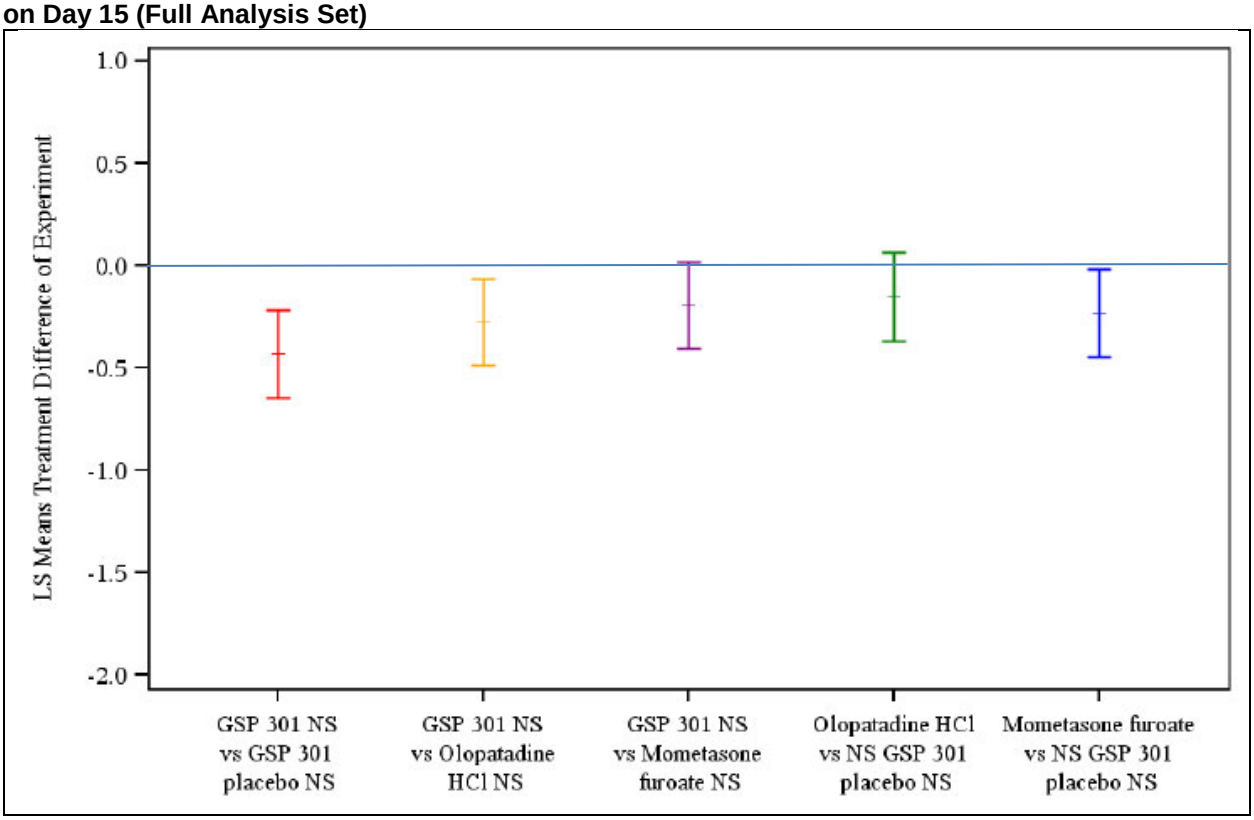
Table 28. Summary of Analysis of Covariance Results for Overall RQLQ Score on Day 15 (Full Analysis Set)

Treatment Group (TRT1 vs. TRT2)	Number of Subjects (n) (TRT1, TRT2)	LS Means Difference	95% CI	P-value
GSP 301 NS vs. GSP 301 placebo NS	298, 279	-0.43	-0.64, -0.21	<0.0001*
GSP 301 NS vs. Olopatadine HCl NS	298, 293	-0.28	-0.49, -0.07	0.0105*
GSP 301 NS vs. Mometasone furoate NS	298, 293	-0.20	-0.41, 0.02	0.0692
Olopatadine HCl NS vs. GSP 301 placebo NS	293, 279	-0.15	-0.37, 0.06	0.1659
Mometasone furoate NS vs. GSP 301 placebo NS	293, 279	-0.23	-0.45, -0.02	0.0345*

CI=confidence interval; HCl=hydrochloride; LS=least square; NS=nasal spray; TRT1=treatment 1; TRT2=treatment 2; vs=versus
Baseline was defined as the pre-dose time point at the Randomization Visit (Visit 2).
LS Means, 95% confidence intervals and p-values were based on an ANCOVA with change from baseline as dependent variable, treatment group and site as fixed effect and baseline as covariate.
* Statistically significant difference ($p<0.05$).

Source: GSP 301-301 study report, Table 16
Note: this endpoint was not included in the applicant's multiplicity planning
Abbreviations: RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire

Figure 17. Treatment Differences of Least Square Means With 95% CIs for Overall RQLQ(S) Score on Day 15 (Full Analysis Set)



Source: GSP 301-301 Clinical Study Report, Figure F15.2.9, with reference line at zero added
Abbreviations: RQLQ(S)=Rhinoconjunctivitis Quality of Life Questionnaire – Standardized Activities; LS=least square; NS=nasal spray; HCl=hydrochloride;

Integrated Review of Effectiveness

Comparisons were made between GSP 301, its single components, and placebo. Results for rTNSS, iTNSS, iTNSS onset of action, rTOSS, iTOSS, and RQLQ demonstrate a clear and statistically significant separation between patients administered GSP 301 and those administered placebos. However, the other comparisons (i.e., GSP 301 to its single components and the single components to placebo) were not as consistently significantly different.

Note there was no preplanned adjustment for multiplicity, except for within-treatment arm comparisons for rTNSS, iTNSS and rTOSS (i.e., between primary and secondary endpoints). With a gatekeeping multiplicity strategy, the expectation was a fully closed set of comparisons, beginning with the primary endpoint, rTNSS, and extending to any secondary endpoints being considered for the label.

8.1.3. Study Design – GSP 301-304

- Study dates: August 22, 2016 to January 31, 2017
- Study sites: 43 U.S. sites
- Study report date: January 5, 2018

Objectives

Primary:

- To compare the efficacy of GSP 301 with placebo and individual constituent monotherapies at the same dose in the same vehicle as well as the efficacy of these individual constituent monotherapies versus GSP 301 over 14 days of study treatment.

Secondary:

- To assess the safety and tolerability of each treatment.

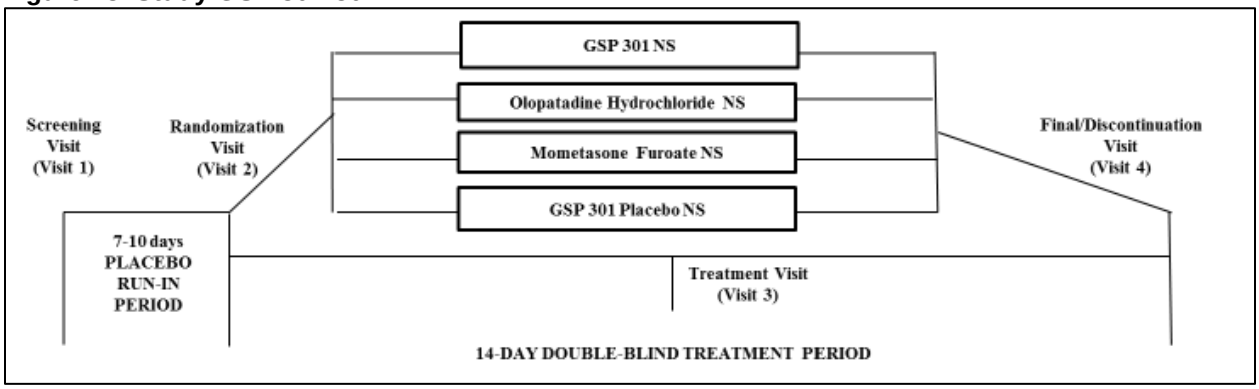
Trial Design

Study 304 was a randomized, double-blind, placebo controlled, parallel group, multicenter study to evaluate the safety, efficacy, and tolerability of GSP 301 administered as two sprays BID compared with GM OLO and GM MF at the same dose and in the same vehicle as subjects with SAR.

Design

Study 304 included a single-blind placebo run-in period, a double-blind treatment period, and four study site visits as described in Section 8.1.1. There was no scheduled posttreatment follow-up visit; however, patients were followed up if there was an AE or at the discretion of the Investigator. A total of 1,808 subjects were screened and 1,176were randomized 1:1:1:1 to four treatment groups. The study design is summarized schematically in Figure 3.

Figure 18. Study GSP 301-304



Source GSP 301-304 CSR Figure 1 page 26
Abbreviations: NS=nasal spray

Schedule of Assessments for Study 304

The schedule of procedures and assessments for study 304 were identical to that of Study 301 (refer to Section 8.1.1 Table 15) except there was no PK sampling or assessments.

Patient Selection Criteria
Similar to Study 301.

Study Endpoints

A brief list is provided here. Refer to Study 301 for a full description of the endpoints.

Primary Endpoints

The primary efficacy endpoint was the change from baseline in average AM and PM subject-reported 12-hour rTNSS over the 14-day treatment period.

Key Secondary Endpoints

- Change from baseline in average AM and PM subject-reported 12-hour iTNSS over the 14-day treatment period
- Change from baseline in average AM and PM subject-reported 12-hour rTOSS over the 14-day treatment period
- Onset of action for each active treatment
- Change from baseline in the overall RQLQ(S) score on day 15 (visit 4)

Safety Assessments

Similar to Study 301.

Statistical Analysis Plan

The SAP for this study was signed off on February 21, 2017. The Applicant stated the SAP was approved prior to database lock and unblinding of the study. The database was locked and approved on March 8, 2017.

The same populations defined in study 301 were used in study 304.

As with study 301, the Applicant's primary analysis, sensitivity and supportive analyses, multiplicity adjustments and secondary analyses were handled in the same way.

Subgroup analyses by age group (12–17, 18–64, 65 and above), sex, race, and ethnicity were conducted for rTNSS and secondary endpoints iTNSS and rTOSS.

The Applicant's focus in their submission was on the pooled analysis of studies 201, 301, and 304, with a proposed label describing the results of study 304 only. This is discussed in Section 8.1.4.

Protocol Amendments

Protocol amendment 1 (March 23, 2018) included an updated statistical analysis (p-values) of three secondary endpoints which did not impact the statistical significance of the result or the overall conclusions of the study.

8.1.4. Study Results

Patient Disposition

Study 304 enrolled 1,808 subjects and randomized 1,176 (65%). Twenty-nine subjects (2.5%) did not complete the study. One subject in the SAS population was randomized to receive GSP 301, but no treatment was given. Another subject was originally randomized to receive MF but was given a kit that contained GSP 301. The subject continued to receive GSP 301 for the rest of the treatment period and all data were included in the GSP 301 group. Two subjects were randomized twice.

Table 29. GSP 301-304 Disposition of Subjects (Safety Analysis Set)

Disposition	GSP 301 Placebo N=294 n (%)	GSP 301 N=294 n (%)	Olopatadine N=294 n (%)	Mometasone N=294 n (%)
Randomized	294 (100.0)	294[a] (100.0)	294 (100.0)	294[b] (99.7)
Terminated early	10 (3.4)	5 (1.7)	7 (2.4)	7 (2.4)
Completed study	284 (96.6)	289 (98.3)	287 (97.6)	287 (97.6)
Early termination reason				
Adverse event	1 (0.3)	0	2 (0.7)	0
Physician decision	2 (0.7)	0	0	4 (1.3)
Lost to follow up	0	0	3 (1.0)	0
Noncompliance with study drug	0	3 (1.0)	0	1 (0.3)
Randomized failure	0	1 (0.3)	0	1 (0.3)
Protocol deviation	1 (0.3)	0	0	0
Withdrawal by subject	4 (1.4)	1 (0.3)	0	1 (0.3)
Other	2 (0.7)	0	2 (0.7)	0

[a] One subject was randomized but did not take any study medication
[b] One subject was randomized to receive mometasone but was given the wrong kit
Percentages are based on the number of randomized subjects.
Source: Study 301-304 CSR Table 14.1.1 and Table 10 page 64
Abbreviations: SAS=safety analysis set

Protocol Violations/Deviations

During the randomized treatment period, protocol deviations occurred in 58 (19.7%) to 65 (22.2%) of subjects per group across treatment groups.

Table 30. Study 304 Protocol Deviations (Safety Analysis Set)

Deviations	GSP 301 Placebo N=294 n (%)	GSP 301 N=294 n (%)	Olopatadine N=294 n (%)	Mometasone N=293 n (%)
Subjects with protocol deviations	58 (19.7)	64 (21.8)	61 (20.7)	65 (22.2)
Total deviations	76	87	77	90
Concomitant medication	1 (0.3)	6 (2.0)	2 (0.7)	0
Exclusion criteria	1 (0.3)	0	0	0
Informed consent	5 (1.7)	6 (2.0)	1 (0.3)	5 (1.7)
Inventory record keeping source documents	3 (1.0)	2 (0.7)	0	3 (1.0)
Study treatment administration/ dispense	0	3 (1.0)	1 (0.3)	3 (1.0)
Study procedures assessments	2 (0.7)	1 (0.3)	1 (0.3)	4 (1.4)
Study treatment compliance	5 (1.7)	8 (2.7)	10 (3.4)	12 (4.1)
Study treatment randomization	5(1.7)	4 (1.4)	7 (2.4)	1 (0.3)
Study treatment supplies/ control	1 (0.3)	0	0	0
Visit scheduling	8 (2.7)	16 (5.4)	6 (2.0)	9 (3.1)
Other	36 (12.2)	33 (11.2)	41 (13.9)	38 (13.0)

Source: GSP 301-304 CSR Table 14.1.2.1 page 60

As shown in Table 31, the mean age of study subjects ranged from 39.2 years to 39.9 years. The majority of subjects were female, white, and not Hispanic or Latino.

Table 31. Study 304 Demographic Characteristics (Full Analysis Set)

Demographics	GSP 301 Placebo N=293	GSP 301 N=293	Olopatadine N=293	Mometasone N=294
Age (years)				
Mean (SD)	39.6 (14.9)	39.8 (14.9)	39.9 (14.6)	39.2 (14.8)
median	40.0	40.0	40.0	38.0
Min, max	12, 82	12, 76	12, 80	12, 77
Sex n (%)				
Male	117 (39.9)	90 (30.8)	104 (35.5)	124 (42.2)
Female	176 (60.1)	202 (69.2)	189 (64.5)	170 (57.8)
Race n (%)				
American Indian or Alaska Native	1 (0.3)	1 (0.3)	1 (0.3)	0
Asian	3 (1.0)	7 (2.4)	4 (1.4)	8 (2.7)
White	229 (78.2)	250 (85.6)	244 (83.3)	233 (79.3)
Black/African American	60 (20.5)	30 (10.3)	41 (14.0)	50 (17.0)
Native Hawaiian or Pacific Islander	0	0	1 (0.3)	0
Other	0	4 (1.4)	2 (0.7)	3 (1.0)
Ethnicity n (%)				
Hispanic or Latino	79 (27.0)	69 (23.6)	96 (32.8)	85 (28.9)
Not Hispanic or Latino	214 (73.0)	223 (76.4)	197 (67.2)	209 (71.1)

Source: Study GSP 301-304 CSR Table 14.1.4.2
Abbreviations: SD=standard deviation

Efficacy Results – Primary Endpoint

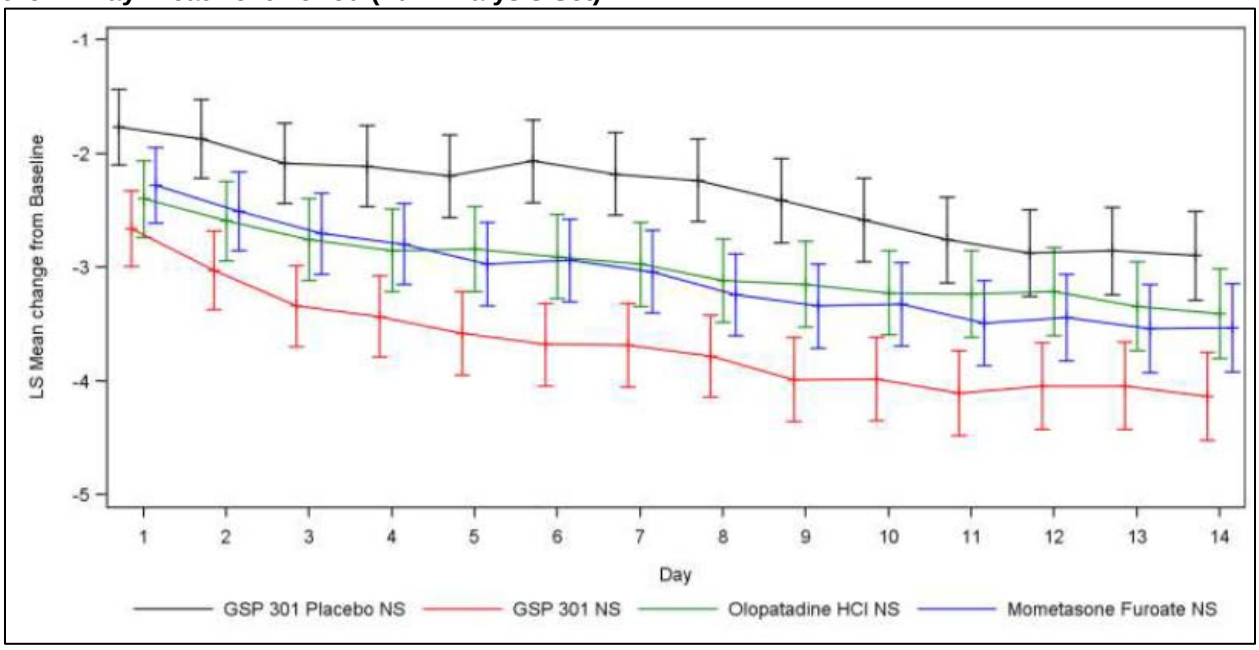
In an analysis of the primary endpoint (AM and PM rTNSS) via MMRM and adjusted for investigational site and patient's baseline value, GSP 301 NS showed statistically significant improvements in symptom scores vs. placebo during the 14-day treatment period (LS mean difference=-1.09) (Table 32). Point estimates for GSP 301 versus single components were -0.44 and -0.47 for OLO and MF, respectively, both being statistically significant. The strength of evidence for single components versus placebo was similar at 0.64- and 0.62-unit reductions, respectively. These treatment group comparisons were statistically significant.

Table 32. Results of Primary Efficacy Analysis, Repeated Measures on AM and PM rTNSS Over 14-Day Treatment (Full Analysis Set)

Treatment Group (Trt 1 vs. Trt 2)	N (Trt 1 vs. Trt 2)	Least Square Mean Difference	Standard Error	95% CI	P-Value
GSP 301 NS vs. placebo	291, 290	-1.08	0.20	-1.48, -0.68	<0.0001*
GSP 301 NS vs. olopatadine HCl	291, 290	-0.46	0.20	-0.85, -0.06	0.0234*
GSP 301 NS vs. mometasone furoate	291, 293	-0.48	0.20	-0.87, -0.08	0.0180*
Olopatadine HCl vs. Placebo	290, 290	-0.63	0.20	-1.02, -0.23	0.0020*
Mometasone furoate vs. Placebo	293, 290	-0.61	0.20	-1.00, -0.21	0.0026*

Source: Statistical reviewer.
Note: Results did not match Applicant's GSP 301-304 Clinical Study Report, Table 13, because their model assumed compound symmetry. This model assumes unstructured covariance.
* Statistically significant, using Applicant's gatekeeping multiplicity plan
ns: not statistically significant, using Applicant's gatekeeping multiplicity plan
Abbreviations: rTNSS=reflective Total Nasal Symptom Score; Trt=treatment; CI=confidence interval; NS=nasal spray; HCl=hydrochloride

Figure 19. Least Square Means With 95% Confidence Intervals of Average AM and PM rTNSS Over the 14-Day Treatment Period (Full Analysis Set)



Statistical Analysis model: MMRM model with change from baseline as the dependent variable, treatment group and site as fixed effects, baseline score as covariate and study day as the within-subject effect.
Source: GSP 301-304 Clinical Study Report, Figure 11.2.1.1.1
Abbreviations: rTNSS=reflective Total Nasal Symptom Score; LS=least square; NS=nasal spray; HCl=hydrochloride

LS means and 95% CIs for each of the four treatments over time are displayed in Figure 19.

The Applicant analyzed the same data using ANCOVA and got results similar to the primary MMRM analysis. The ANCOVA analysis[15] yielded the results in Table 33.

Table 33. Results of Supplementary Analysis, ANCOVA on AM and PM rTNSS Over 14-Day Treatment (Full Analysis Set)

Treatment Group (Trt 1 vs. Trt 2)	N (Trt 1 vs. Trt 2)	Least Square Mean Difference	Standard Error	95% CI	P-Value
GSP 301 NS vs. placebo	291, 290	-1.31	0.07	-1.44, -1.18	<0.0001*
GSP 301 NS vs. olopatadine HCl	291, 290	-0.67	0.07	-0.80, -0.54	<0.0001*
GSP 301 NS vs. mometasone furoate	291, 293	-0.58	0.07	-0.71, -0.46	<0.0001*
Olopatadine HCl vs. placebo	290, 290	-0.63	0.07	-0.76, -0.60	<0.0001*
Mometasone furoate vs. placebo	293, 290	-0.72	0.07	-0.86, -0.60	<0.0001*

Source: GSP 301-304 Clinical Study Report, Table 14.2.1.5
* Statistically significant, using Applicant's gatekeeping multiplicity plan
Abbreviations: ANCOVA=analysis of covariance; rTNSS=reflective Total Nasal Symptom Score; Trt=treatment; CI=confidence interval; NS=nasal spray; HCl=hydrochloride

The Applicant's exploration on the effects of missing data included additional analyses on the primary endpoint with imputation using the J2R and tipping point approaches. Out of the 1,176 randomized patients, 1.7% to 3.4% terminated early, with the GSP 301 arm having the lowest early termination rate and placebo the highest (Table 29).[16] The J2R approach with and without imputation was nearly identical, indicating that the effect of missing data was minimal in this study.[17] The tipping point analysis completed by the Applicant shifted the results by 12 units from the point estimate from GSP 301 group (Table 34). All p-values remained highly statistically significant, indicating that the point estimate was robust to effects of missing data.

[15] Using change from baseline as dependent variable, treatment group and site as fixed effects, and baseline as covariate.

[16] The amount of missing data from patients who remained in the study was not quantified by the Applicant.

[17] See CSR 304, Table 14.2.1.6

Table 34. Tipping Point Analysis in Average AM and PM rTNSS Over the 14-Day Treatment Period (Full Analysis Set)

Result of the Sensitivity Analysis using Tipping Point Approach
Overall 14-day treatment period

Estimates and p-values for Shift Parameters					
Observation	Treatment Comparison	Shift	Estimate of Mean Difference	95% Confidence Interval	P-value
1	GSP 301 NS vs. GSP 301 placebo NS	0	-1.09	(-1.49,-0.70)	<.001
2	GSP 301 NS vs. GSP 301 placebo NS	1	-1.06	(-1.46,-0.66)	<.001
3	GSP 301 NS vs. GSP 301 placebo NS	2	-1.04	(-1.44,-0.64)	<.001
4	GSP 301 NS vs. GSP 301 placebo NS	3	-1.02	(-1.42,-0.62)	<.001
5	GSP 301 NS vs. GSP 301 placebo NS	4	-1.01	(-1.41,-0.61)	<.001
6	GSP 301 NS vs. GSP 301 placebo NS	5	-1.01	(-1.41,-0.61)	<.001
7	GSP 301 NS vs. GSP 301 placebo NS	6	-1.00	(-1.40,-0.60)	<.001
8	GSP 301 NS vs. GSP 301 placebo NS	7	-1.00	(-1.40,-0.60)	<.001
9	GSP 301 NS vs. GSP 301 placebo NS	8	-1.00	(-1.41,-0.60)	<.001
10	GSP 301 NS vs. GSP 301 placebo NS	9	-1.00	(-1.41,-0.60)	<.001
11	GSP 301 NS vs. GSP 301 placebo NS	10	-1.00	(-1.41,-0.60)	<.001
12	GSP 301 NS vs. GSP 301 placebo NS	11	-1.00	(-1.41,-0.60)	<.001

Results displayed for GSP 301 to placebo comparison only.
Source: GSP 301-304 Clinical Study Report, Table 14.2.1.7
Abbreviations: rTNSS=reflective total nasal symptom score; NS=nasal spray

Results of the primary endpoint by age, sex, and race are described in Section 0.

Data Quality and Integrity

No OSI site inspections were performed as part of this NDA.

Efficacy Results – Secondary and Other Relevant Endpoints

Results for iTNSS were similar to the same analysis on rTNSS (Table 35, Figure 20). Point estimates and CIs were similar to rTNSS. With iTNSS, all comparisons were statistically significant, as with rTNSS.

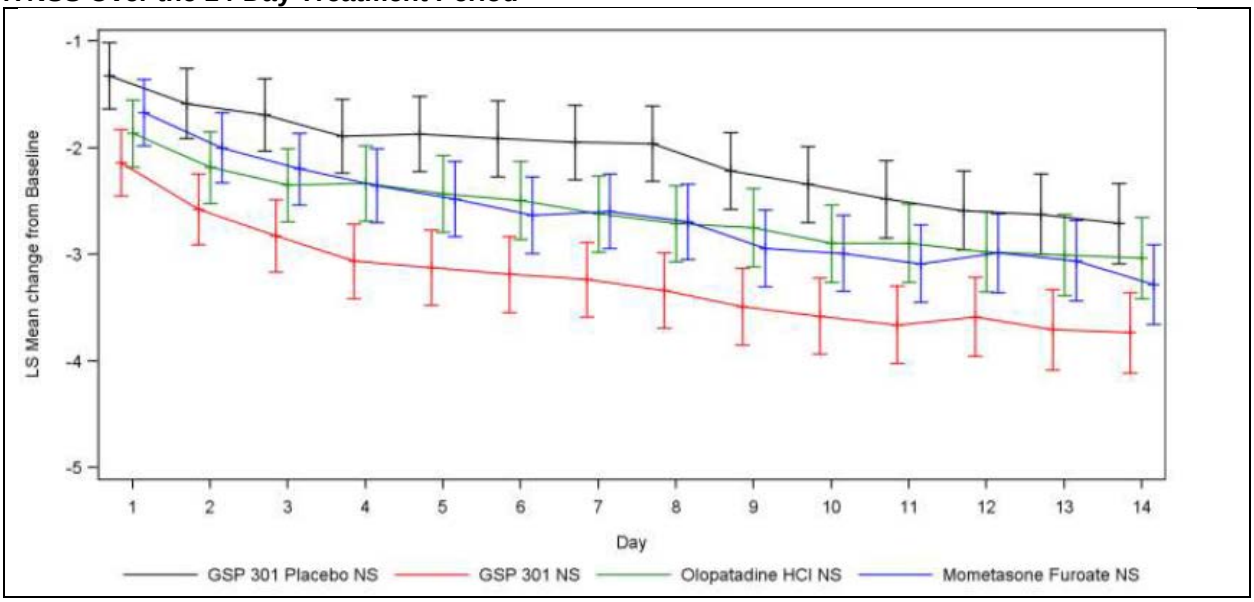
Table 35. Repeated Measures Results for Average AM and PM iTNSS Over the 14-Day Period (Full Analysis Set)

	n		Comparison between TRT 1 and TRT 2		
Treatment Group Comparison (TRT 1 vs. TRT 2)	TRT 1[a]	TRT 2[a]	LS Mean Difference	95% CI	P-value
GSP 301 NS vs. GSP 301 placebo NS	291	290	-0.94	(-1.32,-0.56)	<0.001[b]
GSP 301 NS vs. olopatadine HCl NS	291	290	-0.41	(-0.78,-0.03)	0.035[b]
GSP 301 NS vs. mometasone furoate NS	291	293	-0.51	(-0.88,-0.13)	0.008[b]
Olopatadine HCl NS vs. GSP 301 placebo NS	290	290	-0.54	(-0.92,-0.16)	0.005[b]
Mometasone furoate NS vs. GSP 301 placebo NS	293	290	-0.44	(-0.81,-0.06)	0.023[b]

CI=confidence interval; HCl=hydrochloride; LS = least square; n=number of subjects with data available; NS=nasal spray; TRT1=treatment 1; TRT2=treatment 2; vs=versus
[a] 8 subjects could not be included in the analysis due to no baseline or post-baseline data (Section 11.1).
[b] Statistically significant difference ($p<0.05$) using gatekeeping strategy

Source: GSP 301-304 Clinical Study Report, Table 14
Abbreviations: iTNSS=instantaneous total nasal symptom score

Figure 20. Least Square Means With 95% Confidence Intervals of Change in Average AM and PM iTNSS Over the 14-Day Treatment Period



Source: GSP 301-304 Clinical Study Report, Figure 11.2.1.2.1
Abbreviations: iTNSS=instantaneous total nasal symptom score; LS=least square; NS=nasal spray; HCl=hydrochloride

Results for rTOSS are presented in Table 36 and Figure 21. The comparison between GSP 301 and placebo was statistically significant for this endpoint; however, neither single component, OLO nor MF, was statistically different from GSP 301 by the Applicant's gatekeeping rules.

Furthermore, neither MF nor OLO was statistically different from placebo according to the multiplicity gatekeeping rules established by the Applicant. As with rTNSS and iTNSS, patients treated with GSP 301 demonstrated a consistently better point estimate over time in comparison to the individual components; the point estimates for both single components demonstrated a more favorable trend than placebo.

