CLINICAL STUDY PROTOCOL

Protocol Title	A Double-Blind, Randomized, Parallel-Group Study to Evaluate Long-Term Safety, Tolerability, and Efficacy of a Fixed Dose Combination GSP 301 Nasal Spray Compared with Two Placebo Nasal Spray Formulations in Subjects (Aged 12 Years and Older) with Perennial Allergic Rhinitis (PAR)
Protocol Number **Study Number**	GPL/CT/2014/018/III GSP 301-303
Name of Investigational Product/Code	Fixed Dose Combination of Olopatadine Hydrochloride and Mometasone Furoate (GSP 301)
Phase of Development	Phase 3
Sponsor	Glenmark Specialty S.A. Avenue Léopold-Robert 37 2300 La Chaux-de-Fonds Switzerland
Protocol Version	Version 2.0 Amendment 1.0
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PROTOCOL HISTORY	
Original protocol	Version 1.0 25 Jan 2016

Statement of Confidentiality

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1 ABBREVIATIONS AND SPECIALIST TERMS

Abbreviation	Definition or Explanation
AE	Adverse event
AM	Morning
ANCOVA	Analysis of covariance
AR	Allergic rhinitis
β-HCG	beta human chorionic gonadotropin
BID	Twice daily
^{o}C	Degrees Celsius
CFR	Code of Federal Regulations (of the United States)
CI	Confidence interval
CRF	Case report form
CRO	Contract research organization
CSR	Clinical study report
CYP3A4	Cytochrome P450 system enzyme 3A4
DV	Discontinuation visit
ECG	Electrocardiogram
eCRF	Electronic case report form
ENT	Ears, nose, and throat
EOP2	End-of-Phase 2
^{o}F	Degrees Fahrenheit
FAS	Full Analysis Set
FcεRI	IgE receptor
FDA	Food and Drug Administration (of the United States)
FDC	Fixed dose combination
FV	Final visit
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GRAS	Generally regarded as safe
GSP 301 NS	Fixed dose combination of olopatadine hydrochloride and mometasone furoate nasal spray
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgE	Immunoglobulin E
IL	Interleukin
IND	Investigational New Drug
IP	Investigational product
IRB	Institutional Review Board
iTNSS	instantaneous Total Nasal Symptom Score
IUD	Intrauterine device
LAR	Legally acceptable representative
LASIK	Laser-assisted in situ keratomileusis
LSM	Least squares mean
µg	microgram

MedDRA	Medical Dictionary for Regulatory Activities
NS	Nasal spray
OTC	Over-the-counter
PAR	Perennial allergic rhinitis
PM	Evening
PNSS	Physician assessed Nasal Symptom Score
PPS	Per protocol set
PT	Preferred term
QD	Once daily
QOL	Quality of life
RAST	Radioallergosorbent test
RCAT	Rhinitis Control Assessment Test
RQLQ(S)	Rhinoconjunctivitis Quality of Life Questionnaire - Standardized Activities
rTNSS	reflective Total Nasal Symptom Score
RV	Randomization visit
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Seasonal allergic rhinitis
SAS	Safety analysis set
SD	Standard deviation
SOC	System organ class
SOP	Standard operating procedure
SV	Screening visit
TEAE	Treatment-emergent adverse event
TNSS	Total Nasal Symptom Score
TV	Treatment visit
US	United States
USPI	United States Prescribing Information

2 PROTOCOL SYNOPSIS

Name of Sponsor/Company: Glenmark Specialty S.A.

Protocol Title: A Double-Blind, Randomized, Parallel-Group Study to Evaluate Long-Term Safety, Tolerability, and Efficacy of a Fixed Dose Combination GSP 301 Nasal Spray Compared with Two Placebo Nasal Spray Formulations in Subjects (Aged 12 Years and Older) with Perennial Allergic Rhinitis (PAR)

Protocol Number: GPL/CT/2014/018/III
Study Number: GSP 301-303

Name of Investigational Product(s)/Code(s)

- GSP 301 nasal spray (GSP 301 NS): olopatadine hydrochloride 665 µg and mometasone furoate 25 µg nasal spray (NS)
- GSP 301 placebo NS pH [redacted]
- GSP 301 placebo NS pH[redacted]

Name of Active Ingredient: Olopatadine hydrochloride and mometasone furoate

Phase of Development: Phase 3

Study Rationale

The ideal therapeutic agent for managing the symptoms of allergic rhinitis (AR) is one that effectively addresses the pathophysiology of both the early-phase reaction and the late-phase reaction of the condition.[20] Published studies have indicated that taking both intranasal antihistamine and corticosteroid are more beneficial than either medication alone in the treatment of seasonal allergic rhinitis (SAR).[21]

Olopatadine hydrochloride has been shown to be clinically superior to other anti-allergy molecules because of its strong antihistamine activity and unique ocular mast cell stabilizing properties.[1] Olopatadine hydrochloride NS has been approved in the United States (US) as Patanase® NS for the relief of the symptoms of SAR in adults (in 2008, as 2 sprays per nostril twice daily [BID]; total daily dose of 5320 µg) and in children 6 years of age or older (in 2009, as 1 spray per nostril BID). The efficacy and safety data from adult, adolescent, and pediatric subjects in clinical studies of Patanase® NS are provided in the US Prescribing Information (USPI).[9]

Mometasone furoate NS (Nasonex® NS, 50 µg/spray) has been approved in the US for the treatment of nasal symptoms of AR in patients aged 12 years and older as 2 sprays in each nostril once daily (QD) (200 µg total daily dose) and as 1 spray per nostril QD (100 µg total daily dose) for children aged 2 to 11 years. Other indications include treatment of nasal congestion associated with SAR in patients aged 2 years or older; prophylaxis of SAR in patients aged 12 years or older, and treatment of nasal polyps in adults. The efficacy and safety data from adult, adolescent, and pediatric subjects in clinical studies of Nasonex® NS are provided in the USPI.[10]

[redacted]Currently, only 1 combination product containing an intranasal corticosteroid and intranasal antihistamine is available for SAR treatment (Dymista® USPI),[15] but no such option is available for patients suffering from PAR in the US. Based on the results from a Phase 2 study conducted with GSP 301 (Study GSP 301-201), [redacted] (olopatadine hydrochloride 665 µg and mometasone furoate 25 µg) was found to be op ma y safe and effective for the treatment of SAR in adult and adolescents and will be further evaluated in the Phase 3 studies.

The primary objective of the present study is to evaluate the long-term safety and tolerability of GSP 301 NS administered as [redacted] compared with 2 different formulations of GSP 301 placebo NS formulations that differ in pH. The secondary objective is to evaluate the long-term efficacy of GSP 301 NS compared with GSP 301 placebo NS pH[redacted]

For this study, the subject population will be adult and adolescent subjects (aged ≥12 years) with PAR. The subjects will be asked to take their daily double-blind, study medication for a period of 52 weeks following a 7 to 10 day, single-blind, placebo run-in period.

Study Objectives

Primary Objective:

- To compare the long-term safety and tolerability of GSP 301 NS with 2 GSP 301 placebo NS formulations over 52 weeks of study treatment.

Secondary Objective:

- To evaluate the long-term efficacy of GSP 301 NS compared with GSP 301 placebo NS [redacted] in subjects with PAR.

Planned Number of Subjects: Approximately 600 randomized subjects in a ratio of 4:1:1 (400 subjects in the GSP 301 NS group and 100 subjects in each of the 2 placebo groups) are planned for this study.

Planned Duration of Subject Participation: Subject participation may extend up to 55 weeks with up to 7 to 10 days of a screening/run-in period and a 52-week treatment period, with allowable window periods for the study visits.

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

1. Males and non-pregnant females aged ≥12 years.
2. Signed informed consent/assent form (subject and/or parent/caregiver/legal guardian) that meets all criteria of the current US Food and Drug Administration (FDA)/local regulations.
3. Documented clinical history of PAR (for at least 2 years preceding the Screening Visit [Visit 1]) with exacerbations (clinical evidence of active symptoms) and exhibiting a documented positive skin prick test (wheal diameter at least 3 mm greater than negative diluent control wheal) to at least 1 allergen known to induce PAR. Documentation of a positive result within 12 months prior to the Screening Visit (Visit 1) is acceptable. Additionally, the subject is expected to be exposed to the PAR allergen that he/she tested positive for via the skin prick test for the entire duration of the study.
4. 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.
5. Subjects must be able to demonstrate the correct NS application technique at the Screening Visit (Visit 1).
6. Subjects must be willing and able to comply with all aspects of the protocol.

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

1. Have a positive pregnancy test or established pregnancy, breast-feeding, or planning a pregnancy during the study.
2. Female subjects of child-bearing potential (as judged by the Investigator) who do not agree to remain abstinent or use medically acceptable methods of contraception (e.g., implants, injectables, combined oral contraceptives, intrauterine devices [IUDs], double-barrier protection) during the study. Male participants who do not agree to use a condom with spermicide during intercourse (if not surgically sterilized) during the study.
3. History of significant atopic dermatitis or rhinitis medicamentosa (within 60 days prior to the Screening Visit [Visit 1]).
4. Treatment with any known potent CYP3A4 inducers (carbamazepine, dexamethasone, phenytoin, rifabutin, rifampin, pioglitazone, etc.) or potent inhibitors (azole antifungals, macrolide antibiotics, etc.) within 30 days prior to or during the study.
5. Non-vaccinated exposure to or active infection with chickenpox or measles within 21 days preceding the Screening Visit (Visit 1).
6. Known hypersensitivity to any corticosteroids or antihistamines or to the study medication or its excipients.
7. History of anaphylaxis and/or other severe local reaction(s) to skin testing.

8. History of alcohol or drug dependence within 2 years preceding the Screening Visit (Visit 1).

9. History of a positive test for human immunodeficiency virus (HIV), Hepatitis B, or Hepatitis C infection.

10. Evidence of acute or significant chronic sinusitis or chronic purulent postnasal drip.

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

12. Any major surgery (as assessed by the Investigator) within 4 weeks preceding the Screening Visit (Visit 1).

13. Requirement for the chronic use of tricyclic anti-depressants.

14. Dependence (in the opinion of the Investigator) on nasal, oral, or ocular decongestants, nasal topical antihistamines, or nasal steroids.

15. Active pulmonary disorder or infection (including but not limited to bronchitis, pneumonia, or influenza), or upper respiratory tract or sinus infection within the 14 days prior to the Screening Visit (Visit 1) or the development of respiratory infections during the run-in period. Subjects with mild asthma are allowable on the condition that treatment is limited to inhaled short-acting beta-agonists only (up to 8 puffs per day).

16. Use of antibiotic therapy for acute conditions within 14 days prior to the 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.

17. Posterior subcapsular cataracts or glaucoma, or any other ocular disturbances, or other listed related conditions including:
    - History of increased intraocular pressure
    - History of retinal detachment or surgery
    - History of incisional eye surgery (other than cataract extraction or laser-assisted in situ keratomileusis [LASIK])
    - History of penetrating ocular trauma or severe blunt ocular trauma
    - Evidence of uveitis, iritis, or other inflammatory eye disease during screening
    - Presence of ocular herpes simplex

18. Known history of hypothalamic-pituitary-adrenal axis impairment.

19. Existence of any significant surgical or medical condition, or clinically significant physical finding (e.g. 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 Sponsor's medical monitor, 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 complete or reliably complete the AR Assessment Diary.

20. 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.

21. Initiation of immunotherapy injections or 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) within 60 days preceding the Screening Visit (Visit 1). A 180-day washout period is required following the last dose of sublingual immunotherapy (investigational or other) prior to the Screening Visit (Visit 1).

22. 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 during the clinical study duration.

23. Study participation by clinical investigational site employees and/or their immediate relatives.

24. Study participation by more than 1 subject from the same household at the same time. However, after completion/discontinuation by 1 subject in the household, another subject from the same household may be screened.

25. Known to have failed to show symptom improvement with any approved/marketed monotherapy component of GSP 301 NS (i.e., Nasonex® NS or Patanase® NS or both) as judged by the Investigator.

