A Double-Blind, Randomized, Parallel-Group Study to Evaluate the Efficacy, Safety and Tolerability of Fixed Dose Combination GSP 301 Nasal Spray Compared With Placebo Nasal Spray in Pediatric Subjects (Aged 6 to Under 12 Years) With Seasonal Allergic Rhinitis (SAR)

Identifiers NCT03463031

Date of Document 18 July 2018

glenmark

GSP 301 NS

GSP 301-305

A DOUBLE-BLIND, RANDOMIZED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY, SAFETY AND TOLERABILITY OF FIXED DOSE COMBINATION GSP 301 NASAL SPRAY COMPARED WITH PLACEBO NASAL SPRAY IN PEDIATRIC SUBJECTS (AGED 6 TO UNDER 12 YEARS) WITH SEASONAL ALLERGIC RHINITIS (SAR).

Phase of Development	Phase 3
Sponsor	Glenmark Specialty SA Avenue Léopold-Robert 37 2300 La Chaux-de-Fonds Switzerland
Study Number	GSP 301-305
IND Number	123164
Approved by	[redacted]
Protocol Version	Version 3.0
Date	18-Jul-2018
Supersedes	Version 2.0, 05-Apr-2018

This study must be conducted in accordance with International Council on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and with the applicable regulatory requirements.

INVESTIGATOR'S AGREEMENT

I have received and read the Investigational Brochure for fixed dose combination (FDC) of olopatadine hydrochloride and mometasone furoate nasal spray (GSP 301 NS). I have read the GSP 301-305 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

SPONSOR'S SIGNATURE

This protocol reflects the Sponsor's current knowledge of FDC of olopatadine hydrochloride and mometasone furoate nasal spray (GSP 301 NS) as applicable to this study. It has been designed to achieve the stated objectives while minimizing exposure to, and risk from, both the products being used and the assessments. The assessments are all considered to be appropriate, capable of validating the stated objectives of the study, and of providing the necessary information to ensure subject safety. The protocol has been designed according to the principles of the ICH guidelines for GCP, and the Declaration of Helsinki. It has undergone both medical and scientific review by the Sponsor. The Sponsor is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the study as regards ethics, protocol compliance, integrity and validity of the data recorded on the case report forms (CRFs).

- We hereby agree to conduct the study in accordance with this protocol and the above-mentioned guidance/ regulation.
- We agree to comply with all relevant standard operating procedures required for the conduct of this study.
- We further agree to ensure that all associates assisting in the conduct of study are informed regarding their obligations.

Signed on behalf of the Sponsor, Glenmark Specialty SA, Switzerland:

[redacted]

18-July-2018

Date:

Vice President, Clinical Development
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Reviewed and Approved by:

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24-July 2018

Date:

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1. SYNOPSIS

Name of Sponsor/Company: Glenmark Specialty SA
Name of Study Drug: GSP 301 NS - Fixed dose combination of olopatadine hydrochloride and mometasone furoate
Title of Study: A Double-Blind, Randomized, Parallel-Group Study to Evaluate the Efficacy, Safety and Tolerability of Fixed Dose Combination GSP 301 Nasal Spray Compared With Placebo Nasal Spray in Pediatric Subjects (Aged 6 to Under 12 Years) With Seasonal Allergic Rhinitis (SAR)
IND no: 123164 | **EudraCT no:** Not applicable
Phase of development: Phase 3
Indication: Seasonal allergic rhinitis (SAR)
Objectives: **Primary:** • To compare the efficacy of GSP 301 nasal spray (NS) (administered a[redacted] with placebo NS over 14 days of study drug in pediatric subjects (aged ≥6 to <12 years) with SAR. **Secondary:** • To assess the safety and tolerability over 14 days of study drug in pediatric subjects (aged ≥6 to <12 years) with SAR.
Study population: Male and non-pregnant female subjects aged ≥6 to <12 years with documented clinical history of SAR (for at least 2 years preceding the Screening Visit) with exacerbations (clinical evidence of active symptoms) during the spring or fall allergy seasons for the relevant seasonal allergen (eg, tree/grass pollen or ragweed pollen).
Study design: This is a phase 3, double-blind, randomized, parallel-group, placebo-controlled, multicenter study to compare the efficacy and safety of GSP 301 NS with placebo NS in pediatric subjects (aged ≥6 to <12 years) with SAR. A total of approximately 450 subjects (225 subjects randomized to each treatment group) are planned to be randomized in the study. The subject participation may be 22 days up to 27 days with 7 to 10 days of a placebo run-in period and 14 days of treatment period, with allowable window periods for the study visits.
Study endpoints: **Primary Endpoint(s):** • Change from baseline in average morning (AM) and evening (PM) subject-reported 12-hour reflective total nasal symptom score (rTNSS) over the 14-day treatment period. **Secondary Endpoint(s):** • Change from baseline in average AM and PM subject-reported 12-hour instantaneous Total Nasal Symptom Score (iTNSS) over the 14-day treatment period. • Change from baseline in the overall Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) score on Day 15 (Visit 4) between treatment groups. • Change from baseline in average AM and PM subject-reported 12-hour reflective Total Ocular Symptom Score (rTOSS) over the 14-day treatment period. **Other Endpoint(s):** **Nasal symptoms:** • Change from baseline in AM subject-reported rTNSS over the 14-day treatment period.

- Change from baseline in AM subject-reported iTNSS over the 14-day treatment period.
- Change from baseline in PM subject-reported rTNSS over the 14-day treatment period.
- Change from baseline in PM subject-reported iTNSS over the 14-day treatment period.
- Change from baseline in subject-reported reflective individual nasal symptoms over the 14-day treatment period (AM, PM and average of AM and PM).
- Change from baseline in subject-reported instantaneous individual nasal symptoms over the 14-day treatment period (AM, PM and average of AM and PM).
- Change from baseline in average AM and PM subject-reported rTNSS and iTNSS for each day.
- Change from baseline in AM subject-reported rTNSS and iTNSS for each day.
- Change from baseline in PM subject-reported rTNSS and iTNSS for each day.

Ocular symptoms:

- Change from baseline in average AM and PM subject-reported instantaneous Total Ocular Symptom Score (iTOSS) over the 14-day treatment period.
- Change from baseline in AM subject-reported rTOSS over the 14-day treatment period.
- Change from baseline in AM subject-reported iTOSS over the 14-day treatment period.
- Change from baseline in PM subject-reported rTOSS over the 14-day treatment period.
- Change from baseline in PM subject-reported iTOSS over the 14-day treatment period.
- Change from baseline in subject-reported reflective individual ocular symptoms over the 14-day treatment period (AM, PM, and average AM and PM).
- Change from baseline in subject-reported instantaneous individual ocular symptoms over the 14-day treatment period (AM, PM, and average AM and PM).
- Change from baseline in average of the AM and PM subject-reported rTOSS and iTOSS for each day.
- Change from baseline in AM subject-reported rTOSS and iTOSS for each day.
- Change from baseline in PM subject-reported rTOSS and iTOSS for each day.

Non-nasal symptoms will be assessed in a similar manner to the ocular symptoms above (as described in the Statistical Analysis Plan [SAP]).

Physician assessed Nasal Symptom Score:

- Change from baseline in physician assessed nasal symptom score (PNSS) and physician assessed individual nasal symptoms at Day 15 (Visit 4).

Pediatric Rhinoconjuntivitis Quality of Life Questionnaire:

- Change from baseline in individual domains of the PRQLQ at Day 15.

Number of subjects (planned): A total of approximately 450 subjects (225 subjects randomized to each treatment group) are planned to be randomized in the study.

Main criteria for inclusion:

Subjects eligible for enrolment in the study must meet all of the following criteria:

1. Male or non-pregnant female subjects aged ≥6 to <12 years, at the Screening Visit (Visit 1).
2. Signed informed consent/assent form (subject and parent/caregiver/legal guardian), which meets all criteria of the current Food and Drug Administration/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) during the spring or fall allergy seasons for the relevant seasonal allergen (eg, tree/grass pollen or ragweed pollen). SAR must have been of sufficient

severity to have required treatment (either continuous or intermittent) in the past, and in the Investigator's judgment, is expected to require treatment throughout the study period.

4. Demonstrated sensitivity to at least 1 seasonal allergen (eg, tree/grass pollen or ragweed pollen) known to induce SAR through a documented positive skin prick test (wheal diameter at least 5 mm greater than the negative control) to a relevant seasonal allergen. Documentation of a positive result within 12 months prior to the Screening Visit (Visit 1) is acceptable. The subject's positive allergen must be consistent with the medical history of SAR. Additionally, the subject is expected to be adequately exposed to the SAR allergen that he/she has tested positive for the entire duration of the study.
5. A 12-hour reflective Total Nasal Symptom Score (rTNSS) value of ≥6 (out of a possible 12) for the morning (AM) assessment at the Screening Visit (Visit 1).
6. 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.
7. Able to demonstrate the correct NS application technique (with the help of parents/guardians/caregivers, if needed) at the Screening Visit (Visit 1).
8. Willing and able to comply with all aspects of the protocol (with the help of parents/guardians/caregivers, if needed).

Main criteria for exclusion:

Subjects meeting any of the following criteria must not be enrolled in the study:

1. Eligible females of childbearing potential who are known to be sexually active or pregnant, will be excluded and referred for appropriate evaluation. If a girl has reached puberty and achieved menarche (as determined by the Investigator), parents/guardians/caregivers will be consulted to obtain consent for pregnancy testing and permission to counsel the subject followed by counselling the subject by the Investigator regarding the possible unknown risks associated with study medication during pregnancy. Urine pregnancy test must be negative at the Screening Visit (Visit 1). Male subjects who are known to be sexually active will also be excluded.
2. Plans to travel outside the known pollen area for the investigational site for 24 hours or longer during the last 7 days of the screening/run-in period.
3. Plans to travel outside the known pollen area for the investigational 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).
4. History of significant (based on Investigator's judgement) atopic dermatitis or rhinitis medicamentosa (within 60 days prior to the Screening Visit [Visit 1]).
5. Treatment with any known strong cytochrome P450 (CYP)3A4 inducers (eg, carbamazepine, phenytoin, rifabutin, rifampin, pioglitazone etc.) or strong inhibitors (eg, azole antifungals, macrolide antibiotics) within 30 days prior to the Screening Visit (Visit 1), or during the study.
6. Non-vaccinated exposure to or active infection with chickenpox or measles within the 21 days preceding Screening Visit (Visit 1).
7. A known hypersensitivity to any corticosteroids or antihistamines or to either of the drug components of the Investigational Product or its excipients.
8. History of anaphylaxis and/or other severe local reaction(s) to skin testing.
9. Any history or current use of alcohol or drug dependence at the Screening Visit (Visit 1), as determined by the Investigator.
10. History of positive test for human immune deficiency virus, Hepatitis B or Hepatitis C infection (parents/guardians/caregivers will be consulted to obtain consent).
11. History and evidence of acute or significant chronic sinusitis or chronic purulent post-nasal drip at the Screening Visit (Visit 1).

12. Any of the following conditions (including but not limited to the following) that are judged by the Investigator to be clinically significant and/or to affect the subject's ability to participate in this study:
    - impaired hepatic function.
    - any systemic infection.
    - hematological, hepatic, renal, endocrine disorder (except for hypothyroidism).
    - gastrointestinal disease.
    - malignancy (excluding basal cell carcinoma).
    - current neuropsychological condition with or without drug therapy.
        - Subjects with history or current diagnosis of active Attention Deficit Hyperactivity Disorder (ADHD) can be included in the study if symptoms of ADHD are considered stable by the treating physician and such history is documented by the Investigator.
        - Subjects with history or current diagnosis of ADHD on medications are eligible for inclusion if they are on stable active drug therapy and have stable symptoms for at least 30 days before the screening visit as documented in the medical history by the Investigator. Subjects may not be withdrawn from ADHD treatment medications during screening and/or throughout the study. If ADHD treatment medications are planned to be withdrawn or withdrawn by the treating physician during the study, then the subject should be considered ineligible or early terminated, respectively.
    - cardiovascular disease (eg, uncontrolled hypertension).
    - respiratory disease other than mild asthma (per Investigator clinical judgement).
13. Any major surgery (as assessed by the Investigator) within 4 weeks before the Screening Visit (Visit 1).
14. A requirement for the chronic use of tricyclic anti-depressants.
15. Dependence (in the opinion of the Investigator) on nasal, oral, or ocular decongestants, nasal topical antihistamines, or nasal steroids.
16. Active pulmonary disorder or infection (including but not limited to bronchitis, pneumonia, or influenza), 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 placebo run-in period. Subjects with mild asthma (as judged by the Investigator) are allowable on the condition that treatment is limited to inhaled short-acting beta-agonists only (up to 8 puffs per day).
17. Use of antibiotic therapy for acute conditions within 14 days prior to Screening Visit (Visit 1). Low doses of antibiotics taken for prophylaxis are allowed if the therapy was started prior to the Screening Visit (Visit 1) and is expected to continue at the same stable dose throughout the clinical study duration.
18. Posterior subcapsular cataracts or glaucoma, or any other ocular disturbances or other listed related conditions (as applicable) including:
    - history of increased intraocular pressure.
    - history of retinal detachment surgery.
    - history of incisional eye surgery (other than unilateral cataract extraction or laser-assisted in situ keratomileusis).
    - history of penetrating ocular trauma, severe blunt ocular trauma.
    - evidence of uveitis, iritis, or other inflammatory eye disease during screening.
    - presence of ocular herpes simplex.
19. Known history of hypothalamic-pituitary-adrenal axis impairment.
20. Existence of any significant surgical or medical condition, or clinically significant physical finding (eg, significant nasal polyps or other clinically significant respiratory tract malformations/nasal structural abnormalities, significant nasal trauma [such as nasal piercing] or significant nasal septal deviation) which, in the opinion of the Investigator (or in consultation with the Sponsor's medical monitor/designee),

significantly interferes with the absorption, distribution, metabolism or excretion of the study medication or significantly interferes with nasal air flow or interferes with the subject's ability to reliably complete the AR Assessment Diary.

21. Participation in any investigational non-biological drug clinical study in the 30 days or investigational biological drug in the 120 days preceding the Screening Visit (Visit 1) or planned participation in another investigational clinical study at any time during the current study.
22. Initiation of immunotherapy injections or immunosuppressive/immune-modulator medications within 60 days preceding the Screening Visit (Visit 1) and/or currently undergoing treatment with immunotherapy or immunosuppressive/immune-modulator medications. Topical pimecrolimus cream or tacrolimus ointment treatment, if initiated at least 30 days prior to screening and maintained on stable dose, is acceptable. A 180-day washout period is required following the last dose of sublingual immunotherapy (investigational or other) prior to the Screening Visit (Visit 1).
23. Use of topical corticosteroids in concentrations in excess of 1% hydrocortisone, or equivalent, within 30 days prior to the Screening Visit (Visit 1); use of a topical hydrocortisone or equivalent in any concentration covering greater than 20% of the body surface or the presence of an underlying condition (as judged by the Investigator) that can reasonably be expected to require treatment with such preparations over the clinical study duration.
24. Previous participation in another GSP 301 NS study as a randomized subject.
25. Clinical study participation by clinical investigator site employees and/or their immediate relatives.
26. Study participation by more than 1 subject from the same household at the same time. However, after the completion/discontinuation by 1 subject in the household, another subject from the same household may be screened.
27. Known to have failed to show symptom improvement with any approved/marketed monotherapy component of the GSP 301 NS (ie, NASONEX NS, PATANASE NS, or both) as judged by the Investigator.

Randomization Criteria (at the Randomization Visit (RV) – Visit 2):

1. Continued general good health and continued eligibility according to the inclusion and exclusion criteria.
2. Has not left the known pollen area for the investigative site for 24 hours or longer during the last 7 days of the placebo run-in period.
3. No adverse event (AE) that has altered eligibility according to the inclusion and exclusion criteria.
4. Minimum 12-hour subject-reported rTNSS of an average of 6, (out of a possible 12) during the last 4 days of the placebo run-in period (average of last 8 consecutive AM and PM assessments from the Day -4 PM assessment to the AM assessment on the day of randomization).
5. A 12-hour subject-reported reflective nasal congestion score of an average of 2 or greater during the last 4 days of the placebo run-in period (average of last 8 consecutive AM and PM assessments from Day -4 PM assessment to the AM assessment on the day of randomization).
6. Adequate symptom assessment diary compliance (with assistance from parent/guardian/caregiver, as needed) – inadequate compliance is defined as missing one or more of the entries on 2 or more assessment sessions (AM or PM) during the last 4 days of the placebo run-in period (during the last 8 consecutive AM and PM assessments from Day -4 PM assessment to the AM assessment on the day of randomization).
7. Adequate study medication compliance – each subject must have taken his/her single-blind placebo medication (with assistance from parent/guardian/caregiver, as needed) for at least 80% of the entire placebo run-in period as reported in the symptom assessment diary.
8. Absence of common cold, upper respiratory infections, otitis, lower respiratory infections or acute sinusitis for 14 days prior to the Randomization Visit (Visit 2).
9. No use of prohibited concomitant medications during the placebo run-in period.

Duration of study participation: The subject participation may be 22 days up to 27 days with 7 to 10 days of a placebo run-in period and 14 days of treatment period, with allowable window periods for the study visits.

Duration of treatment: 14-day treatment [redacted]

Investigational product, dosage and mode of administration:
Name of Investigational Product: Fixed dose combination of olopatadine hydrochloride [redacted] and mometasone furoate [redacted] NS
Manufacturing License Name: GSP 301-2 NS
Dosage Form: Spray, metered (Nasal Spray)
Dose: [redacted]
Dosage Frequency: [redacted] for 14 days
Mode of Administration: Intranasal

Placebo therapy, dosage and mode of administration:
Name: GSP 301 Placebo NS
Manufacturing License Name: GSP 301 Placebo NS
Dosage Form: Spray, metered (Nasal Spray)
Dosage: [redacted]
Dosage Frequency: [redacted] for 14 days
Mode of Administration: Intranasal

Criteria for evaluation:

Efficacy: Subject AR symptom assessments (nasal and non-nasal symptoms: rTNSS, iTNSS, rTOSS, iTOSS, and individual symptom assessments reported using a subject diary), PNSS, and PRQLQ.

Safety:

- Monitoring and recording all AEs and SAEs.
- Measurement of vital signs.
- Physical examinations.
- Focused ears, nose, and throat (ENT) examinations

STATISTICAL METHODS:

Detailed statistical methods will be provided in the Statistical Analysis Plan (SAP).

Study Populations:

Full Analysis Set:

The Full Analysis Set will consist of all subjects who are randomized and receive at least 1 dose of investigational product and have at least 1 post-baseline primary efficacy assessment. This will be the primary analysis set for efficacy analyses.

Per Protocol Set:

The Per Protocol Set (PPS) will consist of the subset of the FAS who do not meet criteria for PPS exclusion.

Safety Analysis Set:

The Safety Analysis Set (SAS) will consist of all subjects who are randomized and receive at least one dose of investigational product. This will be the analysis set for safety analyses.

Determination of Sample Size:

A sample size of 382 evaluable subjects, allocated 1:1, will provide 90% power to detect a between-group mean difference (GSP 301 NS vs placebo NS) of 1.0 in the absolute change from baseline in average AM and PM subject-reported 12-hour rTNSS over a 14-day treatment period (assuming a 2-sided alpha of 5%). A standard deviation of 3.0 in the change from baseline in 12-hour rTNSS over a 14-day treatment period has been assumed. Assuming a drop-out rate of 15%, a total of approximately 450 subjects are planned to be randomized (225 subjects in each treatment group). Depending on the actual drop-out rate, the Sponsor may decide to randomize higher or lower number of subjects in order to meet the required sample size of 382 evaluable subjects.

Efficacy Analyses:

The change from baseline in average AM and PM subject-reported 12-hour rTNSS over a 14-day treatment period will be derived by calculating an average score for each subject, based on the post-dose AM and PM assessments over the 14-day treatment period.