Table 36. Summary of Repeated Measures Analysis Results of Average AM and PM rTOSS Over the 14-Day Treatment Period (Full Analysis Set)

	n		Comparison between TRT 1 and TRT 2		
Treatment Group Comparison (TRT 1 vs. TRT 2)	**TRT 1[a]**	**TRT 2[a]**	**LS Mean Difference**	**95% CI**	**P-value**
GSP 301 NS vs. GSP 301 placebo NS	291	290	-0.52	(-0.84, -0.20)	0.001[b]
GSP 301 NS vs. olopatadine HCl NS	291	290	-0.17	(-0.48, 0.15)	0.297
GSP 301 NS vs. mometasone furoate NS	291	293	-0.35	(-0.66, -0.03)	0.030[c]
Olopatadine HCl NS vs. GSP 301 placebo NS	290	290	-0.35	(-0.67, -0.04)	0.029[c]
Mometasone furoate NS vs. GSP 301 placebo NS	293	290	-0.17	(-0.49, -0.14)	0.282

CI=confidence interval; HCl=hydrochloride; LS = least square; n=number of subjects with data available; NS=nasal spray; TRT1=treatment 1; TRT2=treatment 2; vs=versus

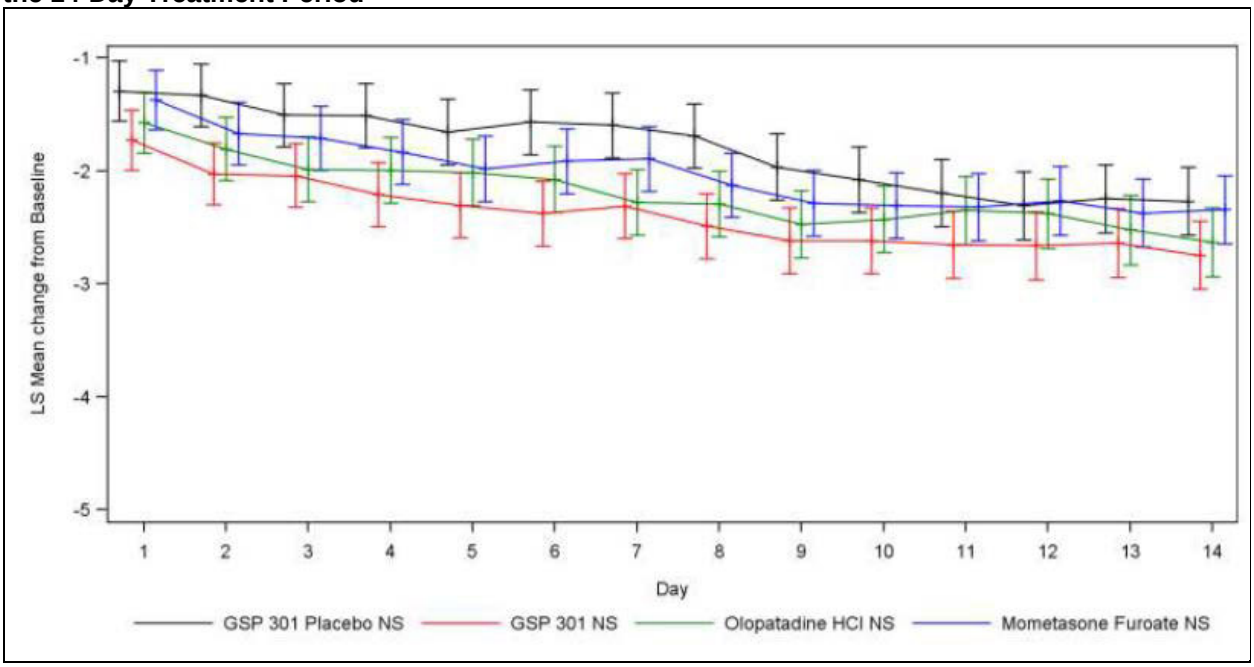
[a] 8 subjects could not be included in the analysis due to no baseline or post-baseline data (Section 11.1).

[b] Statistically significant difference ($p<0.05$) using gatekeeping strategy

[c] Statistically significant difference ($p<0.05$), but did not meet gatekeeping strategy

Source: GSP 301-304 Clinical Study Report, Table 15
Abbreviations: rTOSS=reflective total ocular symptom score

Figure 21. Least Square Means With 95% Confidence Intervals of Average AM and PM rTOSS for the 14-Day Treatment Period



Source: GSP 301-304 Clinical Study Report, Figure 11.2.1.3.1
Abbreviations: rTOSS=reflective total ocular symptom score; LS=least square; NS=nasal spray; HCl=hydrochloride

iTOSS is described in the study report as a tertiary endpoint. It is noted in this section because it was included in the Applicant's proposed label. The iTOSS treatment differences and p-values (Table 37) were similar to those noted in Table 36 for rTOSS.

Table 37. Summary of Repeated Measures Analysis for AM and PM iTOSS Over the 14-Day Treatment Period (Full Analysis Set)

Treatment Group (Trt 1 vs. Trt 2)	N (Trt 1 vs. Trt 2)	Least Square Mean Difference	Standard Error	95% CI	P-Value
GSP 301 NS vs. placebo	291, 290	-0.50	0.16	-0.81, -0.19	0.001*
GSP 301 NS vs. olopatadine HCl	291, 290	-0.19	0.15	-0.49, 0.12	0.227
GSP 301 NS vs. mometasone furoate	291, 293	-0.36	0.15	-0.66, -0.05	0.021[ns]
Olopatadine HCl vs. placebo	290, 290	-0.31	0.16	-0.62, -0.01	0.046[ns]
Mometasone furoate vs. placebo	293, 290	-0.14	0.16	-0.45, 0.16	0.357

Source: GSP 301-304 study report, Table 14.2.3.11.2
* Statistically significant, using Applicant's gatekeeping multiplicity plan
ns Not statistically significant, using Applicant's gatekeeping multiplicity plan

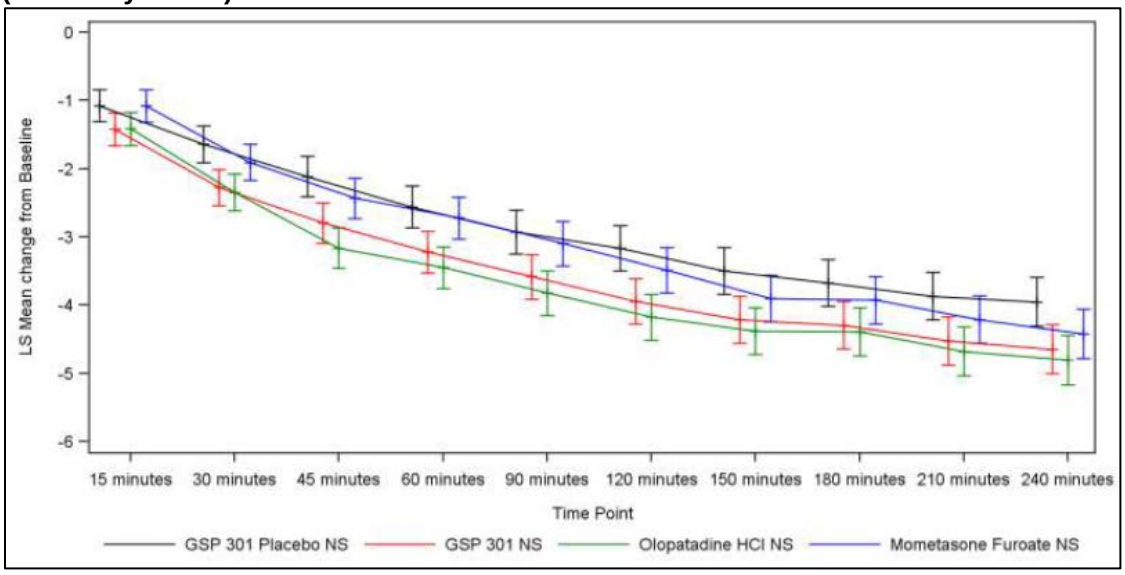
Results for onset of action, as measured by iTNSS, are displayed in Figure 22. There was a statistically significant difference between GSP 301 and placebo within 15 minutes, which was maintained throughout the 4 hours this endpoint was monitored. Similar results were found for the comparison of OLO and placebo at 15 minutes and throughout the 4-hour time course. MF did not achieve statistical significance from placebo at any timepoint.

Table 38. Summary of Repeated Measures Analysis Results of iTNSS Onset of Action (Full Analysis Set)

Treatment Group	Time Point	n Active	n Placebo	LSmean Active	LSmean Placebo	LSmean Difference	95% CI	P-value Active v Placebo
GSP 301 NS	15 minutes	292	292	-1.42	-1.08	-0.34	(-0.65,-0.04)	0.028
	30 minutes	292	292	-2.28	-1.64	-0.64	(-0.99,-0.28)	<.001
	45 minutes	292	292	-2.79	-2.11	-0.68	(-1.07,-0.29)	<.001
	60 minutes	290	289	-3.22	-2.56	-0.66	(-1.07,-0.25)	0.002
	90 minutes	290	289	-3.59	-2.92	-0.66	(-1.10,-0.23)	0.003
	120 minutes	290	289	-3.94	-3.17	-0.78	(-1.23,-0.33)	<.001
	150 minutes	290	289	-4.21	-3.49	-0.72	(-1.18,-0.25)	0.003
	180 minutes	291	291	-4.29	-3.67	-0.62	(-1.09,-0.15)	0.010
	210 minutes	291	292	-4.52	-3.87	-0.65	(-1.13,-0.18)	0.007
	240 minutes	291	292	-4.64	-3.95	-0.70	(-1.19,-0.20)	0.006
Olopatadine HCl NS	15 minutes	292	292	-1.41	-1.08	-0.34	(-0.64,-0.03)	0.029
	30 minutes	292	292	-2.34	-1.64	-0.70	(-1.05,-0.35)	<.001
	45 minutes	292	292	-3.16	-2.11	-1.05	(-1.44,-0.66)	<.001
	60 minutes	287	289	-3.45	-2.56	-0.89	(-1.30,-0.48)	<.001
	90 minutes	288	289	-3.82	-2.92	-0.90	(-1.33,-0.46)	<.001
	120 minutes	288	289	-4.17	-3.17	-1.01	(-1.46,-0.56)	<.001
	150 minutes	287	289	-4.38	-3.49	-0.89	(-1.35,-0.42)	<.001
	180 minutes	291	291	-4.39	-3.67	-0.72	(-1.18,-0.25)	0.003
	210 minutes	291	292	-4.68	-3.87	-0.81	(-1.29,-0.33)	<.001
	240 minutes	291	292	-4.80	-3.95	-0.85	(-1.35,-0.36)	<.001
Mometasone furoate NS	15 minutes	294	292	-1.08	-1.08	-0.00	(-0.30, 0.30)	0.998
	30 minutes	294	292	-1.91	-1.64	-0.27	(-0.62, 0.08)	0.137
	45 minutes	294	292	-2.43	-2.11	-0.32	(-0.71, 0.07)	0.109
	60 minutes	293	289	-2.72	-2.56	-0.16	(-0.57, 0.25)	0.439
	90 minutes	293	289	-3.10	-2.92	-0.17	(-0.61, 0.26)	0.430
	120 minutes	293	289	-3.49	-3.17	-0.33	(-0.77, 0.12)	0.154
	150 minutes	293	289	-3.90	-3.49	-0.41	(-0.87, 0.05)	0.082
	180 minutes	293	291	-3.93	-3.67	-0.25	(-0.72, 0.22)	0.291
	210 minutes	293	292	-4.21	-3.87	-0.34	(-0.82, 0.13)	0.158
	240 minutes	293	292	-4.42	-3.95	-0.47	(-0.96, 0.02)	0.061

iTNSS = sum of four nasal symptom scores (Rhinorrhea, Nasal Congestion, Nasal Itching, Sneezing)
Baseline is defined as the predose time point at the randomization visit (visit 2).
n=number of subjects with data available; LS=least squares; SE=standard error
Statistical Analysis model: MMRM model with change from baseline as the dependent variable, treatment group and site as fixed effects, baseline score as covariate, time as the within-subject effect and treatment*time interaction.
Source: GSP 301-304 study report, Table 14.2.2.3.2
Note: this endpoint was not included in the applicant's multiplicity adjustment plan.
Abbreviations: iTNSS=instantaneous Total Nasal Symptom Score; LSmean=least square mean; CI=confidence interval; NS=nasal spray; HCl=hydrochloride

Figure 22. Least Square Means With 95% Confidence Intervals of Average iTNSS Onset of Action (Full Analysis Set)



Source: GSP 301-304 study report, Figure 11.2.1.4.1
Abbreviations: iTNSS=instantaneous total nasal symptom score; LS=least square; NS=nasal spray; HCl=hydrochloride

Efficacy Results – Secondary or Exploratory Clinical Outcome Assessment (Patient Reported Outcomes) Endpoints

QOL, as assessed by the secondary endpoint RQLQ scores (Table 39 and Figure 23), was statistically significantly improved for patients on GSP 301 compared to that of patients on placebo, with a mean difference of -0.45. RQLQ scores of patients treated with GSP 301 were also compared to those of patients treated with individual components: scores from GSP 301 were statistically lower compared to scores from OLO (mean difference=-0.31), but they were not lower than scores from MF (mean difference=-0.09). Furthermore, the responses of patients on OLO were not statistically improved compared to those of patients on placebo (mean difference=-0.14), while those of patients on MF were statistically improved compared to those of patients on placebo (mean difference=-0.36).

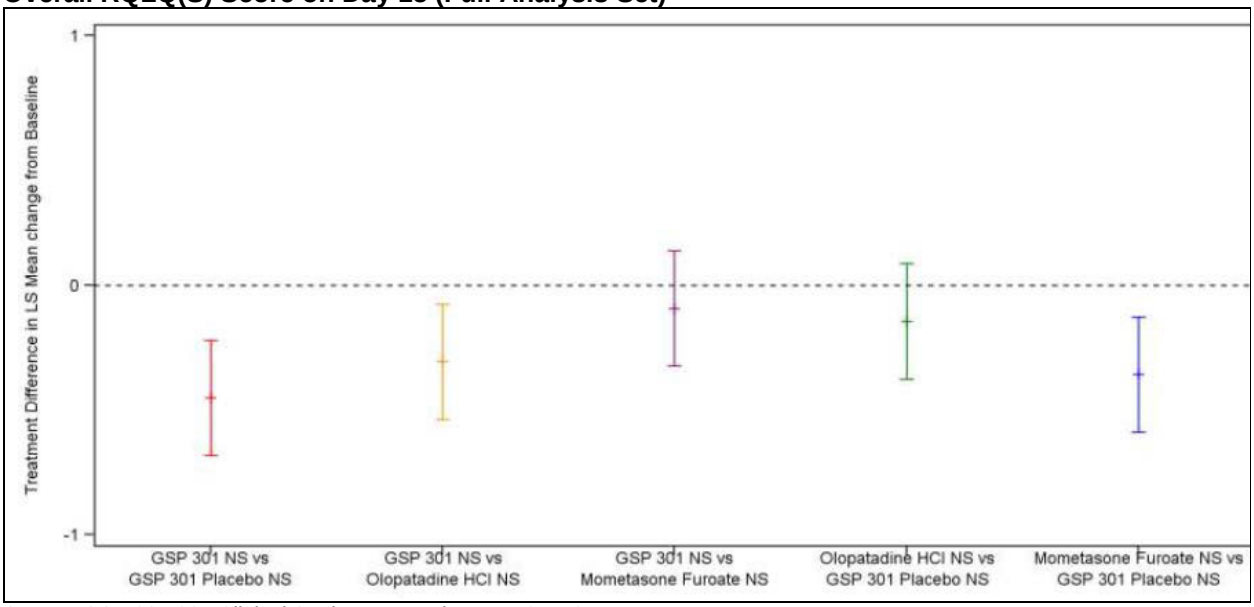
Table 39. Summary of Analysis of Covariance Results for Overall RQLQ Score on Day 15 (Full Analysis Set)

	n		Comparison between TRT 1 and TRT 2		
Treatment Group Comparison (TRT 1 vs. TRT 2)	TRT 1[a]	TRT 2[a]	LS Mean Difference	95% CI	P-value
GSP 301 NS vs. GSP 301 placebo NS	283	280	-0.45	(-0.68, -0.22)	0.0001[b]
GSP 301 NS vs. olopatadine HCl NS	283	276	-0.31	(-0.54, -0.08)	0.0090[b]
GSP 301 NS vs. mometasone furoate NS	283	280	-0.09	(-0.32, 0.14)	0.4236
Olopatadine HCl NS vs. GSP 301 placebo NS	276	280	-0.14	(-0.38, 0.09)	0.2217
Mometasone furoate NS vs. GSP 301 placebo NS	280	280	-0.36	(-0.59, -0.13)	0.0024[b]

CI=confidence interval; HCl=hydrochloride; LS = least square; n=number of subjects with data available; NS=nasal spray; TRT1=treatment 1; TRT2=treatment 2; vs=versus
[a] Number of subjects that had baseline and post-baseline RQLQ measurement.
[b] Statistically significant difference ($p<0.05$).

Source: GSP 301-304 study report, Table 16
Note: this endpoint was not included in the applicant's multiplicity planning
Abbreviations: RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire

Figure 23. Treatment Differences of Least Square Means With 95% Confidence Intervals for Overall RQLQ(S) Score on Day 15 (Full Analysis Set)



Source: GSP 301-304 Clinical Study Report, Figure 11.2.1.13
Abbreviations: RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire; LS=least square; NS=nasal spray; HCl=hydrochloride

Integrated Review of Effectiveness

Comparisons were made between GSP 301, its single components, and placebo. Results for rTNSS, iTNSS, iTNSS onset of action, rTOSS, iTOSS, and RQLQ demonstrate a clear and statistically significant separation between patients administered GSP 301 versus placebo. However, the other comparisons (i.e., GSP 301 to its single components and the single components to placebo) were not as consistently significantly different. This variation among endpoints may be expected since OLO and MF have differing efficacy benefits and onsets of action.

Note there was no preplanned adjustment for multiplicity, with the exception of intra-treatment arm comparisons for rTNSS, iTNSS, and rTOSS between primary and secondary endpoints. With a gatekeeping multiplicity strategy, the expectation is a fully closed set of comparisons beginning with the primary endpoint, rTNSS, and extending to any secondary endpoints being considered for the label.

8.1.5. Study Design- GSP 301-201

This phase 2 study was intended to provide evidence of dose selection, efficacy, and safety for two different dosing regimens of GSP 301 compared to placebo and monotherapies (GM OLO and GM MF). The two dosing regimens were:

- GSP 301-1 NS containing 665 µg OLO/50 µg MF administered QD
- GSP 301-2 NS containing 665 µg OLO/25 µg MF administered BID

Study 201 was conducted in 10 U.S sites during December 5, 2014 to February 22, 2015. A study report was issued on February 16, 2017.

Objectives

Primary:

- To compare the efficacy of GSP 301-1 NS and GSP 301-2 NS with placebo over 14 days of study treatment

Secondary:

- To compare the efficacy of GSP 301-1 NS and GSP 301-2 NS with the individual constituent monotherapies at the same dose in the same vehicle over 14 days of study treatment
- To compare the onset of action between active GSP 301-1 and GSP 301-2 NS with placebo and the individual constituent monotherapies at the same dose in the same vehicle, after the first dose of study drug administration
- To assess the safety and tolerability of individual treatment arms

Trial Design

Study 201 was a phase 2, randomized, double-dummy, double-blind, parallel-group, placebo- and active-controlled comparative study to evaluate the efficacy, safety and tolerability of two FDCs of OLO/MF NS to those of placebo and individual monotherapy formulations (OLO NS and MF NS) in subjects (≥12 years old) with SAR during the mountain cedar pollen season. The monotherapy formulations used in this study were GM formulations. Following a 7- to 10-day single-blind placebo run-in period, eligible subjects were randomized into seven treatment groups in a 1:1:1:1:1:1:1 ratio.

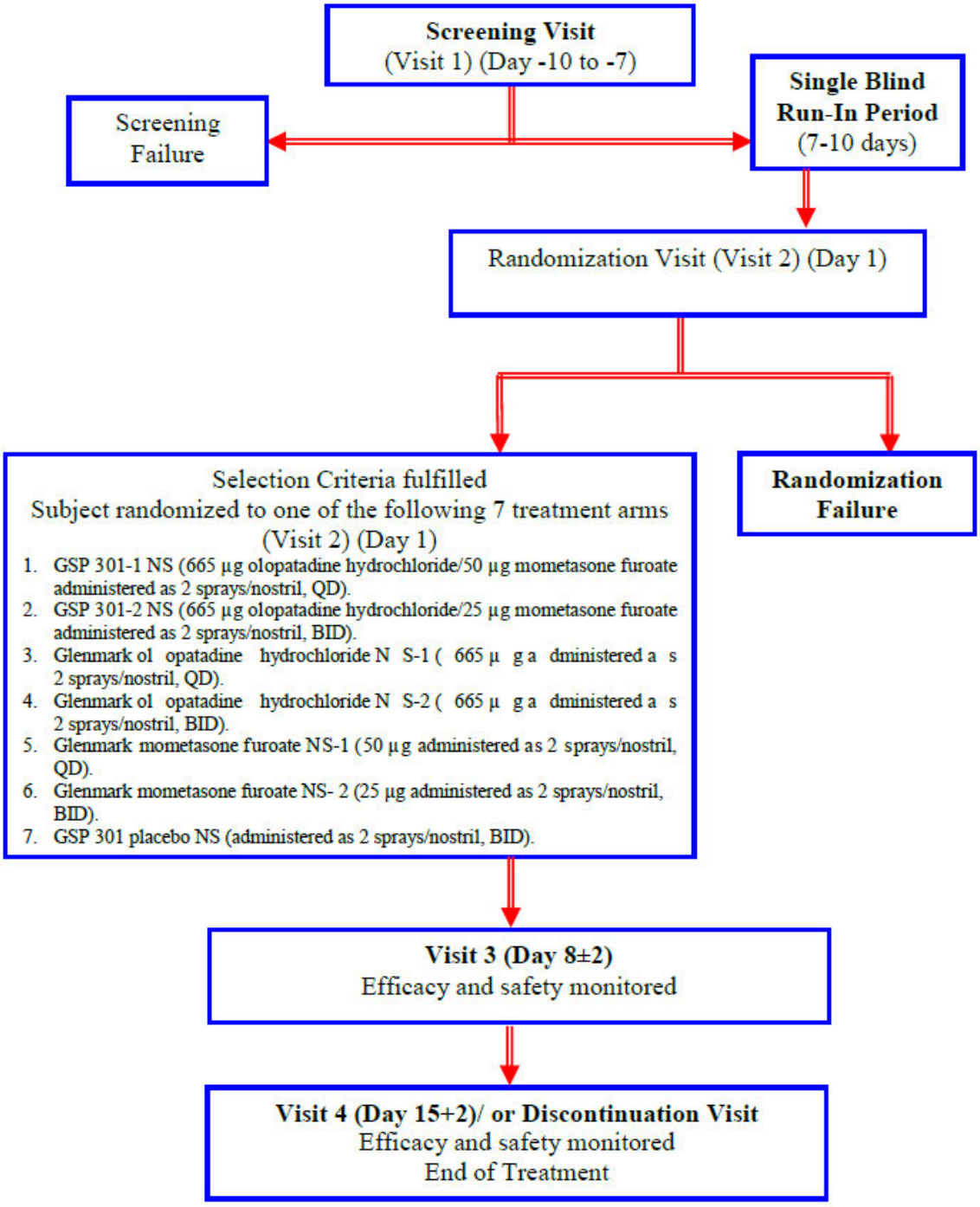
After randomization (visit 2) but before trial medication administration, patients ≥18 years of age were administered the adult RQLQ. Patients were also instructed to record the iTNSS prior to the first dose of trial medication and at prespecified intervals. The first dose of trial medication was self-administered during the clinic visit. Prior to leaving the clinic, patients were given a new diary. During the 14-day treatment period, patients were instructed to record symptoms scores twice daily (AM and PM), and to take the study medication BID after recording the scores.

An interim evaluation (visit 3) was performed on day 8 (+/-2) of the treatment period. Assessments included collection and review of the patient diary, returned trial medication, vital signs, focused nasal examination, AEs, and concomitant medications. A new diary was distributed.

The final evaluation (visit 4) took place on day 15 (+/-2) of the treatment period or at the time of early termination. The first assessment conducted at Visit 4 was the RQLQ for adults. Additional assessments included collection and review of the patient diary, returned trial medication, vital signs, focused nasal examination, urine pregnancy test, AEs, and concomitant medications.

The study design is shown in Figure 24.

Figure 24. Study GSP 301-201 Schema



Source: Study GSP 301-201 CSR p. 29
Abbreviations: NS=nasal spray; QD=once daily; BID=twice daily

Assessments and Procedures

The schedule of assessments and procedures is shown in Table 40. At each visit focused nasal examinations were performed to assess signs of AR as well as known complications of intranasal corticosteroid or antihistamine use (i.e., bleeding, perforation, and ulceration). Throat examinations were performed to evaluate evidence of irritation or candidiasis. Patients were referred to a qualified ENT specialist for and nasal ulceration, nasal mucosal erosion, or nasal septal perforation. Eligibility of the patient to continue to participate in the study was at the investigator's discretion.

Table 40. Study GSP 301-201 Schedule of Procedures and Assessments

Activity/Observation	Screening Visit (Visit 1)	Randomization Visit (Visit 2)	Treatment Visit (Visit 3)	Final Visit (Visit 4)
	Day -7 to -10	Day 1	Day 8±2[a]	Day 15+2[a]
Written informed consent (assent, if applicable) and HIPAA authorization	X			
Inclusion/exclusion criteria review	X			
Demographic data	X			
Medical and treatment history	X			
Concomitant medication evaluation	X	X	X	X
Physical examination	X			X
Vital signs	X	X	X	X
Height and weight measurements	X			X
Laboratory assessments (hematology biochemistry and urine analysis)	X			X
Focused ENT examination	X	X	X	X
Allergy testing (skin prick test for relevant allergen, if required)	X			
12-lead ECG	X			X
Urine pregnancy test (if applicable)	X	X		X
Review instructions and train on proper use of nasal spray using the GSP301 placebo NS device	X			
Review instructions and train on proper use of nasal spray		X	X	
Prime and dispensation and administration of single-blind placebo nasal spray at the clinic	X			
Distribution of symptom assessment diary	X	X	X	
Collection/review of symptom assessment subject diary		X	X	X
Subject assessment of AR symptoms and recording at the clinical site	X			
Subject assessment of AR symptoms and recording	X			
Physician assessment of nasal symptom severity		X		X

Activity/Observation	Screening Visit (Visit 1)	Randomization Visit (Visit 2)	Treatment Visit (Visit 3)	Final Visit (Visit 4)
Review randomization criteria		X		
Randomization/treatment assignment		X		
Prime and dispensing of double-blind study medication		X		
Administration of first dose of double-blind study medication		X		
Onset of action efficacy assessment		X		
Administration of double-blind study medication			X	
Distribution of RQLQ, review instructions with the subject and subject completion of RQLQ		X		X
Adverse event monitoring	X	X	X	X
Return of study medication		X		X
Return of subject diary				X
Subject compliance check (study procedures, diary and study medication)		X	X	X
Concomitant medication evaluation	X	X	X	X

Source: Study GSP 301-201 CSR Table 6 page 36
Abbreviations: AR = allergic rhinitis; ECG = Electrocardiogram; ENT = Ear, Nose and Throat; HIPPA = Health Insurance Portability and Accountability Act; RAST = radioallergosorbent test; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire

Key Inclusion Criteria

- Documented clinical history of SAR (for at least 2 years preceding the screening visit (visit 1) with exacerbations during the study season for mountain cedar pollen and exhibiting a documented positive skin prick test to mountain cedar allergen. Documentation of a positive result within 12 months prior to visit 1 was acceptable.
- A 12-hour rTNSS ≥8 out of a possible 12 and a congestion score of ≥2 for the morning (AM) assessment at visit 1.
- Male or female aged 12 years or older.

Key Exclusion Criteria

- Planned to travel outside the known pollen area for the investigative site for 24 hours or longer during the last 7 days of the run-in period.
- Planned to travel outside the known pollen area for the investigative site for 2 or more consecutive days OR 3 or more days in total between the randomization visit (visit 2) and the final treatment visit (visit 4).
- History of nasal polyps or clinically significant respiratory tract malformations, recent nasal biopsy, nasal trauma or surgery, atopic dermatitis, or rhinitis medicamentosa (within 60 days prior to the visit 1).

- Nasal structure abnormalities, including nasal ulceration, nasal mucosal erosion, and septal deviation that interfered with nasal air flow.
- Treatment with any CYP3A4 inducers or inhibitors within 30 days prior to or during study.
- Nonvaccinated exposure to or active infection with chickenpox or measles within 21 days preceding visit 1.
- Known hypersensitivity to any corticosteroids or antihistamines or to the study drug or its excipients.
- History of anaphylaxis and/or local reaction to skin testing.
- Any severe neuropsychiatric, gastrointestinal, hematologic, hepatic, renal, cardiovascular or respiratory disease or infection other than asthma.
- Dependence on nasal, oral, or ocular decongestants, nasal topical antihistamines, or nasal steroids.
- History of posterior subcapsular cataracts or glaucoma, increased ocular pressure, incisional eye surgery, or ocular herpes simplex.
- History of hypothalamic-pituitary-adrenal axis impairment.
- Previous participation in another GSP 301 study.
- Use of topical corticosteroids in concentrations in excess of 1% hydrocortisone or equivalent within 30 days of visit 1.

Treatment Groups

The seven treatment groups were comprised of three QD groups (one each for GSP 301, MF, and OLO), three BID groups, and one placebo group. Subjects in every treatment group self-administered two sprays of product per nostril each morning and evening. Subjects in the BID groups received active treatment both morning and evening. The QD groups received active treatment in the morning and placebo in the evening.

Concomitant Medications

Prohibited Medications

The medications listed in Table 41 were prohibited during this trial for the indicated number of days prior to the screening visit as well as throughout the study.