26. Previous participation in a GSP 301 NS study as a randomized subject.

Randomization Criteria:

1. Continued general good health meeting the Screening inclusion criteria.
2. Has not experienced an adverse event (AE) that would result in not meeting the Screening inclusion criteria.
3. Minimum morning (AM) subject-reported reflective Total Nasal Symptom Score (rTNSS) of an average of 5 (out of a possible 12) during the last 4 days of the run-in period (last 4 consecutive AM assessments from the Day -3 AM assessment to the AM assessment on the day of randomization).
4. Has an AM subject-reported reflective nasal congestion score ≥2 during the last 4 days of the run-in period (last 4 consecutive AM assessments from the Day -3 AM assessment to the AM assessment on the day of randomization).
5. Adequate AR Assessment Diary compliance – inadequate compliance is defined as missing 1 or more of the entries on 2 or more assessment sessions (AM) during the last 4 days of the run-in period (during the last 4 consecutive AM assessments from the Day -3 AM assessment to the AM assessment on the day of randomization).
6. Adequate study medication compliance – each subject must have taken his/her single-blind medication for at least 80% of the entire run-in period as reported in the AR Assessment Diary.
7. Has not suffered from the common cold, upper respiratory infections, otitis media, lower respiratory infections, or acute sinusitis within the 14 days prior to the Randomization Visit (Visit 2).
8. Has not used any of the prohibited concomitant medications during the run-in period.

Study-Specific Discontinuation/Withdrawal Criteria

A subject may voluntarily discontinue study participation at any time after giving informed consent and before the completion of the last visit of the study. 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 by the subject to continue in the study.
2. Development of a serious or intolerable AE that necessitates discontinuation at the discretion of the Investigator

(AE section of the case report form/electronic case report form [CRF/eCRF] must be completed; includes serious adverse event [SAE], 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.

Lifestyle and/or Dietary Restrictions: Not applicable.

Investigational Products, Dose, and Mode of Administration

Name of Investigational Product: Fixed dose combination (FDC) of olopatadine hydrochloride 665 µg and mometasone furoate 25 µg NS (GSP 301 NS)
License Name: GSP 301-2 NS
Dosage Form: NS
Dosage: [redacted]
Dosage Frequency: [redacted]
Mode of Administration: Intranasal

Reference Product 1: GSP 301 Placebo NS [redacted]
License Name: GSP 301 Placebo NS [redacted]
Dosage Form: NS
Dosage: [redacted]
Dosage Frequency: [redacted]
Mode of Administration: Intranasal

Reference Product 2: GSP 301 Placebo NS [redacted]
License Name: GSP 301 Placebo NS [redacted]
Dosage Form: NS
Dosage: [redacted]
Dosage Frequency: [redacted]
Mode of Administration: Intranasal

Duration of Treatment: 52 weeks

Prior and Concomitant Drug/Therapy
Exclusion of Medication Prior to the Screening Visit (Visit 1):

1.	Vasoconstrictors (e.g., epinephrine, sumatriptan)	3 days
2.	Major tranquilizers (e.g., antipsychotics such as chlorpromazine, haloperidol, risperadol, clonazepam)	3 days
3.	Short-acting antihistamines (oral, ocular, or intranasal antihistaminic – e.g., azelastine)	7 days
4.	Over-the-counter (OTC) cough and cold preparations or sleep aids containing antihistamines	7 days
5.	Topical/oral/nasal decongestants (e.g., oxymetazoline, pseudoephedrine, tetrahydrozoline)	7 days
6.	OTC food supplement/diet to reduce leukotrienes (Airozin™)	7 days
7.	Leukotriene antagonists or arachidonate 5-lipoxygenase inhibitors	7 days
8.	Inhaled/oral/intranasal anticholinergics	7 days
9.	Long-acting antihistamines (e.g., cetirizine, fexofenadine)	10 days

10.	Cromolyn (all forms), nedocromil, or lodoxamide (intranasal, ocular, or oral)	14 days
11.	Systemic antibiotic (see excluded concomitant medications)	14 days
12.	Ocular mast cell stabilizers	14 days
13.	Monoamine oxidase inhibitors	14 days
14.	Tricyclic antidepressants	14 days
15.	All intranasal/topical/ocular corticosteroids (except study medication)	30 days
16.	Inhaled corticosteroids	30 days
17.	Any other investigational non-biological drug	30 days
18.	Treatment with any known potent CYP3A4 inducers (carbamazepine, dexamethasone, phenytoin, rifabutin, rifampin, pioglitazone, etc.)	30 days
19.	Treatment with any known potent CYP3A4 inhibitors (azole antifungals, macrolide antibiotics, etc.)	30 days
20.	Systemic corticosteroids (intermittent or chronic including intra-articular)	60 days
21.	Immunotherapy injections and immunosuppressive/immune-modulator medications (except topical pimecrolimus cream or tacrolimus ointment if initiated at least 30 days prior to screening and maintained on stable dose)	60 days
22.	Immunoglobulin E (IgE) antagonist or any other anti-IgE therapy	120 days
23.	Any other investigational biological drug.	120 days
24.	Anti-interleukin-5 (anti-IL-5) therapy (e.g., reslizumab, mepolizumab, etc.)	120 days
25.	Sublingual immunotherapy (investigational or other)	180 days

These above medications are also prohibited throughout the entire study except for rescue medications (see **Rescue Medication** text). In addition, the following medications are prohibited throughout the entire study:

1. All intranasal therapies (including saline) other than study medication
2. Topical corticosteroids (except for the treatment of small, localized lesions)
3. Radiation therapy
4. Initiation of immunotherapy
5. Any investigational drug being used in another clinical study
6. Herbal medications/supplements to treat AR, or any other alternative therapies to treat AR
7. St. John's Wort (*Hypericum perforatum*)
8. Guaifenesin-containing products (e.g., Mucinex®)

Excluded Concomitant Medications:

1. No 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).

2. Subjects can receive topical immunotherapy (e.g., 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.

3. Potent CYP3A4 inhibitors (such as ketoconazole, itraconazole, erythromycin) and potent CYP3A4 inducers (such as carbamazepine, dexamethasone, phenytoin, rifabutin, rifampin, pioglitazone) are prohibited 30 days prior to the Screening Visit (Visit 1) as well as during the study.

4. Use of antibiotic therapy for acute conditions within 14 days prior to the 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.

Rescue Medications:

The following rescue medication, non-nasal formulations only, is allowed in the study ONLY after Treatment Visit 4 (Week 6):

- Loratadine (10 mg/day)

The use of rescue medications will be available only after the first 6 weeks of treatment (after Treatment Visit 4). No rescue medication will be provided or allowed during the placebo run-in period or prior to Day 43 of the treatment period. Subjects should be instructed that rescue medication use should be minimal and used only as needed when the subject's symptoms are intolerable. Additional rescue medication should be prescribed only if the provided rescue medication (loratadine 10 mg/day) is not effective in relieving the symptoms as judged by the Investigator (e.g. topical/oral decongestants [e.g., oxymetazoline, pseudoephedrine, tetrahydrozoline], short-acting ocular antihistamines, long-acting antihistamines [e.g., desloratadine, cetirizine, fexofenadine], OTC cough and cold preparations or sleep aids containing antihistamines). Once the symptoms are deemed to be under control, rescue medication usage should be minimized or discontinued. Rescue medications should be used as prescribed by the Investigator/designee at approved dosages as applicable per the prescribing information of the medication.

Permitted Medications:

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

Endpoints
Primary Endpoints

- Proportion of subjects with treatment-emergent adverse events (TEAEs).
- Proportion of subjects with treatment-related TEAEs.
- Incidence, type, and severity of the TEAEs after 30 weeks of study treatment.
- Incidence, type, and severity of the TEAEs after 52 weeks of study treatment.
- Clinical laboratory assessments (hematology, serum biochemistry, and urinalysis) at baseline, Week 30, and Week 52.
- Vital signs, physical examinations (PE), and focused ears, nose, and throat (ENT) and eye examinations at baseline, Week 30, and Week 52.

Secondary Endpoints
Efficacy Endpoints

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

treatment.

- Change from baseline in the average AM subject-reported instantaneous Total Nasal Symptom Score (iTNSS) over the first 6, 30, and 52 weeks of treatment.
- Change from baseline in the overall Rhinoconjunctivitis Quality of Life Questionnaire – Standardized Activities (RQLQ(S)) score at Weeks 6, 30, and 52 for the Full Analysis Set (FAS).

Other Efficacy Endpoints

Nasal symptoms:

- Change from baseline in the average AM subject-reported reflective individual nasal symptoms over the first 6, 30, and 52 weeks of treatment.
- Change from baseline in the average AM subject-reported instantaneous individual nasal symptoms over the first 6, 30, and 52 weeks of treatment.
- Change in the average AM subject-reported rTNSS and iTNSS from baseline to the end of each treatment week.
- Change in the average AM subject-reported reflective individual nasal symptoms from baseline to the end of each treatment week.
- Change in the average AM subject-reported instantaneous individual nasal symptoms from baseline to the end of each treatment week.

Physician assessed Nasal Symptom Score (PNSS), Rhinoconjunctivitis Quality of Life Questionnaire – Standardized Activities (RQLQ(S)), and Rhinitis Control Assessment Test (RCAT):

- Change from baseline in PNSS and physician assessed individual nasal symptoms at Weeks 6, 30, and 52.
- Change from baseline in individual domains of the RQLQ(S) at Weeks 6, 30, and 52 for the FAS.
- Change from baseline in overall RQLQ(S) score and individual domains of the RQLQ(S) at Weeks 6, 30, and 52 for the RQLQ(S) Analysis Set.
- Change from baseline in the RCAT at Weeks 6, 30, and 52.
- Change from baseline in individual domains of the RCAT at Weeks 6, 30, and 52.

Exploratory Endpoints:
Not applicable

Pharmacokinetic, Pharmacodynamic, Biomarker, and Pharmacogenomic Assessments
Pharmacokinetic Assessments
Not applicable.
Pharmacodynamic Assessments
Not applicable.
Biomarker Assessments
Not applicable.
Pharmacogenomic Assessments
Not applicable.

Bioanalytical Methods: Not Applicable

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

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

The Safety Analysis Set (SAS) will consist of all subjects who took at least 1 dose of study medication following randomization and will be used for all safety analyses.

The RQLQ(S) Analysis Set will consist of all English-speaking subjects ≥18 years old with impaired quality of life (QOL) at baseline as defined by a RQLQ(S) score at the Randomization Visit (Visit 2) of 3.0 or greater.

Determination of Sample Size
The sample size of 600 subjects for this study (400 subjects on GSP 301 NS and 100 subjects in each of the 2 placebo groups) is based on the International Conference on Harmonisation (ICH) Guideline E1[19] and the FDA Guidance on Allergic Rhinitis,[14] which requires treatment of at least 300 subjects for 6 months and 100 subjects for

1 year. Based on an estimated attrition rate of 25% at the 6 month time point and 50% by 52 weeks, 400 subjects in the GSP 301 NS treatment group are considered sufficient to meet the above requirements.

Efficacy Analyses
Change from baseline in average AM subject-reported rTNSS and iTNSS over the first 6, 30, and 52 weeks of treatment will be analyzed using an analysis of covariance (ANCOVA) model adjusting for study treatment group, site, and baseline (defined as the average of the last 4 consecutive AM assessments during the last 4 days of the run-in period from the Day -3 AM assessment to the AM assessment on the day of randomization). At least 2 out of 4 assessments (scores) should be available in order to calculate the baseline scores for the AM rTNSS and iTNSS (linear, continuous covariate). Least square means (LSMs) of the treatment differences and associated 95% confidence intervals (95% CIs) and p-values will be presented. A multiple, imputation-based approach where complete data sets are drawn will be used for handling missing data in the efficacy analysis. The imputation model will be defined and fully detailed in the statistical analysis plan (SAP).

Changes from baseline in rTNSS and iTNSS at the end of each week of treatment and changes from baseline in individual nasal symptom scores over the first 6, 30, and 52 weeks (and at the end of each treatment week) of the treatment period will be analyzed in a similar manner as described above.

Changes from baseline in RQLQ(S) at Weeks 6, 30, and 52 will be analyzed for the FAS and the RQLQ(S) Analysis Set using ANCOVA models adjusting for study treatment group, site, and baseline RQLQ(S) (linear, continuous covariate). For subjects who withdrew early from the study, the RQLQ(S) score at their discontinuation visit will be used.