The primary endpoint, change from baseline in average AM and PM subject-reported 12-hour rTNSS over a 14 day treatment period, will be evaluated using a repeated measures analysis of covariance (ANCOVA) model, adjusting for study drug group, site, and baseline 12-hour rTNSS (linear, continuous covariate - defined as the average of the last 8 consecutive AM and PM assessments during the last 4 days of the placebo run-in period (from Day -4 PM assessment to the AM assessment on the day of randomization) and study day as the within-subject effect. The interactions of site-by-treatment and baseline-by-treatment will be investigated separately and will only be included in final model if they are statistically significant at the 5% level. At least 6 out of 8 assessments (reading scores) should be available in order to calculate baseline score of 12 hour rTNSS (linear, continuous covariate). An unstructured covariance will be assumed. Least square means of the treatment differences and associated 95% confidence intervals and p-values will be presented. Additional details or any changes will be provided in the SAP.

The efficacy comparison of GSP 301 NS, administered a[redacted] with placebo NS over 14 days of study drug will be tested at 0.05 significance level.

The primary analysis will be based on the FAS and a supportive analysis will be based on the PPS. Analyses of the secondary and other endpoints will be performed using a similar method as described for the primary endpoint. Efficacy within pre-specified subgroups of clinical interest (eg, age, sex, race, and ethnicity) will be examined.

Detailed statistical analysis and methods will be provided in the SAP.

Pharmacokinetic Analyses: Not applicable.

Pharmacodynamic Analyses: Not applicable.

Biomarker Analyses: Not applicable.

Pharmacogenomic Analyses: Not applicable.

Safety Analyses:

Descriptive statistics will be used to summarize AEs, vital signs, physical examination, focused ENT data and a comparison of the incidence rate of AEs between study drug groups will be presented. Detailed statistical analysis and methods will be provided in the SAP.

Interim analyses: No interim analysis is planned.

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	adverse event
AM	Morning
AR	Allergic rhinitis
BID	Twice daily
CI	Confidence interval
C_{max}	Maximum plasma concentration
CRF	Case report form
CRO	Contract research organization
CSR	clinical study report
CYP3A4	Cytochrome P450 system enzyme 3A4
eCRF	electronic case report form
ENT	Ears, nose, and throat
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	Fixed dose combination
GCP	Good Clinical Practice
HCl	Hydrochloride
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent Ethics Committee
IgE	Immunoglobulin E
IL	Interleukin
IP	Investigational product
IRB	Institutional Review Board
iTNSS	Instantaneous Total Nasal Symptom Score
iTOSS	Instantaneous Total Ocular Symptom Score
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LAR	legally acceptable representative

Abbreviation or Specialist Term	Explanation
LSM	Least squares mean
NS	Nasal spray
OTC	Over the counter
QD	Once daily
QOL	Quality of Life
PM	Evening
PNSS	Physician Assessed Nasal Symptom Score
PPS	Per Protocol Set
PRQLQ	Pediatric Rhinoconjunctivitis Quality of Life Questionnaire
PT	Preferred term
rTNSS	Reflective Total Nasal Symptom Score
rTOSS	Reflective Total Ocular Symptom Score
RV	Randomization visit
SAE	serious adverse event
SAS	Safety Analysis Set
SAR	Seasonal Allergic Rhinitis
SAP	Statistical Analysis Plan
SOC	System organ class
TEAE	Treatment-emergent adverse event
TNSS	Total Nasal Symptom Score
US	United States of America
USPI	United States Prescribing Information

4. INTRODUCTION

4.1. Background Information

Rhinitis is defined as inflammation of the nasal membranes and is characterized by the presence of the following: nasal congestion, rhinorrhea, sneezing, nasal itching, and nasal obstruction. Allergic rhinitis (AR) is the most common cause of rhinitis and represents a global health problem affecting approximately 10% to 30% of the general adult population and its prevalence is increasing worldwide (Tran et al, 2011; Naclerio et al, 2010). In the United States (US), AR affects 10% to 30% of the adult general population and up to 40% of children. This accounts for 30 to 60 million people in the US. In the US, the direct medical costs (eg, physician services, diagnostics, medications) increased approximately 2-fold from US $6.1 billion in 2000 to US $11.2 billion in 2005 (Tran et al, 2011).

The high frequency of AR and prevalence in children underscores the importance of AR in health care because the condition can result in absenteeism, diminished learning capacity, and an overall poorer quality of life at school and at home (Jauregui et al, 2009; Blaiss, 2008; Nathan, 2007; Lai et al, 2005). The comprehensive Pediatric Allergies in America survey estimates an almost 30% loss in productivity on a child's most symptomatic days (Meltzer et al, 2009). Further, according to the American Academy of Allergy, Asthma, and Immunology task force on allergic disorders, more than 2 million missed school days are attributed to AR each year (Baena-Cagnani and Patel, 2010). Children with AR tend to be more limited in their activities. Further, improperly managed AR may contribute to the worsening of comorbid conditions, including asthma, rhinosinusitis, and otitis media, in pediatric subjects (Baena-Cagnani and Patel, 2010).

Allergic rhinitis (AR) has been traditionally subdivided into seasonal, perennial, and occupational rhinitis and involves the inflammation of the mucous membranes of the nose, eyes, eustachian tubes, middle ear, sinuses, and pharynx. Inflammation of the mucous membranes is characterized by a complex interaction of inflammatory mediators but ultimately is triggered by an immunoglobulin E (IgE)-mediated response to extrinsic proteins, such as pollens or molds (food allergies rarely cause AR, except as part of a multiorgan reaction) (Kaliner et al, 2010; Min, 2010; Rosenwasser et al, 2005). When 2 or more symptoms such as watery rhinorrhea, sneezing, nasal obstruction, and nasal pruritus persist for 1 hour or more, AR is strongly suspected.

After allergens are inhaled into the nasal mucosa of sensitized subjects, they bind to IgE on the surface of mast cells, resulting in aggregation of IgE receptors (FcεRI) and the release of chemical mediators including histamine. Binding of histamine to the H1 receptor increases paracellular permeability, which contributes to the early-phase response of AR, characterized by sneezing, rhinorrhea, and nasal congestion. Infiltration of inflammatory cells (activated eosinophils and T-helper type 2 cells) into the nasal mucosa is induced by chemo-attractant factors (including various cytokines) and results in edema of the nasal mucosa. This inflammation, the late-phase response of AR, develops 6 to10 hours after allergen challenge and causes prolonged nasal congestion (Okano, 2009).

Many pharmacologic agents are available to treat AR. They target different symptoms and include oral antihistamines, intranasal corticosteroids, intranasal antihistamines, decongestants,

mast cell stabilizers, leukotriene modifiers, anticholinergics, and allergen immunotherapy (Tran et al, 2011; Nasser et al, 2010; Shapiro and Nassef, 2005). Systemic antihistamines generally do not provide the degree of targeted relief of nasal sprays (NSs) (Prenner and Schenkel, 2006). Topical (intranasal) antihistamines (H1 receptor antagonists) are prescribed to treat the nasal itch, sneezing, and rhinorrhea caused by the release of histamine and inflammatory mediators due to the allergic reaction (Okano, 2009). Intranasal corticosteroids inhibit both early and late reactions and reduce IgE production and eosinophilia by inhibiting the secretion of cytokines including interleukin (IL)-4, IL-5, and IL-13 (Okano, 2009; Rosenwasser et al, 2005).

Medicinal options for children suffering with seasonal allergic rhinitis (SAR) include intranasal antihistamines (eg, azelastine hydrochloride and olopatadine hydrochloride), oral (prescription or over the counter) second-generation antihistamines (eg, levocetirizine, cetirizine, desloratadine, loratadine, and fexofenadine), intranasal corticosteroids (eg, beclomethasone, budesonide, ciclesonide, fluticasone furoate, fluticasone propionate, triamcinolone acetonide, flunsolide, and mometasone furoate), and oral leukotriene receptor antagonists (montelukast) (Meltzer et al, 2011). Some of these products are also approved for the treatment of perennial allergic rhinitis (PAR) in children, but the approved age range varies among these treatment options.

The ideal therapeutic agent for managing the symptoms of AR effectively addresses the pathophysiology of both the early-phase reaction and the late phase reaction of the condition (Spector, 1999). It is hypothesized that 2 agents with different mechanisms of action could have the potential for a greater effect when used in combination than when used as monotherapies. Currently, only 1 combination product containing an intranasal corticosteroid and intranasal antihistamine (DYMISTA) is available for SAR treatment in subjects 6 years of age and older (DYMISTA USPI, 2015), but no such option is available for subjects suffering from perennial AR in the United States of America (US) (DYMISTA USPI, 2015). GSP 301 nasal spray (NS) is a FDC of an intranasal antihistamine (olopatadine hydrochloride) and corticosteroid (mometasone furoate) under clinical development for SAR in children and adults.

4.2. Description of Study Drug

Olopatadine is a histamine H1-receptor antagonist. Intranasal antihistamines have the potential to provide quick symptomatic relief but do not provide substantial benefits for the late-phase reaction of the allergic response that leads to nasal congestion. The antihistaminic activity of olopatadine has been documented in isolated tissues, animal models, and humans (PATANASE USPI, 2012). It has been suggested that olopatadine is clinically superior to other anti-allergy molecules because of its strong antihistamine activity and unique ocular mast cell stabilizing properties (PATANASE USPI, 2012; Rosenwasser et al, 2005).

Mometasone is a corticosteroid demonstrating potent anti-inflammatory properties. Although intranasal corticosteroids act on both early-phase and late-phase reactions, they have a slow onset of action and can take hours to several days to reach their maximum benefit with some subjects failing to achieve full relief of symptoms. 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 (eg, mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (eg, histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation

(NASONEX USPI, 2013). Mometasone furoate has a high affinity for the glucocorticoid receptor and a highly lipophilic nature; these characteristics contribute to its minimal systemic absorption and prolonged nasal contact time.

4.3. Nonclinical Experience

The toxicity of both olopatadine hydrochloride (HCl) and mometasone furoate has been extensively assessed in multiple species by various routes of administration including intranasal administration. The Sponsor has conducted a 13-week intranasal toxicity study in rats in order to assess the potential toxicity of GSP 301 and to determine if any synergistic or additive toxicity was seen compared to the individual monotherapies. GSP 301 NS (olopatadine HCl [redacted] and mometasone furoate [redacted] [same as the formulation planned for the phase 3 clinical studies]) was administered to rats by the nasal route up to 4 times daily. The high dose represented overages to the proposed dose to be studied in the phase 3 clinical studies of 2.3 fold based on nasal surface area and approximately 50-fold based on a mg/kg basis. Equivalent concentrations of the individual components and a placebo were used as comparators. No nasal irritancy or systemic toxicity was noted in any groups in the study. Therefore, co administration of the 2 components of the GSP 301 NS did not lead to any adverse effects.

The acute toxicity of olopatadine HCl and mometasone furoate is low.

Repeat dose studies by the intranasal route have been conducted for both olopatadine HCl and mometasone furoate in rats for durations up to 6 months and dogs for up to 12 months. Both compounds showed no nasal irritancy at concentrations equivalent to, or slightly greater than, those proposed in the FDC GSP 301 NS (NDA Number 20-762, 2014; NDA number 21-861, 2008).

Toxicity studies with olopatadine indicated no significant toxicity in repeated dose studies and other than typical corticosteroid effects, no target organ toxicity was determined with mometasone. Carcinogenicity studies have not been conducted by the intranasal route but neither compound was carcinogenic in rats or mice by the oral route. There was no evidence of genotoxicity with either compound. Therefore, the FDC is not considered to pose a genetic hazard or increase the risk of cancer to subjects.

No effect on fertility was observed with mometasone furoate but olopatadine HCl administered orally to rats at 400 mg/kg/day resulted in a decrease in fertility index and reduced mean implantations. No effect on fertility was observed at [redacted] (approximately 100 times the maximum human dose of [redacted] on a body surface area basis).

Olopatadine HCl was not teratogenic in rabbits and rats by the oral route however, mometasone furoate has been shown to induce teratogenicity in multiple species by multiple routes; typical malformations and skeletal variations (reduced ossification) considered to be glucocorticoid class effects. It is known that the sensitivity of rodents to teratogenic effects of corticosteroids is greater than for humans; however, mometasone furoate should be used during pregnancy only if the potential benefits justify the potential risk to the fetus. Difficult and prolonged parturition observed in Segment I and Segment III reproduction studies may be related to the progestational effect of mometasone furoate. Both molecules are considered a Pregnancy Category C drug.

Olopatadine HCl tested negative for antigenic potential in mice and guinea pigs and was non-sensitizing in the guinea pig maximization test.

4.4. Clinical Experience

Two phase 1 pharmacokinetic studies, 1 proof-of concept SAR study, 1 large phase 2 SAR study, and 2 phase 3 SAR studies in subjects aged ≥12 years and older were completed. In addition, 1 long-term (52-week) phase 3 safety study in subjects with PAR was completed. The phase 1 studies were open-label, 3-period, 3-treatment, cross-over randomized studies with 30 healthy subjects (aged ≥18 and ≤65 years) in each study. The results of the 2 phase 1 studies demonstrated that the olopatadine systemic exposure of the FDC GSP 301 NS is comparable to the olopatadine exposure of the marketed monotherapy PATANASE NS and suggested that the mometasone furoate systemic exposure of the FDC GSP 301 NS is generally comparable to the mometasone furoate exposure of the marketed monotherapy NASONEX NS. A higher maximum plasma concentration (C_{max}) (by approximately 42%) for the FDC GSP 301 NS compared with NASONEX NS treatment was observed. The mometasone systemic exposure with GSP 301 NS falls within the range of mometasone exposures associated with other products for which no substantial systemic effect (ie effect on hypothalamic–pituitary–adrenal axis) has been identified. The steady state C_{max} and area under the curve (AUC) of mometasone furoate administered as GSP 301 NS [redacted] was lower based on pharmacokinetic data from a subset of SAR subjects in the GSP 301-301 study) and comparable to NASONEX 200 µg once daily (QD). Moreover, the safety profile of GSP 301 NS seen to date from the clinical program supports the systemic safety of the proposed GSP 301 NS product. It is unlikely that the difference in mometasone furoate systemic exposure seen in this study (especially in terms of increased C_{max}) is clinically significant concerning systemic safety. It should be noted that both of these phase 1 studies used single doses of the GSP 301 NS formulation referred to as GSP 301-1 NS [redacted] formulation of the FDC [olopatadine HCl [redacted] and mometasone furoate [redacted] at [redacted] sprays per nostril]) in the phase 2 Study GSP 301-201.

A proof-of-concept study was conducted to evaluate FDC GSP 301 NS in the treatment of SAR. This was a double-blind, double-dummy, randomized, parallel-group, comparative environmental exposure chamber study to evaluate efficacy, safety, and tolerability of 2 Sponsor-formulated FDC products of olopatadine HCl and mometasone furoate NS [redacted] formulation; olopatadine HCl [redacted] and mometasone furoate [redacted] at [redacted] sprays per nostril and [redacted] formulation; olopatadine HCl [redacted] µg and mometasone furoate [redacted] µg at [redacted] sprays per nostril) compared with an approved FDC of azelastine HCl and fluticasone propionate NS (DYMISTA NS), an approved olopatadine HCl NS (PATANASE NS), and Sponsor-formulated placebo in subjects with SAR. The study population consisted of 180 subjects (aged ≥18 and ≤65 years) who were allergic to ragweed allergen and had SAR for the 2 years prior to study entry. Subjects were treated with study drug for 2 weeks. Both Sponsor-formulated FDC products showed statistically significant and clinically meaningful improvements (Barnes et al, 2010); Brixner et al, 2016; and Meltzer et al, 2016) versus placebo and PATANASE NS for the change from baseline in mean instantaneous total nasal symptom score (iTNSS). However, the Sponsor-formulated FDC products were not statistically superior to DYMISTA NS although showed clinically meaningful numerical improvement. All treatment-emergent adverse events (TEAEs) were mild to moderate. Headache was the most common TEAE in all treatment groups, including placebo. Dysgeusia was noted in all active treatment groups. Epistaxis was observed with the active comparators but not with either GSP 301 NS regimen.

The phase 2, double-blind, randomized, multicenter, study (GSP 301-201) included 1111 subjects with a history of SAR for at least 2 years and allergic to mountain cedar allergen. Subjects were randomized to 1 of 7 treatment groups:

- FDC of olopatadine HCl and mometasone furoate NS (GSP 301 NS [olopatadine HCl and mometasone furoate µg]) at sprays per nostril in the morning (AM).
- FDC of olopatadine HCl and mometasone furoate NS (GSP 301 NS [olopatadine HCl µg and mometasone furoate µg]) at sprays per nostril in the AM and evening [PM]).
- Glenmark olopatadine HCl µg) -1 NS, sprays per nostril in the AM.
- Glenmark olopatadine HCl µg) -2 NS, sprays per nostril in the AM and the PM.
- Glenmark mometasone furoate µg) -1 NS, sprays per nostril in the AM.
- Glenmark mometasone furoate µg) -2 NS, sprays per nostril in the AM and the PM.
- GSP 301 placebo NS (GSP 301 vehicle).

The primary endpoint of the study was mean change in the reflective TNSS (rTNSS) from baseline to end of treatment between treatment groups. GSP 301 NS showed statistically significant and clinically meaningful improvements versus placebo (least squares mean [LSM] treatment difference [97.5% confidence interval {CI}] = 1.1703 [1.7315, 0.6090], p<0.0001) for the full analysis set (FAS). The mean change from baseline in the rTNSS also showed statistically significant and clinically meaningful improvements versus both Glenmark mometasone furoate NS (LSM treatment difference [95% CI] = -0.7133 [1.2031, -0.2235], p=0.0043) and Glenmark olopatadine HCl NS (LSM treatment difference [95% CI] = 0.4918 [-0.9810, -0.0025], p=0.0488).

Based on the data from the phase 1 and 2 studies, GSP 301 NS formulation of olopatadine hydrochloride µg and mometasone furoate µg and referred to as GSP 301 NS in this protocol) was found to be optimally safe and effective for the treatment of SAR in adult and adolescents and further used in phase 3 evaluation. This dosing regimen will result in total daily doses that match the approved daily doses for adults and adolescents for the individual monotherapy products (olopatadine hydrochloride µg and mometasone furoate µg).

Two phase 3 studies have been conducted; a double-blind, randomized, parallel-group, comparative, multicenter study (GSP 301-301) in 1180 subjects with a history of SAR for at least 2 years and allergic to spring allergens and a double-blind, randomized, 4-arm, parallel-group, comparative, multicenter study (GSP 301-304) in 1176 subjects allergic to Fall or mountain cedar allergens with a history of SAR for at least 2 years. In both studies, subjects were randomized to the following 4 treatment groups in a 1:1:1:1 ratio:

- GSP 301 NS µg olopatadine HCl µg mometasone furoate administered as sprays/nostril in the AM and PM.

- Glenmark olopatadine HCl NS [redacted] µg administered as [redacted] sprays/nostril [redacted] in the AM and PM).
- Glenmark mometasone furoate NS [redacted] µg administered as [redacted] sprays/nostril [redacted] in the AM and PM).
- GSP 301 placebo NS.