Table 41. Prohibited Concomitant Medications

Type of Medication	Days Prohibited Prior to the Screening Visit
Vasoconstrictors (e.g., epinephrine, sumatriptan).	3 days
Major tranquilizers (e.g., antipsychotics such as chlorpromazine, haloperidol, risperidone, clonazepam)	3 days
Short-acting antihistamines (oral, ocular or intranasal antihistaminic (e.g., azelastine))	5 days
OTC cough and cold preparations or sleep aids containing antihistamines	7 days
Topical/oral/nasal decongestants (e.g., oxymetazoline, pseudoephedrine, tetrahydrozoline)	7 days
OTC food supplement/diet to reduce leukotrienes (AIROZIN)	7 days
Leukotriene antagonists or arachidonate 5-lipoxygenase inhibitors	7 days
Inhaled/oral/intranasal anticholinergics	7 days
Long-acting antihistamines (e.g., cetirizine, fexofenadine.	10 days
Cromolyn (all forms), nedocromil or lodoxamide (intranasal, ocular, or oral)	14 days
Systemic antibiotic	14 days
Ocular mast cell stabilizers	14 days
Monoamine oxidase inhibitors	14 days
Tricyclic antidepressants	14 days
All intranasal/topical/ocular corticosteroids (except study medication)	30 days
Inhaled corticosteroids	30 days
Any other investigational nonbiological drug	30 days
Treatment with any known potent CYP3A4 inducers (carbamazepine, dexamethasone, phenytoin, rifabutin, rifampin, pioglitazone, etc.)	30 days
Treatment with any known potent CYP3A4 inhibitors (azole antifungals, macrolide antibiotics, etc.)	30 days
Systemic corticosteroids (intermittent or chronic including intra-articular)	60 days
Immunotherapy injections and immunosuppressive/immune-modulator medications (except topical pimecrolimus cream or tacrolimus ointment if initiated at least 30 days prior to screening and maintained on stable dose)	60 days
IgE antagonist or any other anti IgE therapy	120 days
Any other investigational biological drug	120 days
Anti-interleukin-5 therapy (reslizumab, mepolizumab, etc.)	120 days
Sublingual immunotherapy (investigational or other)	180 days

Source: CSR Study 301-304 Table 6 page 36

These medications were prohibited from the screening visit to the final visit:

- All intranasal therapies
- Topical corticosteroids
- All eye ophthalmic drops
- Radiation therapy
- Initiation of injectable immunotherapy
- Any investigational drug
- Herbal medication, supplements or other alternative therapies for AR
- St. John's wort

Permitted Medications

Subjects were allowed to use other chronic medications in stable doses.

Study Endpoints

Primary Endpoint

The primary efficacy endpoint was the change from baseline in average AM and PM subject-reported rTNSS over the 14-day treatment period.

Secondary Endpoints

The key secondary endpoints were:

- Change from baseline in average AM and PM subject-reported iTNSS over the 14-day treatment period.
- Change from baseline in average AM and PM subject-reported rTOSS over the 14-day treatment period.
- Onset of action for each treatment by comparing the change from baseline in post treatment iTNSS between each active treatment and placebo at defined timepoints (prior to first dose (predose)) after the first study treatment for 4 hours. Baseline was defined as the time point pre-dosing at the randomization visit (visit 2).
- Change from baseline in RQLQ on day 15 (visit 4) in the RQLQ population (subjects with impaired QOL at baseline, defined by a RQLQ score at visit 2 of ≥3).

Details on the scoring system for the TNSS and TOSS are provided below, along with a description of the RQLQ.

Total Nasal Symptom Score

The TNSS was defined as the sum of the subject-reported symptom scores for the four nasal symptoms (rhinorrhea, sneezing, nasal itching, and nasal congestion) on a four-point scale:

0=Absent (no sign/symptom evident)

1=Mild (sign/symptom present but minimal awareness; easily tolerated)

2=Moderate (definite awareness of sign/symptom that is bothersome but tolerable)

3=Severe (sign/symptom that are hard to tolerate that cause interference with activities of daily living and/or sleeping)

Total Ocular Symptom Score

The TOSS grades each of three symptoms (itching/burning eyes, tearing/watering eyes and redness of the eye) on a four-point scale. The grading scale for itchy eyes and watery eyes is the same as that for the TNSS. The grading scale for eye redness is as follows:

0=None (no redness present)

1=Mild (slightly dilated blood vessels and pinkish color compared to subject's normal color)

2=Moderate (more dilation of blood vessels and red color compared to subject's normal color)

3=Severe (large, numerous dilated blood vessels and deep red color compared to subject's normal color)

Rhinoconjunctivitis Quality of Life Questionnaire

The RQLQ is a tool that measures the subjective impact of SAR on patients' health-related QOL. It is comprised of 28 items in 7 domains evaluated on a 7-point scale where 0=no impairment and 6=maximum impairment. A change from baseline ≥0.5 points is considered to represent a clinically meaningful improvement. The RQLQ was administered to patients 18 years of age and older in the 2-week efficacy and safety trials.

Safety Assessments

Monitored safety parameters included the following and were assessed:

- Spontaneous and elicited AEs, SAEs, discontinuations due to AEs
- Focused ENT examination
- Physical examination
- Clinical laboratory evaluation
- Vital signs
- ECG
- Urine pregnancy testing

Statistical Analysis Plan

The SAP for this study was signed off on February 27, 2015. The Applicant states the SAP was approved prior to database lock and unblinding of the study. The database was locked and approved on April 15, 2015.

Populations used in the analyses include randomized analysis set, SAS, FAS, PPS, and RQLQ(S) analysis set. The Applicant defined these as follows:

> The randomized analysis set consisted of all subjects who took at least one dose of study medication during the run-in period and was used for all run-in period safety analyses. The randomized analysis set included subjects who were never randomized.
>
> The SAS consisted of all subjects who took at least one dose of study medication following randomization and was used for all safety analyses.
>
> The FAS consisted of all subjects who were randomized and received at least one dose of IP and had at least one postbaseline primary efficacy assessment. This was the primary analysis set for efficacy analyses.
>
> The PPS consisted of the subset of the FAS who did not meet criteria for PPS exclusion. These criteria were to capture relevant nonadherence to the protocol (especially those that affected interpretation of the primary endpoint). The PPS was a secondary analysis set for the primary efficacy endpoint and selected secondary endpoints.
>
> The RQLQ(S) analysis set consisted of all English-speaking subjects ≥18 years old with impaired QOL at baseline as defined by RQLQ(S) score at the Randomization Visit (visit 2; baseline) of 3.0 or greater.

There was no imputation for missing data for subject-reported nasal symptom scores, ocular symptom scores, non-nasal symptom scores, or for physician-assessed nasal symptom scores. If any component symptom score was missing for a timepoint, the TNSS score for that time point was also considered missing. The same strategy was implemented for missing TOSS data. For RQLQ, if any of the questions for a given RQLQ domain at a given time point was missing, the average domain score for that time point was considered missing. For the primary efficacy endpoint, in case of dropouts, the repeated measures ANCOVA and a last non-missing symptom score carried forward up to day 17 (LOCF) approach were both used. These analyses were performed on the FAS and considered as sensitivity analyses.

The primary analysis used the FAS population and the ANCOVA model of treatment group and center for with baseline as covariate for 12-hour rTNSS (linear, continuous covariate). The primary analysis was not imputed for missing data. LS means of the treatment differences and

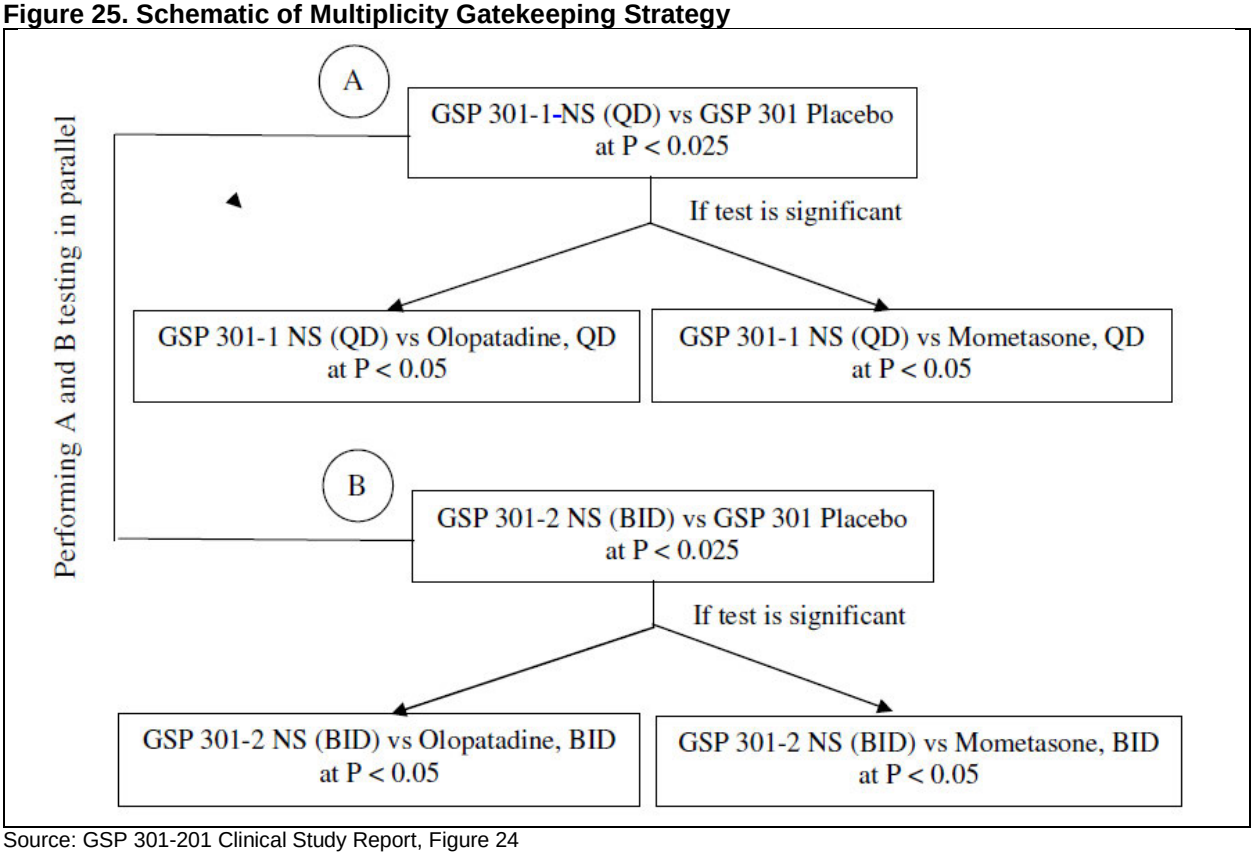
associated 95% CIs and p-values were presented. For the two primary comparisons, GSP 301-1 NS (QD) compared with placebo and GSP 301-2 NS (BID) compared with placebo, 97.5% CIs were presented. The interactions of center-by-treatment group and baseline 12-hour rTNSS-by-treatment group were investigated separately in the ANCOVA model and were removed from the final model if they were not statistically significant at the 5% alpha level.

Comparisons of each of the two IPs (GSP 301-1 NS (QD) and GSP 301-2 NS (BID)) to placebo were compared using pairwise comparisons at a two-sided 0.025 significance level. A Bonferroni correction was used to divide the alpha equally between testing with the BID and QD regimens.

Treatment comparisons were tested using a gate-keeping strategy, as follows (Figure 25):

A1: GSP 301-1 NS (QD) versus placebo (tested at $p<0.025$).
A2: GSP 301-1 NS (QD) versus OLO-1 NS, (QD) (tested at $p<0.05$ if A1 significant).
A3: GSP 301-1 NS (QD) versus MF-1 NS, (QD) (tested at $p<0.05$ if A1 significant).
B1: GSP 301-2 NS (BID) versus placebo (tested at $p<0.025$).
B2: GSP 301-2 NS (BID) versus OLO-2 NS, (BID) (tested at $p<0.05$ if B1 significant).
B3: GSP 301-2 NS (BID) versus MF-2 NS, (BID) (tested at $p<0.05$ if B1 significant).

Figure 25. Schematic of Multiplicity Gatekeeping Strategy



Source: GSP 301-201 Clinical Study Report, Figure 24
Abbreviations: NS=nasal spray; QD=once daily; BID=twice daily

A repeated measure mixed model was applied as a secondary analysis to support the primary endpoint using the FAS. The model adjusted for study treatment, center, baseline 12-hour rTNSS (linear, continuous covariate), and study day as the within-subject effect. The Applicant did not perform a sensitivity analysis for this phase 2 study.

The same methodology was applied to secondary endpoints of change from baseline in average AM and PM 12-hour iTNSS and rTOSS. If either baseline or postbaseline results were missing, change from baseline and percent change were also set to missing.

Comparisons of each of the two IPs (GSP 301-1 NS (QD) and GSP 301-2 NS (BID)) to placebo were compared using pairwise comparisons at a two-sided 0.025 significance level. A Bonferroni correction was used to divide the alpha equally between testing with the BID and QD regimens.

Secondary endpoints, ordered by clinical importance, were as follows:

1. Change from baseline in average AM and PM subject-reported iTNSS over the 14-day treatment period.
2. Change from baseline in average AM and PM subject-reported 12-hour rTOSS over the 14-day treatment period.
3. Onset of action for each treatment assessed by comparing the change from baseline in posttreatment iTNSS between each active treatment and placebo at defined timepoints (prior to first dose (predose), 15±3min, 30±3 min, 45±3 min, 60±5 min, 90±5 min, 120±10 min, 150±10 min, 180±10 min, 210±10 min, and 240±10 min) after the first study treatment for 4 hours. Baseline was defined as the time point predosing at the Randomization Visit (V2).
4. Change from baseline in the RQLQ on Day 15 in the RQLQ population (subjects with impaired QOL at baseline, defined by a RQLQ score at the Randomization Visit (V2) of ≥3.0).

No multiplicity plan was indicated for the secondary endpoints, iTNSS, rTOSS, onset of action, or RQLQ.

Subgroup analyses by age group (12–17, 18–64, 65 and above), sex, race, and ethnicity were conducted for rTNSS and secondary endpoints iTNSS, rTOSS, onset of action, and RQLQ.

The Applicant's focus in their submission was on the pooled analysis of studies 201, 301, and 304, with a proposed label describing the results of study 304 only. This is discussed in Section 8.1.4.

Protocol Amendments

Version 1.0 dated October 7, 2014 was replaced by Version 2.0 dated December 3, 2014, which provided minor revisions to the protocol and changes for clarity, accuracy, and consistency of the protocol. The changes made in Version 3.0 on March 5, 2015 included the clarification of the definition of the baseline rTNSS in the statistical methods section. Planned analyses were defined in the protocol and the SAP dated February 26, 2015, and no changes were made to the planned analyses.

8.1.6. Study Results GSP 301-201

Study 201 enrolled 1,366 subjects and randomized 1,111 subjects. Ten subjects discontinued participation due to an AE. Six subjects withdrew consent. Each treatment group had similar number of subjects who completed the study (Table 42).

Table 42. Summary of Subject Disposition Study GSP 301-201 (Safety Analysis Set)

Disposition	GSP 301 Placebo N=159 n (%)	GSP 301-1 QD N=158 n (%)	Mometasone furoate-1 QD N=160 n (%)	Olopatadine HCl-1 QD N=158 n (%)	GSP 301-2 BID N=157 n (%)	Mometasone furoate-2 BID N=159 n (%)	Olopatadine HCl-2 BID N=160 n (%)
Randomized	159 (100.0)	158 (100.0)	160 (100.0)	158 (100.0)	157 (100.0)	159 (100.0)	160 (100.0)
Terminated early	4 (2.5)	3 (1.9)	3 (1.9)	3 (1.9)	5 (3.2)	6 (3.8)	2 (1.3)
Completed study	155 (97.5)	155 (98.1)	157 (98.1)	155 (98.1)	152 (96.8)	153 (96.2)	158 (98.8)
Early termination reason							
Adverse event	0	2 (1.3)	2 (1.3)	1 (0.6)	2 (1.3)	1 (0.6)	2 (1.3)
Death	0	0	0	0	0	0	0
Investigator's Discretion	0	0	0	0	0	1 (0.6)	0
Lost to follow up	1 (0.6)	0	0	0	0	0	0
Noncompliance with study procedure	0	0	0	0	2 (1.3)	0	0
Other	0	1(0.6)	0	1 (0.6)	1 (0.6)	1 (0.6)	0
Pregnancy	0	0	0	0	0	0	0
Protocol deviation	0	0	0	1 (0.6)	0	1 (0.6)	0
Withdrawal of consent	3 (1.9)	0	1 (0.6)	0	0	2 (1.3)	0

Source: Study GSP 301-201 CSR Table 7 page 55 and Table 14.1.9.1
Abbreviations: MF=mometasone furoate; QD=once daily; BID=twice daily; HCl=hydrochloride; SAS=safety analysis set

Protocol Violations/Deviations

During the randomized treatment period, protocol deviations occurred in 6 (3.8%) to 15 (9.4%) subjects across all treatment groups. The most commonly listed deviation was “other” and “outside visit window.”

Table 43. Protocol Violations/Deviations (Safety Analysis Set)

Violation/Deviation	GSP 301 Placebo N=159 n (%)	GSP 301-1 QD N=158 n (%)	Mometasone Furoate-1 QD N=160 n (%)	Olopatadine HCl-1 QD N=158 n (%)	GSP 301-2 BID N=157 n (%)	Mometasone Furoate-2 BID N=159 n (%)	Olopatadine HCl-2 BID N=160 n (%)
Total patients with Deviations	9 (5.7)	7(4.4)	6 (3.8)	12 (7.6)	9 (5.7)	15 (9.4)	9 (5.6)
Total deviations	10	7	8	15	11	16	10
Outside visit window	2	3	2	2	6	5	3
Enrolled in error	0	0	0	0	0	0	0
Randomized in error	2	0	0	1	0	0	2
Dosing noncompliance	0	0	0	1	0	0	0
Restricted medication	0	0	3	1	1	2	3
TNSS rating Noncompliance	0	0	0	1	1	0	0
Lost to follow up	1	0	0	0	0	0	0
Other	5	4	3	9	3	9	2

Source: GSP 301-201 CSR Table 14.1.9.2.1
Abbreviations: SAS=safety analysis set; QD=once daily; BID=twice daily; HCl=hydrochloride

Demographic Characteristics

Table 44 shows that all groups in study 201 were similar in terms of demographics for the full analysis set. The majority of subjects in all groups were female, white, and not Hispanic or Latino, and the mean age of subjects ranged from 41.9 years to 45.3 years across treatment groups.

Table 44. Demographic Data Set Study 301-201 (Full Analysis Set)

Demographic	GSP 301 Placebo	GSP 301-1 QD	Mometasone Furoate-1 QD	Olopatadine HCl-1 QD	GSP 301-2 BID	Mometasone Furoate-2 BID	Olopatadine HCl-2 BID
Age (years)							
N	158	158	160	158	157	159	160
Mean (SD)	45.4 (14.9)	43.8 (113.6)	44.4 (14.3)	41.9 (12.5)	43.4 (14.1)	44.6 (13.7)	43.5 (13.9)
Median	46.7	44.8	45.5	42.0	44.2	46.2	43.1
Min, max	12, 78	12, 78	13, 76	12, 66	14, 75	15, 75	12, 78
Sex n (%)							
Male	47 (29.7)	58 (36.7)	45 (28.1)	53(33.5)	46 (29.3)	63 (39.6)	59 (36.9)
Female	111 (70.3)	100(63.3)	115 (71.9)	105 (66.5)	111 (70.7)	96 (60.4)	101 (63.1)
Race n (%)							
American Indian or Alaska Native	1 (0.6)	1 (0.6)	1 (0.6)	0	0	0	0
Asian	1 (0.6)	4 (2.5)	4 (2.5)	1 (0.6)	3 (1.9)	5 (3.1)	3 (1.9)
White	133 (84.2)	132 (83.5)	127 (79.4)	131 (82.9)	129 (82.2)	126 (79.2)	132 (82.5)
Black/African American	23 (14.6)	20 (12.7)	28 (17.5)	26 (16.5)	23 (14.6)	27 (17.0)	24 (15.0)
Native Hawaiian or Pacific Islander	0	0	0	0	0	0	0
Other	0	1 (0.6)	0	0	2 (1.3)	1 (0.6)	1 (0.6)
Ethnicity n (%)							
Hispanic or Latino	58 (36.7)	60 (38.0)	68 (38.1)	68 (43.0)	79 (50.3)	66 (41.5)	72 (45.0)
Not Hispanic or Latino	100 (63.3)	98 (62.0)	99 (61.9)	90 (57.0)	78 (49.7)	93 (58.5)	88 (55.0)

Source: Study GSP 301-201 CSR Table 14.1.9.4.2
Abbreviations: FAS=full analysis set; QD=once daily; BID=twice daily; HCl=hydrochloride; SD=standard deviation

Efficacy Results – Primary Endpoint

In an analysis of rTNSS based on the FAS,[18] statistically significant mean differences between both combination sprays and their respective placebos were observed (1.17 units higher for GSP 301-2 NS BID and 1.11 units higher for GSP 301-1 NS QD) (Table 45 and Figure 26). Means for GSP 301 versus its single components were -0.49 and -0.77 units for OLO BID and QD respectively, and -0.71 and -0.36 units for MF BID and QD respectively. According to the Applicant's multiplicity testing rules, p-values of 0.025 were required for significance and the gatekeeping order for each regimen begins with the comparison to placebo, then OLO and finally MF.

[18] AM and PM rTNSS over the 14-day treatment period, adjusted for investigational site and patient's baseline value in an ANCOVA analysis with change from baseline as the response variable, treatment group and study site as fixed effects and baseline value as covariate

Table 45. Results of Primary Efficacy Analysis, ANCOVA on AM and PM rTNSS Over 14-Day Treatment (Full Analysis Set)

	GSP 301 placebo NS N=158	GSP 301-1 NS (QD) N=158	Mometasone furoate-1 NS (QD) N=160	Olopatadine HCl-1 NS (QD) N=158	GSP 301-2 NS (BID) N=157	Mometasone furoate-2 NS (BID) N=159	Olopatadine HCl-2 NS (BID) N=160
Baseline mean (SD)	10.3 (1.18)	10.4 (1.24)	10.4 (1.30)	10.3 (1.26)	10.4 (1.19)	10.5 (1.13)	10.3 (1.24)
LS mean change from baseline	-1.4143	-2.5230	-2.1667	-1.7513	-2.5846	-1.8713	-2.0928
LS mean (SE) difference from placebo	--	-1.1087# (0.2496)	--	--	-1.1703# (0.2501)	--	--
97.5% CI		-1.6690, -0.5485			-1.7315, -0.6090		
p-value		<0.0001★			<0.0001★		
LS mean (SE) difference from monotherapies[a]	--	--	-0.3563 (0.2488)	-0.7718* (0.2496)	--	-0.7133* (0.2496)	-0.4918* (0.2493)
95% CI			-0.8445, 0.1319	-1.2616, -0.2820		-1.2031, -0.2235	-0.9810, -0.0025
p-value			0.1524	0.0020★		0.0043	0.0488

ANCOVA = analysis of covariance; BID = twice daily; CI = confidence interval; HCl = hydrochloride; LS = least squares; N = number of subjects in the treatment group; NS = nasal spray; QD = once daily; SD = standard deviation; SE = standard error.

LS Means (SE), confidence intervals and p-values are based on an ANCOVA with change from baseline as dependent variable, treatment group and center as fixed effect and baseline as covariate.

Monotherapy formulations used are Glenmark Formulations.

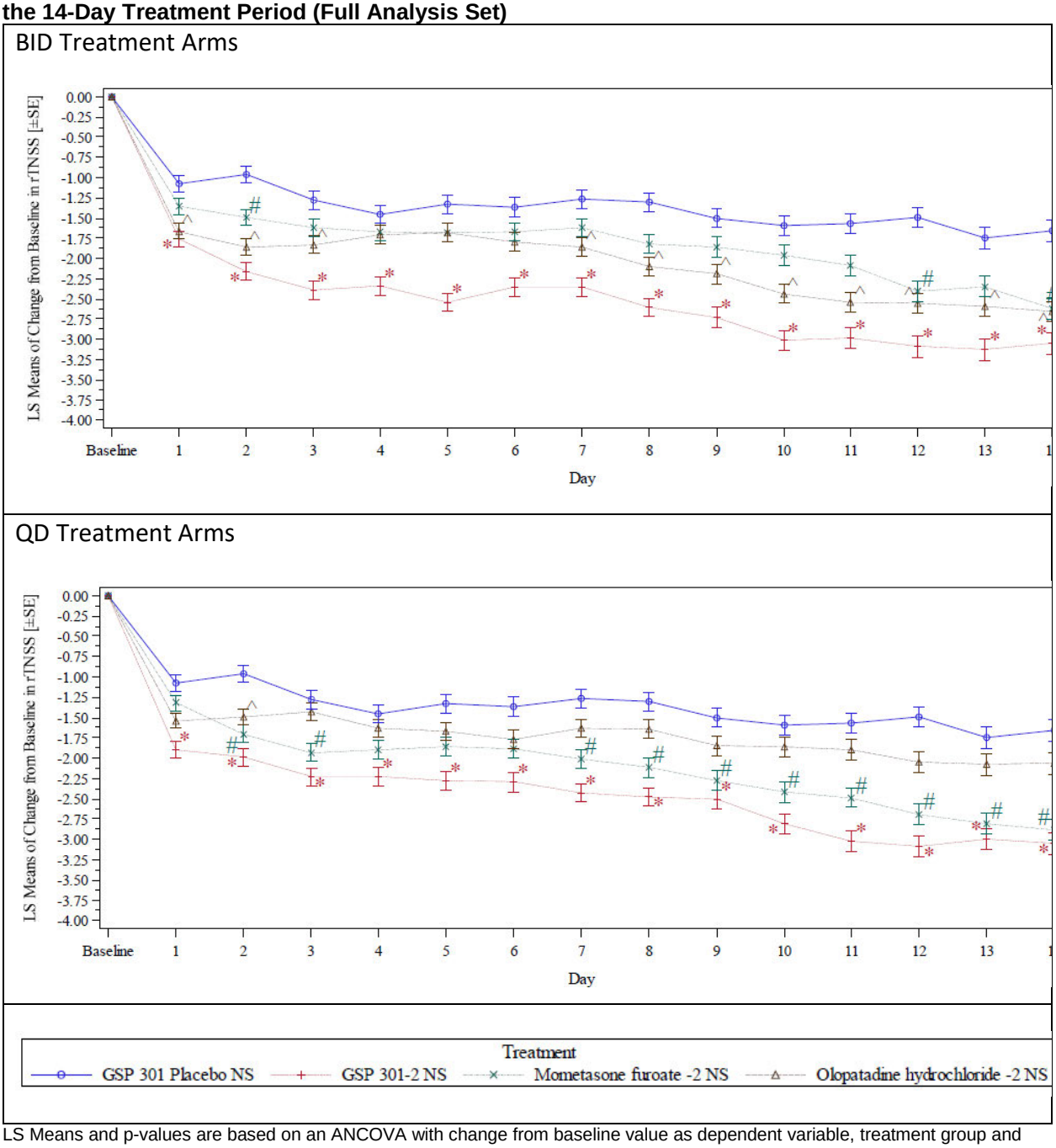
statistically significant difference ($p<0.025$) between GSP 301 NS and placebo.

* statistically significant difference ($p<0.05$) between GSP 301 NS and constituent monotherapies; statistical significance only interpreted if the difference from placebo was statistically significant.

[a] GSP 301 NS (QD) compared with olopatadine hydrochloride-1 NS (QD) and mometasone furoate-1 NS (QD). GSP 301-2 NS (BID) compared with olopatadine hydrochloride-2 NS (BID) and mometasone furoate-2 NS (BID)

★ Statistically significant, based on applicant's multiplicity plan (added by reviewer).
Source: GSP 301-201 Clinical Study Report, Table 12

Figure 26. Least Square Means With 95% Confidence Intervals of Average AM and PM rTNSS Over the 14-Day Treatment Period (Full Analysis Set)



LS Means and p-values are based on an ANCOVA with change from baseline value as dependent variable, treatment group and center as fixed effects and baseline as a covariate.
*, ^, # indicates a significant difference when compared to placebo ($p < 0.05$).
Note: these statistical significances have not been adjusted for multiplicity
Source: GSP 301-201 Clinical Study Report, Figures 15.2.1.2 and 15.2.1.1.
Abbreviations: rTNSS=reflective Total Nasal Symptom Score; BID=twice daily; LS=least square; NS=nasal spray; SE=standard error

The Applicant analyzed the same data using MMRM and got results similar results to the primary MMRM analysis. The MMRM analysis[19] yielded the results in Table 46.

Table 46. Results of Additional Efficacy Analysis, MMRM on AM and PM rTNSS Over 14-Day Treatment (Full Analysis Set)

Treatment Group (Trt 1 vs. Trt 2)	N (Trt 1 vs. Trt 2)	Least Square Mean Difference	Standard Error	95% CI	P-Value
GSP 301 NS (BID) vs. placebo	157, 158	-1.06	0.21	-1.54, -0.59*	<0.001
GSP 301 NS (BID) vs. olopatadine HCl	157, 160	-0.35	0.21	-0.76, 0.06	0.093
GSP 301 NS (BID) vs. mometasone furoate	157, 159	-0.55	0.21	-0.96, -0.14	0.009
GSP 301 NS (QD) vs. placebo	158, 158	-1.07	0.21	-1.54, -0.60*	<0.001
GSP 301 NS (QD) vs. olopatadine HCl	158, 158	-0.70	0.21	-1.11, -0.29	<0.001
GSP 301 NS (QID) vs. mometasone furoate	158, 160	-0.35	0.21	-0.76, 0.06	0.100

Baseline score is derived as the mean of the last 8 reading scores, during the last 4 days of the run-in period prior to randomization, including the AM assessment on the day of randomization.
LS Means, Std Error of LS Means, 95% CI are based on a repeated measure with change from baseline as dependent variable, treatment group and site as fixed effect, baseline as covariate, and study day as the within-patient effect.
* 97.5% confidence interval
Source: GSP 301-201 Clinical Study Report, Table 14.1.9.5.5
Abbreviations: MMRM=mixed-effects for repeated measures; rTNSS=reflective Total Nasal Symptom Score; FAS=full analysis set; Trt=treatment; CI=confidence interval; BID=twice daily; QD=once daily; QID=four times daily; NS=nasal spray

Results of the primary endpoint by age, sex, and race are described in Section 0.