The analyses of RCAT results will be similar to the RQLQ(S) analyses except the RQLQ(S) analysis set will not apply.

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

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses: Not applicable.

Safety Analyses
Adverse events (including TEAEs) will be classified using the current version of the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by treatment group. Summary tables comparing the type, incidence, severity and drug relationship will be presented by treatment group. If sufficient data exist, TEAE frequencies will be compared across treatment groups using Fisher's exact test or a similar test.
Detailed statistical analysis and methods will be provided in the SAP.

Interim Analyses: No interim analysis is planned for the study.

3 INVESTIGATOR'S SIGNATURE

- I have reviewed the clinical protocol.
- I have fully discussed the objective(s) of this study and the contents of this protocol with the Sponsor's representative.
- I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the Sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.
- I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), and with the applicable regulatory requirements.
- I understand that failure to comply with the requirements of the protocol may lead to my participation as an Investigator for this study to be terminated.
- I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the Sponsor.

_____ _____

Name of Investigator, degree Date

Title

Address and contact details

4 SPONSOR'S SIGNATURE

This protocol reflects the Sponsor's current knowledge of Fixed Dose Combination (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 whilst 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 International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP), 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/electronic case report forms (CRFs/eCRFs).

- 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 (SOPs) 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]

31-Aug-2016
Date:

Vice President, Clinical Development
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Reviewed and Approved by:

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31/Aug/2016
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5 BACKGROUND INFORMATION

5.1 Introduction

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.[1,2] In the United States (US), it 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 (physician services, diagnostics, medications, etc.) nearly doubled from US $6.1 billion in 2000 to US $11.2 billion in 2005.[1]

Allergic rhinitis 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 multi-organ reaction).[3,4,5] When 2 or more symptoms such as watery rhinorrhea, sneezing, nasal obstruction, and nasal pruritus persist for ≥1 hour, 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 histamine 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.[6]

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.[1,7,8] Topical (intranasal) antihistamines (histamine 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.[6] Intranasal corticosteroids inhibit both early and late reactions and reduce IgE production and eosinophilia by inhibiting the secretion of cytokines including interleukin 4 (IL-4), IL-5, and IL-13.[3,6]

5.2 Investigational Product: Mechanism of Action

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.[9] 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.[3,9]

Mometasone is a corticosteroid that demonstrates 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 patients 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 (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation.[10] 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.

5.3 Preclinical Experience

The toxicity of both olopatadine hydrochloride and mometasone fuorate 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 nasal spray (GSP 301 NS) and [redacted] GSP 301 NS (6650 µg/mL olopatadine hydrochloride and 250 µg/mL mometasone furoate [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 of 2.3-fold based on nasal surface area and approximately 50-fold on a mg/kg basis to the proposed dose to be studied in the Phase 3 clinical studies. 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 hydrochloride and mometasone furoate is low.

Repeat dose studies by the intranasal route have been conducted for both olopatadine hydrochloride and mometasone furoate in rats for up to 6 months and in dogs for up to 12 months. Both compounds showed no nasal irritancy at concentrations equivalent to, or slightly greater than, those proposed in the fixed dose combination (FDC) GSP 301 NS.[11,12,13]

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 patients.

No effect on fertility was observed with mometasone furoate but olopatadine hydrochloride 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 50 mg/kg/day (approximately 100 times the maximum human dose of 4800 µg/day on a body surface area basis).

Olopatadine hydrochloride 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 with 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 defined as Pregnancy Category C.

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

5.4 Clinical Experience

A proof-of-concept study was conducted to evaluate FDC GSP 301 NS in the treatment of seasonal allergic rhinitis (SAR). This was a double-blind, double-dummy, randomized, parallel-group, comparative environmental chamber study to evaluate efficacy, safety, and tolerability of 2 Sponsor-formulated FDC products of olopatadine hydrochloride and mometasone furoate nasal spray (NS) (referred to as Molo 1 and Molo 2 in that study) compared with an approved FDC of azelastine hydrochloride and fluticasone propionate NS (Dymista® NS), an approved olopatadine hydrochloride NS (Patanase® NS), and Sponsor-formulated placebo in subjects with SAR. The study population consisted of 180 subjects who were allergic to ragweed allergen and had SAR for the 2 years prior to study entry. Subjects were treated with study medication for 2 weeks. Both Sponsor-formulated FDC products were superior to 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 but showed numerical improvement. [redacted]

In addition, two Phase 1 pharmacokinetic (PK) studies and a large Phase 2 study were completed. The Phase 1 studies were open-label, 3-period, 3-treatment, crossover, randomized studies with 30 healthy volunteers in each study. The results of the two Phase 1 studies demonstrated that the olopatadine systemic exposure of the FDC GSP 301 NS is similar 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, except for a higher [redacted] maximum plasma concentration (C_{max}) for the FDC GSP 301 NS compared with Nasonex® NS treatment. 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 [redacted] in the Phase 2 Study GSP 301-201.

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 who were allergic to mountain cedar allergen. Subjects were randomized to 1 of 7 treatment groups:

- FDC of olopatadine hydrochloride and mometasone furoate NS (GSP 301-1 NS [olopatadine hydrochloride 665 µg and mometasone furoate 50 µg]) at [redacted] in the morning (AM)
- FDC of olopatadine hydrochloride and mometasone furoate NS (GSP 301-2 NS [olopatadine hydrochloride 665 µg and mometasone furoate 25 µg]) at [redacted] (BID) in the morning and evening (PM)
- Glenmark olopatadine hydrochloride (665 µg)-1 NS, [redacted]
- Glenmark olopatadine hydrochloride (665 µg)-2 NS [redacted]
- Glenmark mometasone furoate (50 µg)-1 NS, [redacted]
- Glenmark mometasone furoate (25 µg)-2 NS, [redacted]
- GSP 301 placebo NS (GSP 301 vehicle)

The primary endpoint of the study was mean change in the reflective Total Nasal Symptom Score (rTNSS) from baseline to end of treatment between treatment groups. The results of the study suggested that GSP 301-2 NS is statistically and clinically superior to 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 score was clinically and statistically superior to both mometasone furoate NS BID (LSM treatment difference [redacted] and olopatadine hydrochloride NS BID (LSM treatment difference [redacted] p=0.0488). Additionally, GSP 301-2 NS [redacted] was also statistically and clinically superior to placebo (LSM treatment difference [97.5% CI] = -1.1089 [-1.6471, -0.5706], p<0.0001) for mean change from baseline in the iTNSS score (key secondary endpoint) for the FAS. However, mean change from baseline in the iTNSS score was clinically and statistically superior to mometasone furoate NS [redacted] (LSM treatment difference [95% CI] = -0.6519 [-1.1211, -0.1826], p=0.0065) but not olopatadine hydrochloride NS [redacted] (LSM treatment difference [95% CI] = -0.4526 [-0.9212, 0.0161], p=0.0584).

Based on the data from the Phase 1 and 2 studies, GSP 301-2 NS [redacted] of olopatadine hydrochloride 665 µg and mometasone furoate 25 µg and referred to as GSP 301 NS hereafter in this protocol) was found to be optimally safe and effective for the treatment of SAR in adult and adolescents and will be further evaluated in the Phase 3 studies. Additional details of the product are provided in the Investigator's Brochure (IB).

5.5 Study Rationale

It has been suggested that olopatadine hydrochloride is clinically superior to other anti-allergy molecules because of its strong antihistamine activity and unique ocular mast cell stabilizing

properties.[3] The efficacy and safety of mometasone furoate NS, 50 µg (Nasonex® NS 200 µg total daily dose, QD) in the prophylaxis and treatment of nasal symptoms of SAR, nasal congestion associated with SAR and the treatment of perennial allergic rhinitis (PAR) have been evaluated in 18 controlled trials, and 1 uncontrolled clinical trial, in approximately 3000 adults (aged 17 to 85 years) and adolescents (aged 12 to 16 years).[10] [redacted] Olopatadine hydrochloride and mometasone furoate, the monocomponents in GSP 301 NS, are approved in the US. The safety, including long-term safety, of these drugs is well established.

As the proposed GSP 301 NS is to be used to treat chronic rhinitis, it is important to evaluate the safety of the product during long-term use. The US Food and Drug Administration (FDA) guidance on the development of drug product for AR recommends that a new product should be evaluated in a long-term (52 weeks) safety study. Therefore, the optimal dose and regimen determined based on the Phase 2 study, will be further tested in this protocol to evaluate the long-term safety and efficacy of GSP 301 NS compared with placebo NS formulations.

GSP 301 NS is an aqueous nasal spray containing olopatadine hydrochloride and mometasone furoate monohydrate as the active ingredients in an aqueous solution with an approximate pH of [redacted] Although, matching pH of the active product [redacted] is essential to maintain blinding for efficacy purposes; the low pH in the placebo treatment may impact the interpretation of the safety data because the frequencies of commonly occurring adverse events (AEs) in the GSP301 NS group may be underestimated when compared with the low pH placebo treatment group. To address this issue, an additional placebo NS with a higher pH of approximately [redacted] is being evaluated in this study as recommended by the US FDA. Thus, the primary objective of this study is to compare the long-term safety and tolerability of GSP 301 NS with two GSP 301 placebo NS formulations over 52 weeks of treatment in subjects (aged ≥12 years) with PAR. Additionally, the long-term efficacy of GSP 301 NS will also be evaluated.

5.6 Benefit-Risk Assessment

Olopatadine hydrochloride NS (Patanase® NS) has been approved for the relief of the symptoms of SAR in adults and children ≥6 years of age since 2008 in the US. It has a fast onset of action and is effective within 30 minutes of administration. The most common (>1% of patients) adverse reactions included bitter taste, headache, epistaxis, pharyngolaryngeal pain, post-nasal drip, cough, and urinary tract infection.[9]

Mometasone furoate NS (Nasonex® NS) is also well tolerated, effective, and safe in the treatment of seasonal and perennial AR. Nasonex® NS was approved in the US in 1997 for the treatment of the nasal symptoms associated with AR and the nasal congestion associated with SAR, respectively. The most common adverse reactions (≥5% of patients) included headache, viral infection, pharyngitis, epistaxis, cough, upper respiratory tract infection, sinusitis, dysmenorrhea, and musculoskeletal pain.[10]

The currently approved dose of olopatadine hydrochloride (Patanase® NS, 665 µg, equivalent to 600 µg olopatadine as base) monotherapy in adults and adolescents ≥12 years old with SAR is 2 sprays in each nostril BID. The currently approved dose of mometasone furoate (Nasonex® NS, 50 µg) monotherapy in adults and adolescents ≥12 years old with AR is 2 sprays in each nostril QD. Thus, the approved total daily doses for the monotherapies are 5320 µg olopatadine

hydrochloride and 200 µg mometasone fu oa e. W h the proposed GSP 301 NS regimen [redacted], the total daily dose of olopatadine hydrochloride and mometasone furoate will be [redacted]

Several clinical studies have already shown that a combination of an intranasal antihistamine and an intranasal corticosteroid is beneficial with respect to local administration and an additive effect on efficacy, resulting in superior relief of SAR symptoms compared with monotherapy.[15] A clinical study demonstrated that a combination of azelastine and fluticasone NS (Dymista® NS) was more effective than either agent alone in the treatment of SAR.[15] In 2012, Dymista® NS (137 µg azelastine hydrochloride and 50 µg fluticasone propionate) was approved in the US.

From a safety perspective, studies done so far with the GSP 301 NS FDC including the Phase 2 study did not report any major AEs or safety concerns.

Therefore, [redacted] FDC of olopatadine hydrochloride and mometasone furoate (GSP 301 NS w proved efficacy compared with each individual monotherapy and that the safety will be similar to the known safety profiles of each monotherapy.

6 STUDY OBJECTIVES

6.1 Primary Objective

- To compare the long-term safety and tolerability of GSP 301 NS with 2 GSP 301 placebo NS formulations over 52 weeks of study treatment.

6.2 Secondary Objective

- To evaluate the long-term efficacy of GSP 301 NS compared with GSP 301 placebo NS pH [redacted] in subjects with PAR.