Overall, both GSP 301-301 and GSP 301-304, demonstrated that GSP 301 NS [redacted] was efficacious in the treatment of subjects with SAR aged 12 years or older using a range of endpoints compared with GSP 301 placebo NS. The primary endpoint for both studies was average AM and PM subject-reported rTNSS change from baseline to end of treatment between treatment groups. For study GSP 301-301, the results indicated a statistically significant and clinically meaningful difference in average AM and PM rTNSS compared with GSP 301 placebo NS (LSM treatment difference [95% CI] -0.98 [-1.38, -0.57], p<0.0001) for the FAS. The LS mean difference between GSP 301 NS and Glenmark olopatadine HCl NS was statistically significant and clinically meaningful (LSM treatment difference [95% CI] -0.61 [-1.01, -0.21], p<0.0029. The LS mean difference of -0.39 between GSP 301 NS and Glenmark mometasone furoate NS was not statistically significant (p=0.0587); although, the change was in the direction favoring improvement in symptoms and considered clinically meaningful. For study GSP 301-304, the results indicated a statistically significant and clinically meaningful difference in average AM and PM rTNSS compared with GSP 301 placebo NS (LSM treatment difference [95% CI] -1.09 [-1.49, -0.69], p<0.001) for the FAS. The LS mean difference between GSP 301 NS and Glenmark olopatadine HCl NS was statistically significant and clinically meaningful (LSM treatment difference [95% CI] -0.44 [-0.84, -0.05], p=0.028. The LS mean difference between GSP 301 NS and Glenmark mometasone furoate HCl NS was also statistically significant and clinically meaningful (LSM treatment difference [95% CI] -0.47 [-0.86, -0.08], p=0.019.

GSP 301 NS administered for 2 weeks was well-tolerated and showed no clinically meaningful difference compared with GSP 301 placebo NS or the individual monotherapies in the incidence of AEs or in other safety assessments.

The long-term phase 3 safety study (GSP 301-303) was double-blind, randomized, parallel-group, multicenter 52-week study in 601 subjects with a history of PAR for at least 2 years. Subjects were randomized to 1 of 3 treatment groups in a 4:1:1 ratio:

- GSP 301 NS [redacted] µg olopatadine hydrochloride [redacted] µg mometasone furoate administered as [redacted] sprays/nostril [redacted] in the AM and PM)
- GSP 301 placebo NS pH 3.7 administered as [redacted] sprays/nostril [redacted] in the AM and PM
- GSP 301 placebo NS pH 7.0 administered as [redacted] sprays/nostril [redacted] in the AM and PM

The results of this study demonstrated that GSP 301 NS administered for 52 weeks to subjects (aged ≥12 years) with PAR was well-tolerated and showed no clinically meaningful difference in the incidence of AEs or in other safety assessments compared with GSP 301 placebo NS pH 3.7 and GSP 301 placebo NS pH 7.0. The incidence of TEAEs in the GSP 301 NS treatment group was generally low and was comparable to placebo treatment groups. The most frequently reported TEAEs (>3.0% subjects) in the GSP 301 NS treatment group were upper respiratory tract infection (25 [6.4%] subjects), epistaxis (18 [4.6%] subjects), headache (16 [4.1%]

subjects), and nasopharyngitis (12 [3.1%] subjects). The majority of TEAEs were mild or moderate in intensity. The incidence of treatment-related TEAEs with the GSP 301 NS treatment group was generally low and was comparable to placebo treatment groups (7.1% in GSP 301 placebo NS pH 3.7, 9.9% in GSP 301 placebo NS pH 7.0, and 11.2% in GSP 301 NS). The frequency of SAEs with GSP 301 NS treatment group was low and comparable to placebo treatment groups. Eleven subjects experienced SAEs; none of the SAEs were considered by the Investigator to be related to study drug. No deaths occurred during the study. In addition, the frequency of withdrawals with GSP 301 NS treatment group was also low and comparable to placebo treatment groups.

Treatment with GSP 301 NS compared with GSP 301 placebo NS pH 3.7 showed statistically significant and clinically meaningful, as well as sustained improvement in nasal symptoms in PAR subjects with no evidence of tachyphylaxis. Specifically, the following were observed when GSP 301 NS was compared with GSP placebo NS pH 3.7 on the efficacy endpoints:

- Clinically meaningful and statistically significant ($p<0.01$) improvements in the change from baseline in average AM rTNSS and average AM iTNSS over the 6, 30, and 52 weeks treatment period using repeated measures analyses.
- Statistically significant improvements in all 4 AM reflective and AM instantaneous individual nasal symptoms (rhinorrhea, nasal congestion, nasal itching, and sneezing) over the first 6, 30, and 52 weeks treatment duration ($p<0.05$).
- Clinically meaningful improvements in efficacy endpoints (rTNSS and iTNSS) over first 6 weeks of treatment and the efficacy was sustained over the 52 weeks treatment.
- Statistically significant improvements were also observed on changes from baseline in Rhinoconjunctivitis Quality of Life Questionnaire RQLQ (Standardized activities) at 6 and 30 weeks treatment.

Overall, based on the results from the clinical studies conducted as part of the clinical development of GSP 301 NS, the [redacted] formulation of the GSP 301 NS [redacted] sprays/nostril [redacted] of olopatadine hydrochloride [redacted] µg and mometasone furoate [redacted] µg) was found to be safe and effective for the treatment symptoms of SAR in adults and adolescent subjects (aged >12 years).

4.5. Benefit-Risk Assessment

Olopatadine HCL NS (PATANASE NS; 665 µg olopatadine hydrochloride) is approved for the relief of the symptoms of SAR in adults and children aged 6 years and older in the US (12 years of age and older as 2 sprays per nostril twice daily [BID]) and in children 6-11 years of age as 1 spray per nostril BID). The most common (>1%) adverse reactions to olopatadine HCl included bitter taste, headache, epistaxis, pharyngolaryngeal pain, post-nasal drip, cough, and urinary tract infection (PATANASE USPI, 2012).

Mometasone furoate NS (NASONEX NS; 50 µg per spray) has been approved for the treatment of nasal symptoms of AR in subjects 12 years and older (as 2 sprays in each nostril once daily [QD], 200 µg total daily dose) and in subjects ≥2 to 11 years of age (as 1 spray per nostril QD; 100 µg total daily dose). Other approved indications include treatment of nasal congestion associated with SAR in subjects ≥2 years of age, prophylaxis of SAR in subjects ≥12 years of age, and treatment of nasal polyps in subjects ≥18 years of age (NASONEX USPI, 2013). The

most common adverse reactions (≥5%) included headache, viral infection, pharyngitis, epistaxis, cough, sinusitis, upper respiratory infection, dysmenorrhea, and musculoskeletal pain (NASONEX USPI, 2013).

GSP 301 NS [redacted] is being considered for evaluation in this pediatric efficacy and safety study in subjects aged ≥6 to <12 years with SAR. The Sponsor is proposing to match the approved pediatric daily doses for the individual monotherapy products and evaluate [redacted] of the adult and adolescent daily dosage [redacted] spray per nostril, [redacted] - olopatadine hydrochloride [redacted] µg and mometasone furoate [redacted] µg) resulting in a total daily dose of olopatadine hydrochloride [redacted] µg and mometasone furoate [redacted] µg. This proposed pediatric dosage will provide the equivalent total daily dose of the individual monotherapy products as currently approved in the commercially available products, PATANASE NS and NASONEX NS.

No nasal irritancy is expected when GSP 301 NS is administered based on evidence from the approved/marketed monotherapy formulations and the fact that the excipients in GSP 301 NS are all generally regarded as safe-approved by the intranasal route.

The efficacy and safety of another similar FDC product (DYMISTA - FDC of an antihistamine azelastine HCL and an intranasal corticosteroid fluticasone propionate) in pediatric subjects has been previously reported without any safety concerns. The efficacy and safety of DYMISTA was evaluated in a randomized, multicenter, double-blind, placebo-controlled study in 304 children aged 6 to 11 years with SAR. Subjects were randomized 1:1 to receive either one spray per nostril BID of DYMISTA or placebo for 14 days. The primary efficacy endpoint was the mean change from baseline in combined AM+PM rTNSS over 2 weeks. DYMISTA was not statistically significantly different from placebo (p=0.099), but the results were numerically supportive (DYMISTA USPI, 2015). No clinically meaningful difference in the incidence of AEs or in other safety assessments compared with placebo were reported in this study.

Another pediatric study evaluated the efficacy and safety of DYMISTA vs fluticasone propionate (both 1 spray/nostril BID), in subjects aged ≥ 6 to <12 years [DYMISTA: n = 264; fluticasone propionate: n = 89) with AR in an open-label 3 month study. Over the 3-month period, DYMISTA-treated children experienced significantly greater symptom relief than fluticasone propionate-treated children (treatment difference: -0.14; 95% CI: -0.28, -0.01; P = 0.04). Based on the results, this study concluded that DYMISTA provided significantly greater, more rapid and clinically relevant symptom relief than fluticasone propionate in children with AR (Berger et al, 2016). No clinically meaningful difference in the incidence of AEs or in other safety assessments compared with fluticasone propionate were reported in this study.

Therefore, it is anticipated that a FDC of olopatadine HCl and mometasone furoate (GSP 301) NS will provide improved efficacy and that the safety will be comparable to the known safety profiles of each monotherapy in pediatric subject population.

5. STUDY OBJECTIVES AND PURPOSE

5.1. Primary Objective

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

5.2. Secondary Objective

To assess the safety and tolerability over 14 days of study drug in pediatric subjects (aged ≥6 to <12 years) with SAR.

5.3. Exploratory Objective

Not applicable.

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This is phase 3, double-blind, randomized, parallel-group, placebo-controlled study conducted in multiple centers in the US. All study sites will enroll subjects during the spring or fall allergy season, as applicable. The study will evaluate the efficacy and safety of GSP 301 NS administered as [redacted] spray/nostril [redacted] compared with placebo NS in the same vehicle in pediatric subjects with SAR.

Subjects will be randomized to treatment in a 1:1 ratio to the following 2 treatment groups:

- GSP 301 NS [redacted] µg olopatadine HCl [redacted] µg mometasone furoate administered as [redacted] spray/nostril BID in the AM and PM).
- Placebo NS (administered as [redacted] spray/nostril [redacted] in the AM and PM).

This study consists of 4 visits to the study site (Figure 1). After the initial Screening Visit (Visit 1), subjects (aged ≥6 to <12 years) with SAR who meet all study selection criteria will undergo a single-blind, placebo run- in period for 7 to 10 days. Following the completion of the placebo run-in period, eligible subjects meeting the randomization criteria will be randomized to 1 of the 2 treatment groups. Randomized subjects will undergo a 2-week (14-day) treatment period to assess the efficacy and safety of the assigned treatment. The end of the study will be the date of the last study visit for the last subject in the study.

Pollen counts will be obtained each weekday, and when possible, each weekend day at each investigational site, either by study staff or by a community counting station located within approximately 30 miles of the study site. Three (3) consecutive days of moderate pollen counts will be accepted as the start to that pollen's given allergy season. The definition of 'moderate' varies depending on the allergen. Guidelines for identifying a moderate range can be found at http://www.aaaai.org/global/nab-pollen-counts/reading-the-charts.aspx or local guidelines can be used. However, the first subject should be screened only after meeting the moderate pollen count criteria for that relevant pollen season and upon consultation with the Sponsor's study team and approval. Pollen counts will be entered as part of the data entry in the case report forms/electronic case report forms (CRFs/eCRFs) or other methods as provided by the Sponsor or designee.

An overview of the study design is shown in Figure 1 and the Schedule of Assessments is outlined in Table 2. The endpoints to be measured in this study are described in Section 13.3.

Table 2: Schedule of Assessments

Study Period	Screening Visit (SV) Visit 1	Randomization Visit (RV) Visit 2	Treatment Visit (TV) Visit 3	Final Visit/ Discontinuation Visit (FV/DV) Visit 4
Activity / Observation	**(Day -7 to -10)**	**Day 1 [a]**	**Day 8±2 [a]**	**Day 15+2 [a]**
Written informed consent, assent and HIPAA authorization	X			
Inclusion/ exclusion criteria review	X	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
Focused ENT/eye examination [b]	X	X	X	X
Allergy testing (skin prick test for relevant allergen, if required) [c]	X			
Urine pregnancy test (as applicable, females of child bearing potential only)	X	X		X
Review instructions and train on proper use of nasal spray using the placebo NS device [c]	X	X	X	
Subject assessment of AR symptoms and recording at the clinical site [d]	X			
Prime, dispense, and administer single-blind placebo nasal spray at the clinic	X			
Distribute AR symptom assessment diary	X	X	X	
Review of AR symptom assessment subject diary		X	X	X
Subject assessment of AR symptoms and recording [d]	→			→
Physician assessment of nasal symptom severity		X		X
Review randomization criteria		X		
Randomization/treatment assignment		X		
Prime and dispense of double-blind study medication		X		
Administer double-blind study medication at clinic [d,e]		X[e]	X[e]	
Distribute PRQLQ, review instructions with the subject and completion of PRQLQ [f]		X		X
Adverse event monitoring	X	X	X	X
Collect study medication		X		X

Table 2: Schedule of Assessments (Continued)

Study Period	Screening Visit (SV) Visit 1	Randomization Visit (RV) Visit 2	Treatment Visit (TV) Visit 3	Final Visit/ Discontinuation Visit (FV/DV) Visit 4
Activity / Observation	**(Day -7 to -10)**	**Day 1[a]**	**Day 8±2[a]**	**Day 15+2[a]**
Collect AR symptom assessment diary		X	X	X
Subject compliance check (study procedures, diary and study medication)		X	X	X

AM = morning; AR = allergic rhinitis; DV = discontinuation visit; eCRF = electronic Case Report Form; ENT = Ear, Nose and Throat; FV = final visit; HIPAA = Health Insurance Portability and Accountability Act; NS = nasal spray; PM = evening; PRQLQ = Pediatric Rhinoconjuntivitis Quality of Life Questionnaire; RV = randomization visit; RAST = radioallergosorbent test; SV = screening visit; TV = treatment visit.

[a] The following visit windows are permitted: ±2 days for the TV (Visit 3) and +2 days for the FV.

[b] Focused nasal exams will be performed to assess signs of AR as well as known complications of intranasal corticosteroid or antihistamine use (ie, bleeding, perforation and ulceration). Throat examination will be conducted to evaluate the evidence of throat irritation and candidiasis. If clinically significant (as judged by the Investigator) nasal ulceration, nasal mucosal erosion, and nasal septal perforation are observed at any visit, the subject should be referred to a qualified ENT specialist or other medically qualified specialist (qualified to evaluate and record these conditions, as judged by the Investigator) for further evaluation. A record from the specialists for such subjects should be maintained including the photographic evidence (imaging of nasal mucosa) of the assessment to allow pre- and post-treatment comparisons for AEs (See details in Section 11.1.7). The Sponsor (or designee) will collect the de-identified information as part of the study data collection. Eligibility of the subject for participation/continued participation in the study will be at the Investigator's discretion based on whether or not the protocol-defined selection criteria are met. These subjects may need to be rescreened due to delay in scheduling an ENT visit to obtain the necessary evaluation, as applicable, upon consultation with the Sponsor's study team and approval.

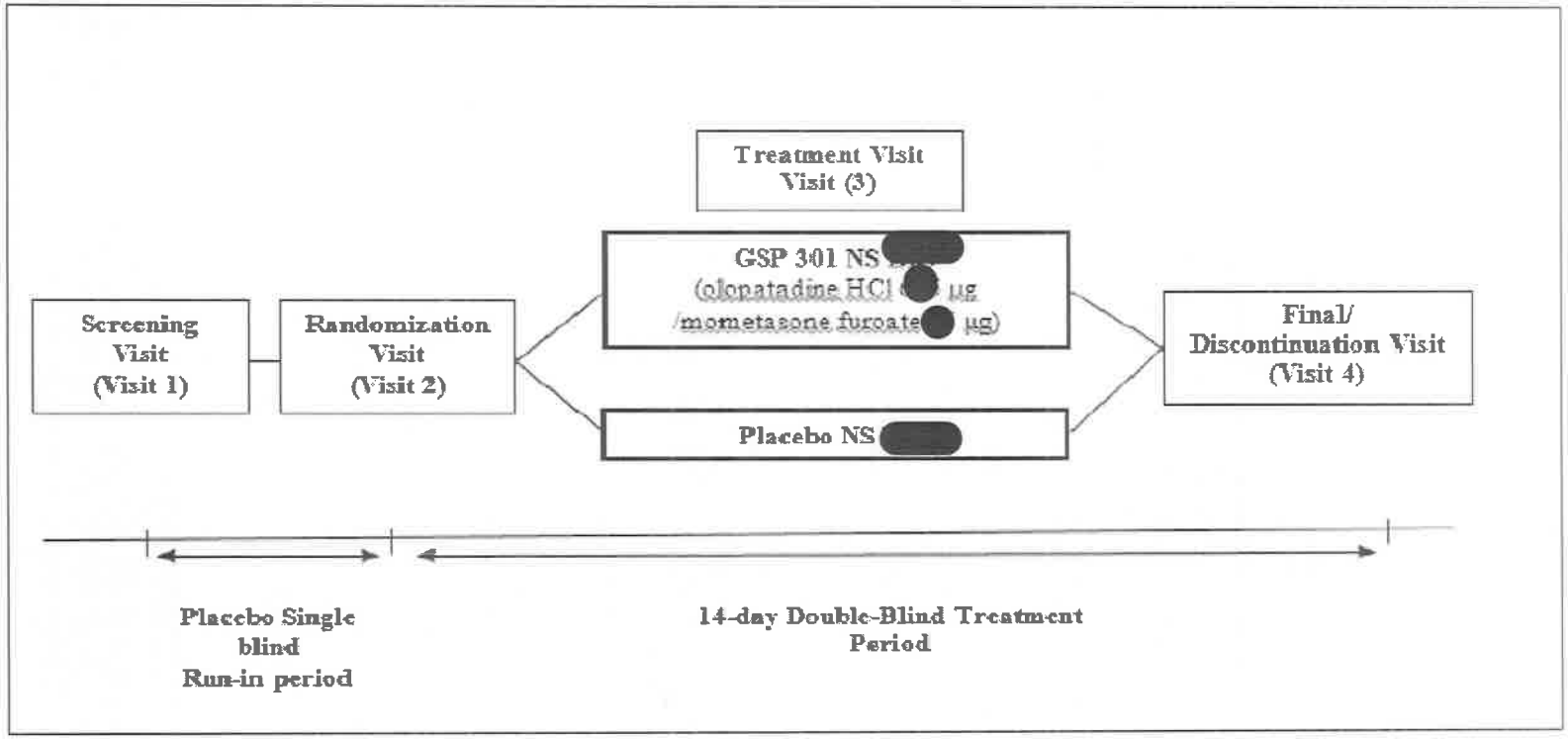
[c] Documentation of a positive result within 12 months before SV is acceptable to meet the eligibility criteria. Intradermal and/or RAST will not be accepted.

[d] Subjects will assess their symptoms (with the help of parents/guardians/caregivers, if needed) at specified clinic visit, as directed by the site personnel. Subject will also assess their symptoms (with the help of parents/guardians/caregivers, if needed) at home every morning and evening prior to self-administering the study medication (with the help of parents/guardians/caregivers, if needed). Study medication during the placebo run-in and treatment periods should be taken immediately following the completion of the AM or PM diary assessment (with assistance from parents/guardians/caregivers, as needed) except on the morning of the RV and TV where the study medication should be administered at the study site under the supervision of site personnel.

[e] All subjects must be told to refrain from taking their study medication on the mornings of the RV (Visit 2) and TV (Visit 3). They will administer the study medication at the clinic under the supervision of the study personnel. At TV (Visit 3), the subject is required to bring back their study drug assigned at Visit 2 and use the same bottle for administering the study drug under the supervision of study personnel. If the subject did take study drug on the morning of the TV (Visit 3) at home, then the date/time of the dose must be recorded but a second dose should not be administered at the clinic. The last dose of the study medication should be the PM dose on the day before the FV/DV (Visit 4). Subjects should be reminded not to take study drug on the morning of the FV/DV (Visit 4). If the subject did take study drug on the morning of the FV/DV (Visit 4), then the date/time of the dose must be recorded in the eCRF.

[f] PRQLQ must be the first procedure conducted at these visits. Subjects returning for the Randomization Visit undergo the PRQLQ assessment (as applicable) before his/her confirmation for randomization in the study. If the subject fails to get randomized due to any reason, the data collected for the PRQLQ will not be analyzed. Subjects that fail to be randomized at any time during Visit 2 will be discharged from the study following collection of the PRQLQ (as applicable), placebo run-in study medication, and placebo run-in diary as well as discussion of AEs and concomitant medications and other safety related procedures, as needed, at the discretion of the Investigator. However, the remaining efficacy-related assessments outlined for this visit may not be needed for the subjects who fail to be randomized.