Data Quality and Integrity

No site inspections were performed by the Office of Scientific Investigations as part of this NDA.

Efficacy Results – Secondary and Other Relevant Endpoints

Results for iTNSS were similar to the same analysis on rTNSS (Table 47, Figure 27).

Point estimates and CIs were similar to rTNSS, and the statistically significant comparisons for rTNSS (both the BID and QD GSP 301 comparisons to placebo and the QD comparison of GSP 301 to OLO), were significant for iTNSS as well.

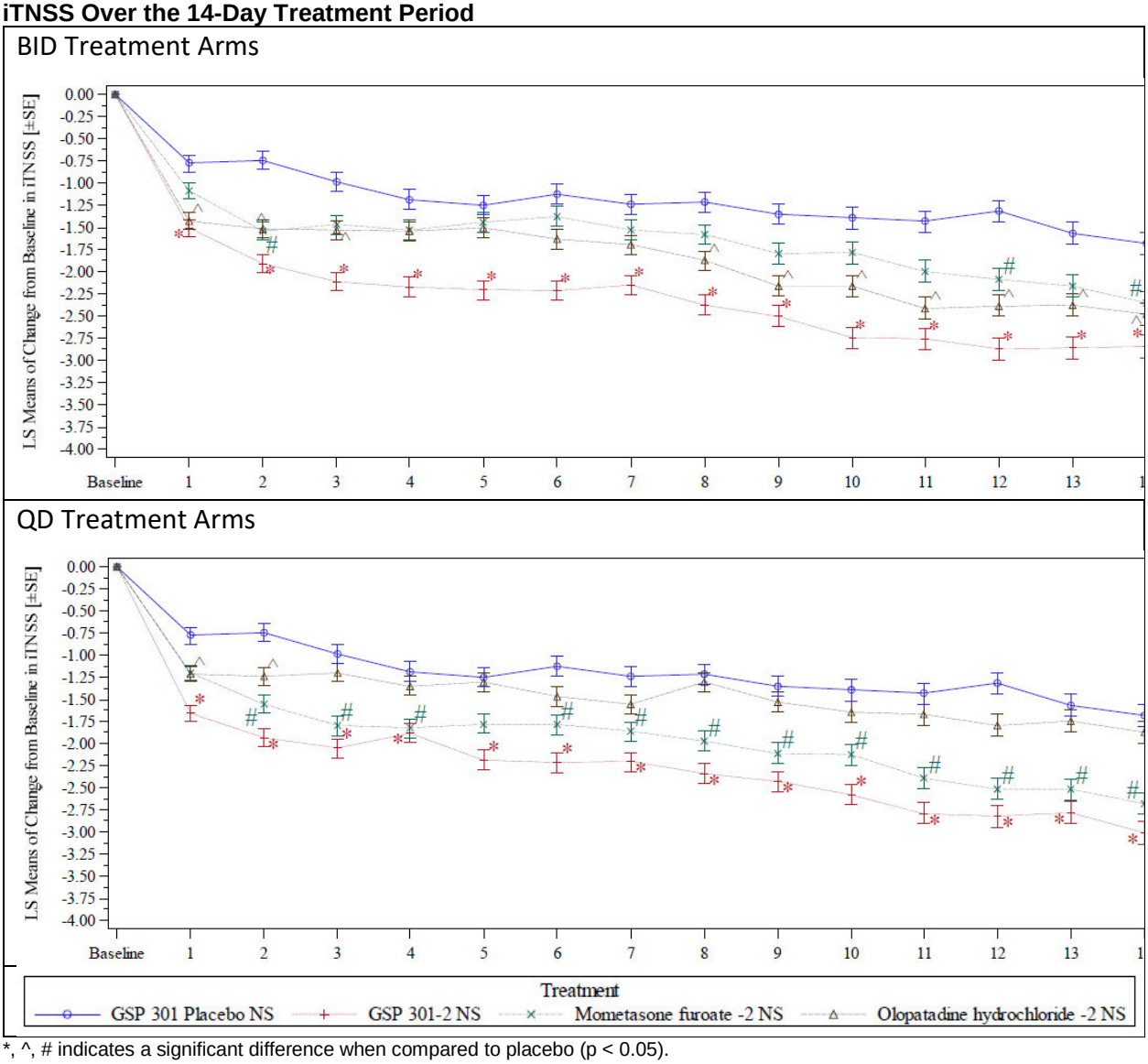
[19] Based on repeated measures with change from baseline as dependent variable, treatment group and site as fixed effect, baseline as covariate, and study day as the within-patient effect.

Table 47. ANCOVA Results for Average AM and PM iTNSS Over the 14-Day Period (Full Analysis Set)

	GSP 301 placebo NS N=158	GSP 301-1 NS (QD) N=158	Mometasone furoate-1 NS (QD) N=160	Olopatadine HCl-1 NS (QD) N=158	GSP 301-2 NS (BID) N=157	Mometasone furoate-2 NS (BID) N=159	Olopatadine HCl-NS (BID) N=160
Baseline mean (SD)	9.6 (1.70)	9.8 (1.67)	9.9 (1.66)	9.7 (1.66)	9.9 (1.65)	10.0 (1.40)	9.7 (1.70)
LS mean change from baseline	-1.2419	-2.3511	-2.0037	-1.4868	-2.3508	-1.6989	-1.8982
LS mean (SE) difference from placebo 97.5% CI p-value	--	-1.1092# (0.2392) -1.6462, -0.5723 <0.0001	--	--	-1.1089# (0.2398) -1.6471, -0.5706 <0.0001	--	--
LS mean (SE) difference from monotherapies[a] 95% CI p-value	--	--	-0.3474 (0.2384) -0.8152, 0.1204 0.1454	-0.8643* (0.2392) -1.3336, -0.3950 0.0003	--	-0.6519* (0.2392) -1.1211, -0.1826 0.0065	-0.4526 (0.2389) -0.9212, 0.0161 0.0584

LS Means (SE), confidence intervals and p-values are based on an ANCOVA with change from baseline as dependent variable, treatment group and center as fixed effect and baseline as covariate.
statistically significant difference (p<0.025) between GSP 301 NS and placebo.
* statistically significant difference (p<0.05) between GSP 301 NS and constituent monotherapies; statistical significance only interpreted if the difference from placebo was statistically significant.
[a] GSP 301 NS (QD) compared with olopatadine hydrochloride-1 NS (QD) and mometasone furoate-1 NS (QD). GSP 301-2 NS (BID) compared with olopatadine hydrochloride-2 NS (BID) and mometasone furoate-2 NS (BID)
Source: GSP 301-201 Clinical Study Report, Table 13
Abbreviations: ANCOVA=analysis of covariance; iTNSS=instantaneous total nasal symptom score; NS=nasal spray; QD=once daily; BID=twice daily; HCl=hydrochloride; SD=standard deviation; SE=standard error; CI=confidence interval

Figure 27. Least Square Means With 95% Confidence Intervals of Change in Average AM and PM iTNSS Over the 14-Day Treatment Period



*, ^, # indicates a significant difference when compared to placebo ($p < 0.05$).
Note: p-values not adjusted for multiplicity
Source: GSP 301-201 Clinical Study Report, Figures 15.2.3.2 and 15.2.3.1
Abbreviations: iTNSS=instantaneous total nasal symptom score; BID=twice daily; QD=once daily; LS=least square; SE=standard error; NS=nasal spray

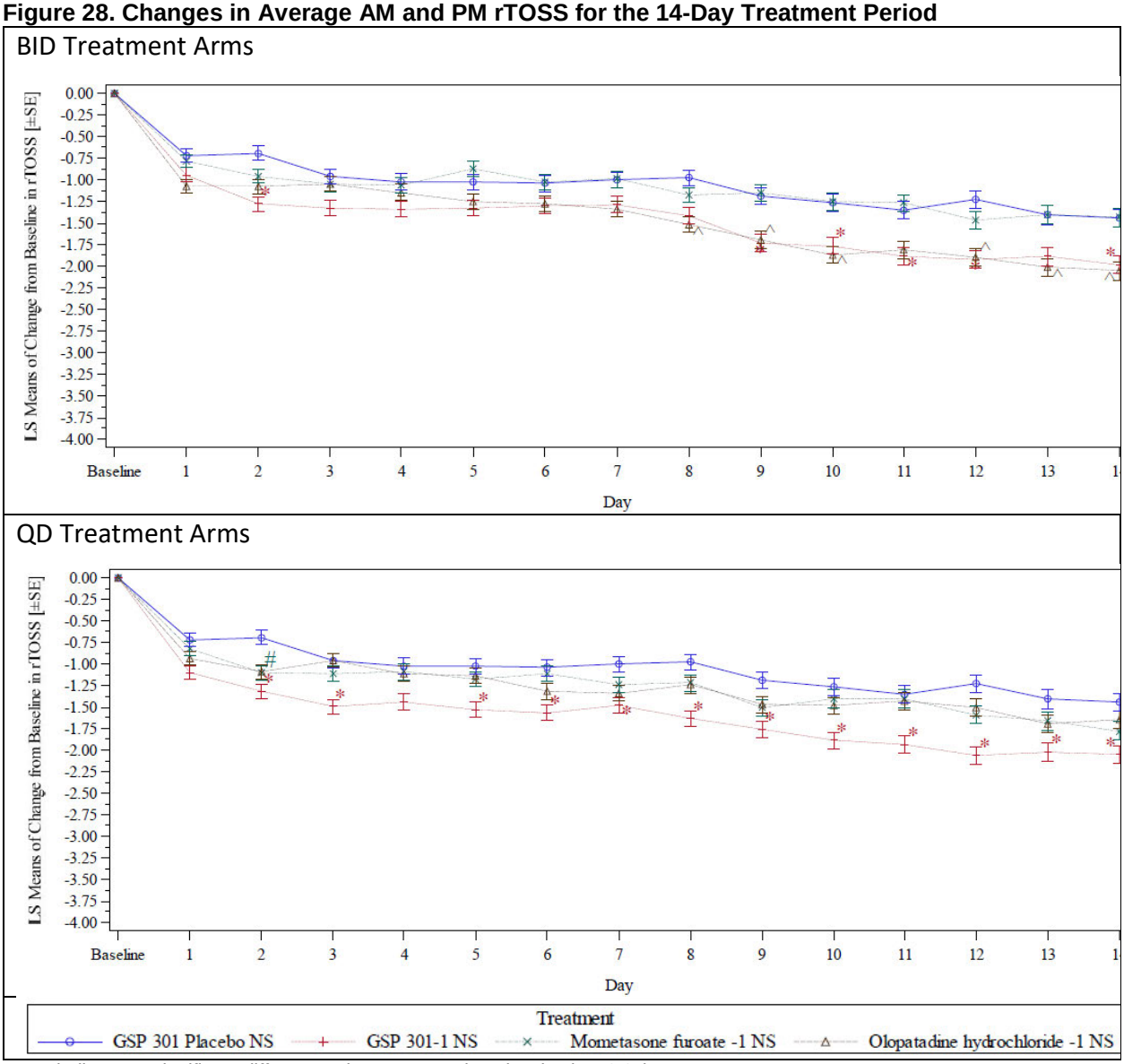
Results for rTOSS are presented in Table 48 and Figure 28. The comparison between GSP 301 and placebo was statistically significant for QD dosing but not for BID dosing at the prespecified 0.025 alpha level. As with rTNSS and iTNSS, there was a trend towards a consistently improved point estimate among patients treated with GSP 301 compared to those treated with placebo. However, the single components appeared to be operating differently, with the OLO arm tracking with GSP 301 and the MF arm tracking with placebo though with more separation in the QD regimen than in the BID regimen.

Table 48. Summary of ANCOVA Analysis of Average AM and PM rTOSS Over the 14-Day Treatment Period (Full Analysis Set)

	GSP 301 placebo NS N=158	GSP 301-1 NS (QD) N=158	Momet-asone furoate-1 NS (QD) N=160	Olopat-adine HCl-1 NS (QD) N=158	GSP 301-2 NS (BID) N=157	Momet-asone furoate-2 NS (BID) N=159	Olopat-adine HCl-2 NS (BID) N=160
Baseline mean (SD)	7.3 (1.38)	7.2 (1.38)	7.4 (1.35)	7.3 (1.29)	7.4 (1.33)	7.5 (1.29)	7.3 (1.36)
LS mean change from baseline	-1.1124	-1.6668	-1.2961	-1.3058	-1.5310	-1.1290	-1.4939
LS mean (SE) difference from placebo	--	-0.5544# (0.1956)	--	--	-0.4186 (0.1959)	--	--
97.5% CI		-0.9933, -0.1155			-0.8583, 0.0212		
p-value		0.0047			0.0329		
LS mean (SE) difference from monotherapies[a]	--	--	-0.3707 (0.1951)	-0.3610 (0.1956)	--	-0.4019 (0.1955)	-0.0371 (0.1953)
95% CI			-0.7535, 0.0122	-0.7448, 0.0228		-0.7856, -0.0182	-0.4202, 0.3461
p-value			0.0578	0.0653		0.0401	0.8494

LS Means (SE), confidence intervals and p-values are based on an ANCOVA with change from baseline as dependent variable, treatment group and center as fixed effects and baseline as covariate.
statistically significant difference (p<0.025) between GSP 301 NS and placebo.
[a] GSP 301 NS (QD) compared with olopatadine hydrochloride-1 NS (QD) and mometasone furoate-1 NS (QD). GSP 301-2 NS (BID) compared with olopatadine hydrochloride-2 NS (BID) and mometasone furoate-2 NS (BID)
Source: GSP 301-201 Clinical Study Report, Table 14
Abbreviations: ANCOVA=analysis of covariance; rTOSS=reflective total ocular symptom score; NS=nasal spray; QD=once daily; BID=twice daily; HCl=hydrochloride; SD=standard deviation; LS=least square; SE=standard error; CI=confidence interval

Figure 28. Changes in Average AM and PM rTOSS for the 14-Day Treatment Period



*, ^, # indicates a significant difference when compared to placebo ($p < 0.05$).
Note: p-values not adjusted for multiplicity
Source: GSP 301-201 Clinical Study Report, Figures 15.2.5.2 and 15.2.5.1
Abbreviations: rTOSS=reflective total ocular symptom score; LS=least square; BID=twice daily; QD=once daily; SE=standard error; NS=nasal spray

Results for onset of action, as measured by iTNSS, are displayed in Table 49 and Figure 29. Time to onset of action for GSP-301 QD was 150 mins after the first dose (LS mean difference from placebo, -0.64, 95% CI -1.18 to -0.10). GSP-301 BID onset of action was not significant at any timepoint measured in the 4 hour time window.

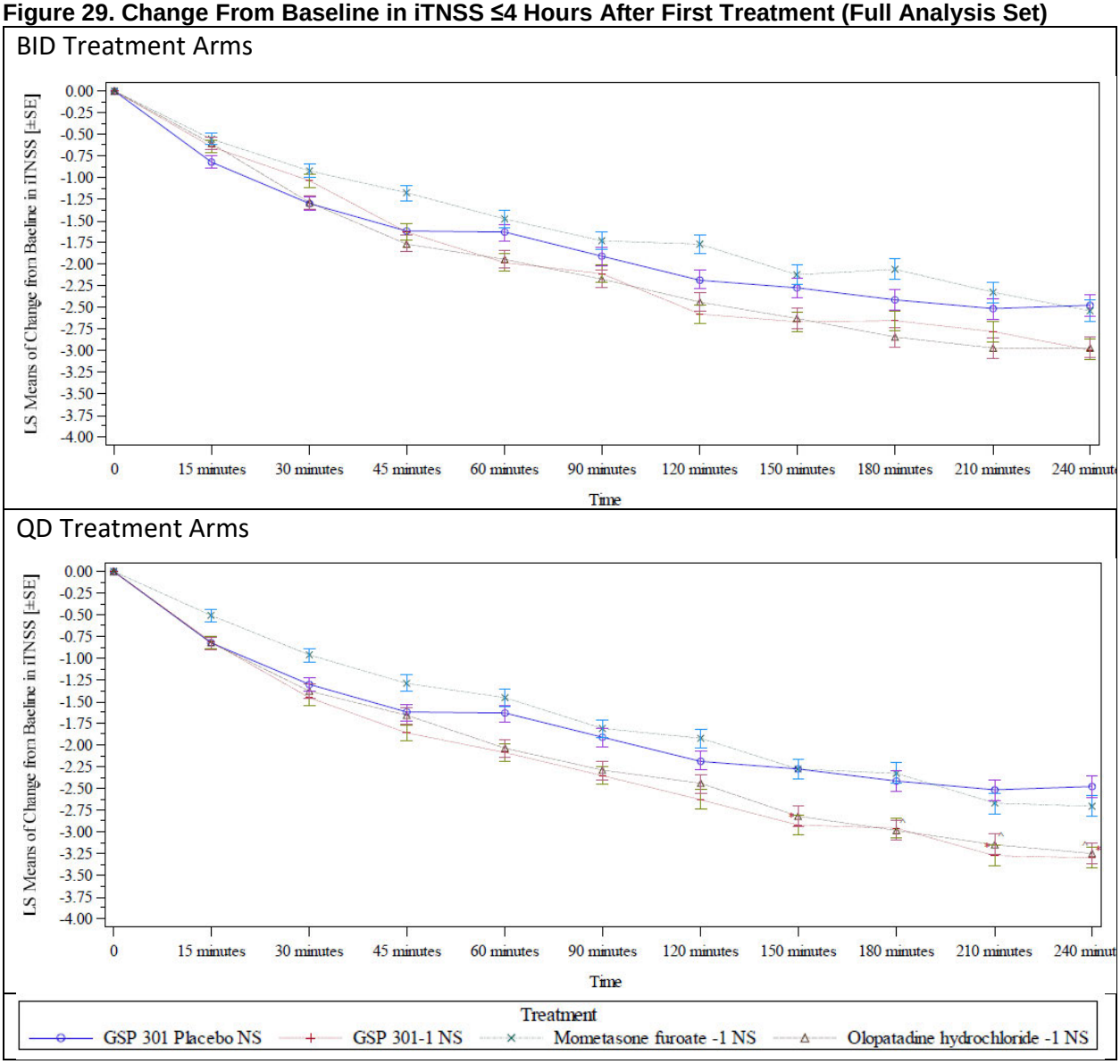
Table 49. Summary of ANCOVA Analysis of Onset of Action in iTNSS (Full Analysis Set)

Treatment Group	Time Point	n Active	n Placebo	LSmean Difference	95% CI	P-values Active vs. Placebo
GSP 301-1 NS (QD)	15 minutes	158	158	0.0049	-0.3248 , 0.3346	0.9766
	30 minutes	158	158	-0.1554	-0.5420 , 0.2313	0.4306
	45 minutes	158	158	-0.2356	-0.6838 , 0.2125	0.3024
	60 minutes	158	158	-0.4433	-0.9262 , 0.0397	0.0720
	90 minutes	158	158	-0.4367	-0.9345 , 0.0611	0.0855
	120 minutes	158	158	-0.4380	-0.9542 , 0.0782	0.0962
	150 minutes	158	158	-0.6382	-1.1818 , -0.0945	0.0215
	180 minutes	158	158	-0.5489	-1.1092 , 0.0115	0.0549
	210 minutes	158	158	-0.7511	-1.3286 , -0.1735	0.0109
	240 minutes	158	158	-0.8192	-1.4022 , -0.2362	0.0059
GSP 301-2 NS (BID)	15 minutes	157	158	0.1775	-0.1527 , 0.5078	0.2918
	30 minutes	157	158	0.2665	-0.1208 , 0.6537	0.1773
	45 minutes	157	158	-0.0041	-0.4530 , 0.4447	0.9857
	60 minutes	157	158	-0.3426	-0.8263 , 0.1412	0.1650
	90 minutes	157	158	-0.1992	-0.6978 , 0.2994	0.4333
	120 minutes	157	158	-0.3987	-0.9157 , 0.1183	0.1306
	150 minutes	157	158	-0.3861	-0.9306 , 0.1585	0.1645
	180 minutes	157	158	-0.2436	-0.8049 , 0.3177	0.3946
	210 minutes	157	158	-0.2650	-0.8435 , 0.3135	0.3689
	240 minutes	157	158	-0.5151	-1.0990 , 0.0688	0.0838

iTNSS = sum of four nasal symptom scores (Rhinorrhea, Nasal Congestion, Nasal Itching, Sneezing)
Baseline is defined as the time point pre-dosing at the Randomization Visit (Visit 2).
P-values are based on an ANCOVA with change from baseline as dependent variable, treatment and center as fixed effect and baseline as covariate.
n: Number of patients with data available at each timepoint in the specific treatment group.

Note: This endpoint was not included in the applicant's multiplicity plan.
Source: GSP 301-201 Clinical Study Report, Table 14.1.9.8.3
Abbreviations: ANCOVA=analysis of covariance; NS=nasal spray; QD=once daily; BID=twice daily; LS=least square; CI=confidence interval

Figure 29. Change From Baseline in iTNSS ≤4 Hours After First Treatment (Full Analysis Set)



*, ^, # indicates a significant difference when compared to placebo ($p < 0.05$).
LS Means and p-values are based on an ANCOVA with change from baseline value as dependent variable, treatment group and center as fixed effects and baseline as a covariate.
Source: GSP 301-201 study report, Figures 15.3.2 and 15.3.1
Note: this endpoint was not included in the applicant's multiplicity plan.
Abbreviations: iTNSS=instantaneous total nasal symptom score; BID=twice daily; QD=once daily; LS=least square; SE=standard error; NS=nasal spray

Efficacy Results – Secondary or Exploratory Clinical Outcome Assessment (Patient Reported Outcome) Endpoints

Results for RQLQ are presented in Table 50. Patients' QOL improved on GSP 301 in comparison to placebo, with significantly lower RQLQ scores for GSP 301 than for placebo in both BID and QD treatment regimens, with a mean difference of -0.57 and -0.49, respectively. Patients' RQLQ scores on GSP 301 were not statistically lower in comparison to those of patients on OLO, with

a mean difference of 0.26 (BID) and 0.29 (QD). Scores of patients on GSP 301 were statistically lower than those of patients on MF for the BID regimen but not for QD with mean differences of 0.42 (BID) and 0.13 (QD).

Table 50. Summary of ANCOVA Results for Overall RQLQ Score on Day 15 (RQLQ Population)

	GSP 301 placebo NS N=133	GSP 301-1 NS (QD) N=129	Mometasone furoate-1 NS (QD) N=134	Olopatadine HCl-1 NS (QD) N=138	GSP 301-2 NS (BID) N=128	Mometasone furoate-2 NS (BID) N=137	Olopatadine HCl-2 NS (BID) N=131
Baseline mean (SD)	4.7 (0.76)	4.7 (0.84)	4.6 (0.83)	4.6 (0.76)	4.7 (0.84)	4.7 (0.76)	4.7 (0.82)
LS mean change from baseline	-0.9309	-1.4176	-1.2806	-1.1239	-1.4985	-1.0814	-1.2428
LS mean (SE) difference from placebo	--	-0.4866# (0.1715)	--	--	-0.5675# (0.1704)	--	--
97.5% CI		-0.8718, -0.1015			-0.9502, -0.1849		
p-value		0.0047			0.0009		
LS mean (SE) difference from monotherapies[a]	--	--	-0.1370 (0.1731)	-0.2937 (0.1708)	--	-0.4171* (0.1706)	-0.2557 (0.1711)
95% CI			-0.4767, 0.2028	-0.6290, 0.0416		-0.7520, -0.0823	-0.5916 0.0802
p-value			0.4290	0.0859		0.0147	0.1355

LS Means (SE), confidence intervals and p-values are based on an ANCOVA with change from baseline as dependent variable, treatment group and center as fixed effect, treatment*center as mixed effect, and baseline as covariate.
statistically significant difference (p<0.025) between GSP 301 NS and placebo.
* statistically significant difference (p<0.05) between GSP 301 NS and constituent monotherapies; statistical significance only interpreted if the difference from placebo was statistically significant.
[a] GSP 301-1 NS (QD) compared with olopatadine hydrochloride-1 NS (QD) and mometasone furoate-1 NS (QD). GSP 301-2 NS (BID) compared with olopatadine hydrochloride-2 NS (BID) and mometasone furoate-2 NS (BID)
Note: The treatment-by-center interaction was statistically significant (p<0.05) in the analysis of the RQLQ and so this term was included in this model.
Source: GSP 301-201 study report, Table 15
Note: this endpoint was not included in the applicant's multiplicity planning
Abbreviations: ANCOVA=analysis of covariance; RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire; NS=nasal spray; QD=once daily; BID=twice daily; HCl=hydrochloride; SD=standard deviation; LS=least square; SE=standard error; CI=confidence interval

Integrated Review of Effectiveness

Comparisons were made between the combination, GSP 301, its single components, and placebo in both BID and QD dosing regimens. Results for rTNSS, iTNSS, iTNSS onset of action, rTOSS, and RQLQ demonstrated a clear and statistically significant separation between patients administered GSP 301 versus those administered placebos. However, the comparisons between GSP 301 and its single components were not consistently significantly different. The variation of statistical significance among the endpoints were expected since OLO and MF have differing efficacy benefits and onsets of action. The Applicant did not compare the single components to placebo in this phase 2 study, but these comparisons were made in the phase 3 studies.

The Applicant's multiplicity plan included a gatekeeping order for each regimen that began with the comparison to placebo, then OLO, and finally MF, but only for the primary endpoint.

8.1.7. Study Design GSP 301-303

Study 303 was a double-blind, randomized, parallel group study to evaluate the long-term safety of GSP 301 compared with two placebo formulations in subjects 12 years and older with PAR to assess any differences in the safety profile due to pH. GSP 301 is an aqueous NS with an approximate pH of 3.7. Matching the pH of the active product in placebo was necessary to maintain blinding for efficacy purposes. The low pH in placebo could impact the interpretation of the safety data because the frequency of common AEs in the GSP 301 treatment group could be underestimated when compared to the low pH treatment group. A second placebo with a higher pH of approximately 7 was included in this 52-week study.

- Study dates: April 1, 2016 to July 24, 2017
- Study sites: 33 sites in the United States
- Study report date: March 23, 2018

Objectives

Primary:

- To compare the long-term safety and tolerability of GSP 301 with two placebo formulations of differing pH over 52 weeks of study treatment in subjects with PAR.

Secondary:

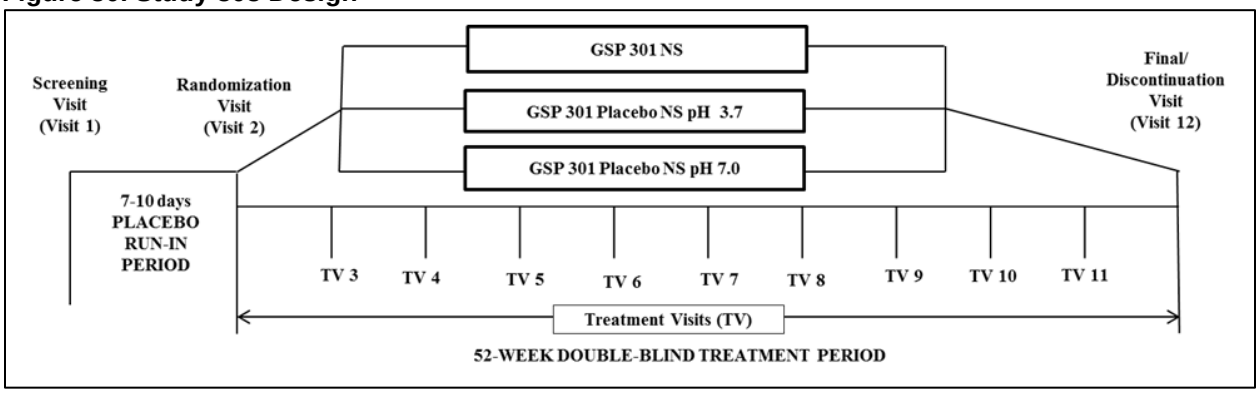
- To evaluate the long-term efficacy of GSP 301 compared with placebo pH 3.7 in subjects with PAR.

Trial Design

Design

A total of 847 subjects were screened and after the run-in period, 601 subjects were randomized (4:1:1) to either GSP 301, placebo pH 3.7, or placebo pH 7.0 treatment groups. The trial design of study 303 incorporated a screening visit, a 7- to 10-day run-in period, and a 52-week randomized treatment period. The single-blind placebo run-in period was to ensure baseline disease severity uniformity and potentially noncompliant subjects. During the treatment period, clinic assessment occurred at weeks 3, 6, 12, 18, 24, 30, 36, 42, 48, and 52. The study design is summarized schematically in Figure 30. Study assessments are summarized in Table 51.

Figure 30. Study 303 Design



Abbreviations: NS=nasal spray

Table 51. Schedule of Procedures and Assessments

			Treatment Visits (TV)									
Visits	**Screening Visit (Visit 1)**	**Randomization Visit (Visit 2)**	**TV 3**	**TV 4**	**TV 5**	**TV 6**	**TV 7**	**TV 8**	**TV 9**	**TV 10**	**TV 11**	**Final Visit/ Discontinuation Visit (Visit 12)**
Week	-1	1	3	6	12	18	24	30	36	42	48	52
Day ± Window	(-7 to-10)	1	22±3	43±3	85±5	127±7	169±7	211±7	253±7	295±7	337±7	365+10
Activity/Observation												
Written informed consent (assent, if applicable) and HIPAA authorization	X											
Inclusion/exclusion criteria review	X											
Demographic data	X											
Medical & treatment History	X											
Concomitant medication evaluation	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X							X				X
Vital signs	X	X						X				X
Height and weight Measurements	X							X				X
Clinical laboratory investigations (hematology, biochemistry, urinalysis)	X							X				X
Focused ENT and eye examination	X	X	X	X	X	X	X	X	X	X	X	X
Allergen testing (skin prick test for relevant allergen, if required)	X											
12-lead ECG	X											X
Urine pregnancy test (if applicable)	X	X	X	X	X	X	X	X	X	X	X	X

Visits	Screening Visit (Visit 1)	Randomization Visit (Visit 2)	Treatment Visits (TV)									Final Visit/ Discontinuation Visit (Visit 12)
			TV 3	TV 4	TV 5	TV 6	TV 7	TV 8	TV 9	TV 10	TV 11	
Review instructions and train on the proper use of the nasal spray using the GSP 301 placebo NS pH 3.7 bottle	X											

Source: Study GSP 301-303 CSR Table 4 page 628
Abbreviations: HIPAA=Health Insurance Portability and Accountability Act of 1996; ENT=ear, nose, and throat; ECG=electrocardiogram; NS=nasal spray

Inclusion and Exclusion Criteria

Key Inclusion Criteria

- Males and females ≥12 years.
- Documented clinical history of PAR (for at least 2 years preceding the screening visit (visit 1) with exacerbations (clinical evidence of active symptoms) and exhibiting a documented positive skin prick test (wheal diameter at least 3 mm greater than negative diluent wheal) to at least 1 allergen known to induce PAR. Documentation of a positive result within 12 months prior to the screening visit was acceptable. Additionally, the subject was expected to be exposed to the PAR allergen that he/she tested positive for via the skin prick test for the entire duration of the study.