6.3 Exploratory Objective

Not applicable.

7 STUDY DESIGN

7.1 Study Type/Design

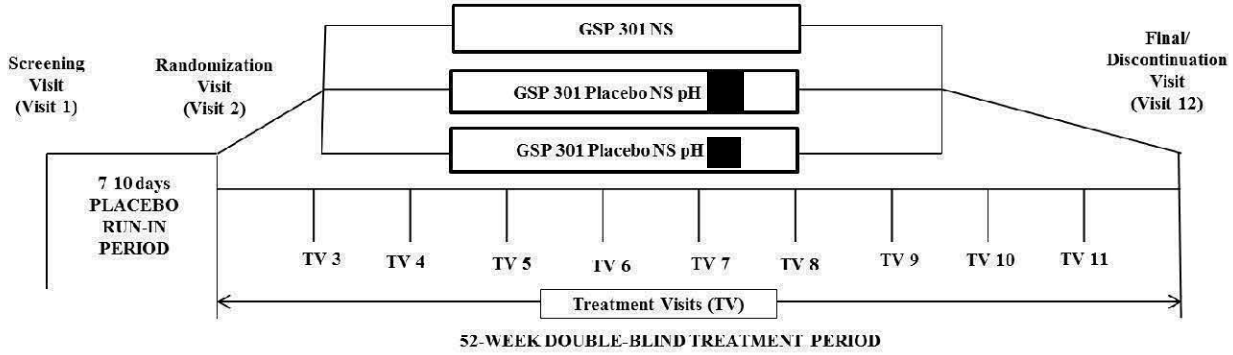
This is a multi-center, double-blind, randomized, parallel-group, 52-week study conducted in subjects with PAR. The subjects will be randomized to the following 3 treatment groups in a ratio of 4:1:1:

- GSP 301 N 665 µ opa ne droch oride/25 µg mometasone furoate) administered as [redacted]
- GSP 301 placebo NS pH [redacted] administered as [redacted]

- GSP 301 placebo NS [redacted] administered as [redacted]

This study consists of 12 visits to the study site (Figure 1). After the initial Screening Visit (Visit 1), subjects 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 run-in period, eligible subjects who meet the randomization criteria will be enrolled and randomized to 1 of the 3 treatment groups. Randomized subjects will undergo a 52-week treatment period to assess the efficacy and safety of the assigned treatment.

Figure 1: Study Design Schematic



The Screening Visit (Visit 1) will occur 7 to 10 days before the Randomization Visit (Visit 2). The purposes of the Screening Visit (Visit 1) are to obtain informed consent, establish protocol eligibility, and enter eligible subjects into the placebo run-in period. Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 15.3. The Screening Disposition case report form/electronic case report form (CRF/eCRF) page must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable. Eligible subjects will be given an AR Assessment Diary to record AR symptoms (morning [AM] rTNSS and iTNSS) during the 7 to 10 day run-in period.

After screening, all eligible subjects will participate in a single-blind, placebo (GSP 301 placebo NS pH[redacted], run-in period. This is to ensure the subjects qualify for the study and to identify any potentially non-compliant subjects. Subjects will assess their symptoms and complete the AR Assessment Diary every morning during the run-in period. The AM dose of single-blind study medication will be taken immediately after completing the diary. Subjects must meet the key randomization criteria required for the run-in period (minimum AM subject-reported rTNSS, AM subject-reported reflective nasal congestion score, adequate AR Assessment Diary compliance, and compliance with avoiding prohibited concomitant medications) to continue in the study.

The treatment period consists of 52 weeks. During this time, subjects will continue to assess their symptoms and complete the AR Assessment Diary every morning[redacted]

[redacted] (Visit 12).

No scheduled post-treatment follow-up visit is planned for this study. However, subjects will be followed up if there is any ongoing AE or for any other reason as per the Investigator's and Sponsor's discretion.

A telephone follow-up will be carried out for this study for any reason as per the Investigator's judgment. If needed, additional unscheduled visits may be conducted to ensure subject safety or to perform other study-related procedures at the discretion of the Investigator or the Sponsor.

No extension phase is planned for this study.

7.2 Discussion of Study Design, Including Choice of Control Groups

This will be a multi-center, double-blind, randomized, parallel-group study conducted in approximately 600 subjects with PAR. These subjects will be randomized to 1 of the 3 treatment arms in a ratio of 4:1:1. Randomization will be stratified by study site.

The study is designed as a double-blind study to reduce treatment and randomization bias. The overall study design is consistent with other similar studies reported in the literature. Furthermore, the overall study design is also based on the FDA guidance document for Allergic Rhinitis: Clinical Development Programs for Drug Products by the US FDA.[14]

This current study is planned to compare the long-term safety and efficacy of GSP 301 NS to 2 different GSP 301 placebo NS formulations as agreed at an End-of-Phase 2 (EOP2) meeting with the FDA. [redacted] All NS bottles for all treatment groups will be identical in appearance. Thus, other than the active components and/or pH of the placebo formulations (as appropriate), there are no other differences in the formulations or the bottles of the 3 treatments.

8 STUDY ENDPOINTS

8.1 Primary Endpoints

- Proportion of subjects with TEAEs.
- Proportion of subjects with treatment-related TEAEs.
- Incidence, type, and severity of the TEAEs after 30 weeks of study treatment.
- Incidence, type, and severity of the TEAEs after 52 weeks of study treatment.
- Clinical laboratory assessments (hematology, serum biochemistry, and urinalysis) at baseline, Week 30, and Week 52.
- Vital signs, physical examinations (PE), and focused ears, nose, and throat (ENT) and eye examinations at baseline, Week 30, and Week 52.

8.2 Secondary Endpoints

8.2.1 Efficacy Endpoints

- Change from baseline in the average AM subject-reported rTNSS over the first 6, 30, and 52 weeks of treatment.
- Change from baseline in the average AM subject-reported iTNSS over the first 6, 30, and 52 weeks of treatment.
- Change from baseline in the overall Rhinoconjunctivitis Quality of Life Questionnaire – Standardized Activities (RQLQ(S)) score at Weeks 6, 30, and 52 for the FAS.

8.2.2 Other Efficacy Endpoints

Nasal Symptoms:

- Change from baseline in the average AM subject-reported reflective individual nasal symptoms over the first 6, 30, and 52 weeks of treatment.
- Change from baseline in the average AM subject-reported instantaneous individual nasal symptoms over the first 6, 30, and 52 weeks of treatment.
- Change in the average AM subject-reported rTNSS and iTNSS from baseline to the end of each treatment week.
- Change in the average AM subject-reported reflective individual nasal symptoms from baseline to the end of each treatment week.
- Change in the average AM subject-reported instantaneous individual nasal symptoms from baseline to the end of each treatment week.
- Physician assessed Nasal Symptom Score (PNSS), Rhinoconjunctivitis Quality of Life Questionnaire – Standardized Activities (RQLQ(S)), and Rhinitis Control Assessment Test (RCAT):
- Change from baseline in PNSS and physician assessed individual nasal symptoms at Weeks 6, 30, and 52.
- Change from baseline in individual domains of the RQLQ(S) at Weeks 6, 30, and 52 for the FAS.
- Change from baseline in overall RQLQ(S) score and individual domains of the RQLQ(S) at Weeks 6, 30, and 52 for the RQLQ(S) Analysis Set.
- Change from baseline in the RCAT at Weeks 6, 30, and 52.
- Change from baseline in individual domains of the RCAT at Weeks 6, 30, and 52.

8.3 Exploratory Endpoint

Not applicable.

8.4 Appropriateness of Measurements

The planned safety analysis and the change in the rTNSS as an efficacy endpoint for the current study are as per the available safety data on the individual monotherapies and the other available FDC product on the US market (Dymista® USPI),[15] and the US FDA guidance on the development of AR medication.[14]

9 SUBJECT SELECTION AND WITHDRAWAL CRITERIA

Approximately 600 subjects (both male and female) will be randomized at multiple sites in the US. Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to enter in the study.

Subject eligibility should be reviewed and documented by an appropriately qualified member of the Investigator's study team before each subject is included in the study.

Any subject who fails screening on any single criterion where there is the potential for them to subsequently become eligible may be re-screened on 1 occasion, dependent upon consultation with the Sponsor's study team and approval.

9.1 Inclusion Criteria

Subjects must meet all of the following criteria to be enrolled in the study:

1. Males and non-pregnant females aged ≥12 years.
2. Signed informed consent/assent form (subject and/or parent/caregiver/legal guardian) that meets all criteria of the current US FDA/local regulations.
3. Documented clinical history of PAR (for at least 2 years preceding the Screening Visit [Visit 1]) with exacerbations (clinical evidence of active symptoms) and exhibiting a documented positive skin prick test (wheal diameter at least 3 mm greater than negative diluent control wheal) to at least 1 allergen known to induce PAR. Documentation of a positive result within 12 months prior to the Screening Visit (Visit 1) is acceptable. Additionally, the subject is expected to be exposed to the PAR allergen that he/she tested positive for via the skin prick test for the entire duration of the study.
4. 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.
5. Subjects must be able to demonstrate the correct NS application technique at the Screening Visit (Visit 1).
6. Subjects must be willing and able to comply with all aspects of the protocol.

9.2 Exclusion Criteria

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

1. Have a positive pregnancy test or established pregnancy, breast-feeding, or planning a pregnancy during the study.
2. Female subjects of child-bearing potential (as judged by the Investigator) who do not agree to remain abstinent or use medically acceptable methods of contraception (e.g., implants,

injectables, combined oral contraceptives, intrauterine devices [IUDs], double-barrier protection) during the study. Male participants who do not agree to use a condom with spermicide during intercourse (if not surgically sterilized) during the study.

3. History of significant atopic dermatitis or rhinitis medicamentosa (within 60 days prior to the Screening Visit [Visit 1]).
4. Treatment with any known potent CYP3A4 inducers (carbamazepine, dexamethasone, phenytoin, rifabutin, rifampin, pioglitazone, etc.) or potent inhibitors (azole antifungals, macrolide antibiotics, etc.) within 30 days prior to or during the study.
5. Non-vaccinated exposure to or active infection with chickenpox or measles within 21 days preceding the Screening Visit (Visit 1).
6. Known hypersensitivity to any corticosteroids or antihistamines or to the study medication or its excipients.
7. History of anaphylaxis and/or other severe local reaction(s) to skin testing.
8. History of alcohol or drug dependence within 2 years preceding the Screening Visit (Visit 1).
9. History of a positive test for human immunodeficiency virus (HIV), Hepatitis B, or Hepatitis C infection.
10. Evidence of acute or significant chronic sinusitis or chronic purulent postnasal drip.
11. 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 including alcohol-related liver disease or cirrhosis
    - Any systemic infection
    - Hematological, hepatic, renal, endocrine disorder (except for postmenopausal symptoms or hypothyroidism)
    - Gastrointestinal disease
    - Malignancy (excluding basal cell carcinoma)
    - Current neuropsychological condition with or without drug therapy
    - Cardiovascular disease (e.g., uncontrolled hypertension)
    - Respiratory disease other than mild asthma
12. Any major surgery (as assessed by the Investigator) within 4 weeks preceding the Screening Visit (Visit 1).
13. Requirement for the chronic use of tricyclic anti-depressants.
14. Dependence (in the opinion of the Investigator) on nasal, oral, or ocular decongestants, nasal topical antihistamines, or nasal steroids.
15. Active pulmonary disorder or infection (including but not limited to bronchitis, pneumonia, or influenza), or upper respiratory tract or sinus infection within the 14 days prior to the Screening Visit (Visit 1) or the development of respiratory infections during the run-in

period. Subjects with mild asthma are allowable on the condition that treatment is limited to inhaled short-acting beta-agonists only (up to 8 puffs per day).