Figure 1: Study Design



BID = twice daily; HCl = hydrochloride; NS = nasal spray.

6.1.1. Rationale for Study Design, Dose(s) and Comparator(s)

This is randomized, double-blind, parallel-group, placebo-controlled study conducted in approximately 450 subjects with SAR. Subjects will be randomized to 1 of the 2 treatment groups in a 1:1 ratio. Randomization will be performed centrally using Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS).

The overall study design is consistent with other similar studies reported in the literature (Berger et al, 2016; Storms et al, 2013). Furthermore, the overall study design is also based on the US Food and Drug Administration (FDA) guidance document: Allergic Rhinitis: Developing Drug Products for Treatment – Guidance for Industry (Draft Guidance) (FDA Guidance for Industry, 2000; FDA Guidance for Industry, 2016).

This current study is planned to evaluate the superiority of GSP 301 NS to placebo NS. The placebo used in the study is formulated in the same vehicle as GSP 301 NS and all the NS bottles are identical in appearance. Thus, other than the active component, there are no other differences in the formulation or the bottle of each treatment.

6.1.2. Estimated Duration of Subject Participation

The expected total duration of subject participation in the study is up to 27 days. This includes a placebo run-in period of 7 to 10 days and 14 days of treatment period, with allowable window periods for the study visits (see schedule of assessments, Table 2).

6.2. Number of Subjects

A total of approximately 450 subjects (225 subjects randomized to each treatment group) are planned to be randomized in the study.

6.3. Treatment Assignment

Study participation begins once written informed consent is obtained (see Section 16.3 for details).

This is a multicenter, randomized, double-blind, placebo-controlled study. Subjects will be randomized in a 1:1 ratio. Randomization will be performed centrally using Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS).

The procedure for using the IVRS/IWRS will be provided to each site separately.

Details of unblinding in the event of a medical emergency are provided in Section 8.4.1.

6.4. Dose Adjustment Criteria

Not applicable.

6.5. Criteria for Study Termination

The Sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators/Institutions and regulatory authorities of the termination or suspension and the

reason(s) for the termination or suspension. The Institutional Review Board (IRB)/independent Ethics Committee (IEC) will also be informed promptly and provided with the reason(s) for the termination or suspension by the Sponsor or by the Investigator/Institution, as specified by the applicable regulatory requirement(s).

The Investigator reserves the right to discontinue participation in the study should his/her judgment so dictate. If the Investigator terminates or suspends a study without prior agreement of the Sponsor, the Investigator should inform the Institution where applicable, and the Investigator/Institution should promptly inform the Sponsor and the IRB/IEC and provide the Sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted in Section 17.

6.6. End of the Study

The end of the study (study completion) is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last subject in the study. All materials or supplies provided by the Sponsor will be returned to the Sponsor or designee upon study completion, as directed by the site monitor. The Investigator will notify the IRB/IEC when the study has been completed.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Subject Inclusion Criteria

Subjects eligible for enrolment in the study must meet all of the following criteria:

1. Male or non-pregnant female subjects aged ≥6 to <12 years, at the Screening Visit (Visit 1).
2. Signed informed consent/assent form (subject and parent/caregiver/legal guardian), which meets all criteria of the current Food and Drug Administration/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) during the spring or fall allergy seasons for the relevant seasonal allergen (eg, tree/grass pollen or ragweed pollen). SAR must have been of sufficient severity to have required treatment (either continuous or intermittent) in the past, and in the Investigator's judgment, is expected to require treatment throughout the study period.
4. Demonstrated sensitivity to at least 1 seasonal allergen (eg, tree/grass pollen or ragweed pollen) known to induce SAR through a documented positive skin prick test (wheal diameter at least 5 mm greater than the negative control) to a relevant seasonal allergen. Documentation of a positive result within 12 months prior to the Screening Visit (Visit 1) is acceptable. The subject's positive allergen must be consistent with the medical history of SAR. Additionally, the subject is expected to be adequately exposed to the SAR allergen that he/she has tested positive for the entire duration of the study.
5. A 12-hour reflective Total Nasal Symptom Score (rTNSS) value of ≥6 (out of a possible 12) for the morning (AM) assessment at the Screening Visit (Visit 1).

6. 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.
7. Able to demonstrate the correct NS application technique (with the help of parents/guardians/caregivers, if needed) at the Screening Visit (Visit 1).
8. Willing and able to comply with all aspects of the protocol (with the help of parents/guardians/caregivers, if needed).

7.2. Subject Exclusion Criteria

Subjects meeting any of the following criteria must not be enrolled in the study:

1. Eligible females of childbearing potential who are known to be sexually active or pregnant, will be excluded and referred for appropriate evaluation. If a girl has reached puberty and achieved menarche (as determined by the Investigator), parents/guardians/caregivers will be consulted to obtain consent for pregnancy testing and permission to counsel the subject followed by counselling the subject by the Investigator regarding the possible unknown risks associated with study medication during pregnancy. Urine pregnancy test must be negative at the Screening Visit (Visit 1). Male subjects who are known to be sexually active will also be excluded and referred appropriately.
2. Plans to travel outside the known pollen area for the investigational site for 24 hours or longer during the last 7 days of the screening/run-in period.
3. Plans to travel outside the known pollen area for the investigational 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).
4. History of significant (based on Investigator's judgement) atopic dermatitis or rhinitis medicamentosa (within 60 days prior to the Screening Visit [Visit 1]).
5. Treatment with any known strong cytochrome P450 (CYP)3A4 inducers (eg, carbamazepine, phenytoin, rifabutin, rifampin, pioglitazone etc.) or strong inhibitors (eg, azole antifungals, macrolide antibiotics) within 30 days prior to the Screening Visit (Visit 1), or during the study.
6. Non-vaccinated exposure to or active infection with chickenpox or measles within the 21 days preceding Screening Visit (Visit 1).
7. A known hypersensitivity to any corticosteroids or antihistamines or to either of the drug components of the Investigational Product or its excipients.
8. History of anaphylaxis and/or other severe local reaction(s) to skin testing.
9. Any history or current use of alcohol or drug dependence at the Screening Visit (Visit 1), as determined by the Investigator.
10. History of positive test for human immunodeficiency virus, Hepatitis B or Hepatitis C infection (parents/guardians/caregivers will be consulted to obtain consent).
11. History and evidence of acute or significant chronic sinusitis or chronic purulent post nasal drip at the Screening Visit (Visit 1).

12. Any of the following conditions (including but not limited to the following) that are judged by the Investigator to be clinically significant and/or to affect the subject's ability to participate in this study:
    - impaired hepatic function.
    - any systemic infection.
    - hematological, hepatic, renal, endocrine disorder (except for hypothyroidism).
    - gastrointestinal disease.
    - malignancy (excluding basal cell carcinoma).
    - current neuropsychological condition with or without drug therapy.
        - Subjects with history or current diagnosis of active ADHD can be included in the study if symptoms of ADHD are considered stable by treating the physician and such history is documented by the Investigator.
        - Subjects with history or current diagnosis of ADHD on medications are eligible for inclusion if they are on stable active drug therapy and have stable symptoms for at least 30 days before the screening visit as documented in the medical history by the Investigator. Subjects may not be withdrawn from ADHD treatment medications during screening and/or throughout the study. If ADHD treatment medications are planned to be withdrawn or withdrawn by the treating physician during the study, then the subject should be considered ineligible or early terminated, respectively.
    - cardiovascular disease (eg, uncontrolled hypertension).
    - respiratory disease other than mild asthma.
13. Any major surgery (as assessed by the Investigator) within 4 weeks before the Screening Visit (Visit 1).
14. A requirement for the chronic use of tricyclic anti-depressants.
15. Dependence (in the opinion of the Investigator) on nasal, oral, or ocular decongestants, nasal topical antihistamines, or nasal steroids.
16. Active pulmonary disorder or infection (including but not limited to bronchitis, pneumonia, or influenza), 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 placebo run-in period. Subjects with mild asthma (as judged by the Investigator) are allowable on the condition that treatment is limited to inhaled short-acting beta agonists only (up to 8 puffs per day).
17. Use of antibiotic therapy for acute conditions within 14 days prior to Screening Visit (Visit 1). Low doses of antibiotics taken for prophylaxis are allowed if the therapy was started prior to the Screening Visit (Visit 1) and is expected to continue at the same stable dose throughout the clinical study duration.

18. Posterior subcapsular cataracts or glaucoma, or any other ocular disturbances or other listed related conditions (as applicable) including:
    - history of increased intraocular pressure.
    - history of retinal detachment surgery.
    - history of incisional eye surgery (other than unilateral cataract extraction or laser-assisted in situ keratomileusis).
    - history of penetrating ocular trauma, severe blunt ocular trauma.
    - evidence of uveitis, iritis, or other inflammatory eye disease during screening.
    - presence of ocular herpes simplex.
19. Known history of hypothalamic-pituitary-adrenal axis impairment.
20. Existence of any significant surgical or medical condition, or clinically significant physical finding (eg, significant nasal polyps or other clinically significant respiratory tract malformations/nasal structural abnormalities, significant nasal trauma [such as nasal piercing] or significant nasal septal deviation) which, in the opinion of the Investigator (or in consultation with the Sponsor's medical monitor/designee), significantly interferes with the absorption, distribution, metabolism or excretion of the study medication or significantly interferes with nasal air flow or interferes with the subject's ability to reliably complete the AR Assessment Diary.
21. Participation in any investigational non-biological drug clinical study in the 30 days or investigational biological drug in the 120 days preceding the Screening Visit (Visit 1) or planned participation in another investigational clinical study at any time during the current study.
22. Initiation of immunotherapy injections or immunosuppressive/immune-modulator medications within 60 days preceding the Screening Visit (Visit 1) and/or currently undergoing treatment with immunotherapy or immunosuppressive/immune-modulator medications. Topical pimecrolimus cream or tacrolimus ointment treatment if initiated at least 30 days prior to screening and maintained on stable dose is acceptable. A 180-day washout period is required following the last dose of sublingual immunotherapy (investigational or other) prior to the Screening Visit (Visit 1).
23. Use of topical corticosteroids in concentrations in excess of 1% hydrocortisone, or equivalent, within 30 days prior to the Screening Visit (Visit 1); use of a topical hydrocortisone or equivalent in any concentration covering greater than 20% of the body surface or the presence of an underlying condition (as judged by the Investigator) that can reasonably be expected to require treatment with such preparations over the clinical study duration.
24. Previous participation in another GSP 301 NS study as a randomized subject.
25. Clinical study participation by clinical investigator site employees and/or their immediate relatives.

26. Study participation by more than 1 subject from the same household at the same time. However, after the completion/discontinuation by 1 subject in the household, another subject from the same household may be screened.
27. Known to have failed to show symptom improvement with any approved/marketed monotherapy component of the GSP 301 NS (ie, NASONEX NS, PATANASE NS, or both) as judged by the Investigator.

7.3. Randomization Criteria (at the Randomization Visit (RV) – Visit 2):

1. Continued general good health and continued eligibility according to the inclusion and exclusion criteria.
2. Has not left the known pollen area for the investigative site for 24 hours or longer during the last 7 days of the placebo run-in period.
3. No adverse event (AE) that has altered eligibility according to the inclusion and exclusion criteria.
4. Minimum 12-hour subject-reported rTNSS of an average of 6, (out of a possible 12) during the last 4 days of the placebo run-in period (average of last 8 consecutive morning [AM] and evening [PM] assessments from the Day -4 PM assessment to the AM assessment on the day of randomization).
5. A 12-hour subject-reported reflective nasal congestion score of an average of 2 or greater during the last 4 days of the placebo run-in period (average of last 8 consecutive AM and PM assessments from Day -4 PM assessment to the AM assessment on the day of randomization).
6. Adequate symptom assessment diary compliance (with assistance from parent/guardian/caregiver, as needed) – inadequate compliance is defined as missing one or more of the entries on 2 or more assessment sessions (AM or PM) during the last 4 days of the placebo run-in period (during the last 8 consecutive AM and PM assessments from Day -4 PM assessment to the AM assessment on the day of randomization).
7. Adequate study medication compliance – each subject must have taken his/her single-blind placebo medication (with assistance from parent/guardian/caregiver, as needed) for at least 80% of the entire placebo run-in period as reported in the symptom assessment diary.
8. Absence of common cold, upper respiratory infections, otitis, lower respiratory infections or acute sinusitis for 14 days prior to the Randomization Visit (Visit 2).
9. No use of prohibited concomitant medications during the placebo run-in period.

7.4. Subject Withdrawal Criteria

A subject (or parent/guardian, as applicable) may voluntarily discontinue study participation at any time after giving informed consent/assent and before the completion of the last visit of the study. Subjects may also be withdrawn from study drug treatment at the discretion of the Investigator or Sponsor for safety, noncompliance, or administrative reasons. The Investigator

may also discontinue the subject's study participation at any time at his/her discretion and for any reason.

The reasons for subject withdrawal will be recorded and may include, but are not limited to:

1. Withdrawal of consent/assent by the subject (or parent/legal guardian, as applicable) to continue in the study. If consent is withdrawn, the subject will not receive any further investigational product (IP) or further study observation. Note that the subject may need to undergo additional tests or tapering of treatment to withdraw safely, as applicable.
2. Development of a serious or intolerable AE that necessitates discontinuation at the discretion of the Investigator (the AE section of the CRF/eCRF must be completed; AE includes serious adverse event (SAE) and death.
3. At the discretion of the Investigator, when he/she believes continued participation is not in the best interest of the subject.
4. At the discretion of the Investigator, when the subject does not adhere to the study procedures.
5. A protocol deviation that, in the opinion of the Sponsor and Investigator, warrants discontinuation from the study.

7.4.1. Lost to Follow-up

A subject will be considered lost-to-follow-up only if no contact has been established by the time the study is completed such that there is insufficient information to determine the subject's status on the Final Visit/Discontinuation Visit 4 (Table 2). Subjects refusing to return to the site or to continue participation in the study should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing subjects throughout the study period. If contact with a missing subject is re-established, the subject should not be considered lost-to-follow-up and any evaluations should resume according to the protocol.

If the subject withdraws consent for the study, no further evaluation will be performed and no additional data or medical records will be collected. The Sponsor may retain and continue to use any data collected before withdrawal of consent.

A subject who discontinues study drug early but does not withdraw consent, should return for end of study assessments, as noted in Section 12.5.

The Investigator will:

- inquire about the reason for withdrawal,
- request that the subject return all unused IP, and
- request that the subject return for the Final Visit/Discontinuation Visit (Visit 4), including examinations and clinical laboratory measurements, as applicable.

If the subject refuses to attend the clinic, efforts will be made and documented, to perform the end of study assessments; collection of visit data during a telephone call is permitted, as applicable.

The Investigator must request follow up with the subject regarding any unresolved AEs/SAEs. At a minimum, at the end of the study, the Investigator should consult public records to determine the subject's circumstances, eg, vital status, incarceration, or relocation.

7.4.2. Permanent Discontinuation of Study Drug

A subject who is permanently discontinued from further receipt of study drug, regardless of the reason (withdrawal of consent, due to an AE, other), will be identified as having permanently discontinued treatment. Subjects who permanently discontinue treatment will be considered not to have completed the study as outlined in the protocol (see Section 8.5 and Section 12.5).

7.4.3. Replacement of Subjects

Discontinued subjects will not be replaced.

8. TREATMENT OF SUBJECTS

8.1. Description of Study Drug

The following study drugs will be supplied by Glenmark for the study:

Table 3: Study Drugs

GSP 301-305	
Product Name	FDC of olopatadine hydrochloride [redacted] µg and mometasone furoate [redacted] µg NS
Manufacturing License Name	GSP 301 [redacted] NS
Dosage Form	Spray, metered (nasal spray)
Dosage	[redacted] in each nostril
Dose frequency	[redacted] for 14 days
Route of Administration	Intranasal
Manufacturer	Glenmark
Placebo	
Product Name	GSP 301 Placebo NS
Manufacturing License Name	GSP 301 Placebo NS
Dosage Form	Spray, metered (nasal spray)
Dosage	[redacted] in each nostril
Dosage frequency	[redacted] for 14 days
Route of Administration	Intranasal
Manufacturer	Glenmark

BID = twice daily; FDC = fixed dose combination; NS = nasal spray

See Section 9 for additional information on study drug supplies.

8.2. Prior and Concomitant Medications

Exclusion of medication prior to the Screening Visit (Visit 1) are summarized in Table 4.

Table 4: Summary of Exclusion of Medication Prior to Screening

Medication	To be Stopped prior Visit 1 (Days)
Vasoconstrictors (eg, epinephrine, sumatriptan).	3
Major tranquilizers (eg, antipsychotics such as chlorpromazine, haloperidol, risperidol, clonazepam).	3
Short-acting antihistamines (oral, ocular, or intranasal antihistaminic – eg, azelastine).	5
OTC cough and cold preparations or sleep aids containing antihistamines.	7
Topical/oral/intanasal decongestants (eg, oxymetazoline, pseudoephedrine, tetrahydrozoline).	7
OTC food supplement/diet to reduce leukotrienes (AIROZIN).	7
Leukotriene antagonists or arachidonate 5-lipoxygenase inhibitors.	7
Inhaled/oral/intranasal anticholinergics.	7
Long-acting antihistamines (eg, cetirizine, fexofenadine).	10
Cromolyn (all forms), nedocromil or lodoxamide (intranasal, ocular, or oral).	14
Systemic antibiotic (see exclusion criterion 17, [Section 7.2]).	14
Ocular mast cell stabilizers.	14
Monoamine oxidase inhibitors.	14
Tricyclic antidepressants.	14
All intranasal/topical/ocular corticosteroids (except study medication - see exclusion criterion 23 [Section 7.2], and for the treatment of small, localized lesions).	30
Inhaled corticosteroids.	30
Any other investigational non-biological drug.	30
Treatment with any known strong CYP3A4 inducers (eg, carbamazepine, dexamethasone, phenytoin, rifabutin, rifampin, pioglitazone).	30
Treatment with any known strong CYP3A4 inhibitors (eg, azole antifungals, macrolide antibiotics).	30
Systemic corticosteroids (intermittent or chronic, including intra-articular).	60
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, see exclusion criterion 22 [Section 7.2]).	60
IgE antagonist or any other anti-IgE therapy.	120
Any other investigational biological drug	120
Anti-interleukin-5 therapy (eg, reslizumab, mepolizumab)	120
Sublingual immunotherapy (investigational or other).	180

CYP3A4 = Cytochrome P450 system enzyme 3A4; IgE = immunoglobulin E; OTC = over the counter

These above medications are also prohibited throughout the entire study (from Screening Visit to Final Visit).

In addition to the above medications, concomitant treatment with any of the following medications is prohibited throughout the study (from Screening Visit to Final Visit):

1. All intranasal therapies (including saline).
2. Topical corticosteroids (except for the treatment of small, localized lesions).
3. All ophthalmic drops (prescription and OTC except lens moisturizing drops).
4. Radiation therapy.
5. Initiation of immunotherapy.
6. Any investigational drug being used in another clinical study.
7. Herbal medication/supplements to treat AR, or any other alternative therapies for AR.
8. St John's Wort (Hypericum perforatum).
9. Guaifenesin containing products (eg, MUCINEX)

8.2.1. Exclusion of Concomitant Medications

1. All above medications (Table 4) are prohibited during the study.
2. No AR or asthma preventive medication will be permitted during the study except for inhaled short acting beta-agonists for mild asthma (up to 8 puffs per day).
3. Radiation therapy, the initiation of immunotherapy, and any drug (investigational or marketed) being used in a clinical study are prohibited during the study.
4. Subjects can receive topical immunotherapy (eg, pimecrolimus cream or tacrolimus ointment), provided initiation of topical immunotherapy was at least 30 days prior to the Screening Visit (Visit 1) and the subject uses a stable maintenance dose (30 days or more) prior to the Screening Visit (Visit 1) as well as during the study.
5. Strong CYP3A4 inhibitors (eg, ketoconazole, itraconazole, and erythromycin) and strong CYP3A4 inducers (eg, carbamazepine, dexamethasone, phenytoin, rifabutin, rifampin, and pioglitazone) are prohibited 30 days prior to the Screening Visit (Visit 1) as well as during the study.