Key Exclusion Criteria

- History of significant atopic dermatitis or rhinitis medicamentosa (within 60 days prior to visit 1).
- Treatment with known potent CYP3A4 inducers (carbamazepine, dexamethasone, phenytoin, rifabutin, etc.) or potent inhibitors (azole antifungals, macrolide antibiotics, etc.) within 30 days prior to or during the study.
- Nonvaccinated exposure to or active infection with chickenpox or measles within 21 days preceding visit 1.
- Known hypersensitivity to corticosteroids or antihistamine or to the study medication or its excipients.
- History of alcohol or drug dependence within 2 years preceding visit 1.
- History of positive test for human immunodeficiency virus, Hepatitis B or Hepatitis C infection.
- Evidence of acute or significant chronic sinusitis or chronic purulent postnasal drip.
- History of anaphylaxis and/or local reaction to skin testing.
- Any severe neuropsychiatric, gastrointestinal, hematologic, hepatic, renal, cardiovascular, or respiratory disease or infection other than asthma.
- Dependence on nasal, oral, or ocular decongestants, nasal topical antihistamines or nasal steroids.
- History of posterior subcapsular cataracts or glaucoma, increased ocular pressure, incisional eye surgery (other than cataract extraction or laser-assisted in situ keratomileusis), retinal detachment or surgery, uveitis, ocular herpes simplex, iritis, or another inflammatory eye disease.
- History of hypothalamic-pituitary-adrenal axis impairment.

- Active pulmonary disorders or infections or upper respiratory tract or sinus infection with the 14 days prior to visit 1 or during the run-in period. Subjects with mild asthma were allowable on the condition that treatment was limited to inhaled short-acting beta-agonists only (up to eight puffs per day).
- Initiation of immunotherapy injections or immunosuppressive/immune-modulator medications within 60 days preceding visit 1. A 180-day washout period was required following last dose of sublingual immunotherapy prior to visit 1.
- Use of topical corticosteroids in concentrations in excess of 1% hydrocortisone or equivalent within 30 days of visit 1, use of topical hydrocortisone or equivalent of any concentration covering greater than 20% of the body surface.
- Participation in any investigational nonbiological drug clinical study in the 30 days or investigational biological drug in the 120 days preceding visit 1
- Any significant surgical or medical condition (e.g., significant nasal polyps or other clinically significant respiratory tract malformations/nasal septal deviation) which in the opinion of the investigator significantly interfered with the absorption, distribution, metabolism or excretion of the study medication or interfered with nasal air flow

Treatment Groups

- GSP 301; 2 sprays per nostril BID
- Placebo pH 3.7;2 sprays per nostril BID
- Placebo pH 7.0; 2 sprays per nostril BID

Restricted Medications

The restricted medications are listed in Table 16.

Study Endpoints

Primary Endpoints:

- Proportion of subjects with treatment-emergent AEs (TEAEs)
- Proportion of subjects with treatment-related TEAEs
- Incidence, type and severity of the TEAEs after 30 weeks of study treatment
- Incidence, type and severity of TEAEs after 52 weeks of study treatment
- Clinical laboratory assessments (hematology, serum biochemistry, and urinalysis) at baseline, week 30 and week 52

Secondary Endpoints:

- Change from baseline in the average AM subject-reported rTNSS over the first 6, 30, and 52 weeks of treatment

- Change from baseline in the average AM subject-reported iTNSS over the first 6, 30, and 52 weeks of treatment
- Change from baseline in the overall RQLQ(S) score at weeks 6, 30, and 52 for the FAS

Statistical Analysis Plan

The SAP for this study was signed off on April 5, 2017. The Applicant stated the SAP was approved prior to database lock and unblinding of the study. The database was locked and approved on August 25, 2017.

Populations used in the analyses include SAS, FAS, PPS, and RQLQ(S) analysis set. The Applicant defined these as follows:

- The SAS consisted of all subjects who took at least one dose of study medication following randomization and was used for all safety analyses.

- The FAS consisted of all subjects who were randomized and received at least one dose of IP and had at least one postbaseline AM rTNSS assessment. This was the primary analysis set for efficacy analyses.

- The PPS consisted of the subset of the FAS who did not meet criteria for PPS exclusion. These criteria were to capture relevant non-adherence to the protocol (especially those that affected interpretation of the primary endpoint). The PPS was a secondary analysis set for the primary efficacy endpoint and selected secondary endpoints.

- The RQLQ(S) analysis set consisted of all English-speaking subjects ≥18 years old with impaired QOL at baseline as defined by RQLQ(S) score at the randomization visit (visit 2; baseline) of 3.0 or greater.

The primary endpoints are safety-related and described in that section. The three secondary efficacy endpoints are changes of rTNSS, iTNSS, and RQLQ(S) scores from their respective baselines over the first 6, 30, and 52 weeks of treatment.

Mixed model for repeated measures analysis was used for endpoints using the FAS. Change from baseline in average AM rTNSS to the end of each treatment week was derived as the average of postbaseline AM rTNSS scores by week. The model adjusted for study treatment, center, baseline 12-hour rTNSS, and study week as the within-subject effect.

The analyses presented by the Applicant are for completers of each respective visit. Missing data was not imputed, with the exception of the Tipping Point sensitivity analysis. The Applicant did not perform a sensitivity analysis for this safety study.

The same methodology was applied to change from baseline in average AM and PM 12-hour iTNSS and RQLQ. If either baseline or postbaseline results were missing, change from baseline was also set to missing.

No multiplicity plan was indicated for this study.

Subgroup analyses by age group (12–17, 18–64, ≥65), sex, race, and ethnicity were conducted for rTNSS and iTNSS.

The Applicant's focus in their submission was on the pooled analysis of studies 201, 301, and 304, with a proposed label describing the results of study 304 only. Study 303 is a 52-week supplemental study with longer-term information on efficacy. This is discussed in Section 8.1.4.

Protocol Amendments

Protocol amendment 1 (August 31, 2016) included minor editorial changes and updated instructions for proper use of the NS bottle and priming. The planned analyses were defined in the protocol and in the SAP, dated April 4, 2017 and did not change.

8.1.8. Study Results

Patient Disposition (All Subjects)

Analysis of subject disposition in trial 303 shows that the total number of subjects withdrawn from the study was similar between placebo pH 3.7 and GSP 301 and slightly lower in placebo pH 7.0. The most common reason for early termination was 'withdrawal by subject' in 51 (8.5%) subjects and "lost to follow up" in 36 (6.0%).

Table 52. Patient Disposition (All Subjects)

Disposition	GSP 301 Placebo pH 3.7 N=100 n (%)	GSP 301 Placebo pH 7.0 N=101 n (%)	GSP 301 N=400 n (%)
Randomized	100 (100.0)[a]	101(100.0)	400 (100.0)[b]
SAS	99 (99.0)	101 (100.0)	393 (98.7)
Terminated early	28 (28.0)	20 (19.8)	113 (28.3)
Completed study	72 (72.0)	81 (80.2)	287 (71.8)
Early termination reason			
Adverse event	2 (2.0)	3 (3.0)	13 (3.3)
Lack of efficacy	0	0	1 (0.3)
Lost to follow up	1 (8.0)	4 (4.0)	24 (6.0)
Non-compliance with study drug	0	0	2 (0.5)
Non-compliance with study procedure	0	0	5 (1.3)
Physician decision	0	0	1 (0.3)
Protocol deviation	4 (4.0)	4 (4.0)	10 (2.5)
Withdrawal by parent/guardian	0	0	1 (0.3)

Disposition	GSP 301 Placebo pH 3.7 N=100 n (%)	GSP 301 Placebo pH 7.0 N=101 n (%)	GSP 301 N=400 n (%)
Withdrawal by subject	7 (7.0)	4 (4.0)	40 (10.0)
Other	7 (7.0)	5 (5.0)	16 (4.0)

[a] One subject was randomized but did not take any study medication
[b] Seven subjects were randomized but did not take any study medication
Percentages are based on the number of randomized subjects.
Source: Study GSP 301-303 CSR table 14.1.9.1 and table 14.1.9.3

Table 53. 303 Protocol Violations/Deviations During Randomized Treatment Period (Safety Analysis Set)

Violation/Deviation	GSP 301 Placebo pH 3.7 N=99 n (%)	GSP 301 Placebo pH 7.0 N=101 n (%)	GSP 301 N=393 n (%)
Subjects with protocol deviations	72 (72.7)	79 (78.2)	319 (81.2)
Total deviations	170	184	651
Restricted medication	67	67	218
Lost to follow-up	7	5	20
Enrolled in error	0	1	0
Randomized in error	1	0	3
Non-compliance with study drug	2	1	14
Non-compliance with study procedure	4	5	31
Outside visit window	33	36	104
Procedure not completed per protocol	0	0	3
Dosing noncompliance	49	57	220
rTNSS rating noncompliance	0	1	2
Other	7	11	36

Source: Study 301-303 CSR Table 14.1.9.2.1
Abbreviations: rTNSS=reflective Total Nasal Symptom Score

Table 54. 303 Demographic Characteristics (Full Analysis Set)

Characteristics	GSP 301 Placebo pH 3.7 N=99 n (%)	GSP 301 Placebo pH 7.0 N=101 n (%)	GSP 301 N=391 n (%)
Age			
n	99	101	391
Mean (SD)	42.1 (15.4)	41.2 (13.5)	40.4 (14.9)
median	42.0	41.0	41.0
Min, max	13, 80	12, 68	12, 81
Sex			
Male	31 (31.3)	33 (32.7)	123 (31.5)
Female	68 (68.7)	68 (67.3)	268 (68.5)
Race			
American Indian or Alaska Native	1 (1.0)	0	2 (0.5)
Asian	1 (1.0)	2 (2.0)	10 (2.6)
White	78 (78.8)	76 (75.2)	281 (71.9)
Black/African American	17 (17.2)	22 (21.8)	94 (24.0)
Other	2 (2.0)	1 (1.0)	24 (1.0)

Characteristics	GSP 301 Placebo pH 3.7 N=99 n (%)	GSP 301 Placebo pH 7.0 N=101 n (%)	GSP 301 N=391 n (%)
Ethnicity			
Hispanic or Latino	26 (26.3)	28 (27.7)	113 (28.9)
Not Hispanic or Latino	73 (73.7)	73 (72.3)	278 (71.1)

Source: Study GSP 301-303 CSR Table 14.1.9.4.2
Abbreviations: SD=standard deviation

Efficacy Results – Primary Endpoint

Primary endpoints for this study are safety endpoints. See secondary efficacy section for review of efficacy for this study.

Efficacy Results – Secondary and Other Relevant Endpoints

Secondary efficacy endpoints for this study were rTNSS, iTNSS and RQLQ. There were no planned adjustments for multiplicity.

(b) (4)

Results for iTNSS (b) (4) were similar to rTNSS. Point estimates were (b) (4) (b) (4) at 6, 30, and 52 weeks, respectively. All comparisons were statistically significant.

(b) (4)

Efficacy Results – Secondary or Exploratory Clinical Outcome Assessment (Patient Reported Outcome) Endpoints

Results for RQLQ are presented in Table 57 and Figure 33. Patients' QOL significantly improved on GSP 301 in comparison to placebo at weeks 6 and 30, but not at week 52, with point estimates of (b) (4) units of improvement, respectively.

(b) (4)

Integrated Review of Effectiveness

Comparisons were made between GSP 301 and the pH 3.7 placebo. Results support those from the three efficacy studies with statistically significant separation between patients administered GSP 301 and those administered placebo at weeks 6, 30, and 52 for rTNSS and iTNSS, and weeks 6 and 30 for RQLQ. It is noted there was no preplanned adjustment for multiplicity.

8.1.9. Assessment of Efficacy Across Trials

Primary Endpoints

Results of average AM and PM rTNSS across the three efficacy studies and in a pooled analysis are displayed in Table 58 and Figure 34. The Applicant used ANCOVA as the primary analysis for study 201, MMRM for 301 and 304 (compound symmetry variance structure) and MMRM (unstructured variance) for their pooled primary Integrated Summary of Efficacy (ISE) analysis. In our review, we confirmed the Applicant's findings from the pooled analysis and re-ran each individual study analysis with that same model for consistency across each of the studies. Unstructured variance is considered a more reasonable and conservative assumption, and the Applicant acknowledged this model by using it for the ISE.

All comparisons between GSP 301 and placebo in the three pooled studies were statistically significant. Many, but not all, of the single study comparisons were also statistically significant, based on the Applicant's multiplicity plan.

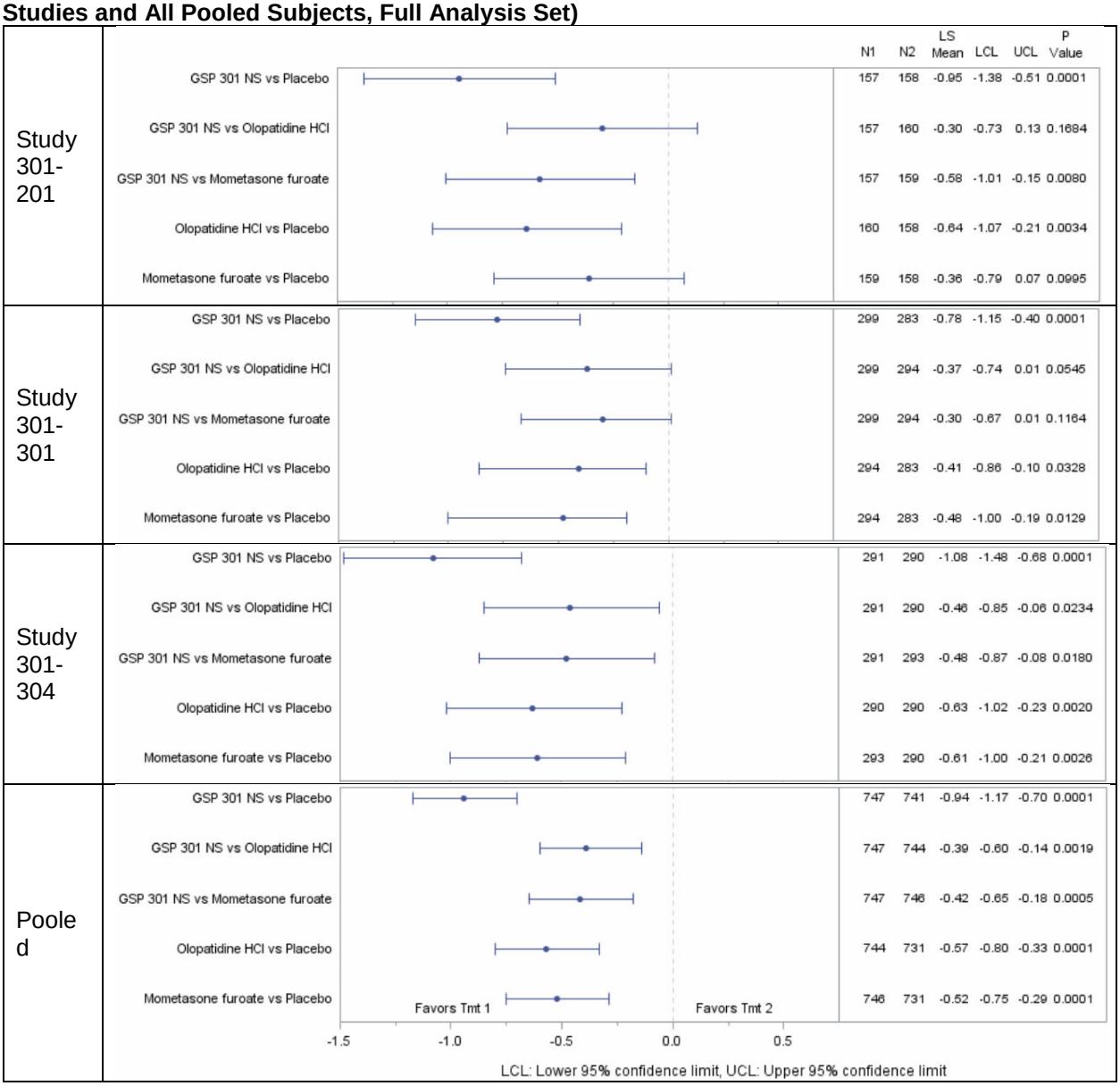
The Applicant's choice of gatekeeping order for multiplicity adjustment indicates that study 301 was only significant for the initial comparison of GSP 301 to placebo. Even that being the case, there is substantial evidence across these three studies demonstrating that GSP 301 is superior to placebo as well as to the single components, and the single components are significantly better than placebo, as per the rhinitis guidance. When data from the three studies is pooled (due to similar design, population, no interaction of effect by study), the greater power to detect a difference from the larger sample size offers additional evidence that the effects seen in the individual studies is a real effect. Statistical significance in the individual studies was not on every comparison in every study, but in totality, the three studies confirm the results are replicable.

Table 58. Primary Analysis Results for Average AM and PM rTNSS Over 14 Day Treatment Period (Individual Studies and Pooled Subjects, Full Analysis Set)

Treatment Group (Trt 1 vs. Trt 2)	N (Trt 1 vs. Trt 2)	Least Square Mean Difference	Standard Error	95% CI	P-Value
Pooled					
GSP 301 NS vs. placebo	747, 731	-0.94	0.12	-1.17, -0.70	<0.0001
GSP 301 NS vs. olopatadine HCl	747, 744	-0.39	0.12	-0.60, -0.14	0.0019
GSP 301 NS vs. mometasone furoate	747, 746	-0.42	0.12	-0.65, -0.18	0.0005
Olopatadine HCl vs. Placebo	744, 731	-0.57	0.12	-0.80, -0.33	<0.0001
Mometasone furoate vs. Placebo	746, 731	-0.52	0.12	-0.75, -0.29	<0.0001
Study 301-201					
GSP 301 NS vs. placebo	157, 158	-0.95	0.22	-1.38, -0.51	<0.0001*
GSP 301 NS vs. olopatadine HCl	157, 160	-0.30	0.22	-0.73, 0.13	0.1684[ns]
GSP 301 NS vs. mometasone furoate	157, 159	-0.58	0.22	-1.01, -0.15	0.0080*
Olopatadine HCl vs. Placebo	160, 158	-0.64	0.22	-1.07, -0.21	0.0034[ns]
Mometasone furoate vs. Placebo	159, 158	-0.36	0.22	-0.79, 0.07	0.0995[ns]
Study 301-301					
GSP 301 NS vs. placebo	299, 283	-0.78	0.19	-1.15, -0.40	<0.0001*
GSP 301 NS vs. olopatadine HCl	299, 294	-0.37	0.19	-0.74, 0.01	0.0545[ns]
GSP 301 NS vs. mometasone furoate	299, 294	-0.30	0.20	-0.67, 0.01	0.1164[ns]
Olopatadine HCl vs. Placebo	294, 283	-0.41	0.19	-0.86, -0.10	0.0328[ns]
Mometasone furoate vs. Placebo	294, 283	-0.48	0.21	-1.00, -0.19	0.0129[ns]
Study 301-304					
GSP 301 NS vs. placebo	291, 290	-1.08	0.20	-1.48, -0.68	<0.0001*
GSP 301 NS vs. olopatadine HCl	291, 290	-0.46	0.20	-0.85, -0.06	0.0234*
GSP 301 NS vs. mometasone furoate	291, 293	-0.48	0.20	-0.87, -0.08	0.0180*
Olopatadine HCl vs. Placebo	290, 290	-0.63	0.20	-1.02, -0.23	0.0020*
Mometasone furoate vs. Placebo	293, 290	-0.61	0.20	-1.00, -0.21	0.0026*

Source: Statistical review, efficacy_mmrm, ISE folder.
Note: Results matched Applicant's ISE analysis, using MMRM with unstructured covariance matrix assumed in the model. Results did not match Applicant's GSP 301-304 Clinical Study Report, Table 13, because their model assumed compound symmetry.
* Statistically significant, using Applicant's gatekeeping multiplicity plan
ns: not statistically significant, using Applicant's gatekeeping multiplicity plan
Abbreviations: rTNSS=reflective Total Nasal Symptom Score; Trt=treatment; CI=confidence interval; NS=nasal spray; HCl=hydrochloride

Figure 34. Mean Change From Baseline to Day 14 of Average AM and PM rTNSS (Individual Studies and All Pooled Subjects, Full Analysis Set)



Source: statistical reviewer
Abbreviations: CI=confidence interval; rTNSS=reflective Total Nasal Symptom Score; NS=nasal spray; HCl=hydrochloride

Secondary and Other Endpoints

As with the primary endpoint, the Applicant used ANCOVA as the primary analysis for study 201, MMRM for 301 and 304 (compound symmetry variance structure), and MMRM (unstructured variance) for their pooled primary ISE analysis of iTNSS and rTOSS. In our review, we re-ran each individual study analysis with that same model for consistency across each of the studies. Unstructured variance is a more reasonable and conservative assumption, and the Applicant acknowledged this model by using it for the ISE.

Similar to the primary (reflective) endpoint, average AM and PM iTNSS, across the three efficacy studies and in a pooled analysis are displayed in Table 59.

We confirmed the Applicant's findings from their pooled analysis,[20] shown in Table 59. All comparisons between GSP 301 and placebo in the three pooled studies were statistically significant. Many, but not all the single study comparisons were also statistically significant, based on the Applicant's multiplicity plan.

Onset of action, pooled across the three studies, is shown in Table 60 and Figure 35. We confirmed the Applicant's findings from their pooled analysis. There were significant differences compared to placebo for both GSP 301 and OLO treatment arms starting at 15 minutes and 30 minutes, respectively, and the differences were consistent throughout the 4-hour period of study. By comparison, the comparison of MF to placebo arms was not significant until the last timepoint at 4 hours, indicating that the antihistamine was responsible for a majority of the result. LS means for GSP 301 trended toward a stronger reduction than OLO alone.

Average AM and PM rTOSS, across the three efficacy studies and in a pooled analysis are displayed in Table 59. We confirmed the Applicant's findings from their pooled analysis. All comparisons between GSP 301 and placebo in the three pooled studies were statistically significant. Many, but not all the single study comparisons were also statistically significant, based on the Applicant's multiplicity plan.

[20] LS means and standard errors were identical. CIs and p-values were slightly different.

Table 59. Analysis Results for Average AM and PM iTNSS Over 14-Day Treatment Period (Individual Studies and Pooled Subjects, Full Analysis Set)

Treatment Group (Trt 1 vs. Trt 2)	N (Trt 1 vs. Trt 2)	Least Square Mean Difference	Standard Error	95% CI	P-Value
Pooled					
GSP 301 NS vs. placebo	747, 731	-0.91	0.11	-1.28, -0.58	<0.0001*
GSP 301 NS vs. olopatadine HCl	747, 744	-0.37	0.11	-0.65, -0.22	0.0001*
GSP 301 NS vs. mometasone furoate	747, 746	-0.44	0.11	-0.65, -0.21	0.0008*
Olopatadine HCl vs. placebo	744, 731	-0.54	0.11	-0.76, -0.33	<0.0001*
Mometasone furoate vs. placebo	746, 731	-0.48	0.11	-0.70, -0.26	<0.0001*
Study 301-201					
GSP 301 NS vs. placebo	157, 158	-0.89	0.21	-1.29, -0.48	<0.0001*
GSP 301 NS vs. olopatadine HCl	157, 160	-0.22	0.21	-0.62, 0.18	0.2861[ns]
GSP 301 NS vs. mometasone furoate	157, 159	-0.48	0.21	-0.88, -0.07	0.0202*
Olopatadine HCl vs. placebo	160, 158	-0.67	0.20	-1.07, -0.26	0.0011[ns]
Mometasone furoate vs. placebo	159, 158	-0.41	0.21	-0.81, -0.01	0.0463*
Study 301-301					
GSP 301 NS vs. placebo	299, 283	-0.93	0.18	-1.15, -0.40	<0.0001*
GSP 301 NS vs. olopatadine HCl	299, 294	-0.50	0.18	-0.85, -0.15	0.0049*
GSP 301 NS vs. mometasone furoate	299, 294	-0.36	0.18	-0.71, -0.01	0.0420*
Olopatadine HCl vs. placebo	294, 283	-0.43	0.18	-0.78, -0.07	0.0181*
Mometasone furoate vs. placebo	294, 283	-0.57	0.18	-0.92, -0.21	0.0017*
Study 301-304					
GSP 301 NS vs. placebo	291, 290	-0.94	0.19	-1.31, -0.55	<0.0001*
GSP 301 NS vs. olopatadine HCl	291, 290	-0.39	0.19	-0.76, -0.01	0.0451*
GSP 301 NS vs. mometasone furoate	291, 293	-0.51	0.19	-0.89, -0.14	0.0077*
Olopatadine HCl vs. placebo	290, 290	-0.55	0.19	-0.93, -0.17	0.0044*
Mometasone furoate vs. placebo	293, 290	-0.42	0.19	-0.80, -0.05	0.0272*

* Statistically significant, using Applicant's phase 3 gatekeeping multiplicity plan
[ns] not statistically significant, using Applicant's phase 3 gatekeeping multiplicity plan
Source: Statistical reviewer.
Note: Note: Results matched Applicant's ISE analysis for LS mean and standard error but not the confidence intervals and p-values. Our MMRM model with unstructured covariance matrix is consistent with the primary endpoint model.
Abbreviations: iTNSS=instantaneous Total Nasal Symptom Score; Trt=treatment; CI=confidence interval; NS=nasal spray; HCl=hydrochloride

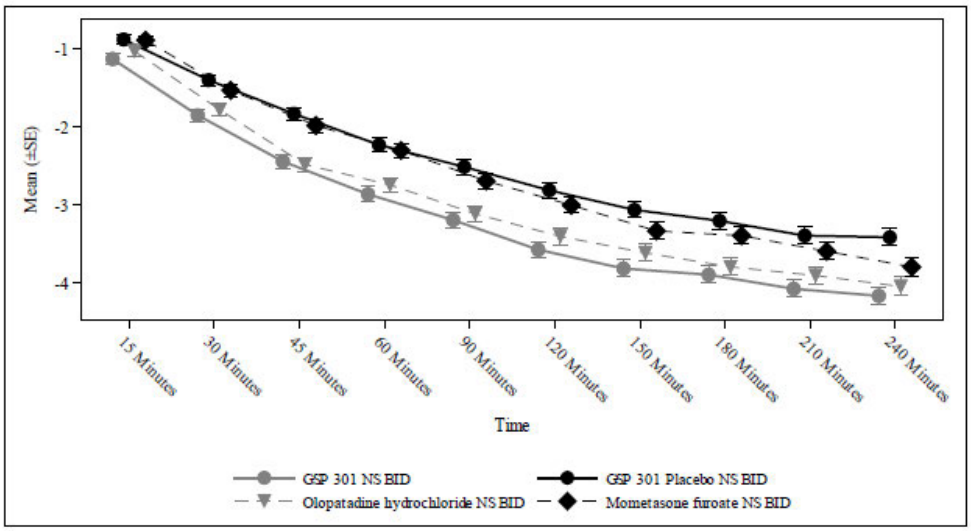
Table 60. Summary of Repeated Measures Analysis of iTNSS Onset of Action for GSP 301 (Pooled Subjects, Full Analysis Set)

Treatment Group	Time Point [1]	n Active	n Placebo	LSmean Active	LSmean Placebo	LSmean Difference	95% CI	P-values Active vs. Placebo
GSP 301 NS BID (N = 747)	15 minutes	741	730	-1.18	-0.95	-0.23	(-0.41, -0.05)	0.0110*
	30 minutes	741	729	-1.90	-1.46	-0.43	(-0.64, -0.23)	<0.0001*
	45 minutes	741	730	-2.49	-1.90	-0.59	(-0.82, -0.35)	<0.0001*
	60 minutes	739	726	-2.91	-2.30	-0.61	(-0.86, -0.36)	<0.0001*
	90 minutes	738	726	-3.24	-2.58	-0.66	(-0.92, -0.39)	<0.0001*
	120 minutes	737	727	-3.62	-2.89	-0.73	(-1.01, -0.46)	<0.0001*
	150 minutes	736	726	-3.86	-3.13	-0.73	(-1.02, -0.45)	<0.0001*
	180 minutes	739	728	-3.93	-3.27	-0.67	(-0.96, -0.38)	<0.0001*
	210 minutes	739	728	-4.12	-3.46	-0.66	(-0.96, -0.36)	<0.0001*
	240 minutes	739	730	-4.20	-3.48	-0.72	(-1.03, -0.42)	<0.0001*
Olopatadine HCl NS BID (N = 744)	15 minutes	738	730	-1.07	-0.95	-0.12	(-0.30, 0.05)	0.1746
	30 minutes	736	729	-1.83	-1.46	-0.36	(-0.57, -0.15)	0.0007*
	45 minutes	736	730	-2.51	-1.90	-0.61	(-0.84, -0.38)	<0.0001*
	60 minutes	731	726	-2.79	-2.30	-0.49	(-0.74, -0.24)	0.0001*
	90 minutes	732	726	-3.16	-2.58	-0.58	(-0.84, -0.31)	<0.0001*
	120 minutes	732	727	-3.46	-2.89	-0.57	(-0.84, -0.30)	<0.0001*
	150 minutes	734	726	-3.67	-3.13	-0.54	(-0.83, -0.25)	0.0002*
	180 minutes	735	728	-3.83	-3.27	-0.57	(-0.86, -0.28)	0.0001*
	210 minutes	737	728	-3.94	-3.46	-0.49	(-0.78, -0.19)	0.0014*
	240 minutes	736	730	-4.09	-3.48	-0.61	(-0.91, -0.30)	<0.0001*
Mometasone Furoate NS BID (N = 734)	15 minutes	729	720	-1.02	-1.05	0.03	(-0.23, 0.29)	0.8039
	30 minutes	729	719	-1.66	-1.57	-0.09	(-0.35, 0.17)	0.4981
	45 minutes	730	720	-2.11	-2.00	-0.11	(-0.37, 0.15)	0.3962
	60 minutes	729	716	-2.41	-2.40	-0.01	(-0.27, 0.25)	0.9470
	90 minutes	728	716	-2.82	-2.68	-0.14	(-0.39, 0.12)	0.3051
	120 minutes	729	717	-3.13	-2.99	-0.15	(-0.40, 0.11)	0.2703
	150 minutes	729	716	-3.46	-3.23	-0.23	(-0.49, 0.03)	0.0812
	180 minutes	727	718	-3.53	-3.38	-0.15	(-0.41, 0.11)	0.2664
	210 minutes	729	718	-3.73	-3.57	-0.17	(-0.43, 0.09)	0.2064
	240 minutes	727	720	-3.91	-3.59	-0.32	(-0.58, -0.06)	0.0145*