16. Use of antibiotic therapy for acute conditions within 14 days prior to the 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.
17. Posterior subcapsular cataracts or glaucoma, or any other ocular disturbances, or other listed related conditions including:
    - History of increased intraocular pressure
    - History of retinal detachment or surgery
    - History of incisional eye surgery (other than cataract extraction or laser-assisted in situ keratomileusis [LASIK])
    - 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
18. Known history of hypothalamic-pituitary-adrenal axis impairment.
19. Existence of any significant surgical or medical condition, or clinically significant physical finding (e.g. 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 Sponsor's medical monitor, 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 complete or reliably complete the AR Assessment Diary.
20. 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.
21. Initiation of immunotherapy injections or 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) within 60 days preceding the Screening Visit (Visit 1). A 180-day washout period is required following the last dose of sublingual immunotherapy (investigational or other) prior to the Screening Visit (Visit 1).
22. 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 during the clinical study duration.
23. Study participation by clinical investigational site employees and/or their immediate relatives.

24. Study participation by more than 1 subject from the same household at the same time. However, after completion/discontinuation by 1 subject in the household, another subject from the same household may be screened.
25. Known to have failed to show symptom improvement with any approved/marketed monotherapy component of GSP 301 NS (i.e., Nasonex® NS or Patanase® NS or both) as judged by the Investigator.
26. Previous participation in a GSP 301 NS study as a randomized subject.

9.3 Randomization Criteria

1. Continued general good health meeting the Screening inclusion criteria.
2. Has not experienced an AE that would result in not meeting the Screening inclusion criteria.
3. Minimum AM subject-reported rTNSS of an average of 5 (out of a possible 12) during the last 4 days of the run-in period (last 4 consecutive AM assessments from the Day -3 AM assessment to the AM assessment on the day of randomization).
4. Has an AM subject-reported reflective nasal congestion score ≥2 during the last 4 days of the run-in period (last 4 consecutive AM assessments from the Day -3 AM assessment to the AM assessment on the day of randomization).
5. Adequate AR Assessment Diary compliance – inadequate compliance is defined as missing 1 or more of the entries on 2 or more assessment sessions (AM) during the last 4 days of the run-in period (during the last 4 consecutive AM assessments from the Day -3 AM assessment to the AM assessment on the day of randomization).
6. Adequate study medication compliance – each subject must have taken his/her single-blind medication for at least 80% of the entire run-in period as reported in the AR Assessment Diary.
7. Has not suffered from the common cold, upper respiratory infections, otitis media, lower respiratory infections, or acute sinusitis within the 14 days prior to the Randomization Visit (Visit 2).
8. Has not used any of the prohibited concomitant medications during the run-in period.

9.4 Subject Discontinuation/Withdrawal Criteria

A subject may voluntarily discontinue study participation at any time after giving informed consent 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 by the subject to continue in the study.
2. Development of a serious or intolerable AE that necessitates discontinuation at the discretion of the Investigator (AE section of the CRF/eCRF must be completed; includes serious adverse event [SAE], 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.

In the case of premature discontinuation, the reason must be documented. The Investigator (or designee) must document the reason for withdrawal in the Study Conclusion section of the CRF/eCRF.

All follow-up assessments should be conducted as outlined for the Final Visit/Discontinuation Visit (Visit 12) (Appendix 1). 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 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 treatment early but does not withdraw consent, should return for end of study assessments, as noted in Section 11.4.

The investigator will:

- inquire about the reason for withdrawal,
- request that the subject return all unused investigational product(s), and
- request that the subject return for the Final Visit/Discontinuation Visit (Visit 12).

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.

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

Discontinued subjects will not be replaced.

9.5 Sponsor Discontinuation Criteria

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), drug safety problems, or at the discretion of the Sponsor for any other reason. In addition, the Sponsor retains the right to discontinue development of GSP 301 NS at any time.

If this study is prematurely terminated or discontinued, the Sponsor will promptly notify the Investigator. After notification, the Investigator must contact all participating subjects and the hospital pharmacy (if applicable) within a time period set by the Sponsor. As directed by the Sponsor, all study materials must be collected and all CRFs/eCRFs completed to the greatest extent possible.

9.6 Prior and Concomitant Medications

Exclusion of Medication Prior to the Screening Visit (Visit 1):

1.	Vasoconstrictors (e.g, epinephrine, sumatriptan)	3 days
2.	Major tranquilizers (e.g., antipsychotics such as chlorpromazine, haloperidol, risperadol, clonazepam)	3 days
3.	Short-acting antihistamines (oral, ocular, or intranasal antihistaminic– e.g., azelastine)	7 days
4.	Over-the-counter (OTC) cough and cold preparations or sleep aids containing antihistamines	7 days
5.	Topical/oral/nasal decongestants (e.g., oxymetazoline, pseudoephedrine, tetrahydrozoline)	7 days
6.	OTC food supplement/diet to reduce leukotrienes (Airozin™)	7 days
7.	Leukotriene antagonists or arachidonate 5-lipoxygenase inhibitors	7 days
8.	Inhaled/oral/intranasal anticholinergics	7 days
9.	Long-acting antihistamines (e.g., cetirizine, fexofenadine)	10 days
10.	Cromolyn (all forms), nedocromil, or lodoxamide (intranasal, ocular, or oral)	14 days
11.	Systemic antibiotics (see excluded concomitant medications)	14 days
12.	Ocular mast cell stabilizers	14 days
13.	Monoamine oxidase inhibitors	14 days
14.	Tricyclic antidepressants	14 days
15.	All intranasal/topical/ocular corticosteroids (except study medication)	30 days
16.	Inhaled corticosteroids	30 days
17.	Any other investigational non-biological drug	30 days
18.	Treatment with any known potent CYP3A4 inducers (carbamazepine, dexamethasone, phenytoin, rifabutin, rifampin, pioglitazone, etc.)	30 days
19.	Treatment with any known potent CYP3A4 inhibitors (azole antifungals, macrolide antibiotics, etc.)	30 days

20. Systemic corticosteroids (intermittent or chronic including intra-articular)	60 days
21. Immunotherapy injections and immunosuppressive/immune-modulator medications (except topical pimecrolimus cream or tacrolimus ointment if initiated at least 30 days prior to screening and maintained on stable dose)	60 days
22. IgE antagonist or any other anti-IgE therapy	120 days
23. Any other investigational biological drug	120 days
24. Anti-IL-5 therapy (e.g., reslizumab, mepolizumab, etc.)	120 days
25. Sublingual immunotherapy (investigational or other)	180 days

These above medications are also prohibited throughout the entire study except for rescue medications (see **Rescue Medications** text). In addition, the following medications are prohibited throughout the entire study:

1. All intranasal therapies (including saline) other than study medication
2. Topical corticosteroids (except for the treatment of small, localized lesions)
3. Radiation therapy
4. Initiation of immunotherapy
5. Any investigational drug being used in another clinical study
6. Herbal medications/supplements to treat AR, or any other alternative therapies to treat AR
7. St. John's Wort (Hypericum perforatum)
8. Guaifenesin-containing products (e.g., Mucinex®)

Exclusion of Concomitant Medications:

1. No 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).
2. Subjects can receive topical immunotherapy (e.g., 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.
3. Potent CYP3A4 inhibitors (such as ketoconazole, itraconazole, erythromycin) and potent CYP3A4 inducers (such as carbamazepine, dexamethasone, phenytoin, rifabutin, rifampin, pioglitazone) are prohibited 30 days prior to the Screening Visit (Visit 1) as well as during the study.
4. Use of antibiotic therapy for acute conditions within 14 days prior to the 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.

Rescue Medications:

The following rescue medication, non-nasal formulations only, is allowed in the study ONLY after Treatment Visit 4 (Week 6):

1. Loratadine (10 mg/day)

The use of rescue medications will be available only after the first 6 weeks of treatment (after Treatment Visit 4). No rescue medication will be provided or allowed during the placebo run-in period or prior to Day 43 of the treatment period. Usage of rescue medication must be recorded in the AR Assessment Diary that will be provided to the subjects. Subjects should be instructed that rescue medication use should be minimal and used only as needed when the subject's symptoms are intolerable. Additional rescue medication should be prescribed only if the provided rescue medication (loratadine 10 mg/day) is not effective in relieving the symptoms as judged by the Investigator (e.g.topical/oral decongestants [e.g., oxymetazoline, pseudoephedrine, tetrahydrozoline], short-acting ocular antihistamines, long-acting antihistamines [e.g., desloratadine, cetirizine, fexofenadine], OTC cough and cold preparations or sleep aids containing antihistamines). Once the symptoms are deemed to be under control, rescue medication usage should be minimized or discontinued. Rescue medications should be used as prescribed by the Investigator/designee at approved dosages as applicable per the prescribing information of the medication.

The use of all medication and non-medication therapies must be recorded on the concomitant medication pages of the subject's CRF/eCRF.

Permitted Medications:

With the exception of medications listed as excluded, subjects will be allowed to use other chronic medications at stable doses and other medications at the discretion of the Investigator (in consultation with the Sponsor) provided that they do not interfere with the safety and efficacy variables of the study.

9.7 Lifestyle and/or Dietary Restrictions

Not applicable.

10 TREATMENT OF SUBJECTS

10.1 Treatments Administered

Name of Investigational Product: FDC of olopatadine hydrochloride 665 µg and mometasone furoate 25 µg NS (GSP 301 NS)
License Name: GSP 301-2 NS
Dosage Form: NS
Dosage: [redacted]
Dosage Frequency: [redacted]
Mode of Administration: Intranasal

Reference Product 1: GSP 301 Placebo NS [redacted]
License Name: GSP 301 Placebo NS [redacted]
Dosage Form: NS
Dosage: [redacted]
Dosage Frequency: [redacted]
Mode of Administration: Intrana

Reference Product 2: GSP 301 Placebo NS pH [redacted]
License Name: GSP 301 Placebo NS pH [redacted]
Dosage Form: NS
Dosage: [redacted]
Dosage Frequency: [redacted]
Mode of Administration: Intranasa

10.1.1 Administration

Each nasal spray bottle contains [redacted] At the Screening Visit (Visit 1), site personnel will adequately train the subjects on the proper use of the NS bottle (Appendix 2). At each subsequent visit, site personnel will review instructions on the proper use of the NS bottle with the subject and prime the NS bottle as needed. The priming process must be completed in such a way as to avoid any possible inhalation and contamination by the subject.

Each subject will be provided with single-blind, placebo, run-in medication (GSP 301 placebo NS pH [redacted] for use until the Randomization Visit (Visit 2). Subjects will self-administer the first dose of the single-blind GSP 301 placebo NS pH [redacted] in the presence of the Investigator or designee during the Screening Visit (Visit 1). Subjects should be instructed NOT to administer the single-blind study medication on the day of the Randomization Visit (Visit 2).

At the Randomization Visit (Visit 2), each subject will be provided with double-blind study medication according to the randomization scheme. The site personnel will review instructions on the proper use of the NS bottle with the subject and prime the NS bottle as needed. The priming process must be completed in such a way as to avoid any possible inhalation and contamination by the subject. The first dose of double-blind study medication (AM dose on Day 1) will be self-administered in the clinic in the presence of the Investigator or designee during the Randomization Visit (Visit 2). All subsequent doses will be administered at home. The last scheduled dose will be the [redacted] on the day before the Final Visit/Discontinuation Visit (Visit 12). Study medication shou d not be taken (either at home or at the clinic) on the morning of the Final Visit/Discontinuation Visit (Visit 12).

Detailed instructions for the proper use of the treatment NS devices are provided in Appendix 2.

10.1.2 Treatment Adherence/Compliance

All study medication will be self-administered in the clinical facility as well at home in accordance with the protocol-specified subject study medication instructions. Subject adherence/compliance to treatment will be monitored by reviewing the AR Assessment Diary entries as outlined in the Schedule of Procedures and Assessments (Appendix 1). Subjects will be counseled regarding proper treatment adherence/compliance and re-trained in the proper use of the study medication nasal spray bottle at the specified visits as well as reviewing the subject study medication instructions.