8.2.2. Permitted Concomitant Medications

With the exception of medications listed on the exclusion list, subjects will be allowed to use other chronic medications in stable doses and other medications at the discretion of the Investigator (in consultation with the Sponsor), which do not interfere in the safety and efficacy variables of the study.

8.2.3. Rescue Medication

Rescue medications will not be provided and should not be used throughout the duration of the study, including the placebo run-in period.

8.2.4. Lifestyle and/or Dietary Restrictions

As defined in the inclusion/exclusion criteria section (Section 7.1 and Section 7.2), subjects are expected to follow protocol-specific lifestyle and dietary requirements.

8.3. Treatment Compliance

All study medication will be self-administered by the subject in the clinical facility as well at home (with assistance from parents/guardians/caregivers, as needed) in accordance with the protocol-specified subject study medication instructions (Appendix 1). Subject compliance will be monitored by the site personnel by reviewing the AR Assessment Diary entries as outlined in the Schedule of Assessments (Table 2). Subjects (parents/guardians/caregivers) will be counseled regarding proper treatment compliance and re-trained in the proper use of the study medication NS bottle at the specified visits as well as reviewing the subject study medication instructions (Appendix 1).

8.3.1. Treatment of Investigational Product Overdose

Thus far, there are no data available on the effects of acute or chronic overdose with GSP 301 NS based on the completed clinical studies (GSP 301 IB, 2017). Because of the proven safety and efficacy of GSP 301 NS and the approved individual monotherapy components of GSP 301 NS (PATANASE and NASONEX), overdose is unlikely to require any therapy other than observation. There is no specific antidote to be used in the event of overdose. Investigators should use their clinical judgment in treating cases of overdose as indicated by the subject's clinical status.

Overdose information for each individual component of GSP 301 NS (approved monotherapies) is provided in the prescribing information and outlined here (PATANASE USPI, 2012; NASONEX USPI, 2013).

Olopatadine hydrochloride: There have been no reported overdoses with olopatadine HCl NS (PATANASE NS). Symptoms of antihistamine overdose may include drowsiness. There is no known specific antidote to olopatadine HCl NS. Should overdose occur, symptomatic or supportive treatment is recommended, taking into account any concomitantly ingested medications.

Mometasone furoate: No data are available on the effects of acute or chronic overdose with mometasone furoate monohydrate NS (NASONEX NS). Overdose is unlikely to require any therapy other than observation followed by initiation of the appropriate prescribed dosage because of the negligible (<0.1%) systemic bioavailability of mometasone furoate and the absence of acute drug related systemic findings in clinical studies. Intranasal administration of [redacted]µg [redacted]times the recommended dose of mometasone furoate monohydrate NS[redacted]µg for the treatment of AR) daily for[redacted]days to healthy volunteers did not result in increased incidence of AEs. Single intranasal doses up to[redacted]µg and oral inhalation doses up to[redacted]µg have been studied in subjects with no adverse effects reported.

8.4. Randomization and Blinding

Subjects will be assigned to 1 of the 2 treatment groups in a 1:1 ratio based on a computer generated randomization scheme that will be reviewed and approved by a statistician. The

randomization will be performed centrally using IVRS/IWRS. The randomization scheme and treatment allocation for each subject will be included in the final clinical study report (CSR) for this study.

This study is designed as a double-blind study. The blinding will be maintained by packing the active products and placebo in identical bottles and outer cartons. Double blind kits containing the IP will be supplied to the sites and will be dispensed to subjects using IVRS/IWRS.

8.4.1. Unblinding in the Event of a Medical Emergency

In case of any premature unblinding (eg, accidental unblinding or unblinding due to a SAE) of the IPs, subjects will be terminated from the study. In addition, the Investigator should promptly document and explain the situation to the Sponsor. The Sponsor's Medical Monitor or delegate should be contacted either prior to unblinding or soon after, depending on the circumstances. The Investigator will unblind the subject under consideration only, using IVRS/IWRS or the IVRS/IWRS help desk, if knowledge of the randomized treatment is required for the treatment of the AE or SAE. In the event of unblinding, the following minimum information will be recorded in a memo to file, which will be included in the CSR:

1. Date of unblinding.
2. Identification of person(s) requesting the unblinding.
3. Reason for unblinding.
4. Investigator's signature.

8.5. Subject Completion

An individual will be considered to have completed the study if the subject was followed up through the end of the study, defined as Visit 4/Day 15 (+2), regardless of the number of doses of study drug that were received.

Subjects will be considered not to have completed the study if consent was withdrawn or the subject was lost to follow up (see Section 7.4). A subject who discontinues study drug early but does not withdraw consent, should return for end of study assessments, as noted in Section 12.5.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Study Drug

Specific details regarding study drug supplies, dose preparation, and accountability will be provided in the Investigational Product Manual supplied to the sites.

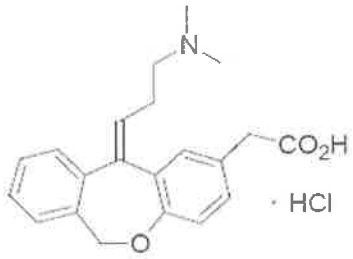
9.1.1. Identity of Study Drug

9.1.1.1. Chemical Name and Structural Formulas

Generic name: Olopatadine hydrochloride

Chemical name: (Z)-11-[3-(dimethylamino)propylidene]-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid hydrochloride

Structural formula:

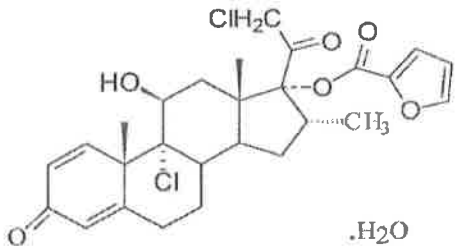


9.1.1.2. Mometasone Furoate

Generic name: Mometasone furoate

Chemical name: 9,21-Dichloro-11ß,17-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione17-(2 furoate) monohydrate

Structural formula:



9.1.2. Placebo

Placebo will be prepared using the same vehicle as the active products. The placebo NS bottle will be identical to that of active treatments. The placebo NS will be packaged in primary and secondary packaging similar to that of the active treatments to maintain study drug blinding.

9.2. Study Drug Packaging and Labeling

Each of the IPs will be packed as per Good Manufacturing Practice guidelines. The IP kits will be packed as per the visit schedule to cover the treatment duration. The individual subject kit will at a minimum be labeled as per FDA guidance (CFR Title 21, 2017).

The Study Monitor should be notified immediately of the details of any supplies that are inadvertently damaged or unaccountable for any reason. These will be documented on drug accountability logs that will be collected by the Study Monitor at the end of the study or on request by the Sponsor.

9.3. Study Drug Storage

The IP should be stored upright, at controlled room temperature 15° to 25° Celsius (59° to 77° Fahrenheit), not frozen or refrigerated, and protected from light. Subjects will be informed about the storage conditions for the IP.

9.4. Study Drug Preparation

9.5. Administration

Each study medication bottle will contain [redacted] metered sprays. The study medication will be dispensed to the subjects (parents/caregivers/legal guardians, as applicable) at the study site after adequate training using a placebo NS bottle.

The subjects (with the assistance from parents/caregivers/legal guardians, as needed) will be asked to take their daily double-blind, study medication for a period of 14 days (2 weeks) following a 7 to 10 day, single-blind, placebo run-in period. The first dose (AM dose on Day 1) will be administered in the clinic at the Randomization Visit (Visit 2). The AM dose of the day of the Treatment Visit (Visit 3) will also be administered at the clinic. All other doses will be self-administered at home (with assistance from parents/guardians/caregivers, as needed). The last scheduled dose will be the PM dose on the day before the Final Visit/Discontinuation Visit (Visit 4). Study drug should not be taken (either at home or at the clinic) on the morning of the Final Visit/Discontinuation Visit (Visit 4).

Subjects will self-administer the study medication during specified study visits under the supervision of the study personnel (with assistance from parents/guardians/caregivers, as needed). Additionally, subjects will self-administer the study medication at home BID per the subject instructions provided during the single blind placebo run-in period and the treatment period (with assistance from parents/guardians/caregivers, as needed). Subjects (parents/legal guardians/caregivers, as needed) will be adequately trained in the proper use of the study medication NS bottle at the specified visits as well as reviewing the subject study medication instructions.

Detailed instructions for the proper use of the treatment NS bottles are provided in Appendix 1.

9.6. Study Drug Accountability

The Investigator (or designee) is responsible for study drug accountability and its documentation at the site. The Investigator must also ensure that the dispensing and recording of study drug is

done only by authorized personnel. The study drug records must be readily available for inspection by the Study Monitor and/or auditor/regulatory agency personnel. Upon completion of the study, copies of study drug accountability records will be returned to the Sponsor or its designee. Refer to the Investigational Product Manual or other written instructions provided by the Sponsor or its designee for contact information and specific shipping and return instructions.

9.7. Study Drug Handling and Disposal

No medication (used or unused) can be returned to the Sponsor or disposed of at the investigational site until the Sponsor's Study Monitor has verified/reconciled the accuracy of the study medication records at the site and indicated whether the medication should be destroyed at the site or returned to the Sponsor. The Study Monitor must indicate the name and address of the individual to whom the returned materials should be shipped.

10. ASSESSMENT OF EFFICACY

10.1. Subject-Reported Nasal Symptoms

The primary efficacy measure in this study is the subject-reported Total Nasal Symptom Score (TNSS). The TNSS is defined as the sum of the subject-reported symptom scores for 4 nasal symptoms: rhinorrhea (runny nose), nasal congestion, nasal itching, and sneezing. The subject will assess and report his/her nasal symptoms twice (AM and PM assessments) on each day of the placebo run-in and double-blind treatment periods prior to administering the study drug (with assistance from parents/guardians/caregivers, as needed). Subjects (with assistance from parents/guardians/caregivers, as needed) will record the symptom scores on a paper AR Assessment Diary. The AM assessment should be performed prior to bathing, consumption of food or beverages, or strenuous activities. The PM assessment should occur approximately 12 hours after the AM assessment. Study medication should be administered immediately after completion of the AR Assessment Diary.

The subject will be asked to assess both reflective (ie, an evaluation of symptom severity over the past 12 hours prior to the recording of the score) and instantaneous (ie, an evaluation of the symptom severity just before taking study medication [within 10 minutes]) nasal symptoms. Each of the following nasal symptoms will be assessed.

- Nasal Congestion
- Rhinorrhea
- Nasal Itching
- Sneezing

Each of the above symptoms will be rated on a 4-point severity scale (Table 5).

Table 5: Nasal Symptom Severity Scale

Score	Grade	Description
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 is hard to tolerate; causes interference with activities of daily living and/or sleeping

10.2. Subject-Reported Non-Nasal Symptoms

The efficacy measures in this study will also include the subject-reported non-nasal symptoms as measured by the Total Non-nasal Symptom Score. The Total Non-nasal Symptom Score is defined as the sum of the subject-reported non-nasal symptom scores for 4 non-nasal symptoms: itching/burning eyes, tearing/watering eyes, redness of eyes, and itching of ears or palate. The subject will assess and report his/her non-nasal symptoms twice (AM and PM assessments) on each day of the placebo run-in and double-blind treatment periods prior to administering the study drug (with assistance from parents/guardians/caregivers, as needed). Subjects will record the symptom scores on a paper AR Assessment Diary (with assistance from parents/guardians/caregivers, as needed). The AM assessment should be performed prior to bathing, consumption of food or beverages, or strenuous activities. The PM assessment should occur approximately 12 hours after the AM assessment. Study medication should be administered immediately after completion of the AR Assessment Diary.

The subject will be asked to assess non-nasal symptoms, both reflective (ie, an evaluation of symptom severity over the past 12 hours prior to the recording of the score) and instantaneous (ie, an evaluation of the symptom severity prior to taking study medication [ie, the last 10 minutes]). Each of the following symptoms will be assessed:

- Itching/burning eyes
- Tearing/watering eyes
- Redness of eyes
- Itching of ears and palate

Each of the above symptoms will be rated on a 4-point severity scale (Table 6).

Table 6: Non-nasal Symptom Severity Scale

Score	Grade	Description
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 is hard to tolerate; causes interference with activities of daily living and/or sleeping

The Total Ocular Symptom Score (TOSS) will be calculated using the 3 eye-related non-nasal symptoms: itching/burning eyes, tearing/watering eyes, and redness of eyes.

10.3. Physician Assessment of Nasal Symptom Severity

The Physician Assessment of Nasal Symptom score (PNSS) will be derived from the intensity of the following nasal symptoms associated with AR: rhinorrhea (runny nose), nasal congestion, nasal itching, and sneezing; each of these symptoms will be assessed as described in Section 10.2 (Raphael et al, 2013). Investigators will assess the severity of these symptoms based on questioning the subjects (overall feeling since last visit), the ear nose and throat (ENT) examination, and other observations by the Investigator.

Whenever possible, the same medically qualified person should complete this assessment for the same subject throughout the subject's participation in this study.

10.4. Pediatric Rhinoconjuntivitis Quality of Life Questionnaire (PRQLQ)

The PRQLQ (Appendix 3) used in this study is a validated, disease-specific, quality-of-life (QOL) questionnaire developed to measure the physical, emotional, and social impairments that are experienced by children (aged ≥6 to <12 years) with rhinoconjunctivitis (Juniper et al, 1998).

The PRQLQ has 23 questions in 5 domains (nose symptoms, eye symptoms, practical problems, activity limitation and other symptoms) (Juniper et al, 1998). Subjects recall how they have been during the previous week and respond to each question on a 7-point scale. The overall PRQLQ score is the mean of all 23 responses and the individual domain scores are the means of the items in those domains.

The interviewer-administered PRQLQ will be provided to subjects at the investigational site at the Randomization Visit (Visit 2) and the Final Visit/Discontinuation Visit (Visit 4). The PRQLQ administration must be the first procedure conducted at these study visits.

The study site personnel and the Investigators will be provided with detailed instructions about conducting QOL assessments in order to achieve maximum compliance with the standards of QOL assessments in a clinical study environment and to maximize data quality. Clinical staff must ask the questions exactly as worded in the questionnaire. Words should not be simplified, skipped or changed. Above all, clinical staff should never attempt to paraphrase or revise the questions. After completion of the PRQLQ, the site personnel will check the questionnaire for completeness and legibility.

An English version of the PRQLQ will be provided to all subjects who provide informed consent/assent in English. However, if a subject consents/assents in a language other than English, the PRQLQ will be provided to the subject in that language provided a validated version of the PRQLQ is available in that language. If a validated version of the PRQLQ is not available in that language, then the subject will be exempt from completing the PRQLQ.

11. ASSESSMENT OF SAFETY

11.1. Safety Parameters

Safety assessments will consist of monitoring and recording all AEs (including severity as mild, moderate or severe as per Section 11.2) and SAEs; periodic measurements of vital signs, ENT examinations, and physical examinations as detailed in the Schedule of Procedures and Assessments (Table 2). Additional details for the safety procedures performed in the study are detailed below.

Safety assessments (eg, vital signs measurements), including those that worsen from baseline, that are considered to be clinically significant in the medical and scientific judgment of the Investigator will be recorded as AEs or SAEs. If a repeat safety or other physical assessment is performed by the Investigator, those results should be entered in the eCRF as an unscheduled assessment.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition, will not be reported as AEs or SAEs.

11.1.1. Demography

Subject demographic information will be collected at the Screening Visit (Visit 1). Demographic information includes date of birth (or age), sex, race/ethnicity, and any other study-specific demography.

11.1.2. Baseline Assessments

11.1.2.1. Medical History and Physical Examinations

Medical and surgical history, current medical conditions, and allergen testing data (skin prick test for relevant allergen, if required), will be recorded at the Screening Visit (Visit 1). All relevant medical and surgical history within 2 years must be noted in the Medical and Surgical History or equivalent CRF/eCRF.

11.1.3. Vital Signs

Vital sign evaluations will be performed as designated in the Schedule of Procedures and Assessments (Table 2). Vital sign evaluations will include sitting blood pressure (mm Hg) and pulse rate (beats/minute) after at least 5 minutes of rest in the seated position. Either an electronic or a manual sphygmomanometer may be used. For each subject, blood pressure measurements will be taken from the same arm throughout the study, if possible. Pulse rate will be measured from the radial pulse counted electronically or manually over at least 15 seconds, adjusted per minute. The methods of assessment should be consistent throughout the study for each subject. A medically qualified staff member will perform the vital sign evaluations. If a clinically important change in vital signs is observed, the assessment should be repeated in 5 to 10 minutes to confirm the change.

11.1.4. Weight and Height

Height (cm) and weight (kg) will be measured at the Screening Visit (Visit 1) and at the Final Visit/Discontinuation Visit (Visit 4).

11.1.5. Physical Examination

Physical examinations (comprehensive) will be performed as designated in the Schedule of Procedures and Assessments (Table 2). Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit (Visit 1) will be recorded on the Medical History and Current Medical Conditions CRF/eCRF. Changes from the screening physical examination findings that meet the definition of an AE will be recorded on the AE CRF/eCRF.

11.1.6. Urine Pregnancy Testing

Urine pregnancy testing will be completed by a dipstick evaluation at the Investigator's clinical facility for all female subjects of child-bearing potential as designated in the Schedule of Procedures and Assessments (Table 2) or as indicated by the subject's condition. The testing, based on beta human chorionic gonadotropin, will be carried out as per the manufacturer's instructions.

A positive finding during the Screening Visit (Visit 1) will prevent the subject from study participation and a positive finding at or after the Randomization Visit (Visit 2) will require immediate Sponsor notification, discontinuation of study medication, and termination from the study with appropriate referral for evaluation and follow-up.

11.1.7. Focused Ears, Nose and Throat (ENT) Examinations

Focused ENT examinations will be performed as designated in the Schedule of Procedures and Assessments (Table 2). The Investigator or medically qualified designee will perform a thorough and focused ENT examination. Whenever possible, the same medically qualified person should complete this assessment for the same subject throughout the subject's participation in the study.

Nasal examinations will be performed to assess signs of AR as well as known complications of intranasal corticosteroid or antihistamine use (eg, bleeding, perforation, and ulceration). The focused ENT examination will include an evaluation of nasal irritation, epistaxis, and additional nasal symptoms, graded according to the criteria in Table 7.

Table 7: Grading Criteria for Nasal Examination Findings

Evaluation	Grading Criteria
Nasal Irritation	0=None
	Grade 1A=Focal irritation (focal nasal inflammation, erythema or hyperemia)
	Grade 1B=Superficial mucosal erosion
	Grade 2=Moderate mucosal erosion
	Grade 3=Ulceration
	Grade 4=Septal perforation
Epistaxis	None
	Mild=Self-limited
	Moderate=Significant, prevents daily activity
	Severe=Emergency room visit or hospitalization
Mucosal Edema, Nasal Discharge, Mucosal Erythema, and Crusting of Mucosa	None
	Mild
	Moderate
	Severe

Note: The epistaxis category may also include mild mucosal bleeding including reports of even a single speck of blood on a tissue based on the Investigator's judgment. However, moderate to severe grading of epistaxis should exclude these minor mucosal bleeding cases and should include only significant cases of epistaxis.

Throat examinations will be conducted to evaluate evidence of throat irritation, candidiasis, and post nasal drip. Any clinically significant new findings, not related to the study indication (SAR), evident at any visit after the Screening Visit (Visit 1), as judged by the Investigator, should be captured as an AE and reported and recorded in the CRF/eCRF. All findings at the Screening Visit (Visit 1) will be captured on the Medical History page of the CRF/eCRF.