Note:
iTNSS = sum of four nasal symptom scores (Rhinorrhea, Nasal Congestion, Nasal Itching, Sneezing).
Baseline is defined as the pre-dose time point at the Randomization Visit (Visit 2).
n= number of subjects with data available; LS = least squares; SE = standard error.
Statistical Analysis model: Mixed-effect repeated measures model with change from baseline as the dependent variable, treatment group and site as fixed effects, baseline score as covariate, time as the within-subject effect and treatment*time interaction; variance covariance matrix Compound Symmetry.
[1] Timepoint was baseline, 15 to 240 minutes (15±3, 30±3, 45±3, 60±5, 90±5, 120±10, 150±10, 180±10, 210±10, and 240±10 minutes).
*** = p-value<0.05**

Note: Statistical reviewer confirmed results above, onset_mmrm.sas
Source: Applicant's Summary of Clinical Efficacy, Table 14.2.2.3.4
Abbreviations: iTNSS=instantaneous Total Nasal Symptom Score; GSP 301=olopatadine/mometasone furoate; NS=nasal spray; BID=twice daily; CI=confidence interval; HCl=hydrochloride

Figure 35. Mean Change From Baseline in iTNSS Onset of Action Over the Initial 4-Hour Treatment Period



Source: ISE, Figure 11.2.1.4.1
Abbreviations: iTNSS=instantaneous Total Nasal Symptom Score; SE=standard error; NS=nasal spray; BID=twice daily

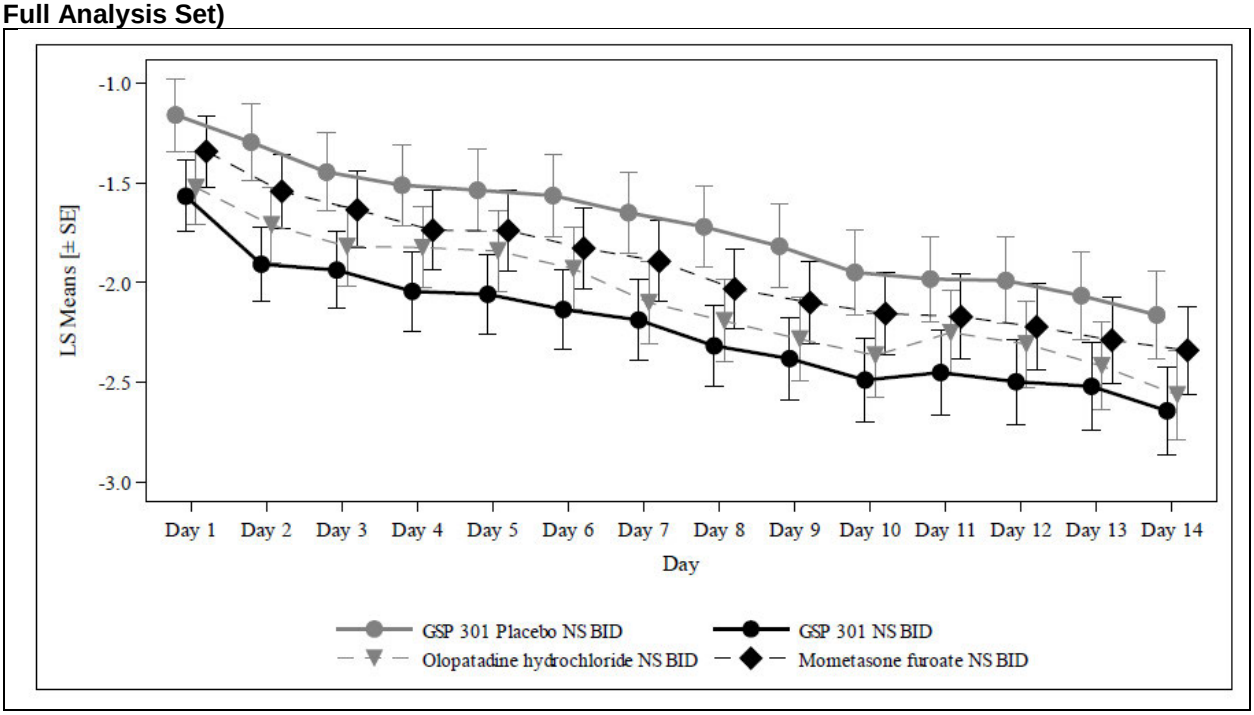
Comparisons of GSP 301 to placebo, GSP 301 to MF, and OLO to placebo were significant in the pooled analysis, indicating that OLO was driving the result for this secondary endpoint (Table 61 and Figure 36). It is noted there was a trend at all timepoints for placebo to have the least reduction, followed by MF, OLO, and finally GSP 301 with the greatest reduction. The consistency in this GSP 301-OLO-MF-placebo order across all the timepoints is indicative of a real effect.

Table 61. Analysis Results for Average AM and PM rTOSS Over 14-Day Treatment Period (Individual Studies and Pooled Subjects, Full Analysis Set)

Treatment Group (Trt 1 vs. Trt 2)	N (Trt 1 vs. Trt 2)	Least Square Mean Difference	Standard Error	95% CI	P-Value
Pooled					
GSP 301 NS vs. placebo	747, 731	-0.47	0.10	-0.66, -0.28	<0.0001*
GSP 301 NS vs. olopatadine HCl	747, 744	-0.10	0.09	-0.28, 0.09	0.3045[ns]
GSP 301 NS vs. mometasone furoate	747, 746	-0.27	0.09	-0.46, -0.09	0.0037*
Olopatadine HCl vs. placebo	744, 731	-0.37	0.10	-0.56, -0.19	<0.0001[ns]
Mometasone furoate vs. placebo	746, 731	-0.19	0.10	-0.36, -0.01	0.0610[ns]
Study 301-201					
GSP 301 NS vs. placebo	157, 158	-0.32	0.18	-0.66, 0.03	0.0742[ns]
GSP 301 NS vs. olopatadine HCl	157, 160	-0.07	0.18	-0.29, 0.40	0.7454[ns]
GSP 301 NS vs. mometasone furoate	157, 159	-0.28	0.18	-0.62, 0.07	0.1155[ns]
Olopatadine HCl vs. placebo	160, 158	-0.37	0.18	-0.72, -0.03	0.0341[ns]
Mometasone furoate vs. placebo	159, 158	-0.04	0.18	-0.38, 0.31	0.8285[ns]
Study 301-301					
GSP 301 NS vs. placebo	299, 283	-0.49	0.15	-0.79, -0.19	0.0015*
GSP 301 NS vs. olopatadine HCl	299, 294	-0.09	0.15	-0.39, 0.21	0.5474[ns]
GSP 301 NS vs. mometasone furoate	299, 294	-0.18	0.15	-0.48, 0.11	0.2264[ns]
Olopatadine HCl vs. placebo	294, 283	-0.40	0.15	-0.70, -0.10	0.0100[ns]
Mometasone furoate vs. placebo	294, 283	-0.31	0.15	-0.61, -0.00	0.0473[ns]
Study 301-304					
GSP 301 NS vs. placebo	291, 290	-0.53	0.16	-0.84, -0.21	0.0012*
GSP 301 NS vs. olopatadine HCl	291, 290	-0.18	0.16	-0.49, 0.13	0.2633[ns]
GSP 301 NS vs. mometasone furoate	291, 293	-0.36	0.16	-0.68, -0.05	0.0231*
Olopatadine HCl vs. placebo	290, 290	-0.35	0.16	-0.66, -0.03	0.0316[ns]
Mometasone furoate vs. placebo	293, 290	-0.16	0.16	-0.48, 0.15	0.3110[ns]

* Statistically significant, using Applicant's phase 3 gatekeeping multiplicity plan
ns not statistically significant, using Applicant's phase 3 gatekeeping multiplicity plan
Source: Statistical review, rtoss_mmrm, ISE folder.
Note: Note: Results matched Applicant's ISE analysis. Our MMRM model with unstructured covariance matrix is consistent with the primary endpoint model.
Abbreviations: rTOSS=reflective Total Ocular Symptom Score; Trt=treatment; CI=confidence interval; NS=nasal spray; HCl=hydrochloride

Figure 36. Change in AM and PM rTOSS Over the 14-Day Treatment Period (All Pooled Subjects, Full Analysis Set)



Source: ISE Figure 11.2.2.3.1
Abbreviations: CI=confidence interval; rTOSS=reflective Total Ocular Symptom Score; LS=least square; SE=standard error; NS=nasal spray; BID=twice daily

RQLQ across the three efficacy studies and in a pooled analysis are displayed in Table 62. We confirmed the Applicant's findings from their pooled analysis,[21] shown in Table 59. All comparisons between GSP 301 and placebo in the pooled analysis were statistically significant. Some, but not all of the single study comparisons were also statistically significant based on the Applicant's multiplicity plan.[22]

[21] LS means and standard errors were identical. CIs and p-values were slightly different.

[22] For consistency, the Applicant's phase 3 multiplicity gatekeeping strategy was applied to the pooled analysis and to each of the individual studies.

Table 62. ANCOVA Results for RQLQ (Individual Studies and Pooled Subjects, Full Analysis Set)

Treatment Group (Trt 1 vs. Trt 2)	N (Trt 1 vs. Trt 2)	Least Square Mean Difference	Standard Error	95% CI	P-Value
Pooled					
GSP 301 NS vs. placebo	725, 707	-0.48	0.07	-0.62, -0.34	<0.0001*
GSP 301 NS vs. olopatadine HCl	725, 721	-0.29	0.07	-0.43, 0.15	<0.0001*
GSP 301 NS vs. mometasone furoate	725, 724	-0.19	0.07	-0.33, -0.06	0.0059*
Olopatadine HCl vs. placebo	721, 707	-0.19	0.07	-0.33, -0.05	0.0070*
Mometasone furoate vs. placebo	724, 707	-0.29	0.07	-0.43, -0.15	<0.0001*
Study 301-201					
GSP 301 NS vs. placebo	128, 133	-0.60	0.15	-0.89, -0.31	<0.0001*
GSP 301 NS vs. olopatadine HCl	128, 138	-0.32	0.15	-0.60, -0.03	0.0314*
GSP 301 NS vs. mometasone furoate	128, 137	-0.38	0.15	-0.67, -0.09	0.0092*
Olopatadine HCl vs. placebo	138, 133	-0.28	0.15	-0.56, 0.01	0.0556[ns]
Mometasone furoate vs. placebo	137, 133	-0.21	0.15	-0.50, 0.07	0.1428[ns]
Study 301-301					
GSP 301 NS vs. placebo	298, 279	-0.43	0.11	-0.64, -0.21	<0.0001*
GSP 301 NS vs. olopatadine HCl	298, 293	-0.28	0.11	-0.49, -0.06	0.0107*
GSP 301 NS vs. mometasone furoate	298, 293	-0.20	0.11	-0.41, 0.02	0.0699[ns]
Olopatadine HCl vs. placebo	293, 279	-0.15	0.11	-0.37, 0.06	0.1643[ns]
Mometasone furoate vs. placebo	293, 279	-0.23	0.11	-0.45, -0.02	0.0344[ns]
Study 301-304					
GSP 301 NS vs. placebo	283, 280	-0.44	0.12	-0.68, -0.22	0.0002*
GSP 301 NS vs. olopatadine HCl	283, 276	-0.31	0.12	-0.54, 0.08	0.0084*
GSP 301 NS vs. mometasone furoate	283, 280	-0.09	0.12	-0.32, 0.14	0.4186[ns]
Olopatadine HCl vs. placebo	276, 280	-0.14	0.12	-0.37, 0.09	0.2411[ns]
Mometasone furoate vs. placebo	280, 280	-0.35	0.12	-0.59, -0.12	0.0026*

* Statistically significant, using Applicant's phase 3 gatekeeping multiplicity plan
[ns] not statistically significant, using Applicant's phase 3 gatekeeping multiplicity plan
Source: Statistical review, rqlq_ancova, ISE folder.
Note: Note: Results matched Applicant's ISE analysis for ls mean and standard error, with slight differences in confidence intervals and p-values.
Abbreviations: ANCOVA=analysis of covariance; RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire; Trt=treatment; CI=confidence interval; NS=nasal spray; HCl=hydrochloride

Subpopulations

Pooled subgroup analysis was conducted by the Applicant using MMRM across studies 201, 301, and 304 and forest plots generated for age category, sex, race, and ethnicity for rTNSS, iTNSS, rTOSS, and RQLQ (Figure 37). Sample sizes were relatively small for youngest and oldest age groups, and for race category "Other" (Table 63). For these smaller sample sizes, a wider CI would be expected. Forest plots for the primary endpoint, rTNSS, are displayed in Figure 37. Pooled from studies 201, 301, and 303 and analyzed with MMRM model change from baseline as the dependent variable, treatment group, study and site as fixed effects, baseline score as covariate and study day as the within-subject effect. Variance-covariance matrix used is unstructured.

Pooled results by subgroup were similar to overall results for rTNSS, except for those with small sample sizes as noted above and for Blacks/African Americans, where mean differences of all treatment comparisons were less strong than for Whites.

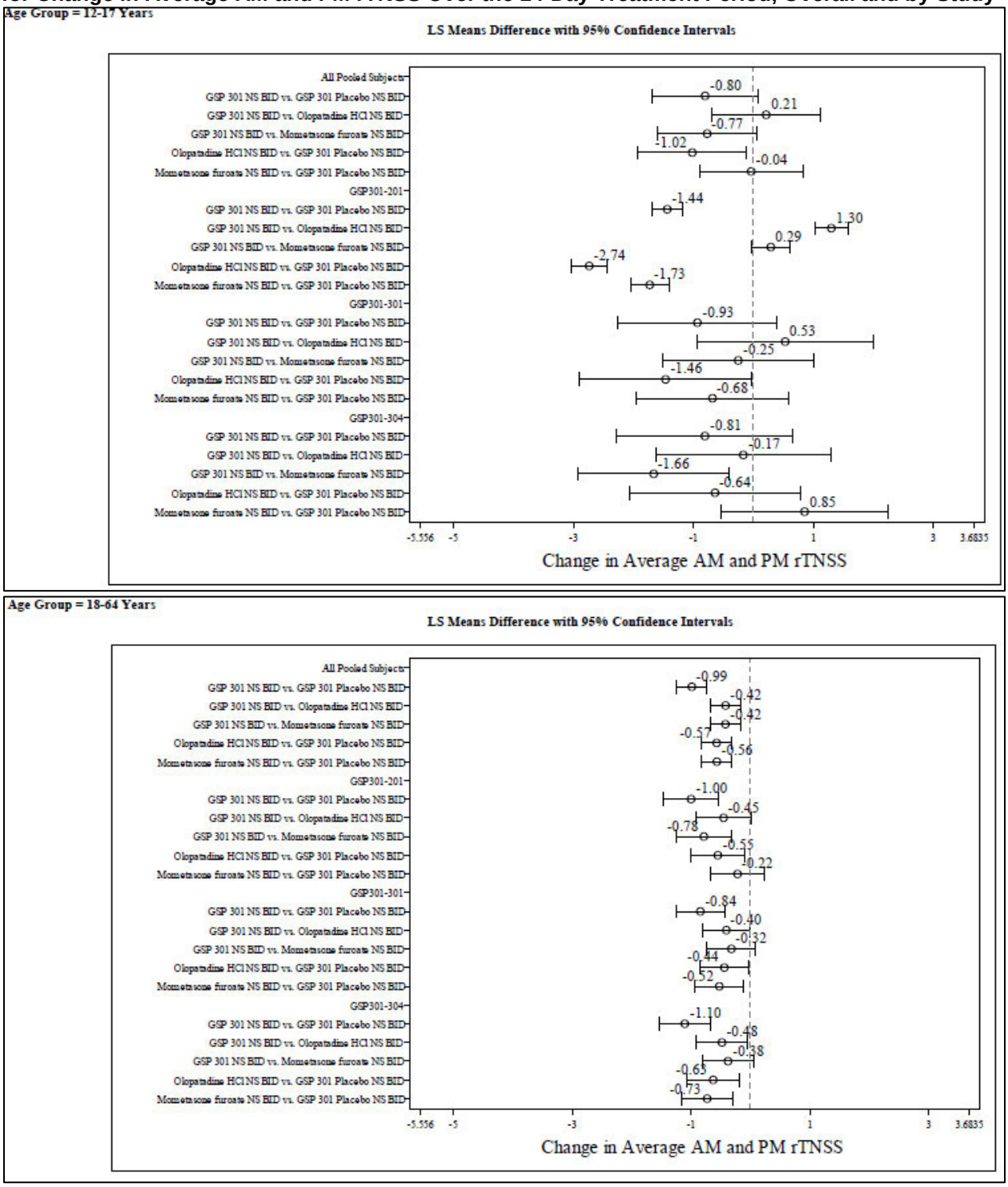
In addition, a Bayesian shrinkage analysis was conducted on the primary efficacy endpoint, rTNSS.

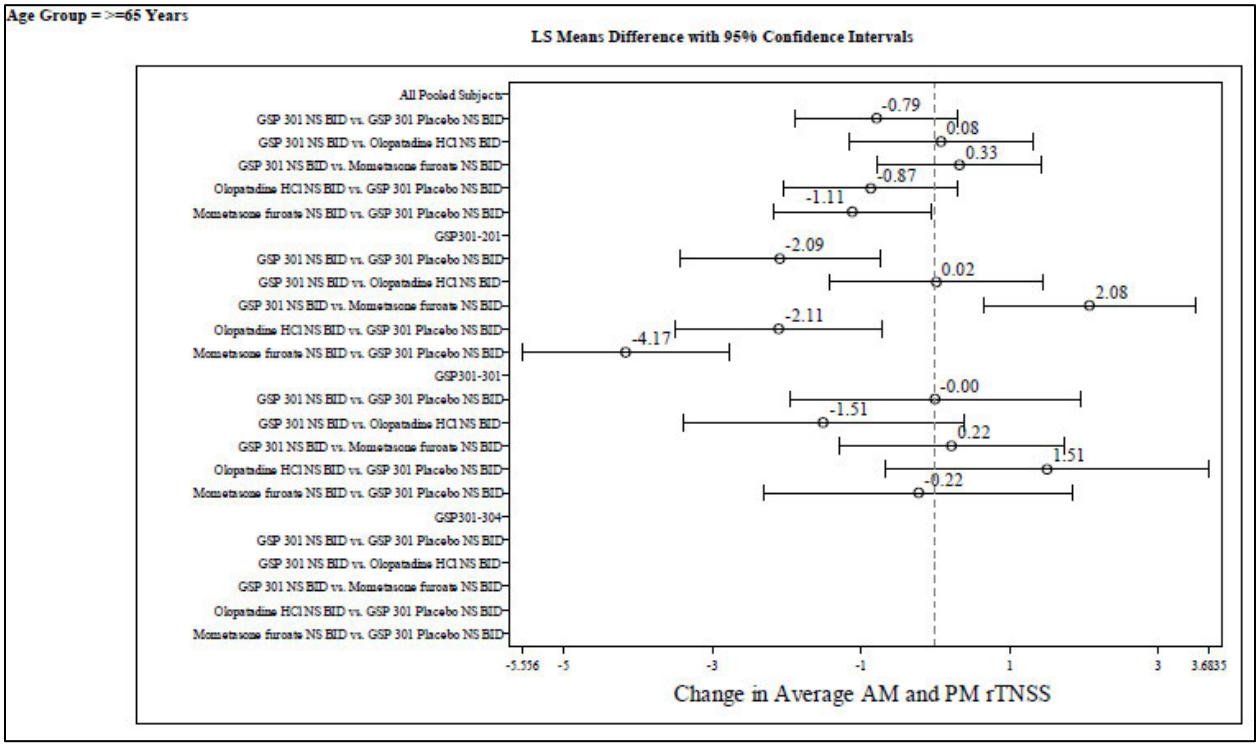
Table 63. Sample Size for the Subgroups, Age Group, Sex, Race and Ethnicity

Subgroup	GSP 301 NS	Placebo	Olopatadine	Mometasone	Total
Age group, years					
12-17	65	62	54	64	245
18-64	649	633	658	638	2581
≥65	33	36	32	44	145
Sex					
Male	235	267	277	283	1062
Female	512	464	467	463	1909
Race					
White	617	589	591	582	2381
Black	108	128	130	136	503
Other	22	14	23	28	87
Ethnicity					
Hispanic	218	202	235	224	879
Non-Hispanic	529	529	509	522	2092

Source: ISE, Tables 30-33
Abbreviations: NS=nasal spray

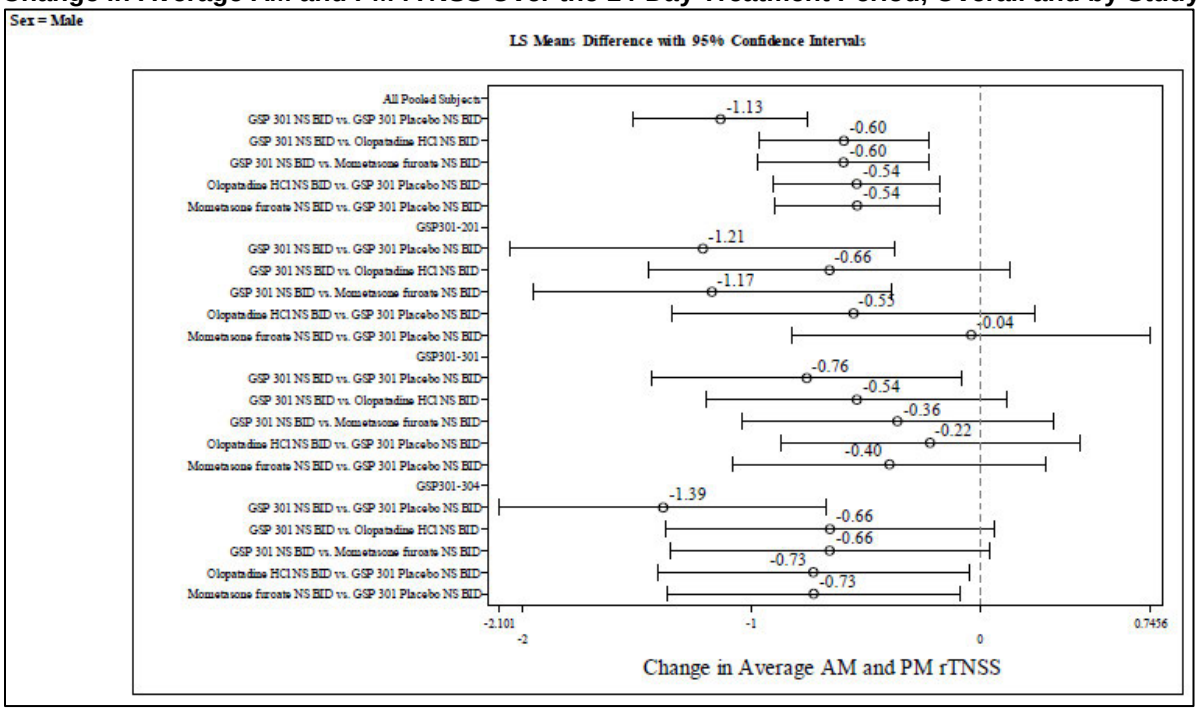
Figure 37. Forest Plot of Least Square Mean Treatment Differences and 95% CIs by Age Category for Change in Average AM and PM rTNSS Over the 14-Day Treatment Period, Overall and by Study





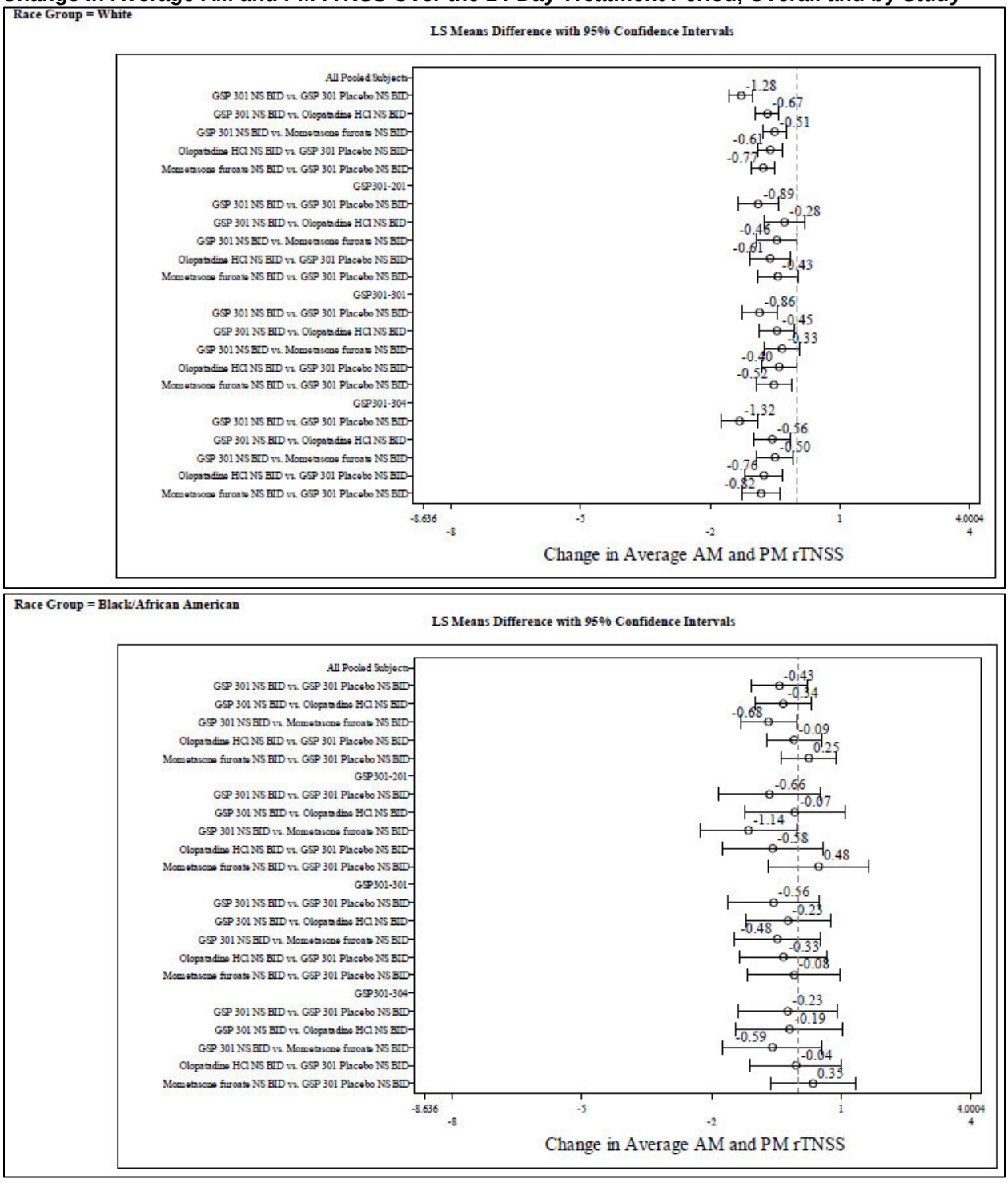
Pooled from studies 301-201, 301-301, and 301-303 and analyzed with MMRM model: change from baseline as the dependent variable, treatment group study and site as fixed effects, baseline score as covariate and study day as the within-subject effect; variance covariance matrix used is Unstructured.
Statistical analysis of each day: ANCOVA model with change from baseline as the dependent variable, treatment group, study and site as fixed effects, baseline score as covariate.
Source: ISE Figure 11.2.4.1.1
Abbreviations: CI=confidence interval; rTNSS=reflective Total Nasal Symptom Score; LS=least square; NS=nasal spray; HCl=hydrochloride; BID=twice daily