10.1.3 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. Because of the proven safety and efficacy of the individual monotherapy components of GSP 301 NS, overdose is unlikely to require any therapy. There is no specific antidote to be used in the event of overdose. The Investigator should observe the subject and use his/her clinical judgment in treating 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.[9,10]

Olopatadine hydrochloride: There have been no reported overdoses with olopatadine hydrochloride NS (Patanase® NS). Symptoms of antihistamine overdose may include drowsiness. There is no known specific antidote to olopatadine hydrochloride 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 because of the negligible (<0.1%) systemic bioavailability of mometasone furoate and the absence of acute drug-related systemic findings in clinical studies; however, observation followed by re-initiation of the appropriate prescribed dosage is recommended. [redacted]

[redacted]

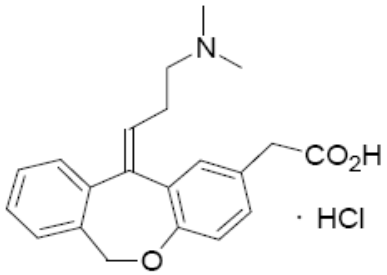
10.2 Identity of Investigational Products

10.2.1 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

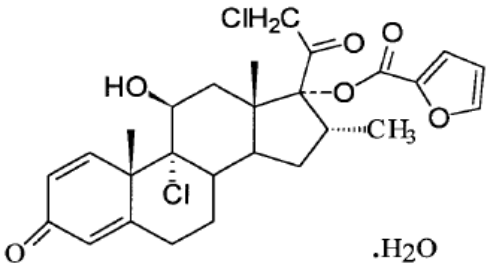
Structural formula:



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:



10.2.2 Placebo

GSP 301 placebo NS formulations will be prepared using the same vehicle as the active products. The GSP 301 placebo NS bottle will be identical to that of active treatments. The GSP 301 placebo NS will be packaged in primary and secondary packaging similar to that of the active treatments to maintain study medication blinding.

Two GSP 301 placebo NS formulations will be used in this study. GSP 301 placebo NS pH [redacted] is a placebo formulation matching the pH of the active product (pH [redacted]. An additional GSP 301 placebo NS pH [redacted] with a higher pH of approximately [redacted] is being evaluated in this study as recommended by the FDA. Other than the differences in pH and active ingredients, both placebo formulations used in the study are formulated in the same vehicle as GSP 301 NS and all NS bottles used for all treatment groups will be identical in appearance.

10.2.3 Packaging and Labeling of Investigational Products

Each of the investigational products (IPs) will be packed as per Good Manufacturing Practice (GMP) 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.

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.

10.3 Allocation to Treatment Groups

Subjects will be assigned to 1 of the 3 treatment groups in a 4:1:1 ratio based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The randomization will be stratified by study site. The randomization scheme and treatment allocation for each subject will be included in the final clinical study report (CSR) for this study.

10.4 Blinding and Unblinding Procedures

This study is designed as a double-blind study. The blinding will be maintained by packaging the active products and placebo in identical bottles and outer cartons. Additionally, an unblinded qualified person not associated with the study team will facilitate the randomization process to ensure that the double-blind design of the study is maintained.

In case of any premature unblinding (e.g., accidental unblinding or unblinding due to a SAE) of the IPs, the Investigator should promptly document and explain it to the Sponsor. The Sponsor's medical monitor or delegate should be contacted either prior to opening the code break card or soon after, depending on the circumstances. The Investigator will open the code break card for the subject under consideration only if knowledge of the randomized treatment is required for the treatment of the AE or SAE. In the event of a code break, the following minimum information will be recorded in a memo to file, which will be included in the CSR:

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

10.5 Preparation, Receipt, Storage, Dispensing and Accountability

The IP should be stored upright between 15° to 25°C (59°F to 77°F) and protected from light. It should not be frozen or refrigerated. Subjects will be instructed on the storage conditions for the IP. The Investigator (or designee) is responsible for IP accountability at the site and its documentation. The Investigator must also ensure that the dispensing and recording of IP is conducted only by authorized personnel. The study medication records must be readily available for inspection by the Study Monitor and/or auditor/regulatory agency personnel. No medication (used or unused) may 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.

11 TIMING OF STUDY PROCEDURES AND ASSESSMENTS

Study procedures and assessments are summarized across all study visits within the Schedule of Procedures and Assessments (Appendix 1).

A focused ENT and eye examination will be done at all visits. If at any visit, clinically significant nasal ulceration, nasal mucosal erosion, and nasal septal perforation are observed, or a finding at a previous visit has worsened (as judged by the Investigator), the subject should be referred to a qualified ENT specialist (medically qualified specialist qualified to evaluate and record these conditions, as judged by the Investigator) for further evaluation. A record from the specialist 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 12.4.11). The Sponsor 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 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. A thorough eye examination will also be performed by the Investigator or medically qualified designee.

11.1 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 any procedures or assessments are performed, the nature of the study and the potential risks associated with the study must be explained to each subject and written informed consent (and assent as applicable) must be obtained. Once informed consent/assent (and Health Insurance Portability and Accountability Act [HIPAA] 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. Clinical laboratory investigations (hematology, biochemistry, urinalysis)
9. Focused ENT and eye examination
10. Allergen testing (if required)
11. A 12-lead electrocardiogram (ECG)
12. Urine pregnancy test, if applicable
13. Review instructions and provide training on the proper use of the NS using the placebo bottle provided in the IP kit provided for the run-in period
14. Priming and dispensation and administration of single-blind GSP 301 placebo NS pH [redacted] at the clinic
15. Distribution of the AR Assessment Diary
16. Subject assessment of AR symptoms and recording
17. AE query, if applicable

Subjects, who fail Screening based 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 1 occasion, dependent upon consultation with the Sponsor study team or designee. The subject may not be re-screened if the Investigator or the Sponsor determines that the failed criterion may impact the efficacy and/or safety assessments. However, subjects who have entered the single-blind,

placebo, run-in period and then fail to meet randomization criteria for any reason are not eligible for re-screening to avoid any undue bias.

11.2 Randomization Visit: Visit 2 (Day 1)

The following procedures and evaluations will be performed at this visit:

1. Distribution of RQLQ(S), review instructions with the subject, and subject completion of RQLQ(S)*
2. RCAT
3. Concomitant medication evaluation
4. Vital signs
5. Focused ENT and eye examination
6. Urine pregnancy test, if applicable
7. Review instructions and provide training on the proper use of the NS
8. Collection/review of the AR Assessment Diary
9. Distribution of the AR Assessment Diary
10. Physician assessment of nasal symptom severity at the clinical site
11. Review randomization criteria
12. Randomization/treatment assignment
13. Return of single-blind, placebo run-in study medication
14. Prime and dispensation of double-blind study medication
15. Administration of double-blind study medication under the supervision of the study personnel
16. AE query, if applicable
17. Subject compliance check (study procedures, AR Assessment Diary, and study medication)

*This must be the first procedure performed. Subjects returning for the Randomization Visit undergo RQLQ(S) and RCAT assessments (as applicable) before confirmation for randomization in the study. If the subject fails randomization criteria for any reason, the data collected for the RQLQ(S) and RCAT 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 RQLQ(S) and RCAT (as applicable), run-in study medication, and run-in diary as well as a 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 randomization criteria.

On the first day of treatment (Randomization Visit [Visit 2]), subjects will be instructed how to self-administer study medication while the first dose is taken at the clinic. Subjects will self-administer study medication [redacted] at home during the treatment period (Weeks 1-52). During the treatment period, subjects will assess their symptoms and complete the AR Assessment Diary every morning (AM).[redacted]

[redacted]

11.3 Treatment Visit: Visit 3 (Week 3 ±3 Days)

The following procedures and evaluations will be performed at this visit:

1. Concomitant medication evaluation
2. Focused ENT and eye examination
3. Urine pregnancy test, if applicable
4. Review instructions and provide training on the proper use of the NS
5. Collection/review of the AR Assessment Diary
6. Distribution of the AR Assessment Diary
7. Physician assessment of nasal symptom severity at the clinical site
8. Return of used double-blind study medication to the clinic
9. Prime and dispensation of double-blind study medication, as applicable
10. AE query, if applicable
11. Subject compliance check (study procedures, AR Assessment Diary, and study medication)

11.4 Treatment Visit: Visit 4 (Week 6 ±3 Days)

The following procedures and evaluations will be performed at this visit:

1. Distribution of RQLQ(S), review instructions with the subject, and subject completion of RQLQ(S). This must be the first procedure performed.
2. RCAT
3. Concomitant medication evaluation
4. Focused ENT and eye examination
5. Urine pregnancy test, if applicable
6. Review instructions and provide training on the proper use of the NS
7. Collection/review of the AR Assessment Diary
8. Distribution of the AR Assessment Diary
9. Physician assessment of nasal symptom severity at the clinical site
10. Return of used double-blind study medication to the clinic
11. Prime and dispensation of double-blind study medication, as applicable
12. AE query, if applicable.
13. Subject compliance check (study procedures, AR Assessment Diary, and study medication).

11.5 Treatment Visit: Visit 5 (Week 12 ±5 Days)

The following procedures and evaluations will be performed at this visit:

1. Concomitant medication evaluation
2. Focused ENT and eye examination
3. Urine pregnancy test, if applicable
4. Review instructions and provide training on the proper use of the NS
5. Collection/review of the AR Assessment Diary
6. Distribution of the AR Assessment Diary
7. Physician assessment of nasal symptom severity at the clinical site
8. Return of used double-blind study medication to the clinic
9. Prime and dispensation of double-blind study medication, as applicable
10. AE query, if applicable
11. Subject compliance check (study procedures, AR Assessment Diary, and study medication)

11.6 Treatment Visit: Visit 6 (Week 18 ±7 Days)

The following procedures and evaluations will be performed at this visit:

1. Concomitant medication evaluation
2. Focused ENT and eye examination
3. Urine pregnancy test, if applicable
4. Review instructions and provide training on the proper use of the NS
5. Collection/review of the AR Assessment Diary
6. Distribution of the AR Assessment Diary
7. Physician assessment of nasal symptom severity at the clinical site
8. Return of used double-blind study medication to the clinic
9. Prime and dispensation of double-blind study medication, as applicable
10. AE query, if applicable
11. Subject compliance check (study procedures, AR Assessment Diary, and study medication)

11.7 Treatment Visit: Visit 7 (Week 24 ±7 Days)

The following procedures and evaluations will be performed at this visit:

1. Concomitant medication evaluation
2. Focused ENT and eye examination
3. Urine pregnancy test, if applicable
4. Review instructions and provide training on the proper use of the NS

5. Collection/review of the AR Assessment Diary
6. Distribution of the AR Assessment Diary
7. Physician assessment of nasal symptom severity at the clinical site
8. Return of used double-blind study medication to the clinic
9. Prime and dispensation of double-blind study medication, as applicable
10. AE query, if applicable
11. Subject compliance check (study procedures, AR Assessment Diary, and study medication)

11.8 Treatment Visit: Visit 8 (Week 30 ±7 Days)

The following procedures and evaluations will be performed at this visit:

1. Distribution of RQLQ(S), review instructions with the subject, and subject completion of RQLQ(S). This must be the first procedure performed.
2. RCAT
3. Concomitant medication evaluation
4. Physical examination
5. Vital signs
6. Height and weight
7. Clinical laboratory investigations (hematology, biochemistry, urinalysis)
8. Focused ENT and eye examination
9. Urine pregnancy test, if applicable
10. Review instructions and provide training on the proper use of the NS
11. Collection/review of the AR Assessment Diary
12. Distribution of the AR Assessment Diary
13. Physician assessment of nasal symptom severity at the clinical site
14. Return of used double-blind study medication to the clinic
15. Prime and dispensation of double-blind study medication, as applicable
16. AE query, if applicable
17. Subject compliance check (study procedures, AR Assessment Diary, and study medication)

11.9 Treatment Visit: Visit 9 (Week 36 ±7 Days)

The following procedures and evaluations will be performed at this visit:

1. Concomitant medication evaluation
2. Focused ENT and eye examination
3. Urine pregnancy test, if applicable

4. Review instructions and provide training on the proper use of the NS
5. Collection/review of the AR Assessment Diary
6. Distribution of the AR Assessment Diary
7. Physician assessment of nasal symptom severity at the clinical site
8. Return of used double-blind study medication to the clinic
9. Prime and dispensation of double-blind study medication, as applicable
10. AE query, if applicable
11. Subject compliance check (study procedures, AR Assessment Diary, and study medication)

11.10 Treatment Visit: Visit 10 (Week 42 ±7 Days)

The following procedures and evaluations will be performed at this visit:

1. Concomitant medication evaluation
2. Focused ENT and eye examination
3. Urine pregnancy test, if applicable
4. Review instructions and provide training on the proper use of the NS
5. Collection/review of the AR Assessment Diary
6. Distribution of the AR Assessment Diary
7. Physician assessment of nasal symptom severity at the clinical site
8. Return of used double-blind study medication to the clinic
9. Prime and dispensation of double-blind study medication, as applicable
10. AE query, if applicable
11. Subject compliance check (study procedures, AR Assessment Diary, and study medication)

11.11 Treatment Visit: Visit 11 (Week 48 ±7 Days)

The following procedures and evaluations will be performed at this visit:

1. Concomitant medication evaluation
2. Focused ENT and eye examination
3. Urine pregnancy test, if applicable
4. Review instructions and provide training on the proper use of the NS
5. Collection/review of the AR Assessment Diary
6. Distribution of the AR Assessment Diary
7. Physician assessment of nasal symptom severity at the clinical site
8. Return of used double-blind study medication to the clinic
9. Prime and dispensation of double-blind study medication, as applicable

10. AE query, if applicable
11. Subject compliance check (study procedures, AR Assessment Diary, and study medication)

11.12 Final Visit: Visit 12 (Week 52 + 10 Days)

The following procedures and evaluations will be performed at this visit:

1. Distribution of RQLQ(S), review instructions with the subject, and subject completion of RQLQ(S). This must be the first procedure performed.
2. RCAT
3. Concomitant medication evaluation
4. Physical examination
5. Vital signs
6. Height and weight
7. Clinical laboratory investigations (hematology, biochemistry, urinalysis)
8. Focused ENT and eye examination
9. A 12-lead ECG
10. Urine pregnancy test, if applicable
11. Collection/review of the AR Assessment Diary
12. Physician assessment of nasal symptom severity at the clinical site
13. Return of used double-blind study medication to the clinic
14. AE query, if applicable
15. Subject compliance check (study procedures, AR Assessment Diary, and study medication)

11.13 Discontinuation Visit

The process to be followed for a subject who discontinues treatment or withdraws from the study is described in Section 9.4. If at any time point, a subject is deemed ineligible to continue in the study, the Final Visit/Discontinuation Visit (Visit 12) procedures will be conducted and recorded in the Early Withdrawal/Termination/Discontinuation pages of the CRF/eCRF. After completion of study participation, 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.

11.14 Unscheduled Visit

An unscheduled visit (or telephone contact) 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 (e.g., AEs, concomitant medications/treatments, and results from procedures or tests).

11.15 Follow-Up Visit

No Follow-up Visit is planned during the study.

12 STUDY PROCEDURES AND ASSESSMENTS

12.1 Demography and Other Pretreatment Assessments

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. Allergen testing data will be recorded in the source documents and CRF/eCRF with the description of the allergen.

Medical and surgical history and current medical conditions will be recorded at the Screening Visit (Visit 1). All relevant medical and surgical history within 2 years must be noted in the Medical History and Current Medical Conditions CRF/eCRF.

Other baseline and pretreatment assessments will be performed as designated in the Schedule of Procedures and Assessments (Appendix 1).

12.2 Efficacy Assessments

The primary objective of the study is to evaluate the long-term safety of GSP 301 NS. However, the long-term efficacy will also be evaluated.

12.2.1 Subject-Reported Nasal Symptoms

An 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 [redacted] The subjec will a ess and report his/her nasal symptoms in the morning (AM assessment) on each day of the placebo run-in and double-blind treatment periods prior to administering the study treatment. The subject will record the scores for each symptom in an AR Assessment Diary. The AM assessment should be performed prior to bathing, consumption of food or beverages, or strenuous activities. The morning dose of study medication should be administered immediately after completion of the AR Assessment Diary.

The subject will be asked to assess both reflective (i.e., an evaluation of symptom severity over the past 24 hours prior to the recording of the score) and instan aneous (i.e., an evaluation of the symptom severity just before taking study medication [redacted] nasal symptoms. Each of the following symptoms will be assessed.

Nasal Symptoms	
1. Nasal Congestion	2. Rhinorrhea (Runny Nose)
3. Nasal Itching	4. Sneezing

Each of the above symptoms will be rated on a 4-point severity scale as follows:

Score	Grade	Description
0	Absent	No sign/symptom evident
1	Mild	Signs/symptoms clearly present but minimal awareness; easily tolerated
2	Moderate	Definite awareness of signs/symptoms which are bothersome but tolerable
3	Severe	Signs/symptoms are hard to tolerate; cause interference with activities of daily living and/or sleeping

The subject will not assess AR symptoms in the evening. Howeve , e s ect will self-administer study medication in the evening [redacted]

12.2.2 Physician Assessment of Nasal Symptom Severity

The PNSS will be derived from the intensity of the following nasal symptoms associated with AR: rhinorrhea (runny nose), nasal congestion, nasal itching, and sneezing.[16] Clinicians will assess the severity of the above symptoms based on questioning the subjects (overall feeling since last visit), the ENT and eye examination, and other observations.

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

12.2.3 Rhinoconjunctivitis Quality of Life Questionnaire - Standardized Activities

The RQLQ(S) (Appendix 4) used in this study is a disease-specific, validated, quality-of-life (QOL) questionnaire developed to measure the functional problems (physical, emotional, and social) that are troublesome to adults and adolescents (aged ≥12 years) with allergies. The RQLQ(S) measures both atopic and non-atopic experiences as a result of subjects' nasal and ocular symptoms.

The RQLQ(S) has 28 questions in 7 domains (activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional).[17] The subject is asked to recall their experiences during the previous week and to give responses on a 7-point scale (0=not troubled to 6=extremely troubled) for the domains of activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, and eye symptoms. The domain "emotional" utilizes a 7-point scale (0=none of the time to 6=all of the time). This questionnaire should be completed as the first activity of visits that include this assessment.

The self-administered version of the RQLQ(S) will be completed by the subject at the investigational site at the Randomization Visit (Visit 2), Treatment Visit 4 (Week 6), Treatment Visit 8 (Week 30), and the Final Visit/Discontinuation Visit (Visit 12 at Week 52). The RQLQ(S) administration must be the first procedure conducted at these study visits.

The study site personnel and the Investigators will be provided with detailed instructions for 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. Caregivers or study site personnel are not allowed to interfere or communicate with the subject completing the questionnaire over and above re-stating the question(s) on the questionnaire exactly as written. Completion of the questionnaire may take approximately 10 minutes depending on the experience and capability of the individual completing the questionnaire. After completion of the RQLQ(S), the site personnel will check the questionnaire for completeness and legibility.

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

12.2.4 Rhinitis Control Assessment Test

The RCAT (Appendix 5) is a brief, patient-completed tool to evaluate rhinitis symptom control.[18] This questionnaire asks the subject about nasal and other allergy symptoms that are not related to a cold or flu, and the control of these symptoms over the past week. Responses to the questions are scored by the number next to the response box. The total RCAT score is calculated by adding individual RCAT item or domain scores. The total RCAT score can range from 6 to 30.

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

12.3 Pharmacokinetic, Pharmacodynamic, Biomarker and Pharmacogenomic Assessments

Not applicable.

12.4 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs, (including severity as mild, moderate and severe as per Section 12.4.1.2), and SAEs; regular monitoring of hematology, biochemistry, and urinalysis values (as applicable per the protocol or for safety reasons); periodic measurement of vital signs and ECGs; and physical examinations as detailed in the Schedule of Procedures and Assessments (Appendix 1). Additional details on the safety procedures performed in the study are detailed below.

Any abnormal laboratory test result (hematology, biochemistry, or urinalysis) or other safety assessment (eg, 12-lead ECGs, radiological scans, vital signs measurements), including any that worsen from baseline, that is considered to be clinically significant in the medical and scientific judgment of the Investigator will be recorded as an AE or SAE.

However, any clinically significant safety assessment that is 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 an AE or SAE.

12.4.1 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 the IB Section 6.4.8.2 Reference Safety Information within the Summary of Data and Guidance for Investigators.

12.4.1.1 Adverse Events

An AE is defined as any untoward medical occurrence in a subject administered IP 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 an IP, whether or not related to the IP. An AE includes any event, regardless of the presumed causality between the event and the IP.

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:

- IP overdose, whether accidental or intentional.
- IP abuse.
- An event occurring from IP withdrawal.
- Inadvertent or accidental IP exposure (e.g., product leaking or being spilled onto a subject or care-giver).
- Unexpected therapeutic or clinical benefit from the IP.
- Medication errors (i.e., 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 (e.g., endoscopy, appendectomy); the condition that led 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.

12.4.1.2 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 12.4.2 for the definition of a SAE).

12.4.1.3 Assessment of Relationship to Study Medication

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

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

Related: A causal relationship between the study treatment and the AE is a reasonable possibility

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

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment 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 treatment-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 adverse event?

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 (run-in or double-blind), the answer must be no.

12.4.2 Serious Adverse Events

A 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.

- Requires hospitalization or prolongation of existing hospitalization.
  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.
- 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 (e.g., 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 1 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.

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

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

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

Fax: + 44 1923 251137

Email: GlobalClinicalSAE@glenmarkpharma.com

When further information becomes available, the SAE Form should be updated with the new information and reported immediately using 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.

12.4.3 Pregnancy

Any subject who has a positive pregnancy test after signing the informed consent form (ICF) should be withdrawn from the study immediately and study medication should be discontinued immediately.

Any pregnancy that occurs during study participation must be reported to the Sponsor, using a Clinical Study 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: + 44 1923 251137

Email: GlobalClinicalSAE@glenmarkpharma.com

When further information becomes available, the Clinical Study Pregnancy Form should be updated with all new information and reported immediately using the same contact information above. The pregnancy must be followed up to determine the 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 that occurs in association with a pregnancy that is brought to the Investigator's attention after the subject has completed the study, and is considered by the Investigator as possibly related to the investigational product, must be promptly reported to the Sponsor.

The Investigator must attempt to collect pregnancy information on any female partner, of a male study subject, who becomes pregnant while the male partner is participating in this study. The Investigator must 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 must also be followed up to determine the outcome of the pregnancy. Information on the status of the mother and child must 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 must be reported.

12.4.4 Adverse Events of Special Interest

Not applicable.

12.4.5 Collection and Recording of Adverse Events and Serious Adverse Events

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

Adverse events will be collected from the time of signing the ICF until the last contact.

Serious adverse events will be collected over the same time period as stated above for AEs. However, any SAEs assessed as related to study participation (e.g., IP, protocol mandated procedures, invasive tests, or change in existing therapy) or related to a concomitant medication that is a Sponsor 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 12.4.2.

The Investigator will enquire about the occurrence of AEs/SAEs at every visit throughout the study (including Follow-up and Discontinuation 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.

All AEs regardless of seriousness, severity, or relationship to the study medication must be recorded on the AE pages of the CRFs/eCRFs.

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 unavailable, each sign and symptom should be recorded as an AE. Update the AE CRF/eCRF record with the relevant diagnosis alone, when this is available.

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

12.4.6 Clinical Laboratory Tests

Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures and Assessments (Appendix 1) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study. Lists of clinical laboratory tests are provided in Appendix 3 List of Clinical Laboratory Tests. A central laboratory will be used to measure laboratory parameters that are part of the safety assessments.

12.4.7 Urine Pregnancy Testing

Urine pregnancy testing will be completed by a dipstick evaluation at the Investigator's clinical facility for all female subjects of childbearing potential as designated in the Schedules of Procedures and Assessments (Appendix 1) or as indicated by the subject's condition. The testing, based on beta human chorionic gonadotropin (β-HCG), 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 Randomization Visit (Visit 2) will require immediate Sponsor notification, discontinuation of study medication, and termination from the study.

12.4.8 Vital signs

Vital signs evaluation will be performed as designated in the Schedule of Procedures and Assessments (Appendix 1). 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. For each subject, blood pressure measurements will be taken from the same arm throughout the study. Pulse rate will be measured from the radial pulse counted electronically or manually over at least 15 seconds and adjusted to a per minute value. 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.