If clinically significant nasal structural abnormalities (as judged by the Investigator) including, but not limited to, nasal ulceration, nasal mucosal erosion, and significant septal deviation are observed during any visit, the subject should be referred to qualified ENT specialists or other medically qualified specialists (qualified to evaluate and record these conditions, as judged by the Investigator) for further evaluation, as soon as possible. A record from the specialists for such subjects should be maintained including the photographic evidence (imaging of nasal mucosa) of the assessment to allow pre- and post-treatment comparisons for AEs (see details at the beginning of Section 11.2, Section 11.4.1, and Section 11.4.2). The Sponsor will collect the de-identified information as part of the study data collection. Eligibility of such subjects for participation in the study will be at the Investigator's discretion based on the ability to meet the study protocol defined selection criteria.

11.1.8. Confirmation of Medical Care by Another Physician

The Investigator will instruct subjects (parents/legal guardians/caregivers, as applicable) to inform site personnel when they are planning to receive medical care by another physician. At each visit, the Investigator will ask the subject whether he/she has received medical care by another physician since the last visit or is planning to do so in the future (parents/legal guardians/caregivers, as applicable). When the subject is going to receive medical care by another physician, the Investigator, with the consent of the subject (parents/legal guardians/caregivers, as applicable), will inform the other physician that the subject is participating in the clinical study.

11.2. Adverse and Serious Adverse Events

The Investigator or site staff will be responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE.

The reference safety information for this study is provided in the Investigational Brochure Section 6.4.8.2 within the Summary of Data and Guidance for Investigators Definition of Adverse Events (GSP 301 IB, 2017).

List of contact details are provided in Appendix 2.

11.2.1. Adverse Event

An AE is defined as any untoward medical occurrence in a subject administered study drug that does not necessarily have a causal relationship with the treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease (new or exacerbated) temporally associated with the use of the study drug, whether or not related to the study drug. An AE includes any event, regardless of the presumed causality between the event and the study drug.

Events that, while not necessarily meeting the definition of AEs, should be treated as such because they may be reportable to Regulatory Authorities according to AE reporting regulations, whether or not considered causally associated with IP, include the following:

- Study drug overdose, whether accidental or intentional
- Study drug abuse
- An event occurring from study drug withdrawal
- Any failure of expected pharmacological action
- Inadvertent or accidental study drug exposure (eg, product leaking or being spilled onto a subject or care-giver)
- Unexpected therapeutic or clinical benefit from the study drug
- Medication errors (ie, incorrect route of administration, incorrect dosage, use of incorrect product).

Events that do not meet the definition of an AE include:

- Medical or surgical procedure (eg, endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

Note that significant worsening of symptoms (ie, requiring systemic steroids, antibiotics, or hospitalization) will be reported as an AE.

11.2.1.1. Assessment of Severity of Adverse Events

The severity of AEs is classified as follows:

- Mild:
  - The AE is a transient discomfort and does not interfere in a significant manner with the subject.
  - The AE resolves spontaneously or may require minimal therapeutic intervention.
- Moderate:
  - The AE produces limited impairment of function and may require therapeutic intervention.
  - The AE produces no sequelae.
- Severe:
  - The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern.
  - The AE produces sequelae, which require (prolonged) therapeutic intervention.

The criteria for assessing severity are different from those used for seriousness (see Section 11.2.1.2 for the definition of an SAE).

11.2.1.2. Serious Adverse Event

An SAE is any untoward medical occurrence that, at any dose:

- Results in death.
- Is life-threatening.
  - NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

- May result in inpatient hospitalization or prolongation of existing hospitalization. Hospitalization is defined as any inpatient admission (even if less than 24 hours). Inpatient admission does not include the following:
  - Emergency room department visits.
  - Outpatient/same day/ambulatory procedures/observation/short-stay units.
  - Hospice facilities/respite care.
  - Rehabilitation facilities.
  - NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
  - A hospitalization planned prior to study enrollment is to be considered a therapeutic intervention and not the result of a new SAE. If the planned hospitalization or procedure is executed as planned, it will be recorded in the subject's medical history or procedures. However, if the event/condition worsens during the study, it must be reported as an AE.
  - Emergency room visits that do not result in a hospital admission should be evaluated for one of the other serious outcomes (eg, life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).
- Results in disability/incapacity.
  - NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect.
- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or

convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

11.3. Relationship to Study Drug

The relationship of AEs to study medication is classified as follows:

- Not Related: A causal relationship between the study drug and the AE is not a reasonable possibility.
- Related: A causal relationship between the study drug and the AE is a reasonable possibility.

Items to be considered when assessing the relationship of an AE to the study drug are:

- Temporal relationship of the onset of the event to the initiation of the study drug.
- The course of the event, especially the effect of discontinuation of study drug or reintroduction of study drug, as applicable.
- Whether the event is known to be associated with the study drug or with other similar treatments.
- The presence of risk factors in the study subject known to increase the occurrence of the event.
- The presence of non-study drug–related factors that are known to be associated with the occurrence of the event.

For each AE, the Investigator should answer the following question with Yes or No:

- Was there a reasonable possibility (evidence) that the drug caused the AE?
  - A reasonable possibility means that there are facts (evidence) or arguments to suggest a causal relationship.
  - NOTE: For subjects that have not started receiving study medication, or placebo run-in phase medications, the answer must be no.

11.4. Recording Adverse Events

11.4.1. Collection of Adverse Events

The Investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

AEs will be collected from the time of signing the informed consent form (ICF) until the follow up contact.

SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed as related to study participation (eg, study drug, protocol mandated procedures, invasive tests, or change in existing therapy) or related to a concomitant medication that is a Glenmark product, will be recorded from the time a subject consents to participate in the study up to and including any follow up contact. All SAEs will be reported to the Sponsor within 24 hours, as indicated in Section 11.5.

The Investigator will enquire about the occurrence of AEs/SAEs at every visit throughout the study (including Follow-up and Early Withdrawal visits where applicable), by asking the following non-leading verbal question of the subject (or care-giver, where appropriate):

- "Have you had any medical problems since your last visit?"

All AEs not resolved by the end of the study or that have not resolved upon the subject's discontinuation in the study must be followed until the event resolves, the event stabilizes or the event returns to baseline if a baseline value is available.

11.4.2. Recording of Adverse Events

All AEs, regardless of the seriousness, severity or relationship to the study medication must be recorded on the AE CRF.

Adverse events that meet the definition of a SAE must be reported on the SAE Form provided for this study.

Adverse events must be documented in clear, unambiguous medical language. Do not use abbreviations or acronyms.

For each AE record only the diagnosis, do not report the characteristic signs and symptoms of the diagnosis as additional AEs.

If a diagnosis is not available record each sign and symptom as an AE, when a diagnosis becomes available, update the AE CRF, to record the relevant diagnosis only.

In general abnormal findings at screening should be recorded in the subject's Medical History or in the Concurrent Conditions section in the CRF. However if, in the Investigators opinion, the finding is clinically significant and represents a condition that was not present at signing of informed consent, then the finding must be reported as an AE.

11.5. Reporting Adverse Events

Prompt notification of SAEs by the Investigator to Glenmark is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

Glenmark has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Glenmark will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC and Investigators.

All SAEs must be reported to the Sponsor immediately or within 24 hours of the Investigator or their staff becoming aware of them. Reporting should be performed by recording as much information as is available at the time on the SAE Form and sending it to the contact information provided below:

Fax: [redacted]

Email: [redacted]

When further information becomes available, the SAE Form should be updated with the new information and reported immediately via the same contact information. Follow-up reports must

be submitted to the Sponsor until the event resolves, the event stabilizes or the event returns to baseline if a baseline value is available.

Additional information will be requested by the Sponsor as necessary.

11.5.1. Pregnancy

The Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study (as applicable). In addition, the underage male subject should also be referred for appropriate evaluation. The Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 2 weeks of learning of the partner's pregnancy. The partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

Any pregnancy that occurs during study participation must be reported to the Sponsor, using a clinical trial pregnancy form, immediately or within 24 hours of the Investigator learning of its occurrence. The report should contain as much information as possible and should be sent to:

Fax: [redacted]

Email: [redacted]

When further information becomes available, the Pregnancy Report Form should be updated with all new information and reported immediately via the same contact information above. The Pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child, and this information must be sent to the Sponsor as above. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Additional information will be requested by the Sponsor as necessary.

Any SAE occurring in association with a pregnancy brought to the Investigator's attention after the subject has completed the study and considered by the Investigator as possibly related to the study drug, must be promptly reported to the Sponsor.

12. TIMING OF STUDY ASSESSMENTS

Study procedures and assessments are summarized across all study visits within the Schedule of Assessments (Table 2).

12.1. Screening Visit: Visit 1 (Day -7 to -10)

A Screening Visit (Visit 1) should be scheduled within 7 to 10 days before the Randomization Visit (Visit 2). Before performing any procedures or assessments, the nature of the study and the potential risks associated with the study must be explained to all subjects (parents/guardians/caregivers, as needed) and written informed consent (and assent) must be obtained. Once informed consent/assent (and Health Insurance Portability and Accountability Act authorization as applicable) has been obtained, the following procedures and evaluations will be performed:

1. Inclusion/exclusion criteria
2. Demographic data
3. Medical and treatment history
4. Concomitant medication evaluation
5. Physical examination
6. Vital signs
7. Height and weight
8. Focused ENT/eye examination[a]
9. Allergen testing (skin prick test for relevant allergen, if required)
10. Urine pregnancy test, if applicable
11. Subject assessment of AR symptoms and recording (rTNSS) at the clinical site (with assistance from parents/guardians/caregivers, as needed)
12. Review instructions and provide training on the proper use of the NS using the placebo bottle provided in the IP kit provided for the placebo run-in period (including parents/guardians/caregivers, as needed)
13. Priming, dispensation and administration of single-blind placebo NS at the clinic (with assistance from parents/guardians/caregivers, as needed)
14. Distribution of AR Assessment Diary
15. AE query, if applicable

[a] Subjects who have clinically significant (as judged by the Investigator) nasal ulceration, nasal mucosal erosion, and nasal septal perforation at the Screening Visit (Visit 1) should be referred to qualified ENT specialists (medically qualified specialists who are qualified to evaluate and record these conditions, as judged by the Investigator) for further evaluation. A record from the specialists for such subjects should be maintained including the photographic evidence (imaging of nasal mucosa) of the assessment to allow pre- and post-treatment comparisons for AEs (see details in Section 11.1.7). The Sponsor will collect the

de-identified information as part of the study data collection. Eligibility of such subjects for participation in the study will be at the Investigator's discretion based on the ability to meet the study protocol defined selection criteria. These subjects may need to be re-screened due to delay in scheduling an ENT visit to obtain the necessary evaluation, as applicable, upon consultation with the Sponsor's study team and approval.

Subjects, who fail screening on any single criterion at the Screening Visit (Visit 1) where there is the prospect of their subsequently becoming eligible, may be re-screened on one occasion only upon consulting the Sponsor study team or designee. If the Investigator or the Sponsor determines the failed criterion may impact the efficacy and/or safety assessments, then the subject may not be re-screened. However, subjects who have entered the single-blind, placebo run-in period and then fail for any reason are not eligible for re-screening to avoid any undue bias.

12.2. Randomization Visit: Visit 2 (Day 1)

1. Distribution of PRQLQ, review instructions with the subject and subject completion of PRQLQ[a]
2. Inclusion/exclusion criteria
3. Concomitant medication evaluation
4. Vital signs
5. Focused ENT/eye examination[b]
6. Urine pregnancy test, if applicable
7. Review instructions and provide training on the proper use of the NS (including parents/guardians/caregivers, as needed)
8. Distribution of AR symptom assessment diary
9. Review of AR symptom assessment diary
10. Physician assessment of nasal symptom severity at the clinical site
11. Review randomization criteria
12. Randomization/treatment assignment
13. Prime and dispensation of double-blind study medication
14. Administration of first dose of double-blind study medication (with assistance from parents/guardians/caregivers, as needed), under the supervision of the study personnel and remind subject not to take study drug before reporting to the clinic for the Treatment Visit (Visit 3).
15. AE query, if applicable
16. Collect study medication (placebo run-in), as applicable
17. Collect AR symptom assessment diary (placebo run-in period), as applicable
18. Subject compliance check (study procedures, diary, and study medication)

[a] Subjects returning for the Randomization Visit undergo the PRQLQ assessment (as applicable) before his/her confirmation for randomization in the study. If the subject fails to get randomized due to any reason, the data collected for the PRQLQ will not be analyzed. Subjects that fail to be randomized at any time during Visit 2 will be discharged from the study following collection of the PRQLQ (as applicable), placebo run-in study medication, and placebo run-in diary as well as discussion of AEs and concomitant medications and other safety related procedures, as needed, at the discretion of the Investigator. However, the remaining efficacy-related assessments outlined for this visit may not be needed for the subjects who fail to be randomized.

[b] If any clinically significant (as judged by the Investigator) nasal ulceration, nasal mucosal erosion, and nasal septal perforation are observed during this visit (newly observed or worsening of previously observed event), the subjects should be referred to qualified ENT specialist (or medically qualified specialists who are qualified to evaluate and record these conditions, as judged by the Investigator) for further evaluation. A record from the specialists for such subjects should be maintained including the photographic evidence (imaging of nasal mucosa) of the assessment to allow pre- and post-treatment comparisons for AEs (see details in Section 11.1.7). The Sponsor will collect the de-identified information as part of the study data collection. Eligibility of such subjects for participation in the study will be at the Investigator's discretion based on the ability to meet the study protocol defined selection criteria.

12.3. Treatment Visit: Visit 3 (Day 8±2)

1. Concomitant medication evaluation
2. Vital signs
3. Focused ENT/eye examination[a]
4. Review instructions and provide training on the proper use of the NS (including parents/guardians/caregivers, as needed)
5. Distribution of AR symptom assessment diary
6. Review of AR symptom assessment diary
7. Administration of double-blind study medication (with assistance from parents/guardians/caregivers, as needed), under the supervision of the study personnel and remind subjects (parents/guardians/caregivers, as needed) that the last dose of study drug should be the PM dose on the day before the Final Visit (Visit 4)
8. AE query, if applicable
9. Collect AR symptom assessment diary, as applicable
10. Subject compliance check (study procedures, diary, and study medication)

[a] Subjects who have clinically significant nasal ulceration, nasal mucosal erosion, and nasal septal perforation (newly observed or worsening of previously observed event - as judged by the Investigator) should be referred to qualified ENT specialists (or medically qualified specialists who are qualified to evaluate and record these conditions, as judged by the Investigator) for further evaluation. A record from the

specialists for such subjects should be maintained including the photographic evidence (imaging of nasal mucosa) of the assessment to allow pre- and post-treatment comparisons for AEs (see details in Section 11.1.7). The Sponsor will collect the de-identified information as part of the study data collection.

12.4. Final Visit/Early Discontinuation Visit: Visit 4 (Day 15+2)

1. Distribution of PRQLQ, review instructions with the subject, and completion of PRQLQ (as applicable
2. Concomitant medication evaluation
3. Physical examination
4. Vital signs
5. Height and weight measurements
6. Focused ENT/eye examination[a]
7. Urine pregnancy test (as applicable)
8. Review of AR symptom assessment diary
9. Physician assessment of nasal symptom severity at the clinical site
10. AE query, if applicable
11. Collect study medication
12. Collect AR symptom assessment diary
13. Subject compliance check (study procedures, diary, and study medication)

[a] Subjects who have clinically significant nasal ulceration, nasal mucosal erosion, and nasal septal perforation (newly observed or worsening of previously observed event - as judged by the Investigator) should be referred to qualified ENT specialists (or medically qualified specialist qualified to evaluate and record these conditions, as judged by the Investigator) for further evaluation. A record from the specialists for such subjects should be maintained including the photographic evidence (imaging of nasal mucosa) of the assessment to allow pre- and post-treatment comparisons for AEs (see details in Section 11.1.7). The Sponsor will collect the de-identified information as part of the study data collection.

12.5. Discontinuation Visit

If at any time point, subjects are deemed ineligible to continue in the study, the Final Visit/Discontinuation Visit (Visit 4) procedures will be conducted and recorded in the Early Withdrawal/Termination/Discontinuation pages of the CRF/eCRF. After the end of participation in the study, the subject will be treated, as needed, at the discretion of the Investigator. Every effort should be made to contact the subject for a follow-up if the subject has not returned to the clinic for scheduled visits (lost-to-follow up subject) to ensure the safety of the subject.

If the subject is withdrawn because of an AE, the AE will be followed until the medical condition returns to baseline or is considered stable or chronic. The Sponsor (or designee)

should be informed of all subjects withdrawn/discontinued for this reason. If there are multiple reasons for early withdrawal/discontinuation, the worst case scenario should be chosen.

12.6. Unscheduled Visit

An unscheduled visit (or telephone follow-up) may be performed at any time during the study at the subject's request or as deemed necessary by the Investigator. The date and reason for the unscheduled visit will be recorded on the CRF/eCRF as well as any other data obtained (eg, AEs, concomitant medications/treatments, and results from procedures or tests).

12.7. Follow-Up Visit

No Follow-up Visit is planned for this study.

13. STATISTICS

The statistical analysis will be coordinated by the responsible Sponsor biostatistician (or designee at the Contract Research Organization [CRO]). The Statistical Analysis Plan (SAP) will be written to provide details of the analyses, along with specifications for tables, listings, and figures to be produced. The SAP will be finalized before the database lock at the latest. If there are differences, the information in the SAP will supersede the information in the protocol. Any changes from the analyses planned in the SAP will be justified in the CSR.

All analyses will be performed by the Sponsor (or designee CRO) using STATISTICAL ANALYSIS SOFTWARE Version 9.3 or above.

In general, all data will be summarized with descriptive statistics (number of subjects, mean, and standard deviation [SD], minimum, median, and maximum) for continuous variables and frequency and percentage for categorical variables.

13.1. Sample Size

A sample size of 382 evaluable subjects, allocated 1:1, will provide 90% power to detect a between-group mean difference (GSP 301 NS vs placebo NS) of 1.0 in the absolute change from baseline in average AM and PM subject-reported 12-hour rTNSS over a 14-day treatment period (assuming a 2-sided alpha of 5%). A standard deviation of 3.0 in the change from baseline in 12-hour rTNSS over a 14-day treatment period has been assumed. Assuming a drop-out rate of 15%, a total of approximately 450 subjects are planned to be randomized (225 subjects in each treatment group). Depending on the actual drop-out rate, the Sponsor may decide to randomize higher or lower number of subjects in order to meet the required sample size of 382 evaluable subjects.

13.2. Analysis Sets

Detailed criteria for analysis sets will be documented in the SAP and the allocation of subjects to analysis sets will be determined prior to database hard-lock.

13.2.1. Full Analysis Set

The FAS will consist of all subjects who are randomized and receive at least 1 dose of IP and have at least 1 post-baseline primary efficacy assessment. This will be the primary analysis set for efficacy analyses.

13.2.1.1. Per Protocol Set

The Per Protocol Set (PPS) will consist of the subset of the FAS who do not meet criteria for PPS exclusion.

13.2.1.2. Safety Analysis Set

The Safety Analysis Set (SAS) will consist of all subjects who are randomized and receive at least one dose of IP. This will be the analysis set for safety analyses.

13.3. Endpoints

13.3.1. Primary Endpoint

Change from baseline in average AM and PM subject-reported 12-hour rTNSS over the 14-day treatment period.

13.3.2. Secondary Endpoints

- Change from baseline in average AM and PM subject-reported 12-hour instantaneous Total Nasal Symptom Score (iTNSS) over the 14-day treatment period.
- Change from baseline in the overall Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) score on Day 15 (Visit 4) between treatment groups.
- Change from baseline in average AM and PM subject-reported 12-hour reflective Total Ocular Symptom Score (rTOSS) over the 14-day treatment period.