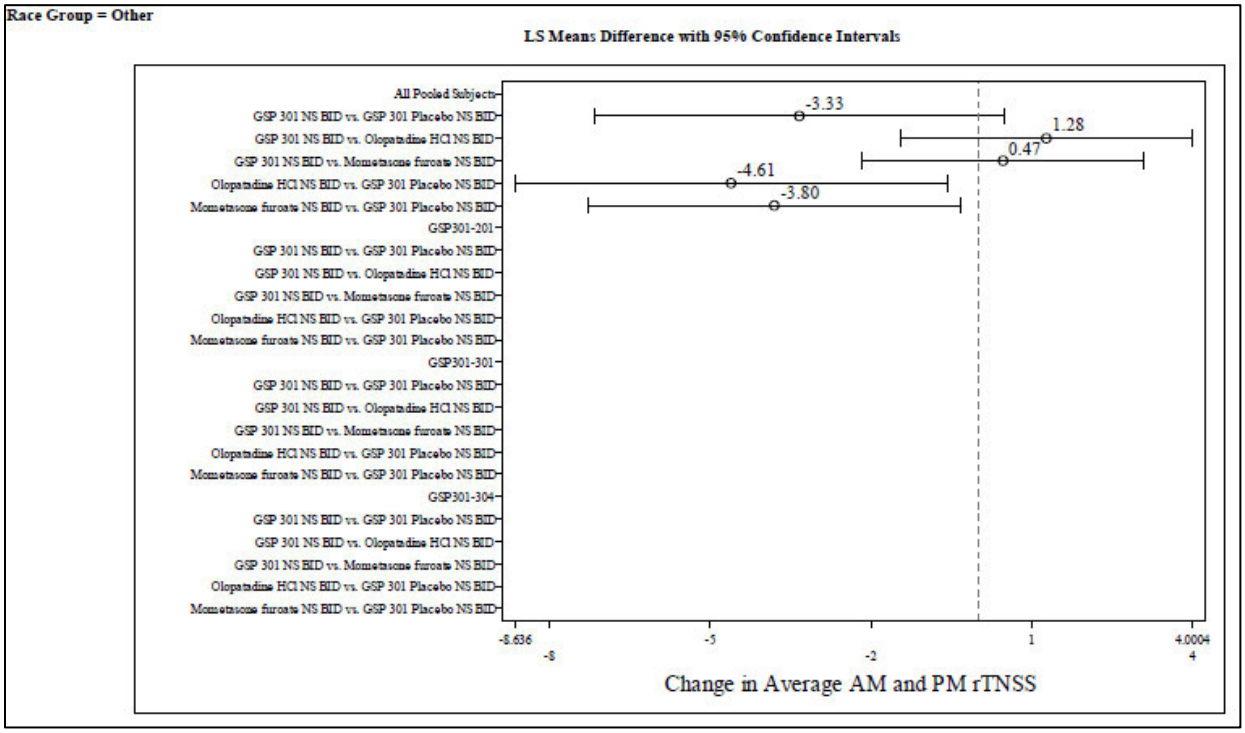
Figure 38. Forest Plot of Least Square Mean Treatment Differences and 95% CIs by Sex for Change in Average AM and PM rTNSS Over the 14-Day Treatment Period, Overall and by Study



Pooled from studies 201, 301, and 303 and analyzed with MMRM model: change from baseline as the dependent variable, treatment group study and site as fixed effects, baseline score as covariate and study day as the within-subject effect; variance covariance matrix used is unstructured.
Statistical analysis of each day: ANCOVA model with change from baseline as the dependent variable, treatment group, study and site as fixed effects, baseline score as covariate.
Source: ISE Figure 11.2.4.1.2
Abbreviations: CI=confidence interval; rTNSS=reflective Total Nasal Symptom Score; LS=least square; NS=nasal spray; BID=twice daily; HCl=hydrochloride

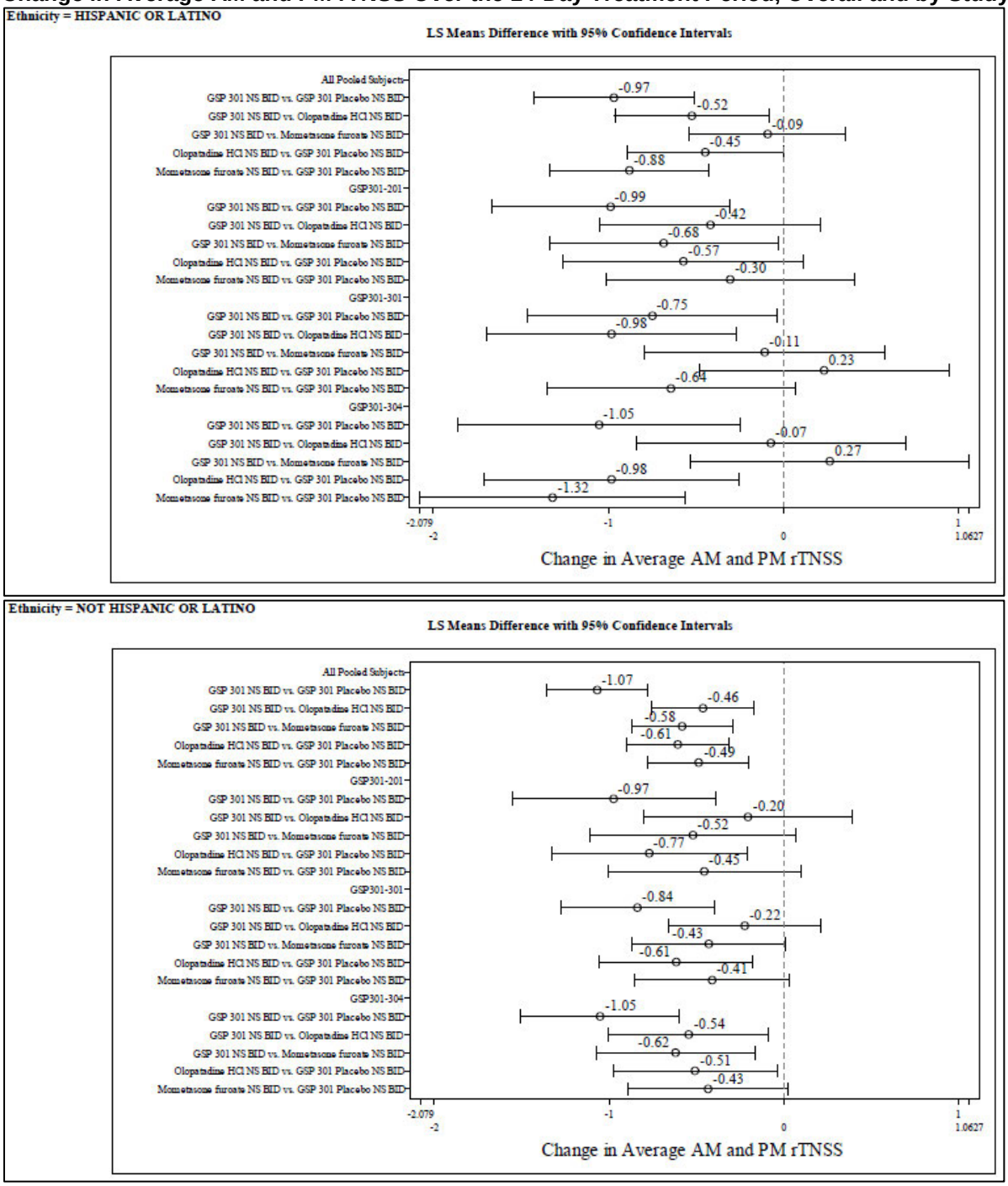
Figure 39. Forest Plot of Least Square Mean Treatment Differences and 95% CIs by Race for Change in Average AM and PM rTNSS Over the 14-Day Treatment Period, Overall and by Study





Pooled from studies 201, 301, and 303 and analyzed with MMRM model: change from baseline as the dependent variable, treatment group study and site as fixed effects, baseline score as covariate and study day as the within-subject effect; variance covariance matrix used is Unstructured.
Statistical analysis of each day: ANCOVA model with change from baseline as the dependent variable, treatment group, study and site as fixed effects, baseline score as covariate.
Source: ISE Figure 11.2.4.1.3
Abbreviations: CI=confidence interval; rTNSS=reflective Total Nasal Symptom Score; LS=least square; NS=nasal spray; BID=twice daily; HCl=hydrochloride

Figure 40. Forest Plot of Least Square Mean Treatment Differences and 95% CIs by Ethnicity for Change in Average AM and PM rTNSS Over the 14-Day Treatment Period, Overall and by Study



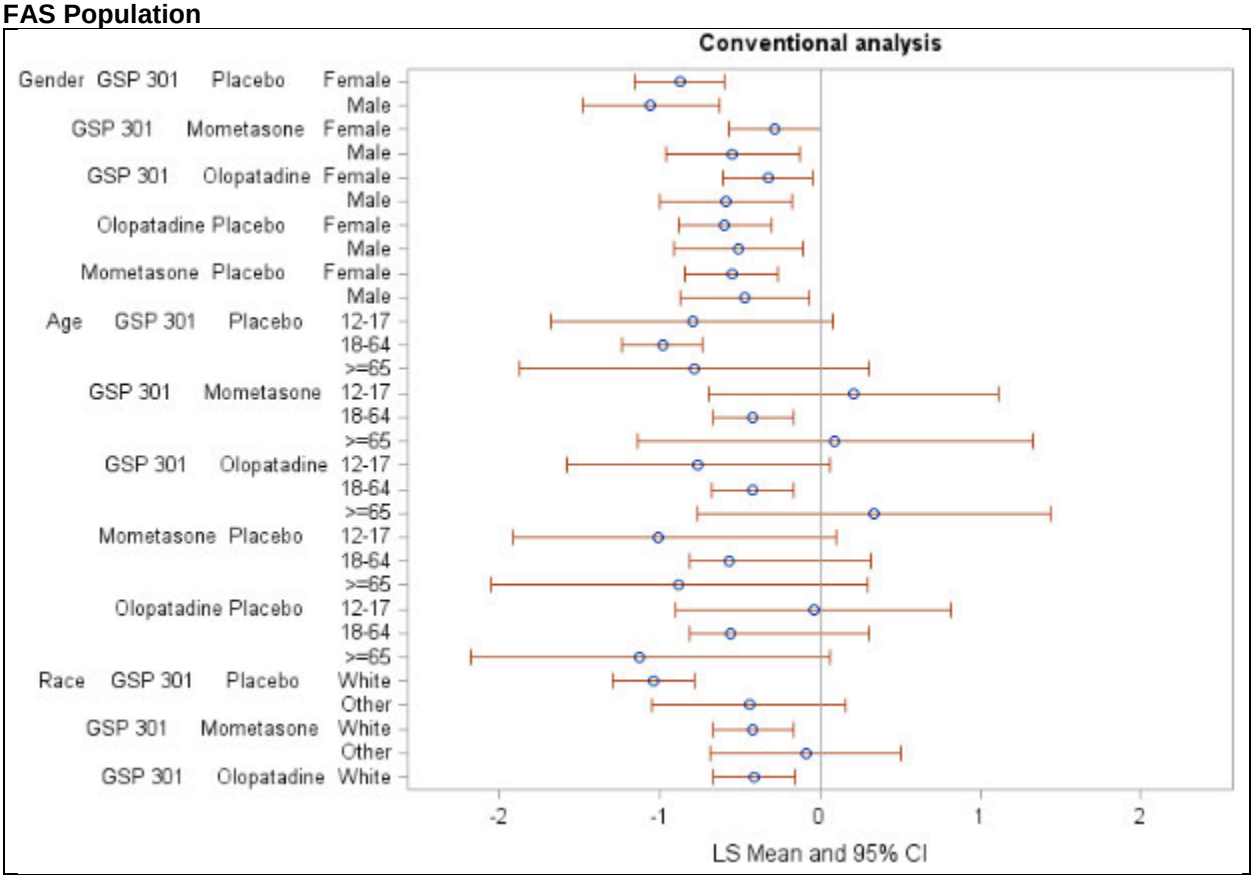
Pooled from studies 201, 301, and 303 and analyzed with MMRM model: change from baseline as the dependent variable, treatment group study and site as fixed effects, baseline score as covariate and study day as the within-subject effect; variance covariance matrix used is Unstructured.
Statistical analysis of each day: ANCOVA model with change from baseline as the dependent variable, treatment group, study and site as fixed effects, baseline score as covariate.
Source: ISE Figure 11.2.4.1.4
Abbreviations: rTNSS=reflective Total Nasal Symptom Score; CI=confidence interval; NS=nasal spray; LS=least square; BID=twice daily; HCl=hydrochloride

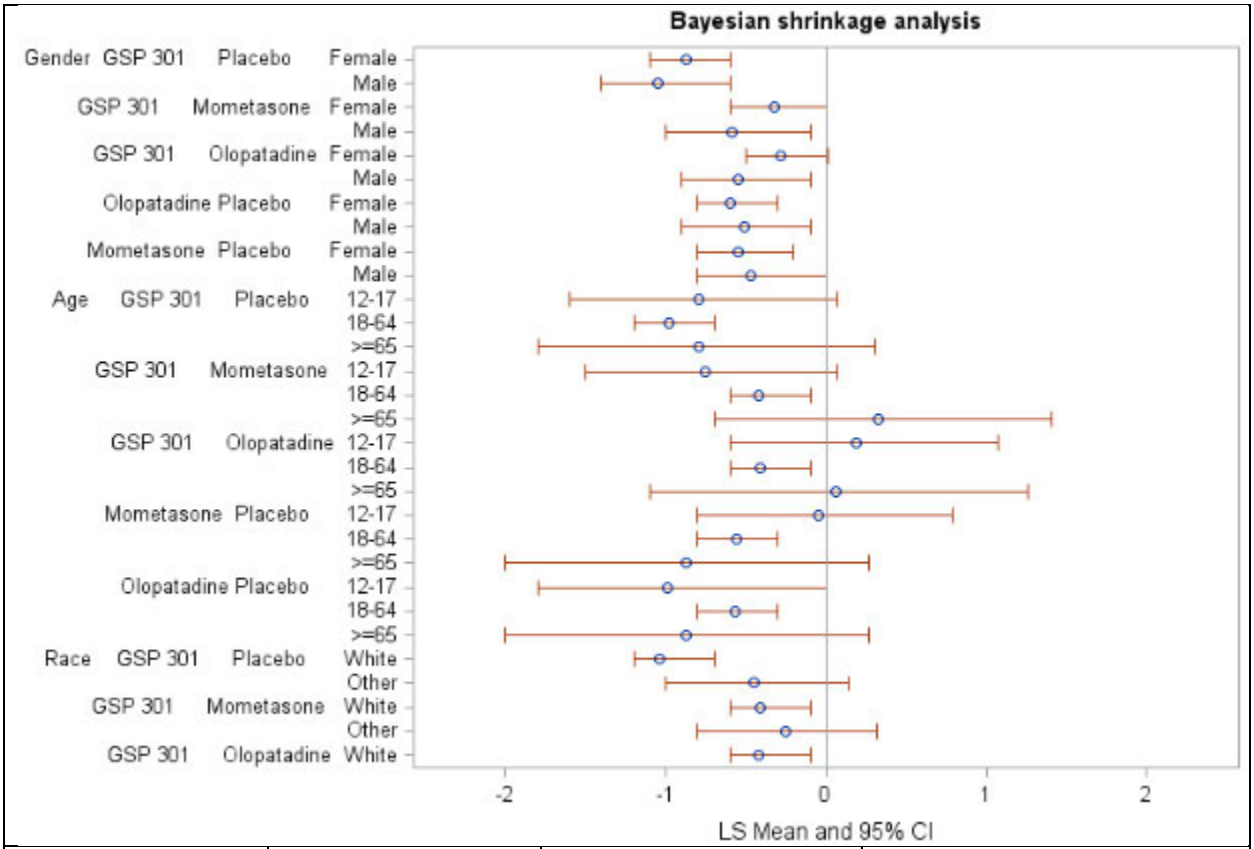
We also determined shrinkage estimates of subgroup treatment effects using a Bayesian hierarchical model. Shrinkage estimates use more information and are more precise, closer to the true subgroup treatment effects than the sample estimates.

Sample estimated treatment effects vary across subgroups more than the true treatment effects. The total variability in the sample estimates is the sum of the within subgroup variability of sample estimator and the across subgroups variability in underlying/true parameter values. As such, the sample estimates are susceptible to random highs and random lows. The shrinkage estimated treatment effects quantitatively address the random highs and random lows. The variance in the collection of shrinkage estimated treatment effects across subgroups is close to what we believe is the variance in the true treatment effects across subgroups. For a given subgroup, information from other subgroups are also used to estimate its treatment effect. Outcomes from all patients are relevant, with an outcome from a patient in the given subgroup more relevant than the outcome of a patient not in the given subgroup. A shrinkage estimate of a treatment effect/difference for a subgroup is a "weighted" average of sample estimate and overall estimate (the shrinkage estimate "borrows" information from the other subgroups). The sample estimate is "shrunk" towards the overall estimate, as seen in the comparison of the conventional, non-weighted forest plot in comparison to that weighted via the Bayesian hierarchical approach (Figure 41). The weights are based on the ratio of the between subgroup variability to the within subgroup variability. The greater that ratio the smaller the weight on the overall estimate (the less the shrinkage).

In the Bayesian hierarchical modeling approach, the conventional subgroup analysis was conducted first, then the estimated sample means, and standard errors were used in the Bayesian hierarchical modeling by assuming the subgroup sample means are random samples of a normal distribution. Subgroup analysis using Bayesian shrinkage estimate exhibits narrower confidence interval, and the shrinkage subgroup estimate is closer to the overall mean.

Figure 41. Comparison of frequentist and Bayesian Means and 95% CIs on LS Mean Treatment Differences in Change in Average AM and PM rTNSS Over the 14-Day Treatment Period, Pooled FAS Population





Subgroup	GSP 301 Comparison to	Without shrinkage Mean (95% CI)	With shrinkage Mean (95% CI)
Gender			
Female	Placebo	-0.88 (-1.16, -0.59)	-0.88 (-1.16, -0.61)
Male		-1.06 (-1.48, -0.63)	-1.05 (-1.48, -0.62)
Female	Mometasone	-0.33 (-0.61, -0.04)	-0.33 (-0.61, -0.04)
Male		-0.59 (-1.00, -0.17)	-0.59 (-1.02, -0.17)
Female	Olopatadine	-0.28 (-0.56, 0.00)	-0.28 (-0.56, 0.01)
Male		-0.5 (-0.96, -0.13)	-0.55 (-0.95, -0.13)
Age			
12-17	Placebo	-0.80 (-1.68, 0.08)	-0.80 (-1.69, 0.07)
18-65		-0.99 (-1.24, -0.73)	-0.98 (-1.24, -0.73)
>65		-0.79 (-1.88, 0.31)	-0.79 (-1.85, 0.31)
12-17	Mometasone	-0.76 (-1.59, 0.06)	-0.76 (-1.56, 0.08)
18-65		-0.42 (-0.67, -0.17)	0.42 (-0.67, -0.16)
>65		0.34 (-0.75, 1.44)	0.32 (-0.74, 1.41)
12-17	Olopatadine	0.21 (-0.70, 1.11)	0.19 (-0.66, 1.08)
18-65		-0.42 (-0.67, -0.17)	-0.41 (-0.66, -0.16)
>65		0.09 (-1.14, 1.33)	0.06 (-1.16, 1.27)
Race			
White	Placebo	-1.04 (-1.29, -0.79)	-1.04 (-1.30, -0.79)

Other		-0.44 (-1.05, 0.16)	-0.45 (-1.03, 0.15)
White	Mometasone	-0.41 (-0.66, -0.16)	-0.41 (-0.66, -0.15)
Other		-0.26 (-0.85, 0.32)	-0.26 (-0.85, 0.32)
White	Olopatadine	-0.42 (-0.67, -0.17)	-0.42 (-0.67, -0.16)
Other		-0.09 (-0.69, 0.51)	-0.09 (-0.68, 0.51)

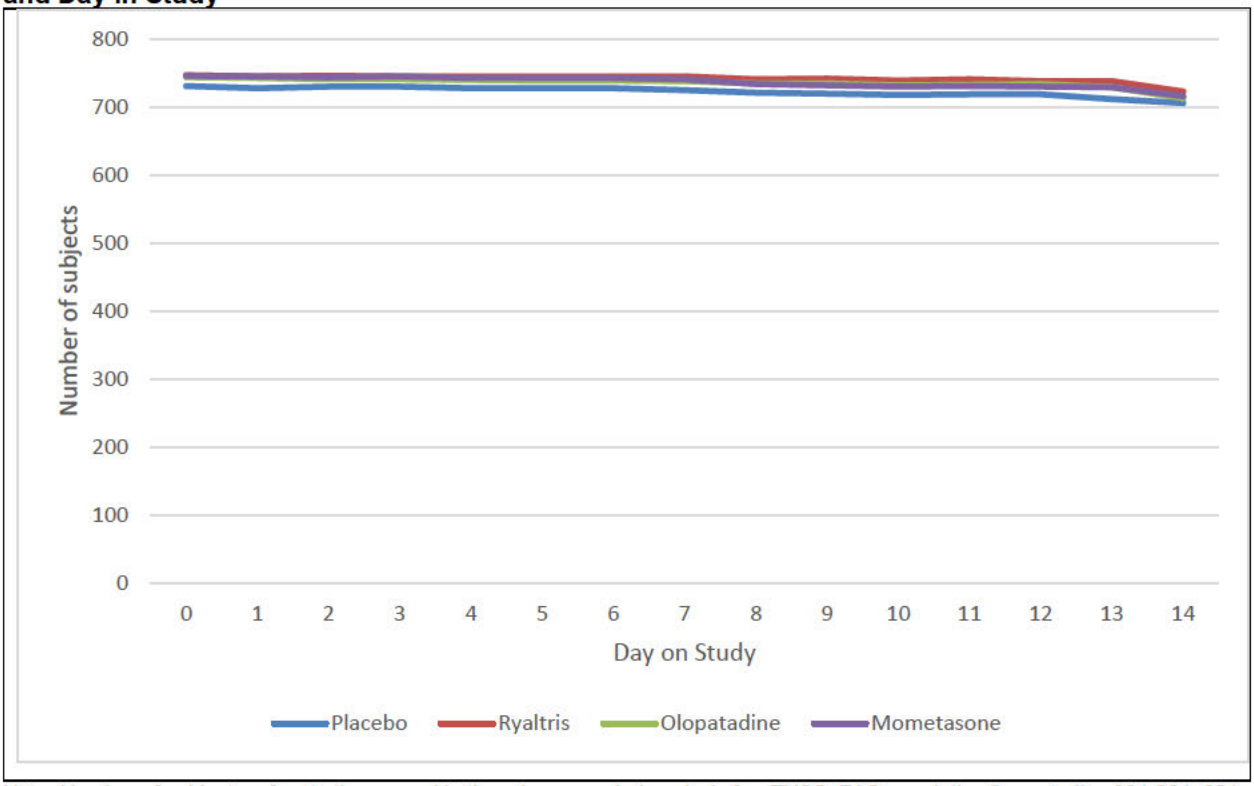
Source: Statistical reviewer

Integrated Assessment of Effectiveness

For rTNSS, evidence of effectiveness meets the statutory evidentiary standard: GSP 301 treatment reduces rTNSS clinically and statistically better than placebo and its constituent monotherapies, and the monotherapies are significantly better than placebo (Figure 34, Table 58). This was most cleanly demonstrated in the results from study 304 with confirmatory evidence from studies 301 and 201. The pooled analysis across these three trials showed a reduction of 0.94 in rTNSS point estimate (95% CI: 0.70, 1.17) relative to placebo.
Due to the brief length of study, missing data was of minimal concern in the pooled efficacy analysis (Figure 42). The tipping point analysis conducted in both pivotal studies, where all p-values remained highly statistically significant, indicated that the point estimate was robust to effects of missing data.

[23] With the exception of the GSP 301 versus olopatadine arm, which was marginally non-significant in study 301 (p-value 0.0545 and non-significant in study 201 (p-value 0.1684), the phase 2 study which has a lower sample size.

Figure 42. Number of Subjects Contributing to the Pooled Efficacy Analysis, by Treatment Arm and Day in Study



Note: Number of subjects refers to those used in the primary pooled analysis for rTNSS, FAS population from studies 301-201, 301-301, and 301-304.
Source: Statistical reviewer, efficacy_mmrm.sas

As shown in Table 59, Table 61, and Figure 36 results from two pivotal studies showed significant difference in rTOSS for GSP 301 versus placebo (a reduction of 0.49 and 0.53 in studies 301 and 304, respectively). Many of the other comparisons were not significant due to the greater effect of OLO on eye symptoms relative to MF. RQLQ (Table 62) was significantly different for GSP 301 compared to placebo (a reduction in rTOSS of 0.60, 0.43 and 0.44 for studies 201, 301 and 304, respectively). Onset of action (Table 60, Figure 35) was statistically significantly different (0.01 at 15min, <0.0001 at subsequent timepoints) for GSP 301-treated patients relative to placebo-treated patients for all recorded timepoints. Results for the OLO and placebo groups were similar; they were statistically significantly different at 30 minutes postdose and continued so for the duration of the 4 hours. However, the results for patients treated with MF were not statistically different from those of patients treated with placebo until the last timepoint, indicating that onset of action is primarily driven by OLO. The GSP 301 means had a consistently greater amount of reduction than OLO alone, indicating that MF was having a small additional effect on onset of action.

[24]

8.2. Review of Safety

8.2.1. Safety Review Approach

As studies 201, 301, 304, and the POC study were similar in design, it was deemed acceptable to pool subjects to examine the emergence of any safety signals. The safety information for the 52-week phase 3 safety study (Study 303) was not included because of its longer duration and different patient population; the safety results for study 303 will be described separately.

Safety assessments in studies 201, 301, 304, and the long-term safety trial included vital signs, physical examinations (both general and focused nasal examinations), clinical laboratory testing, 12-lead ECGs, and AE monitoring. In the POC study, AEs were collected just as in the other studies, but physical examination and focused ENT examinations were only done once (at the predose visit), and clinical laboratory tests, vital signs, and 12-lead ECGs were not performed.

8.2.2. Review of the Safety Database

Overall Exposure

The overall exposure to GSP 301 in the clinical development program was adequate for the premarket evaluation of safety. A total of 3,062 subjects in the pool 1 (BID) SAS were exposed to one of four treatments for a mean duration of 14 days (Table 64). A high compliance rate of ≥75% was achieved in >98% of subjects.

Exposure for Study 303 is summarized in Table 65. A compliance rate of ≥75% was achieved by >90% of subjects in each treatment group. Compliance was slightly higher in the two placebo groups, with 94% and 97% demonstrating ≥75% compliance as compared to 91% of patients on GSP 301. A total of 326 subjects were exposed to GSP 301 for 6 months and 250 subjects for 1 year.

Table 64. Extent of Exposure in Pooled Studies (Safety Analysis Set)

	GSP 301 Placebo N=776 n (%)	GSP 301 N=789 n (%)	Olopatadine N=751 n (%)	Mometasone N=746 n (%)
Number of days on treatment				
Mean (SD)	14.2 (1.9)	14.2 (1.4)	14.2 (1.8)	14.3 (1.4)
Median	14.0	14.0	14.0	14
Min, max	1, 16	1, 19	1, 20	4, 19
Treatment compliance, n (%)*				
<75%	10 (1.3)	3 (0.4)	7 (0.9)	5 (0.7)
≥75% to ≤100%	328 (42.3)	356 (45.1)	287 (38.2)	297 (39.8)
>100% to ≤125%	400 (51.5)	405 (51.3)	426 (56.7)	404 (54.2)
>125%	38 (4.9)	25 (3.2)	31 (4.1)	40 (5.4)

*Treatment compliance = (total number of doses actually taken / total number of doses expected) x 100
Source: GSP 301, ISS table 16 page 57

Table 65. Extent of Exposure in 52-Week Safety Study (Safety Analysis Set)

Statistic	GSP 301 Placebo NS pH 3.7 (N=99)	GSP 301 Placebo NS pH 7.0 (N=101)	GSP 301 NS (N=393)
Number of subjects exposed to study treatment, n (%)	99 (100.0)	101 (100.0)	393 (100.0)
Number of days on treatment			
Mean (SD)	322.6 (104.5)	339.9 (77.0)	311.9 (111.3)
Median	366.0	365.0	366.0
Min, max	11.0, 379.0	42.0, 393.0	1.0, 392.0
Treatment compliance, n (%)			
<75%	6 (6.1)	3 (3.0)	36 (9.2)
≥75% to ≤100%	44 (44.4)	50 (49.5)	164 (41.7)
>100% to ≤125%	49 (49.5)	48 (47.5)	193 (49.1)
Number (%) of subject treated for at least:			
6 months (180 days)	85 (85.9)	93 (92.1)	326 (83.0)
1 year (365 days)	65 (65.7)	68 (67.3)	250 (63.6)

Source: GSP 301-303 CSR Table 18 page 59

The pooled population yielded similar demographic characteristics in each treatment group, despite a slightly higher proportion of females in the GSP 301 group than in the comparator groups (Table 66).

Table 66. Demographics of Pooled Studies (Safety Analysis Set)

Statistic	GSP 301 Placebo N=776	GSP 301 N=789	Olopatadine N=751	Mometasone N=746
Age (years)				
Mean (SD)	40.7 (14.9)	40.2 (14.8)	40.3 (14.6)	39.9 (15.4)
Median	41.0	41.0	40.0	40.0
Min, max	12, 83	12, 81	12, 84	12, 87
Sex n (%)				
Male	285 (36.7)	260 (33.0)	279 (37.2)	282 (37.8)
Female	491 (63.3)	529(67.0)	472 (62.8)	464 (62.2)
Race n (%)				
White	612 (78.9)	642 (81.4)	596 (79.4)	582 (78.0)
Black/African American	143 (18.4)	118 (15.0)	132 (17.6)	136 (18.2)
Other	21 (2.7)	29 (3.7)	23 (3.1)	28 (3.8)
Ethnicity n (%)				
Hispanic or Latino	205 (26.4)	225 (28.5)	237 (31.6)	224 (30.0)
Not Hispanic or Latino	571 (73.6)	564 (71.5)	514 (68.4)	522 (70.0)

Source: NDA 211746, ISS Table 19 page 58

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Categorization of Adverse Events

All AEs were coded according to version 20.0 of the Medical Dictionary for Regulatory Activities (MedDRA) however, version 19.0 is incorrectly noted in the ISS tables. For study 303, all AEs were coded using MedDRA Version 18.1.

The clinical program defined an AE as "any untoward medical occurrence in a subject administered IP that did not necessarily have a causal relationship with the treatment. An AE could, therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease (new or exacerbated) temporally associated with the use of an IP".