13.3.3. Other Endpoints

Nasal symptoms:

- Change from baseline in AM subject-reported rTNSS over the 14-day treatment period.
- Change from baseline in AM subject-reported iTNSS over the 14-day treatment period.
- Change from baseline in PM subject-reported rTNSS over the 14-day treatment period.
- Change from baseline in PM subject-reported iTNSS over the 14-day treatment period.
- Change from baseline in subject-reported reflective individual nasal symptoms over the 14-day treatment period (AM, PM and average of AM and PM).

- Change from baseline in subject-reported instantaneous individual nasal symptoms over the 14-day treatment period (AM, PM and average of AM and PM).
- Change from baseline in average AM and PM subject-reported rTNSS and iTNSS for each day.
- Change from baseline in AM subject-reported rTNSS and iTNSS for each day.
- Change from baseline in PM subject-reported rTNSS and iTNSS for each day.

Ocular symptoms:

- Change from baseline in average AM and PM subject-reported instantaneous Total Ocular Symptom Score (iTOSS) over the 14-day treatment period.
- Change from baseline in AM subject-reported rTOSS over the 14-day treatment period.
- Change from baseline in AM subject-reported iTOSS over the 14-day treatment period.
- Change from baseline in PM subject-reported rTOSS over the 14-day treatment period.
- Change from baseline in PM subject-reported iTOSS over the 14-day treatment period.
- Change from baseline in subject-reported reflective individual ocular symptoms over the 14-day treatment period (AM, PM, and average AM and PM).
- Change from baseline in subject-reported instantaneous individual ocular symptoms over the 14-day treatment period (AM, PM, and average AM and PM).
- Change from baseline in average of the AM and PM subject-reported rTOSS and iTOSS for each day.
- Change from baseline in AM subject-reported rTOSS and iTOSS for each day.
- Change from baseline in PM subject-reported rTOSS and iTOSS for each day.

Non-nasal symptoms will be assessed in a similar manner to the ocular symptoms above (as described in the SAP).

Physician assessed Nasal Symptom Score (PNSS):

- Change from baseline in PNSS and physician assessed individual nasal symptoms at Day 15 (Visit 4).

Pediatric Rhinoconjuntivitis Quality of Life Questionnaire (PRQLQ):

- Change from baseline in individual domains of the PRQLQ at Day 15.

13.4. Safety Endpoints

- Adverse events and SAEs.
- Vital signs.

- Physical examinations.
- Focused ears, nose, and throat (ENT)/Eye examinations.

13.5. Subject Disposition

The subject accountability and disposition information will be summarized by study drug group. The number of subjects screened, treated with study medication during the placebo run-in period, randomized, treated with study medication following randomization, and the number of subjects in each analysis set will be tabulated. In addition, completion status and primary reason for withdrawal will be summarized by study drug group.

13.6. Demographic and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized by treatment group for the SAS and other analysis sets as required. Descriptive statistics will include the number of subjects and demographic and baseline characteristics such as age, sex, race, and ethnicity.

13.7. Efficacy Analyses

Efficacy analysis will be conducted on the FAS and PPS (except for PRQLQ that will be performed on the FAS). The interpretation of results from statistical tests will be based on the FAS. The PPS will be used to assess the robustness of the results from the statistical tests based on the FAS.

Efficacy within certain subgroups of clinical interest, (ie, age, sex, race, and ethnicity) will be examined. Further detail on the subgroups of interest will be specified in the SAP.

13.7.1. Analysis of the Primary Efficacy Endpoint

The change from baseline in average AM and PM subject-reported 12-hour rTNSS over a 14-day treatment period will be derived by calculating an average score for each subject, based on the post-dose AM and PM assessments over the 14-day treatment period.

The primary endpoint, change from baseline in average AM and PM subject-reported 12-hour rTNSS over a 14-day treatment period, will be evaluated using a repeated measures analysis of covariance (ANCOVA) model. The model will adjust for study drug, site, baseline 12-hour rTNSS (linear, continuous covariate - defined as the average of the last 8 consecutive AM and PM assessments during the last 4 days of the run-in period from the Day -4 PM assessment to the AM assessment on the day of randomization), study day as the within-subject effect. The interactions of site-by-treatment and baseline-by-treatment will be investigated separately and will only be included in final model if they are statistically significant at the 5% level. At least 6 out of 8 assessments (reading scores) should be available in order to calculate baseline score of 12 hour rTNSS (linear, continuous covariate. An unstructured covariance will be assumed. Least square means (LSMs) of the treatment differences and associated 95% CIs and p-values will be presented. Additional details or any changes will be provided in the SAP.

13.7.2. Analysis of Secondary Efficacy Endpoints

The secondary endpoint of iTNSS and rTOSS will be analyzed using a similar method as described for the primary endpoint. The secondary endpoint of change from baseline in PRQLQ

at Day 15 (Visit 4) will be analyzed for the FAS using an ANCOVA model adjusting for study drug group, site, and baseline PRQLQ (linear, continuous covariate).

Further detail on the analyses of all efficacy endpoints including tertiary endpoints will be detailed in the SAP.

13.7.3. Hierarchical Testing

Treatment comparisons will begin with the primary endpoint versus placebo. If the resulting two-sided p-value is less than 0.05, then the next comparison of the secondary endpoint will be made, in the order of clinical importance, as outlined below. This process continues until either all comparisons of interest are made, or until the point at which the resulting two-sided p-value for a comparison of interest is greater than 0.05.

In order to control the type I error for multiple endpoints, the testing of the secondary endpoints will be performed sequentially in the following order, at the end of the 14 days treatment period:

- Change from baseline in average AM and PM subject-reported 12-hour instantaneous Total Nasal Symptom Score (iTNSS) over the 14-day treatment period.
- Change from baseline in the overall Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) score on Day 15 (Visit 4) between treatment groups.
- Change from baseline in average AM and PM subject-reported 12-hour reflective Total Ocular Symptom Score (rTOSS) over the 14-day treatment period.

Once one of the tests as ordered above is not significant, the testing will no longer be performed for the remainder of the endpoints. No multiplicity adjustments will be made for the 'Other efficacy endpoints'.

13.8. Safety Analyses

All safety analyses will be performed on the SAS. Unless otherwise specified, 'baseline' will be defined as the last available assessment prior to the first dose of study drug following randomization.

13.8.1. Extent of Exposure

The number of subjects exposed to each study drug will be summarized. The number of days on treatment and the number of days on study (placebo run-in plus treatment periods) will be summarized by study drug. In addition, treatment compliance will be summarized by categories (75%, ≥75% to ≤100%, >100% to ≤125%, >125%) and study drug.

13.8.2. Adverse Events

Adverse events will be coded using the current Medical Dictionary for Regulatory Activities (version 19 or higher). The number and percentage of AEs, SAEs, AEs leading to discontinuation, and AEs related to the IP will be summarized by system organ class (SOC), preferred term (PT), and treatment group. The number and percentage of AEs by severity will also be summarized. All AEs will be displayed in listings. Any AE that occurs during the placebo run-in period will be summarized separately. A comparison of the incidence rate of AEs between study drug groups will be presented.

13.8.3. Adverse Events, Concomitant Medications, and Withdrawals

All AEs will be coded according to the current version of Medical Dictionary for Regulatory Activities, version 19 or higher. Adverse events occurring between the signing of informed consent and administration of the first dose (randomized treatment) of study medication will be regarded as pre-treatment AEs and included in the subject listings but not in the summary tables. Adverse events occurring after the first dose of study medication will be defined as TEAEs and will be listed and summarized by SOC and PT.

Summaries of the number of subjects with TEAEs and the number of TEAEs experienced will be presented by treatment. The number of subjects and the number of TEAEs will be presented using frequency counts and percentages, overall and by SOC and PT. Tables of the number and percentage of subjects and the number of TEAEs by intensity and by relationship to study medication will also be presented. Events will be assigned to the study drug administered prior to the start of the TEAE. Events that occurred during the study discontinuation visit and final follow-up will be assigned to the final treatment.

Details of SAEs and AEs leading to withdrawal of the subject from the study will also be presented by treatment group. Withdrawals from the study, and associated details, will be presented by treatment group. Any withdrawals will be listed and summarized by reason for withdrawal, treatment and by any other relevant categorical information.

Concomitant medications will be listed.

13.8.4. Vital Signs

Descriptive statistics will be used to summarize vital sign results and changes from baseline by treatment group and time. Values of potential clinical significance will be defined in the SAP. The number of subjects with values of potential clinical significance will be tabulated. All vital signs data will be displayed in listings.

13.8.5. Physical Examinations

Descriptive statistics will be used to summarize physical examination results and changes from baseline by treatment group and time. The number of subjects with findings of potential clinical significance will be tabulated. All physical examination data will be displayed in listings.

13.8.6. Focused Ears, Nose, and Throat (ENT)/Eye Examinations

Descriptive statistics will be used to summarize ENT/eye results and changes from baseline by treatment group and time. The number of subjects with findings of potential clinical significance will be tabulated. All ENT/eye data will be displayed in listings.

13.9. Interim Analysis

No interim analysis is planned for this study.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Before an investigational site can enter a subject into the study, a representative of the Sponsor (or designee; as applicable) may visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the Investigator.

During the study, a monitor from the Sponsor (or designee) or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the CRF/eCRF, and that IP accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the CRFs/eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (eg, clinic charts).
- Record and report any protocol deviations not previously sent to the Sponsor.
- Confirm AEs and SAEs have been properly documented on CRFs/eCRFs and confirm any SAEs have been forwarded to the Sponsor and those SAEs that met criteria for reporting have been forwarded to the IRB.
- Any other monitoring tasks, as appropriate

The monitor will be available between visits if the Investigator or other staff needs information or advice.

14.2. Audits and Inspections

Authorized representatives of the Sponsor (or designee), a regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The Investigator should contact the Sponsor (or designee) immediately if contacted by a regulatory agency about an inspection.

14.2.1. Inspection

An inspection is defined as the act of a regulatory authority of conducting an official review of documents, facilities, records and any other resources that are deemed by the authorities to be related to the clinical study and that may be located at the site of the study, or at the Sponsor's

and/or CRO facilities or any other establishments deemed appropriate by the regulatory authorities.

14.2.2. Audit

An audit is a systematic and independent review of study-related activities and documents to determine whether study-related activities were conducted and the data were accurately recorded and analyzed according to the protocol, standard operating procedures, GCP, and the appropriate requirements.

In conducting this study the Investigator accepts that the Sponsor, IRB/IEC or regulatory body may, at any time by appointment, conduct an audit of the study site.

14.3. Institutional Review Board/Independent Ethics Committee

The Investigator must obtain IRB/IEC approval for the clinical study. Initial IRB/IEC approval, and all materials approved by the IRB/IEC for this study including the subject consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

15. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, The Sponsor may conduct a quality assurance audit. Please see Section 14.2 for more details regarding the audit process.

16. ETHICS

16.1. Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit written approval to the Sponsor (or designee) before he or she can enroll any subject into the study.

The Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising material used to recruit subjects for the study, as well as any materials (eg subject diaries, subject questionnaires) to be given to subjects. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Investigator is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the IP. The Sponsor (or designee) will provide this information to the Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

In the case of early termination/temporary halt of the study, the Investigator or Sponsor should notify the IRB/IEC and Regulatory Authority in accordance with applicable regulatory

requirements, and a detailed written explanation of the reasons for the termination/halt should be given.

16.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP guidelines, applicable regulatory requirements and the Sponsor's policy on Bioethics.

16.3. Written Informed Consent

The Investigator will ensure that the subject (parents/guardians/caregivers, as needed) is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects (parents/guardians/caregivers, as needed) must also be notified that they are free to discontinue from the study at any time. The subject (parents/guardians/caregivers, as needed) should be given the opportunity to ask questions and allowed time to consider the information provided.

The Investigator is responsible for obtaining informed consent from each subject/legally acceptable representative (LAR) participating in the study. An ICF will contain all US (federal and state specific) requirements, all ICH-required elements, and Health Insurance Portability and Accountability Act information in a language that is understandable to the subject. The process of obtaining informed consent will be in compliance with all US federal regulations, ICH requirements, and local laws. All pertinent aspects of the study must be explained to the subject/LAR before he or she signs the ICF. The subject's signed and dated informed consent/assent must be obtained before conducting any study procedures.

Informed consent/assent must be obtained from the subject/LAR before any activity or treatment is undertaken which is not part of routine care. This includes, but is not limited to, the performance of diagnostic or therapeutic screening procedures and the administration of the first dose of the study medication. Each subject (parents/guardians/caregivers, as needed) must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject/LAR should understand the statement before signing and dating it and will be given a copy of the signed document.

Each subject/LAR must sign an approved ICF(s) before study participation. The form(s) must be signed and dated by the appropriate parties. The Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject.

The subject (parents/guardians/caregivers, as needed or the subject's LAR should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented. If required, informed consent should be obtained using an amended ICF(s) for the subject's continuation in the study.

16.4. Approval of the Protocol and Amendments

Subjects will not be admitted to the study before approval of the study protocol and other relevant study documents by the IRB/IEC and Regulatory Authority.

Any change or addition to this protocol requires a written protocol amendment that must be approved by the Sponsor, Principal Investigator and IRB/IEC before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study will require additional approval by the IRB/IEC and the Regulatory Authority.

These requirements for approval will in no way prevent any immediate action from being taken by the Principal Investigator in the interests of preserving the safety of the subjects included in the study. If an immediate change to the protocol is considered necessary by the Principal Investigator and is implemented for safety reasons the IRB/IEC will be informed within 7 working days. Changes affecting only administrative aspects of the study will not require formal protocol amendments or IRB/IEC approval but the IRB/IEC will be kept informed of such administrative changes.

Protocol amendments that affect only administrative aspects of the study may not require submission to Health or Regulatory Authority or the IRB/IEC, but the Health or Regulatory Authority and IRB/IEC should be kept informed of such changes as required by local regulations. In these cases, the Investigator or Sponsor (or designee), may be required to send a letter to the IRB/IEC and the Regulatory Authorities notifying them of such changes.

16.5. Protocol Deviation

The Investigator is responsible for the conduct of the study in accordance with the study protocol. It is the responsibility of the site/Investigator to use continuous vigilance to identify and report any deviations from the protocol. Any deviation from the protocol will be recorded as a protocol deviation. Protocol deviations are defined as 'major' if they have significant influence on efficacy – these are the criteria for subjects being excluded from PPS. Major protocol deviations will be defined in the SAP and by clinical review prior to unblinding.

17. DATA HANDLING AND RECORDKEEPING

17.1. Data Collection

As part of the responsibilities assumed by participating in the study, the Investigator agrees to maintain adequate and accurate case histories for the subjects treated under this protocol. Case histories include CRFs and supporting data including, but not limited to, signed and dated informed consent forms, progress notes, hospital charts, nurse's notes, diary cards, laboratory reports, ECG strips, etc.

Subject demographics will be collected, as available, for all subjects who provide written informed consent. For subjects who provide informed consent and were not assigned to treatment/randomized into the study, the reason the subject was not assigned to treatment/randomized, ie, did not meet one or more inclusion criteria, met one or more exclusion criteria, or other (eg, lost to follow-up, consent withdrawn), will also be collected.

17.2. Inspection of Records

The Sponsor (or designee) will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

17.3. Confidentiality and Intellectual Property

All information disclosed to the Investigator by the Sponsor or persons assigned by the Sponsor shall be treated by the Investigator as strictly confidential. The Investigator shall only use such information for the purpose of conducting the clinical study described in this protocol and agrees not to disclose such information to any third party except those of his/her colleagues and employees who are assisting in the conduct of the study and who are bound by the obligations of confidentiality.

Information concerning the IP, patent applications, processes, unpublished scientific data, the investigational brochure and other pertinent information is confidential and remains the property of the Sponsor. Details should be disclosed only to the persons involved in the approval or conduct of the study. The Investigator may use this information for the purpose of the study only. It is understood by the Investigator that the Sponsor will use the information obtained during the clinical study in connection with the development of the drug and therefore may disclose it as required to other clinical Investigators or to regulatory agencies. In order to allow for the use of the information derived from this clinical study, the Investigator understands that he/she has an obligation to provide the Sponsor with all data obtained during the study. The Institution and/or the Investigator undertake that they will not reverse-engineer, decompile or dissemble the information or make any variant out of the information.

All intellectual property arising out of, or in connection with, the conduct of the clinical study described in this protocol ("Derivative Intellectual Property") shall be promptly disclosed to the Sponsor. Any such Derivative Intellectual Property shall be the sole property of the Sponsor. The Institution and/or the Investigator, its affiliates and any person claiming through them shall do all acts and things as shall be necessary to vest all right, title and interest therein in the Sponsor. The Institution and/or the Investigator shall keep the said Derivative Intellectual Property confidential in accordance with this Agreement.

In the event of inconsistency between the above and the study contract, the terms of the study contract would prevail to the extent of such inconsistency.

17.4. Retention of Records

The Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for the Sponsor or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

17.5. Financing and Insurance

The Sponsor will provide clinical study insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

18. PUBLICATION POLICY

The Sponsor recognizes and supports the publication and dissemination of scientific information as a means of furthering knowledge. The general strategy regarding publication of the study (what, when, where, etc.) will be mutually agreed upon by the Investigator and Sponsor. However, in order to protect its commercial interests, the Sponsor reserves the right to manage the publication of all study results. The Investigator agrees that oral and written communication to third parties of any procedures or results from the study is subject to prior written consent of the Sponsor. Presentation material and/or manuscript(s) for publication will be reviewed by Sponsor prior to submission for publication. This review will be completed within 30 days of receiving presentation material and 60 days of receiving the manuscript from the Investigator. Alterations in the material will only be made in agreement between the Investigator and the Sponsor.

In the event of inconsistency between the above and the study contract, the terms of the study contract would prevail to the extent of such inconsistency.

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APPENDIX 1. SUBJECT INSTRUCTIONS FOR PROPER USE OF NASAL SPRAY BOTTLE USED IN THE STUDY

Subjects will administer their assigned study medication on their own (self-administration; with assistance from parents/legal guardians/caregivers, as needed) [redacted] using the subject instructions below. If needed, parents/guardians/caregivers can assist subjects with administering the study nasal spray medication (helping the subject perform certain tasks to ensure that the bottle is used properly) but they should be reminded that "you" as stated in the instructions below, refers to the subject and not the person assisting the subject.

Preparing the Nasal Spray Bottle for Use (prior to the first use ONLY)

As with all nasal spray medications, the bottle must be primed prior to the first use. The priming process must be performed by the study personnel but away from the study subjects to avoid any possible inhalation and contamination.

Priming should be done as follows:

- Nasal spray bottle should be shaken well before priming.
- Remove the protective (dust) cap from the bottle.
- Hold the nasal spray bottle firmly with your index and middle finger on either side of the applicator (on finger rests) while supporting the base of the bottle with your thumb.
- Release 6 sprays into the air, away from the eyes and face, by pressing down and releasing the pump 6 times.

Using Nasal Spray Bottle [redacted]

Shake the bottle well before each use [redacted]

1. Blow your nose to clear your nostrils.
2. Remove the dust cap from the nasal spray bottle.
3. Hold the bottle firmly with your index and middle finger on either side of the applicator (on finger rests) while supporting the base of the bottle with your thumb.
4. Insert the end of the nasal tip into one nostril, pointing it slightly toward the outside nostril wall away from the nasal septum (the wall between the two nostrils), while holding your other nostril closed with one finger.
5. Tilt your head forward slightly. Keep the bottle upright, and press down the finger rests quickly and firmly to activate the pump. Breathe in (inhale) gently through your nose as you spray. Then breathe out through your mouth. Try not to get any spray in your eyes or directly on your nasal septum (the wall between the two nostrils).
6. Repeat Steps 3 through 5 for the 2nd spray (in the other nostril).
7. Replace the protective (dust) cap on the nasal spray bottle.

8. Avoid blowing your nose for the next 15 minutes. Do not tip your head back or blow your nose right after using the Nasal Spray. This will help to keep the medicine from going into your throat.

Notes:

- You will be given study medication kits. Remember to take your study medication treatment [redacted]
- Prime the nasal spray bottle only 1 time (releasing 6 sprays) prior to the First Use. DO NOT prime the bottle every day. In some instances, study personnel may ask you to prime a new bottle at home prior to first use.
- If unused for more than 1 week, reprime by spraying 2 times following the priming instructions.
- This medicine is for use in the nose only. Avoid spraying in your eyes.
- Shake well before each use [redacted].
- After you finish administering the medication, wipe the tip with a clean dry tissue or cloth, replace cap, and store the nasal spray bottle in an upright position in the bottle carton.
- Store study medication between 15°C and 25°C (59°F and 77°F).
- If the nasal spray bottle appears to be blocked or not spraying properly, contact your study site/doctor immediately.
- Please contact your study nurse/coordinator or study doctor immediately if you have questions regarding the use of your medications.

APPENDIX 2. LIST OF CONTACT DETAILS

Additional information and contact details related to the study will be provided to each clinical site separately in relevant documents and procedural manuals.

SAE and Pregnancy Reporting:
Fax: [redacted]
Email: [redacted]

Medical Monitor (Chiltern):
[redacted]
Medical Officer
Chiltern, a Covance company
1016 West Ninth Avenue
King of Prussia, PA 19406
Mobile: [redacted]
Email: [redacted]

Medical Monitor (Glenmark):
[redacted]
Vice President, Clinical Sciences-Respiratory
461 From Road, Paramus, NJ 07652, USA
Office: [redacted]
Mobile: [redacted]
Email: [redacted]

APPENDIX 3. PEDIATRIC RHINOCONJUNTIVITIS QUALITY OF LIFE QUESTIONNAIRE (PRQLQ)

General Instructions:

1. A paper version of interviewer-administered PRQLQ will be provided to subjects.
2. Subjects should be placed in a quiet room to fill out the PRQLQ.
3. All parents/guardians/caregivers/friends/relatives should be asked to wait in a separate room.
4. Clinical coordinator/study site personnel (interviewer) will administer this questionnaire.
5. Additional instructions/guidelines will be provided to each site that needs to be followed for the proper administration/completion of PRQLQ.

Specific Instructions for the Clinical Coordinators/Site Personnel Administering the PRQLQ:

The PRQLQ administration must be the first procedure conducted at these study visits. After the completion of the PRQLQ, the completed questionnaire should be reviewed to ensure that all questions have been answered.

The clinical staff must:

1. Ask the questions exactly as worded in the questionnaire. Do not skip words or try to simplify or change the questions. Above all, never attempt to paraphrase or revise the questions.
2. Never "help" the subject choose the answer.
3. Be neutral in your response to the child's answer.
4. Ask subjects about impairments that they have experienced during the last week as a result of their rhinoconjunctivitis.
5. Parents/guardians/caregivers must not be present at the interview.
6. Be looking at the child during the interview.
7. Follow additional instructions/guidelines that will be provide to each site for proper administration/completion of the PRQLQ.

PAEDIATRIC RHINOCONJUNCTIVITIS QUALITY OF LIFE QUESTIONNAIRE (PRQLQ)

INTERVIEWER-ADMINISTERED

For further information:

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MARCH 2000

QUALITY OF LIFE QUESTIONNAIRE FOR 6-12 YEAR OLDS WITH ALLERGIC RHINOCONJUNCTIVITIS

THE PAEDIATRIC RHINOCONJUNCTIVITIS QUALITY OF LIFE QUESTIONNAIRE HAS BEEN TESTED AND VALIDATED USING THE WORDING AND FORMAT THAT FOLLOWS. IT IS IMPORTANT THAT INTERVIEWERS ADHERE TO THE EXACT WORDING WHEN ADDRESSING THE PATIENT (REGULAR TYPE) AND FOLLOW THE INSTRUCTIONS (ITALICS). DEVIATION FROM BOTH WORDING AND INSTRUCTIONS MAY IMPAIR THE RELIABILITY AND VALIDITY OF THE QUESTIONNAIRE.

PARENTS SHOULD NOT BE PRESENT DURING THE INTERVIEW. IT IS THE CHILD'S OWN EXPERIENCES THAT YOU WANT TO EVALUATE. SOME PARENTS MAY WANT TO INFLUENCE THIS EVALUATION AND SOME CHILDREN MAY WANT TO LOOK TO THE PARENT FOR GUIDANCE.

REASSURE THE CHILD THAT THERE ARE NO RIGHT OR WRONG ANSWERS. DO NOT INTERPRET QUESTIONS FOR CHILDREN. IF THEY HAVE DIFFICULTY, JUST ASK THEM TO DO THE BEST THEY CAN.

MAKE SURE THAT THE CHILD UNDERSTANDS THE TIME FRAME OF "DURING THE LAST WEEK". IF IN DOUBT, ASK THE PARENT TO IDENTIFY AN EVENT THAT OCCURRED A WEEK PREVIOUSLY (E.G., A FOOTBALL MATCH) AND THEN ASK THE CHILD TO THINK ABOUT HOW SHE/HE HAS BEEN SINCE THAT EVENT.

SHOW THE BLUE AND GREEN RESPONSE CARDS TO THE CHILD AND EXPLAIN THE OPTIONS. FOR CHILDREN WHO CAN READ, WE SUGGEST THAT YOU ASK THEM TO READ ALOUD EACH OF THE RESPONSE OPTIONS. FOR YOUNGER CHILDREN, READ THROUGH EACH OF THE RESPONSES WITH THEM. MAKE SURE THAT THE CHILD UNDERSTANDS THE CONCEPT OF THE GRADING FROM 0 (NOT BOTHERED/ NONE OF THE TIME) TO 6 (EXTREMELY BOTHERED/ ALL OF THE TIME).

I want you to tell me how much you have been bothered by your nose and eye allergies during the past week. I will tell you which card to use. Pick the number that best describes how much you were bothered by your allergies during the past week. *Make sure that when you ask about "allergies" the child understands that you mean their nose and eye symptoms.*

N 1. How much were you bothered by a **STUFFY, BLOCKED NOSE** during the past week? [BLUE CARD]

N 2. How much were you bothered by **SNEEZING** during the past week? [BLUE CARD]

N 3. How much were you bothered by a **RUNNY NOSE** during the past week? [BLUE CARD]

N 4. How much were you bothered by an **ITCHY NOSE** during the past week? [BLUE CARD]

E 5. How much were you bothered by **ITCHY EYES** during the past week? [BLUE CARD]

E 6. How much were you bothered by **WATERY EYES** during the past week? [BLUE CARD]

E 7. How much were you bothered by **SWOLLEN/PUFFY EYES** during the past week? [BLUE CARD]

E 8. How much were you bothered by **SORE EYES** during the past week? [BLUE CARD]

P 9. How much were you bothered by **HAVING TO RUB YOUR EYES AND NOSE** during the past week? [BLUE CARD]

P 10. How much were you bothered by **HAVING TO BLOW YOUR NOSE** during the past week? [BLUE CARD]

P 11. How much were you bothered by **HAVING TO CARRY KLEENEX** during the past week? [BLUE CARD]

P 12. How much were you bothered by **HAVING TO TAKE MEDICATIONS FOR YOUR ALLERGIES** during the past week? [BLUE CARD]

O 13. How much were you bothered by **THIRST** during the past week? [BLUE CARD]

O 14. How much were you bothered by a **SCRATCHY/ITCHY THROAT** during the past week? [BLUE CARD]

O 15. How much were you bothered by having a **HEADACHE** during the past week? [BLUE CARD]

A 16. How much were you bothered by your allergies **PLAYING OUTDOORS** during the past week? [BLUE CARD]

Change to the GREEN card

O 17. How often did your allergies make you feel **TIRED** during the past week? [GREEN CARD]

O 18. How often did your allergies make you feel **NOT WELL ALL OVER** during the past week? [GREEN CARD]

O 19. How often did your allergies make you feel **IRRITABLE (cranky/grouchy*)** during the past week? [GREEN CARD]
(*use only if child does not understand the word "irritable")

P 20. How often did your allergies make you feel **EMBARRASSED** during the past week? [GREEN CARD]

A 21. How often did your allergies make it **HARD TO GET TO SLEEP** during the past week? [GREEN CARD]

A 22. How often did your allergies **WAKE YOU UP DURING THE NIGHT** during the past week? [GREEN CARD]

A 23. How often did your allergies **MAKE IT HARD TO PAY ATTENTION** during the past week? [GREEN CARD]

DOMAIN CODE:		
N	=	Nose Symptoms
E	=	Eye Symptoms
P	=	Practical Problems
O	=	Other Symptoms
A	=	Activity Limitations

3

RESPONSE SHEET

NAME: _____ NUMBER: _____

DATES OF COMPLETION:

1st: _____ 2nd: _____

3rd: _____ 4th: _____

ITEM	RESPONSES			
	1st	2nd	3rd	4th
1. Stuffy/ blocked nose	___	___	___	___
2. Sneezing	___	___	___	___
3. Runny nose	___	___	___	___
4. Itchy nose	___	___	___	___
5. Itchy eyes	___	___	___	___
6. Watery eyes	___	___	___	___
7. Swollen/ puffy eyes	___	___	___	___
8. Sore eyes	___	___	___	___
9. Rub your eyes and nose	___	___	___	___
10. Blow your nose	___	___	___	___
11. Carry Kleenex	___	___	___	___
12. Take medication	___	___	___	___
13. Thirsty	___	___	___	___
14. Scratchy and itchy throat	___	___	___	___
15. Headache	___	___	___	___
16. Playing outdoors	___	___	___	___
17. Tired	___	___	___	___

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18.	Not well all over	____	____	____	____
19.	Irritable	____	____	____	____
20.	Embarrassed	____	____	____	____
21.	Hard to get to sleep	____	____	____	____
22.	Wake up during the night	____	____	____	____
23.	Pay attention	____	____	____	____

RESPONSE OPTIONS

GREEN CARD

6. ALL OF THE TIME
5. MOST OF THE TIME
4. QUITE OFTEN
3. SOME OF THE TIME
2. ONCE IN A WHILE
1. HARDLY ANY OF THE TIME
0. NONE OF THE TIME

BLUE CARD

6. EXTREMELY BOTHERED
5. VERY BOTHERED
4. QUITE BOTHERED
3. SOMEWHAT BOTHERED
2. BOTHERED A BIT
1. HARDLY BOTHERED AT ALL
0. NOT BOTHERED

APPENDIX 4. SUMMARY OF CHANGES IN CURRENT PROTOCOL AMENDMENT

Study Number: GSP 301-305

PROTOCOL AMENDMENT 2.0

SUMMARY OF CHANGES

A Double-Blind, Randomized, Parallel-Group Study to Evaluate the Efficacy, Safety and Tolerability of Fixed Dose Combination GSP 301 Nasal Spray Compared With Placebo Nasal Spray in Pediatric Subjects (Aged 6 to Under 12 Years) With Seasonal Allergic Rhinitis (SAR)

PROTOCOL HISTORY

PROTOCOL VERSION 1.0, 08-Jan-2018

PROTOCOL VERSION 2.0, 05-Apr-2018

PROTOCOL VERSION 3.0, 18-Jul-2018

Description of Changes in Protocol Version 3.0 (Amendment 2.0) dated 18-Jul-2018

Minor editorial changes for accuracy, clarity, formatting and consistency have been made throughout the document and are not included in the description(s) below.

Key: **Bold**: Newly added text

~~Strikethrough text~~: Deleted text from the previous version of the protocol.

A. Details of Substantial Changes to the Protocol, from Protocol Version 2.0 (Amendment 1) to Protocol Version 3.0 (Amendment 2)

From Protocol Version 2.0 (Amendment 1.0) 05-Apr-2018	To Protocol Version 3.0 (Amendment 2.0) 18-Jul-2018	Rationale for Amendment
1. Protocol Synopsis, Study Population		
Used to read: Male and non-pregnant female subjects aged ≥6 to <12 years with documented clinical history of SAR (for at least 2 years preceding the Screening Visit) with exacerbations (clinical evidence of active symptoms) during the study season for the relevant seasonal allergen (eg, tree/grass pollen).	Now reads: Male and non-pregnant female subjects aged ≥6 to <12 years with documented clinical history of SAR (for at least 2 years preceding the Screening Visit) with exacerbations (clinical evidence of active symptoms) during the ~~study season~~ **spring or fall allergy seasons** for the relevant seasonal allergen (eg, tree/grass pollen **or ragweed pollen**).	Clarified that the study season may be either the spring or fall allergy season. Clarified that seasonal allergen would include ragweed pollen.
2. Protocol Synopsis, Inclusion Criteria 3 and 4; Section 7.1, Subject Inclusion Criteria, Criteria 3 and 4.		
Used to be: 3. Documented clinical history of SAR (for at least 2 years preceding the Screening Visit [Visit 1]) with exacerbations (clinical evidence of active symptoms) during the study season for the relevant seasonal allergen (eg, tree/grass pollen). SAR must have been of sufficient severity to have required treatment (either continuous or intermittent) in the past, and in the Investigator's judgment, is expected to require treatment throughout the study period. 4. Demonstrated sensitivity to at least 1 seasonal allergen (eg, tree/grass pollen) known to induce SAR through a documented positive skin prick test (wheal diameter at least 5 mm greater than the negative control) to a relevant seasonal allergen. Documentation of a positive result within 12 months	Now reads: 3. Documented clinical history of SAR (for at least 2 years preceding the Screening Visit [Visit 1]) with exacerbations (clinical evidence of active symptoms) during the ~~study season~~ **spring or fall allergy seasons** for the relevant seasonal allergen (eg, tree/grass pollen **or ragweed pollen**). SAR must have been of sufficient severity to have required treatment (either continuous or intermittent) in the past, and in the Investigator's judgment, is expected to require treatment throughout the study period. 4. Demonstrated sensitivity to at least 1 seasonal allergen (eg, tree/grass pollen **or ragweed pollen**) known to induce SAR through a documented positive skin prick test (wheal diameter at least 5 mm greater than the negative control) to a relevant seasonal allergen. Documentation of a positive result within 12 months prior to the	Clarified that the study season may be either the spring or fall allergy season. Clarified that seasonal allergen would include ragweed pollen.

From Protocol Version 2.0 (Amendment 1.0) 05-Apr-2018	To Protocol Version 3.0 (Amendment 2.0) 18-Jul-2018	Rationale for Amendment
prior to the Screening Visit (Visit 1) is acceptable. The subject's positive allergen must be consistent with the medical history of SAR. Additionally, the subject is expected to be adequately exposed to the SAR allergen that he/she has tested positive for the entire duration of the study.	Screening Visit (Visit 1) is acceptable. The subject's positive allergen must be consistent with the medical history of SAR. Additionally, the subject is expected to be adequately exposed to the SAR allergen that he/she has tested positive for the entire duration of the study.	
3. Protocol Synopsis, Determination of Sample Size; Section 13.1, Sample Size.		
Used to read: A sample size of 382 evaluable subjects, allocated 1:1, will provide 90% power to detect a between-group mean difference (GSP 301 NS vs placebo NS) of 1.0 in the absolute change from baseline in average AM and PM subject-reported 12-hour rTNSS over a 14-day treatment period (assuming a 2-sided alpha of 5%). A standard deviation of 3.0 in the change from baseline in 12-hour rTNSS over a 14-day treatment period has been assumed. Assuming a drop-out rate of 15%, a total of approximately 450 subjects will be randomized (225 subjects in each treatment group).	Used to read: A sample size of 382 evaluable subjects, allocated 1:1, will provide 90% power to detect a between-group mean difference (GSP 301 NS vs placebo NS) of 1.0 in the absolute change from baseline in average AM and PM subject-reported 12-hour rTNSS over a 14-day treatment period (assuming a 2-sided alpha of 5%). A standard deviation of 3.0 in the change from baseline in 12-hour rTNSS over a 14-day treatment period has been assumed. Assuming a drop-out rate of 15%, a total of approximately 450 subjects **are planned to** ~~will~~ be randomized (225 subjects in each treatment group). **Depending on the actual drop-out rate, the Sponsor may decide to randomize higher or lower number of subjects in order to meet the required sample size of 382 evaluable subjects.**	Clarified that the higher or lower number of subjects may be randomized depending on the actual drop-out rate.
4. Section 6.1, Overall Study Design		
Used to read: This is phase 3, double-blind, randomized, parallel-group, placebo-controlled study conducted in multiple centers in the US. All study sites will enroll subjects during the spring allergy season. . . . Pollen counts will be obtained each weekday, and when possible, each weekend day at each investigational site, either by study staff or by a community counting station located within	Now reads: This is phase 3, double-blind, randomized, parallel-group, placebo-controlled study conducted in multiple centers in the US. All study sites will enroll subjects during the spring **or fall** allergy season**, as applicable**. . . . Pollen counts will be obtained each weekday, and when possible, each weekend day at each investigational site, either by study staff or by a community counting station located within	Clarified that the study season may be either the spring or fall allergy season.

From Protocol Version 2.0 (Amendment 1.0) 05-Apr-2018	To Protocol Version 3.0 (Amendment 2.0) 18-Jul-2018	Rationale for Amendment
approximately 30 miles of the study site. Three (3) consecutive days of moderate pollen counts will be accepted as the start to that pollen's given allergy season. The definition of 'moderate' varies depending on the allergen. Guidelines for identifying a moderate range can be found at http://www.aaaai.org/global/nab-pollen-counts/reading-the-charts.aspx or local guidelines can be used. However, the first subject should be screened only after meeting the moderate pollen count criteria and upon consultation with the Sponsor's study team and approval. Pollen counts will be entered as part of the data entry in the case report forms/electronic case report forms (CRFs/eCRFs) or other methods as provided by the Sponsor or designee. . . .	approximately 30 miles of the study site. Three (3) consecutive days of moderate pollen counts will be accepted as the start to that pollen's given allergy season. The definition of 'moderate' varies depending on the allergen. Guidelines for identifying a moderate range can be found at http://www.aaaai.org/global/nab-pollen-counts/reading-the-charts.aspx or local guidelines can be used. However, the first subject should be screened only after meeting the moderate pollen count criteria **for that relevant pollen season** and upon consultation with the Sponsor's study team and approval. Pollen counts will be entered as part of the data entry in the case report forms/electronic case report forms (CRFs/eCRFs) or other methods as provided by the Sponsor or designee. . . .	

B. Details of Non-Substantial Changes to the Protocol, from Protocol Version 2.0 (Amendment 1) to Protocol Version 3.0 (Amendment 2)

From Protocol Version 2.0 (Amendment 1.0) 05-Apr-2018	To Protocol Version 3.0 (Amendment 2.0) 18-Jul-2018	Rationale for Amendment
1. Appendix 2, List of Contact Details		
Used to read: Medical Monitor (Glenmark): [redacted] Vice President, Clinical Sciences-Respiratory 750 Corporate Drive, Mahwah, NJ 07430, USA Office: [redacted] Mobile: [redacted] Email: [redacted]	Now reads: Medical Monitor (Glenmark): [redacted] Vice President, Clinical Sciences-Respiratory ~~750 Corporate Drive, Mahwah, NJ 07430, USA~~ **461 From Road, Paramus, NJ 07652, USA** Office: [redacted] Mobile: [redacted] Email: [redacted]	Updated office address of Medical Monitor

From Protocol Version 2.0 (Amendment 1.0) 05-Apr-2018	To Protocol Version 3.0 (Amendment 2.0) 18-Jul-2018	Rationale for Amendment
2. Appendix 4, Summary of Changes in Current Protocol Amendment, title of appendix and contents		
Used to read: Appendix 4, Summary of Changes in Protocol Amendments (Contents reflecting a previous amendment [Protocol Version 2.0, Amendment 1] summary of changes.)	Now reads: Appendix 4, Summary of Changes in **Current** Protocol Amendments (Deleted old contents that reflected a previous amendment [Protocol Version 2.0, Amendment 1] summary of changes.) (Added new appendix contents reflecting the current amendment [Protocol Version 3.0, Amendment 2] summary of changes.)	Updated Appendix 4 to show summary of changes in current amendment.