An SAE was defined as "any untoward medical occurrence that, at any dose:

- Resulted in death
- Was life-threatening
- Required hospitalization or prolongation of existing hospitalization
- Resulted in disability/incapacity
- Was a congenital/birth defect"[25]

The Applicant also considered the following AEs of special interest based on safety information presented in the Reference Listed Drugs US prescribing information: "hypersensitivity reactions, metabolism and hormonal disorders, nasal toxicity, neurotoxicity, ophthalmic toxicity and opportunistic infections".[26]

8.2.4. Safety Results

Deaths

There were no deaths in the clinical trials comprising the development program for GSP 301.

Serious Adverse Events

A total of 20 SAEs were reported across the clinical program in 16 subjects (Table 67 and Table 68). In pool 1 (BID only), nine SAEs were reported among 5 (0.2%) subjects. No SAEs were considered related to study treatment. One subject in placebo group had a foot fracture that led to study discontinuation.

[25] Section 1.1.6.2 ISS pg 40–43.
[26] Section 1.1.7.2 ISS p. 47.

Table 67. Treatment-Emergent Serious Adverse Events in Pool 1 (Safety Analysis Set)

SYSTEM ORGAN CLASS Preferred Term	GSP 301 Placebo NS BID (N=776) n (%)	GSP 301 NS BID (N=789) n (%)	Olopatadine HCl NS BID (N=751) n (%)	Mometasone Furoate NS BID (N=746) n (%)	Total (N=3062) n (%)
Any SAE	1 (0.1)	1 (0.1)	2 (0.3)	1 (0.1)	5 (0.2)
GASTROINTESTINAL DISORDERS	0	0	1 (0.1)	0	1 (0.0)
Large intestinal obstruction	0	0	1 (0.1)	0	1 (0.0)
Large intestine perforation	0	0	1 (0.1)	0	1 (0.0)
INFECTIONS AND INFESTATIONS	1 (0.1)	0	1 (0.1)	1 (0.1)	3 (0.1)
Diverticulitis	0	0	1 (0.1)	0	1 (0.0)
Osteomyelitis	1 (0.1)	0	0	0	1 (0.0)
Peritonsillar abscess	0	0	0	1 (0.1)	1 (0.0)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (0.1)	0	0	0	1 (0.0)
Foot fracture	1 (0.1)	0	0	0	1 (0.0)
NERVOUS SYSTEM DISORDERS	1 (0.1)	0	1 (0.1)	0	2 (0.1)
Ischaemic stroke	0	0	1 (0.1)	0	1 (0.0)
Syncope	1 (0.1)	0	0	0	1 (0.0)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	0	1 (0.1)	0	0	1 (0.0)
Abortion spontaneous	0	1 (0.1)	0	0	1 (0.0)

Source: ISS table 36 page 88
Adverse events were coded using MedDRA version 20.0
Abbreviations: NS=nasal spray; BID=twice daily; HCl=hydrochloride; SAE=serious adverse event;

In the 52-week safety study, 11 subjects reported a total of 11 SAEs for a rate of ≤2.0% across the 3 treatment groups. No SAEs were considered to be related to study treatment. Discontinuation of study occurred in subjects with prostate cancer, renal cell carcinoma, anaplastic astrocytoma, and ectopic pregnancy.

Narratives for all SAEs were reviewed. Overall, the number of SAEs in the clinical program was low and without any imbalances between the treatment groups. No new safety signals were revealed.

Table 68. Treatment-Emergent Serious Adverse Events in Study 303 (Safety Analysis Set)

MedDRA Preferred Term	GSP 301 Placebo NS pH 3.7 (N=99) n (%)	GSP 301 Placebo NS pH 7.0 (N=101) n (%)	GSP 301 NS (N=393) n (%)
Subjects with at least 1 SAE	2 (2.0)	2 (2.0)	7 (1.8)
Cholelithiasis	0	1 (1.0)	1 (0.3)
Appendicitis	1 (1.0)	0	0
Cellulitis	0	0	1 (0.3)
Pneumonia	0	0	1 (0.3)
Anaplastic astrocytoma	0	0	1 (0.3)
Prostate cancer	0	0	1 (0.3)
Renal cell carcinoma	0	0	1 (0.3)
Triple negative breast cancer	0	0	1 (0.3)
Ectopic pregnancy	1 (1.0)	0	0
Nephrolithiasis	0	1 (1.0)	0

Source ISS Table 37 page 89
Adverse events coded using MedDRA version 18.1

Dropouts and/or Discontinuations Due to Adverse Effects

In pool 1, the study completion rate for all subjects was 96.7% and rates were similar across the treatment groups (ranging from 96.3% to 97.1%). The early termination rate for all subjects was 3.3% and rates were similar across the treatment groups. Early termination due to AEs was 15 (0.5%) subjects and ranged from 1 (0.1%) in placebo group to 6 (0.8%) in the OLO group.

Significant Adverse Events

The incidence of TEAEs in the pool 1 GSP 301 group was higher (13.9%) than those of placebo, OLO, and MF groups (9.5%, 13.2%, and 7.9%, respectively) (Table 69). Overall, the frequency of AEs leading to discontinuation of treatment was low and balanced in the GSP 301 and placebo arms (0.1% and 0.4% respectively) and slightly higher in the monotherapy comparators (0.9% for OLO and 0.8 % for MF). Fewer than 1% of subjects had a TEAE, SAE, or AE leading to study discontinuation.

Table 69. Treatment Emergent Adverse Events and Serious Adverse Events (14-Day) (Safety Analysis Set)

Subject Level Summary	GSP 301 Placebo N=776 n (%)	GSP 301 N=789 n (%)	Olopatadine N=751 n (%)	Mometasone N=746 n (%)
At least 1 TEAE	74 (9.5)	110 (13.9)	99 (13.2)	59 (7.9)
At least 1 related TEAE	20 (2.6)	51 (6.5)	45 (6.0)	20 (2.7)
At least 1 severe TEAE	4 (0.5)	4 (0.5)	11 (1.5)	6 (0.8)
TEAE leading to discontinuation	1 (0.1)	3 (0.4)	7 (0.9)	6 (0.8)
At least 1 SAE	1 (0.1)	1 (0.1)	2 (0.3)	0
At least 1 related SAE	0	0	0	0
At least 1 severe SAE	1 (0.1)	0	2 (0.3)	0
SAE leading to drug discontinuation	1 (0.1)	0	0	0
At least 1 SAE leading to death	0	0	0	0

Source: GSP 301 ISS table 23 page 66

The number of TEAEs leading to study discontinuation was also low in the long-term safety study. However, TEAEs occurred more frequently in the GSP 301 group (n=15 (3.8%)) than in the two placebo arms (n=2 (2.0%) for placebo pH 3.7, n=3 (3.0%) for placebo pH 7.0).

Table 70. Treatment Emergent Adverse Events and Serious Adverse Events (52-Week) (Safety Analysis Set)

Subject Level Summary	GSP 301 Placebo pH 3.7 N=99 n (%)	GSP 301 Placebo pH 7.0 N=101 n (%)	GSP 301 N=393 n (%)
At least 1 TEAE	41 (41.4)	54 (53.5)	203(51.7)
At least 1 related TEAE	7 (7.1)	10 (9.9)	44 (11.2)
At least 1 severe TEAE	6 (6.1)	3 (3.0)	20 (5.1)
≥1 TEAE leading to discontinuation	2 (2.0)	3 (3.0)	15 (3.8)
At least 1 SAE	2 (2.0)	2 (2.0)	7 (1.8)
At least 1 related SAE	0	0	0
At least 1 severe SAE	1 (1.0)	1 (1.0)	5 (1.3)
≥1 SAE leading to drug discontinuation	1 (1.0)	0	3 (0.8)

Source: NDA 211746, ISS table 25 page 72

Table 71. Adverse Events of Special Interest in Pool 1 (14-Day SAR Studies) (Safety Analysis Set)

Preferred Term	GSP 301 Placebo N=776 n (%)	GSP 301 N=789 n (%)	Olopatadine N=751 n (%)	Mometasone N=746 n (%)
Nasal toxicity				
Epistaxis	5 (0.6)	8 (1.0)	11 (1.4)	6 (0.8)
Nasal mucosal erosion	1 (0.1)	1 (0.1)	0	1 (0.1)
Nasal perforation	0	0	0	0
Nasal septal defect	0	0	0	0
Nasal ulceration	0	0	0	0
Hypersensitivity reactions				
Anaphylaxis	0	0	0	0
Asthma	0	2 (0.2)	2 (0.3)	0
Urticaria	2 (0.2)	0	1 (0.1)	1 (0.1)
Wheezing	0	1 (0.1)	0	0
Neurotoxicity				
Somnolence	0	2 (0.2)	2 (0.3)	2 (0.3)
Syncope	1 (0.1)	0	0	0
Opportunistic infections				
Candida infection	0	0	1 (0.1)	0
Oral candidiasis	1 (0.1)	0	0	0
Oral herpes	2 (0.2)	0	2 (0.3)	0
Tuberculosis	0	0	0	0
Ophthalmic toxicity				
Cataract	0	0	0	0
Glaucoma	0	0	0	0
Intraocular pressure	0	0	0	0
Metabolism and hormonal disorders				
Adrenal suppression	0	0	0	0
Growth retardation	0	0	0	0
Impaired wound healing	0	0	0	0

Source: NDA 211746, ISS Table 44 page 107

Table 72. Adverse Events of Special Interest in 52-Week Safety Study (Safety Analysis Set)

Category/Preferred Term	GSP 301 Placebo pH 3.7 N=99 n (%)	GSP 301 Placebo pH 7.0 N=101 n (%)	GSP 301 NS N=393 n (%)
Nasal toxicity			
Epistaxis	2 (2.0)	2 (2.0)	18 (4.6)
Nasal mucosal erosion	0	0	0
Nasal perforation	0	0	1 (0.3)
Nasal septal defect	0	0	0
Nasal ulceration	0	0	0
Hypersensitivity reactions			
Anaphylaxis	0	0	0
Asthma	1 (1.0)	0	4 (1.0)
Hypersensitivity	0	0	2 (0.5)
Urticaria	0	0	3 (0.8)
Wheezing	0	1 (1.0)	0
Neurotoxicity			
Somnolence	0	0	3 (0.8)
Syncope	1 (0.1)	1 (1.0)	0
Opportunistic infections			
Candida infection	0	0	0
Oral candidiasis	0	0	0
Oral herpes	1 (1.0)	0	2 (0.5)
Tuberculosis	0	0	0
Ophthalmic toxicity			
Cataract	0	1 (1.0)	0
Glaucoma	0	0	1 (0.3)
Intraocular pressure	1 (1.0)	0	0
Metabolism and hormone disorders			
Adrenal suppression	0	0	0
Growth retardation	0	0	0
Impaired wound healing	0	0	0

Source: NDA 211746, ISS table 45 page 110

Common Adverse Events

The overall AE profile for GSP 301 was largely consistent with the safety profiles observed for the constituent monoproducts. The most common TEAEs were dysgeusia, headache, epistaxis and, and nasal discomfort which occurred with ≥1% incidence and were reported more frequently with GSP 301 than placebo in the 2-week placebo controlled studies.

Laboratory Findings

Clinical laboratory evaluations were not done in the POC study; therefore, the pool 1 analysis is based on available data from 2,990 subjects in studies 201, 301, and 304. Overall, mean baseline and mean changes in hematology, biochemistry, and urinalysis parameters did not demonstrate clinically significant changes and were similar across treatment groups. At the end of the treatment, ≤0.4% of subjects in each treatment group had abnormal clinically significant laboratory values as determined by the investigator.

In the long-term safety trial, small mean changes from baseline in biochemistry, hematology,

and urinalysis parameters were seen, and the changes were similar across all three treatment groups. At the end of 52 weeks of treatment, ≤1.0% of subjects in each treatment group had abnormal clinically significant laboratory values.

Vital Signs

Among subjects whose vital signs were measured (studies 201, 301 and 304), abnormal values for systolic blood pressure, diastolic blood pressure, and pulse rate were observed at the end of the treatment in ≤0.3% of subjects in each treatment group. None of the abnormal values were determined to be clinically significant by the investigator.

In the year-long safety trial, abnormal values for diastolic blood pressure, systolic blood pressure, and pulse rate were observed at the end of 52 weeks of treatment in ≤3.1% of subjects in the GSP 301 group and in 2.0% and 7.1% in the two placebo groups. One subject in the GSP 301 group had systolic and diastolic values that were determined to be clinically significant by the investigator. This occurred at the final study visit and was reported as a TEAE. The increased blood pressure was not considered related to study treatment by the investigator.

Electrocardiograms

Among subjects in whom ECGs were performed (studies 201, 301, and 304), the overall ECG interpretation was normal at baseline and at the end of treatment for all subjects except 1 in the MF BID group. This subject's ECG detected supraventricular extra systoles at the last visit, which was considered a potentially clinically significant abnormality by the investigator. The TEAE was reported as moderate, but it was resolved and was considered not related to study treatment by the investigator.

8.2.5. Analysis of Submission-Specific Safety Issues

Local toxicity in the form of nasal septal perforation, ulceration, and epistaxis are safety concerns common to other intranasal products approved for AR. For this reason, the Applicant conducted focused nasal exams throughout the trials and used a prespecified grading system for scoring local toxicity.

Nasal Examinations

There was one instance of nasal perforation across the clinical development program, which was reported for a patient receiving GSP 301 in the long-term safety study. This event was severe though not considered to be related to treatment, and it did not result in permanent discontinuation of study treatment. The patient had a history of substance abuse, and the ENT report indicated that the physical finding was consistent with a chronic, preexisting perforation given history of cocaine use and of the lesion.

There were three cases of nasal mucosal erosion, one in the GSP 301 group and one each in placebo and OLO groups. Reports of epistaxis were infrequent in all treatment arms and were most commonly reported as of mild or moderate intensity.

Ophthalmic Examinations

Ophthalmic exams screening for glaucoma and posterior subcapsular cataracts were also conducted in the long-term safety study since these AEs have been associated with other intranasal corticosteroids. Events were rare (one case each) and similar across treatment arms.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The RQLQ(S) used in the clinical development program is a disease-specific, validated, QOL questionnaire that measures functional impairments (physical, emotional, and social) of adults and adolescents with allergies. The RQLQ(S) had 28 questions in 7 domains (activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional). Subjects recalled experiences during the previous week and gave responses on a seven-point scale (0=not troubled to 6=extremely troubled) for all domains. The self-administered version of the RQLQ(S) was completed by the subjects at the randomization visit (visit 2) and the final visit/discontinuation visit.

The change from baseline RQLQ(S) over the 14-day treatment was a secondary endpoint. In all individual studies, GSP 301 demonstrated a statistically significant improvement compared with placebo.

8.2.7. Safety Analyses by Demographic Subgroups

Stratification of the safety analyses by sex did not reveal clinically meaningful differences in the rates of AEs between males and females.

Stratification of the safety analyses by age group did not reveal clinically meaningful differences in the AE frequencies among the three age groups, ≥12 to ≤ 17 years of age, ≥18 to ≤64 years of age, and ≥65 years of age.

The number of white subjects (N=2,432) greatly exceeded the number of black/African American (N=529) subjects and those of other racial minorities (N=101). For subjects treated with GSP 301, the incidence of TEAEs was similar for white and black/African American subjects (14.3% and 10.2%, respectively) and was higher for subjects of other races (20.7%).

8.2.8. Specific Safety Studies/Clinical Trials

Study 303 was designed as a 52-week, long-term safety study investigating the effect of pH of the TBM product on local nasal toxicities. No additional specific safety issues were identified.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Nonclinical carcinogenicity studies were not conducted given known safety of OLO and MF.

Human Reproduction and Pregnancy

Human reproduction and pregnancy studies were not conducted given known safety of OLO and MF.

Pediatrics and Assessment of Effects on Growth

The clinical development program for GSP 301 did not include an evaluation in children less than 12 years old. The proposed label includes class labeling that describes the association between intranasal corticosteroids and reduced growth velocity in pediatric patients and recommends that the growth of pediatric patients receiving GSP 301 be monitored routinely.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The application does not address the issue of overdose but does comment that no withdrawal or rebound effects would be predicted based on past experience with OLO and MF.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

There has been no postmarket experience with GSP 301.

Expectations on Safety in the Postmarket Setting

No postmarketing risk evaluation and management strategies are recommended.

8.2.11. Integrated Assessment of Safety

The safety population pooled from the four 2-week efficacy and safety trials is comprised of subjects treated with GSP 301 BID (n=789), placebo (n=776), OLO monotherapy comparator (n=751), and MF monotherapy comparator (n=746). The mean treatment duration, mean total number of doses taken, and rate of compliance were comparable across treatment groups. The

safety population from the long-term safety trial 303 was comprised of subjects treated with GSP 301 (n=393), placebo pH 3.7 (n=99), and placebo pH 7.0 (n=101).

There were no deaths across the seven clinical trials comprising the development program for GSP 301. A total of five SAEs were reported across the clinical program, one of which was not considered treatment-related and did not lead to discontinuation.

The overall AE profile for GSP 301 was largely consistent with the safety profiles observed for the constituent monoproducts. The most common TEAEs were dysgeusia, headache, epistaxis and, and nasal discomfort which occurred with ≥1% incidence and were reported more frequently with GSP 301 than placebo in the 2-week placebo controlled studies.

In study 303 (52-week treatment), the most commonly reported TEAE in each treatment group was upper respiratory infection (6.4% for GSP 301, 6.1% for pH 3.7 placebo, and 8.9% for pH 7 placebo). There was no significant difference in the most common TEAEs (≥2% of subjects) observed between GSP 301 and either placebo group.

The placebo-controlled trials 201, 301, and 304, in conjunction with the 52-week trial 303, provide adequate support for the safety of GSP 301 for the treatment of symptoms associated with SAR in patients ≥12 years of age (b) (4) . Prospective examinations for local toxicity did not suggest an additive or synergistic effect of the combination compared to the active comparators. Overall, the nature and frequency of the AEs were consistent with the safety profile of commercially available monoproducts.

8.3. Summary and Conclusions

8.3.1. Statistical Issues

Statistical issues will be described in the context of the efficacy estimand for this development program. An estimand is described by four features:

1. Population of interest: Patients with SAR, from 12 years and older, duplicated in one phase 2 and two phase 3 confirmatory studies.
2. Variable or endpoint of interest: rTNSS measured identically across the three trials for 14 days in AM and PM, prior to the next treatment dose.
3. Measure of intervention effect: Difference in mean AM and PM daily scores over 14 days, adjusting for baseline as a covariate in an MMRM analysis.
4. How potential intercurrent events were reflected: missing data were not imputed; sensitivity analysis was conducted with a Tipping Point analysis.

Two supportive analyses were also performed: analysis of covariance (ANCOVA)[27] and MMRM with imputation using Jump to Reference (J2R)[28]. ANCOVA employs a different statistical model from the primary MMRM. J2R estimates a different estimand from the primary analysis.

It is unusual for missing data to not be imputed; we expect missing data handling in most pivotal efficacy trials.

For GSP 301, there were no major concerns with the estimand as described above. The Applicant used an ANCOVA model in study 201, MMRM with compound symmetry variance matrix for studies 301 and 304, and MMRM with unstructured variance matrix for the ISE pooled analysis. For our review (described in the ISE section), we were able to confirm the ISE MMRM with unstructured covariance matrix model. We based our assessment for substantial evidence on the same analysis for the individual studies. When comparing the results of our model to the Applicants for the individual studies, the results were very similar.

We noted an inconsistency in methodology across the clinical program, which is detailed in the Integrated Efficacy section. The pooled analysis used MMRM with the unstructured covariance option in the model. We concur with that analysis. Study 301-201 primary analysis was ANCOVA. Studies 301-301 and 301-304 used MMRM with the compound symmetry covariance option in the model. We do not agree with this approach, as these studies do not adhere to the conditions for assuming compound symmetry. The impact of the revised analysis on study 301 was substantive: our results for the difference between GSP 301 and placebo were 0.78, whereas the Applicant's were 0.98. It also affected the other comparisons, most notably the comparison of GSP 301 to mometasone is not significant in our analysis.

This was not the case in study 304: results using unstructured variance (our analysis) were only slightly different than with compound symmetry (Applicant's analysis). Because the Applicant chose study 304 for the label, we felt it was reasonable to concur with those estimates as a reasonable representation of the results for labelling purposes.

Subgroup analysis of the primary endpoint on demographic characteristics such as gender, age, and race using Bayesian shrinkage estimate exhibits narrower confidence intervals, and the shrinkage subgroup estimate is closer to the overall mean.

While we do see reasonable and consistent evidence of efficacy in this program, the studies are somewhat underpowered. A slightly larger sample size in the pivotal studies would have made a clearer case for substantial evidence.

[27] This model includes treatment, site and baseline 12-hour rTNSS, performed for the FAS only.

[28] This approach represents an estimand (defined as to be estimated in a statistical analysis) where the subject takes no further treatment, and their mean response is now that of the subjects in the reference (placebo) group

The multiplicity gatekeeping strategy used by the Applicant may not have been optimal. The requirement for significance in the comparisons between GSP 301 and its constituent monotherapies may be harder to achieve than in the comparisons between placebo and the monotherapies. The data was compelling and consistent enough that we determined there was substantial evidence despite the stated multiplicity strategy.

8.3.2. Conclusions and Recommendations

The 2-week placebo-controlled trials in conjunction with the results of the 52-week trial, provide adequate support for the efficacy and safety of GSP 301 2 sprays per nostril BID for the treatment of the symptoms associated with SAR in patients 12 years of age and older who require treatment with both OLO and MF for symptomatic relief. Prospective examination for local toxicity did not suggest additive or synergistic effect of the combination compared to the active comparators. The nature and frequency of AEs were consistent with the safety profile of the corresponding commercially available monoproducts as described in the current package inserts for each.

The clinical and statistical review's conclusion is that the risk-benefit assessment is favorable for the proposed product and supports approval.

9 Advisory Committee Meeting and Other External Consultations

As OLO and MF are well-characterized pharmaceutical entities, an advisory committee meeting was not held for this application.

10 Pediatrics

The clinical development program for GSP 301 did not include an evaluation in children less than 12 years of age.

The proposed label includes class labeling that describes the association between intranasal corticosteroids and reduced growth velocity in pediatric patients and recommends that the growth of pediatric patients receiving GSP 301 be monitored routinely.

The NDA includes a request for waiver of pediatric studies for patients less than 2 years of age, based on the prevalence and incidence of SAR in patients <2 years of age and studies of this product in that age range would be impossible to highly impracticable. Currently, neither of the individual monotherapy products of the GSP 301 FDC product are approved for use in the age group <2 years for the treatment of SAR (b) (4). Patanase® NS is approved for SAR patients 6 years of age and older and Nasonex® NS is approved for AR patients 2 years of age and older.

While Patanase® NS was studied in patients 2 to 6 years of age, efficacy and safety were not demonstrated in this age group.

The Applicant's full waiver proposal was discussed at the Pediatric Review Committee on December 20, 2017. The Pediatric Study Plan includes a waiver in patients <6years of age. The reason for the waiver in patients <2 years of age is that studies would be impossible or highly impractical. For patients 2 to <6 years of age, the reason for waiver is that the product would be ineffective and/or unsafe in one or more of the pediatric groups(s) for which the waiver is requested (and should be labeled as it already is labeled for Patanase®). It also includes a deferral of pediatric studies in patients 6 to< 12 years of age until the safety and tolerability of GSP 301 is established in the adult and adolescent (≥12 years) population. The Pediatric Review Committee noted that it would be best to conduct a two-week parallel study in this population employing the same factorial design to avoid the use of a placebo arm.

The Applicant will conduct a multi-center, randomized, double-blind, parallel group, 14-day, efficacy and safety study (study 305) of GSP 301 versus placebo in approximately 450 pediatric subjects aged ≥6 to <12 years with SAR. The primary and secondary efficacy endpoints will be the change from baseline in average AM and PM subject-reported 12-hour rTNSS and iTNSS, respectively over the treatment period.

This pediatric PMR will be communicated to the sponsor in the next review cycle.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

12 Risk Evaluation and Mitigation Strategies (REMS)

No postmarketing risk evaluation and management strategies are recommended.

13 Postmarketing Requirements and Commitment

The agreed upon Pediatric Research Equity Act Postmarketing Requirements study 305 is a multi-center, double-blind, randomized, parallel-group study to evaluate the efficacy, safety, and tolerability of FDC GSP 301 compared with placebo NS in pediatric subjects (aged 6 to under 12 years) with SAR. Approximately 450 pediatric patients will be randomized to the 2 treatment groups in a ratio of 1:1 and receive the assigned NS during the 14-day treatment

period.

Objectives

Primary Objective:

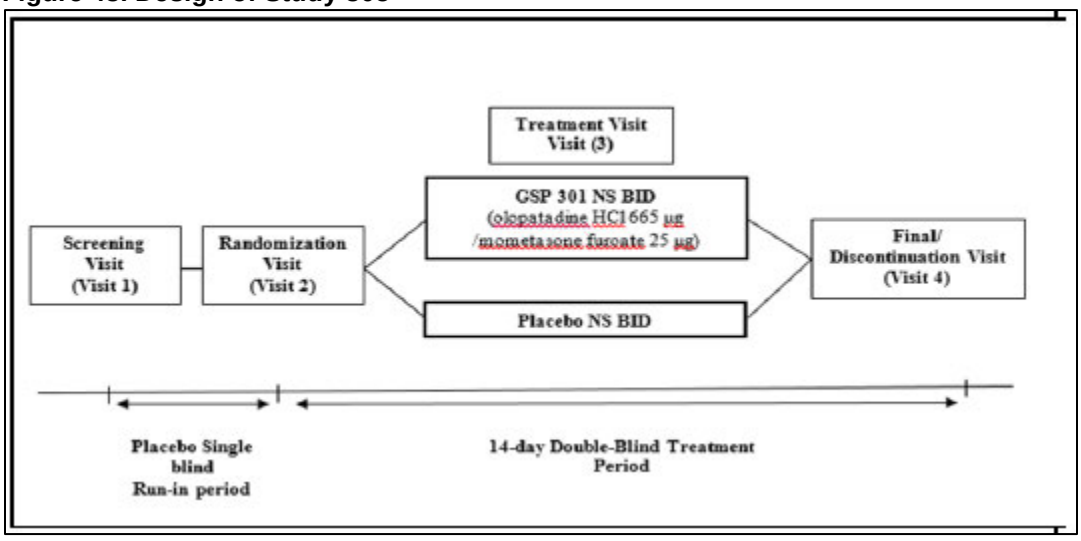
- To compare the efficacy of GSP 301 (administered as 1 spray per nostril BID) with placebo NS over 14 days of study drug in pediatric subjects (aged ≥6 to <12 years) with SAR.

Secondary Objective:

- To assess the safety and tolerability over 14 days of study drug in pediatric subjects with SAR.

Trial Design

Figure 43. Design of Study 305



Abbreviations: NS=nasal spray; BID=twice daily

The study consists of four visits to the study site. After the screening visit (visit 1) subjects who met selection criteria underwent a single-blind, placebo, run-in period for 7 to 10 days. Following the run-in period, eligible subjects were randomized to one of the two treatment groups and underwent a 2-week (14-day) treatment period to assess the efficacy and safety of the assigned treatment.

This PREA PMR will be communicated to the Sponsor in the next review cycle.

14 Division Director (or designated signatory authority)

Ryaltris nasal spray is a fixed-dose combination (FDC) NS of olopatadine hydrochloride (OLO), an H_1-receptor antagonist, and mometasone furoate (MF), a corticosteroid. Each actuation delivers a volume of 0.1 ml suspension containing 665 µg of OLO and 25 µg of MF (665 µg/25 µg). The proposed indication is "the treatment of symptoms associated with seasonal allergic rhinitis (SAR) in patients 12 years of age and older (b) (4) ." The proposed dosing regimen is 2 sprays per nostril twice daily (BID), for a total daily dose of 5,320 µg OLO and 200 µg MF.

The 2-week placebo-controlled trials in conjunction with the results of the 52-week safety trial, provide adequate support for the efficacy and safety of GSP 301 2 sprays per nostril BID for the treatment of the symptoms associated with SAR in patients 12 years of age and older (b) (4) . Prospective examination for local toxicity did not suggest additive or synergistic effect of the combination compared to the active comparators. The nature and frequency of AEs were consistent with the safety profile of the corresponding commercially available monoproducts as described in the current package inserts for each. The clinical and statistical review's conclusion is that the risk-benefit assessment is favorable for the proposed product and supports approval.

From a non-clinical standpoint, a potential issue (b) (4) was identified during the review cycle. Further data was submitted, which constituted a major amendment, and the review timeline was extended 3 months. After extensive evaluation of the newly submitted data, the nonclinical review team concluded that there were no safety issues with respect to the (b) (4) leachable levels. The non-clinical team is also recommending approval.

The recommendations for approval of the clinical, statistical, clinical pharmacology, and non-clinical review disciplines are noted; however, recent surveillance inspections of the drug product manufacturer, Glenmark Pharmaceuticals Ltd. and the proposed contract testing laboratory, (b) (4), revealed significant quality concerns with the facilities. Due to the facilities deficiencies, the Office of Process and Facilities reports that the application cannot be approved at this time.

The regulatory action for this application will be a *Complete Response.* The following language will be included in the *Compete Response* letter:

During recent inspections of the Glenmark Pharmaceuticals Ltd (FEI 3005757050) manufacturing facility and (b) (4) testing facility for this NDA, our field investigator observed objectionable conditions at the facilities and conveyed that information to the representatives of the facilities at the close of the inspections. Satisfactory resolution of the observations is required before this NDA may be approved.

15 Appendices

15.1. Financial Disclosure

Covered Clinical Study (Name and/or Number): GSP 301-101, 102, POC, 201, 301, 303, 304

Was a list of clinical investigators provided?	**Yes ☒**	**No ☐ (Request list from Applicant)**
Total number of investigators identified: 663		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Applicant of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements?	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided?	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason?	Yes ☐	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BANU A KARIMI SHAH
06/18/2019 07:05:40 AM
signing with the delegated authority of Dr. Sally Seymour, Acting Division Director, DPARP