12.4.9 Electrocardiograms

Electrocardiograms will be obtained as designated in the Schedule of Procedures and Assessments (Appendix 1). Subjects must be in the recumbent or supine position for a period of 5 minutes prior to the 12-lead ECG.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Adverse Events, Section 12.4.1) and the CRF/eCRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the AE CRF/eCRF.

For ECG abnormalities that meet criteria for an SAE (Section 12.4.2), the site must fax or email the SAE report, including the ECG tracing and report, to the Sponsor using the SAE form.

12.4.10 Physical Examinations

Physical examinations (comprehensive) will be performed as designated in the Schedule of Procedures and Assessments (Appendix 1). 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 screening physical examination or subsequent findings that meet the definition of an AE will be recorded on the AE CRF/eCRF.

Height (cm) and weight (kg) will also be measured at Screening Visit (Visit 1) and at the Final Visit / Discontinuation Visit (Visit 12).

12.4.11 Focused Ears, Nose, and Throat and Eye Examinations

Focused ENT and eye examinations will be performed as designated in the Schedule of Procedures and Assessments (Appendix 1). The Investigator or medically qualified designee will perform a thorough and focused ENT and eye examination. Whenever possible, the same medically qualified person should complete this assessment for the same subject throughout that 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 (e.g., 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 provided as follows.

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: 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 examination will be conducted to evaluate evidence of throat irritation, candidiasis and postnasal drip. Any clinically significant new findings, not related to the study indication (PAR), 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 a qualified ENT specialist or other medically qualified specialist (qualified to evaluate and record these conditions, as judged by the Investigator) for further evaluation as soon as possible. A record from the specialist 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 12.4 and Section 12.4.5). The Sponsor will collect the de-identified information as part of the study data collection. Eligibility of the subject for participation in the study will be at the Investigator's discretion based on whether or not the protocol-defined selection criteria are met.

A thorough eye examination will also be performed by the Investigator or medically qualified designee to assess signs of AR as well as any known complications of intranasal corticosteroid or antihistamine use. If needed, the subject should be referred to a qualified ophthalmologist for further evaluation as soon as possible.

12.4.12 Confirmation of Medical Care by Another Physician

The Investigator will instruct subjects 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. When the subject is going to receive medical care by another physician, the

Investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

13 DATA ANALYSIS AND STATISTICAL METHODS

The statistical analysis will be coordinated by the responsible Sponsor biostatistician (or designee at the Contract Research Organization [CRO]). A Statistical Analysis Plan (SAP) will be written to provide details of the analysis, along with specifications for tables, listings, and figures to be produced. The SAP will be finalized before the database lock. 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 SAS® 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 endpoints, and frequency and percentage for categorical endpoints.

13.1 Sample Size

The sample size of 600 subjects for this study (400 subjects on GSP 301 NS and 100 subjects in each of the 2 placebo groups) is based on the ICH E1 Guideline (ICH E1)[19] and the FDA Guidance on Allergic Rhinitis,[14] which requires treatment of at least 300 subjects for 6 months and 100 subjects for 1 year. Based on an estimated attrition rate of 25% after 6 months and 50% after 52 weeks, 400 subjects in the GSP 301 NS treatment group are considered sufficient to meet the above requirements.

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.

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 efficacy assessment. This will be the primary analysis set for efficacy analyses.

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

The Safety Analysis Set (SAS) will consist of all subjects who took at least 1 dose of study medication following randomization and will be used for all safety analyses.

The RQLQ(S) Analysis Set will consist of all English-speaking subjects ≥18 years old with impaired QOL at baseline as defined by a RQLQ(S) score at the Randomization Visit (Visit 2) of 3.0 or greater.

13.3 Subject Disposition

The subject accountability and disposition information will be summarized by study treatment group. The number of subjects screened, treated with study medication during the 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 treatment group.

13.4 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.

13.5 Efficacy Analyses

Efficacy analysis will be conducted on the FAS and PPS. 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 (e.g., age, sex, race, and ethnicity) will be examined. Further details on the subgroups of interest will be specified in the SAP.

Change from baseline in average AM rTNSS and iTNSS over the first 6, 30, and 52 weeks of treatment will be analyzed using an analysis of covariance (ANCOVA) model adjusting for study treatment group, site, and baseline (defined as the average of the last 4 consecutive AM assessments during the last 4 days of the run-in period from the Day -3 AM assessment to the AM assessment on the day of randomization). At least 2 out of 4 assessments (scores) should be available in order to calculate the baseline scores for the AM rTNSS and iTNSS (linear, continuous covariate). Least squares means (LSMs) of the treatment differences and associated 95% confidence intervals (95% CIs) and p-values will be presented. A multiple, imputation-based approach where complete data sets are drawn will be used for handling missing data in the efficacy analysis. The imputation model will be defined and fully detailed in the SAP.

Changes from baseline in rTNSS and iTNSS at the end of each week of treatment and changes from baseline in individual nasal symptom scores over the first 6, 30, and 52 weeks (and at the end of each treatment week) of the treatment period will be analyzed in a similar manner as described above.

Changes from baseline in RQLQ(S) at Weeks 6, 30, and 52 will be analyzed for the FAS and the RQLQ(S) Analysis Set using ANCOVA models adjusting for study treatment group, site, and baseline RQLQ(S) (linear, continuous covariate). For subjects who withdraw early from the study, the RQLQ(S) score at their discontinuation visit will be used.

The analyses of RCAT results will be similar to the RQLQ(S) analyses except the RQLQ(S) analysis set will not apply.

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

13.6 Pharmacokinetic, Pharmacodynamic, Biomarker, and Pharmacogenomic/Pharmacogenetic Analyses

Not applicable.

13.7 Safety Analyses

Unless otherwise specified, 'baseline' will be defined as the last available assessment prior to the first dose of study medication following randomization.

13.7.1 Extent of Exposure

The number of subjects exposed to each study treatment will be summarized. The number of days on treatment and the number of days on study (run-in plus treatment periods) will be summarized by study treatment. In addition, treatment compliance will be summarized by categories (details will be provided in the SAP) and study treatment.

13.7.2 Adverse Events

Adverse events will be coded using the current Medical Dictionary for Regulatory Activities (MedDRA). Adverse events occurring between the signing of informed consent and administration of the first dose of randomized 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 randomized study medication will be defined as TEAEs.

The safety endpoints related to AEs are:

- Proportion of subjects with TEAEs.
- Proportion of subjects with treatment-related TEAEs.
- Incidence, type, and severity of the TEAEs after 30 weeks of study treatment.
- Incidence, type, and severity of the TEAEs after 52 weeks of study treatment.

The number and percentage of subjects with TEAEs will be summarized by study treatment group, overall, and by system organ class (SOC) and preferred term (PT) using frequency counts and percentages. The summaries will also include the number of TEAEs experienced. A similar summary will be produced for subjects with treatment-related TEAE.

The number and percentage of subjects with a TEAE that has a start date within 30 weeks of the start of treatment (≤182 days) will be summarized by severity and study treatment group, overall, and by SOC and PT using frequency counts and percentages. A similar summary will be produced including all TEAEs during the study (i.e., after 52 weeks of treatment).

If sufficient data exist, TEAE frequencies will be compared across treatment groups using Fisher's exact test or a similar test.

Additionally, the number and percentage of SAEs, TEAEs leading to discontinuation, and TEAEs related to the IP will be summarized by SOC, PT, and study treatment group. All AEs will be displayed in listings. AEs that occur during the run-in period will be summarized separately.

13.7.3 Laboratory Data

The laboratory data (hematology, biochemistry, and urinalysis), will be summarized for each visit at which laboratory assessments are done (Screening Visit [Visit 1], Week 30 [Visit 8], and Week 52 [Visit 12]). In addition, values outside the normal range and values deemed as

clinically significant by the Investigator will be listed. The data will be summarized using descriptive statistics. All laboratory data will be displayed in listings.

13.7.4 Vital Signs

Descriptive statistics will be used to summarize vital sign results and changes from baseline by treatment group and time point (Week 30 [Visit 8] and Week 52 [Visit 12]). 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.

13.7.5 Electrocardiograms

Descriptive statistics for ECG parameters and changes from baseline will be presented by treatment group. Shift tables will present changes from baseline to end of treatment in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant). All ECG data will be displayed in listings.

13.7.6 Physical Examinations

Descriptive statistics will be used to summarize physical examination results by treatment group and time point (Screening, Week 30 and Week 52). The number of subjects with findings of potential clinical significance will be tabulated. All physical examination data will be displayed in listings.

13.7.7 Focused Ears, Nose, and Throat and Eye Examinations

Descriptive statistics will be used to summarize ENT and eye examination results by treatment group and time point (Week 30 and Week 52). The number of subjects with findings of potential clinical significance will be tabulated. All ENT and eye examination data will be displayed in listings.

13.7.8 Concomitant Medication and Withdrawals

Any withdrawals from the study will be listed and summarized by reason for withdrawal, study treatment group and by any other relevant categorical information. Descriptive statistics will be used to summarize the number (%) of subjects who used rescue medication along with the type, dose, and duration of rescue medication.

Concomitant medications, including rescue medications, will be listed.

13.8 Interim Analysis

No interim analysis is planned for this study.

14 QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor or designee will implement and maintain quality assurance and quality control systems with Standard Operating Procedures (SOP) to ensure that this clinical study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, Good Clinical Practice (GCP) standards, ICH, and other applicable local regulations.

The Sponsor is responsible for securing agreement among collaborating parties to ensure direct access to clinical-study-related sites and material to ensure that all data are reliable and have been processed correctly.

14.1 Procedures for Monitoring Compliance

To ensure the completeness and accuracy of CRFs/eCRFs completion, each site will be monitored by a designated Clinical Study Monitor. At regular intervals, the study monitor will visit the study site(s). The frequency of visits will vary depending on the recruitment rate. It is the duty of the Investigator to provide open access to the monitor of all study related records at previously agreed upon times. The Sponsor, IRB/IEC, and regulatory authorities shall have right to direct access to source data for verification.

14.2 Inspection

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

14.3 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 accurately recorded and analyzed according to the protocol, SOPs, GCP, and other 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.

15 ETHICS

15.1 Ethics Committee Approval

The clinical study protocol, ICF, and any documents that are given to the study subjects (e.g., questionnaires, diaries, etc.) must be reviewed and approved by an IRB or IEC constituted and functioning in accordance with Section 3 of ICH E6 (GCP) and any local regulations. Any protocol amendment, or revision to the ICF or other documents used in the study, will be resubmitted to the IRB/IEC for review and approval. Documentation of IRB/IEC compliance with ICH E6 and any local regulations regarding constitution and review conduct will be provided to the Sponsor.

Any queries raised by the IRB/IEC in regard to the study will be provided in writing to the Investigator. The Investigator will be responsible for providing answers and resolving all queries prior to study start. The Investigator must consult with the Sponsor before providing a response to the IRB/IEC.

A signed letter of study approval from the IRB/IEC chairman must be sent to the Investigator or Sponsor, depending on local regulatory obligations, before study start and the release of any IP to the site by the Sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the Investigator (or if regionally required, the head of the medical

institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the Sponsor (or Investigator), as appropriate.

Written approvals from the IRB/IEC and Regulatory Authority must be obtained before starting the informed consent process for the first subject at the site. The IRB/IEC will also review the ICF and endorse it in writing.

Study progress will be reported to IRBs/IECs annually (or as required) by the Investigator or Sponsor, depending on local regulatory obligations. If the Investigator is required to report to the IRB/IEC, he/she will forward a copy to the Sponsor/designee at the time of each periodic report. The Investigator(s) or the Sponsor will submit, depending on local regulations, periodic reports and inform the IRBs/IECs (or if regionally required, the Investigator and the relevant IRB/IEC via the head of the medical institution) of any reportable AEs per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the Investigator will provide the IRBs/IECs with a brief report of the outcome of the study, if required.

At the end of the study, the Investigator should notify the IRB/IEC and Regulatory Authority in accordance with local regulatory obligations. The end of the study will be the date of the last study visit for the last subject in the study. The Investigator or Sponsor, depending on local regulatory obligations, should also provide the IRB/IEC with an end-of-study notification.

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.

15.2 Ethical Conduct of the Study

This study will be conducted in accordance with the SOPs of the Sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2008.
- ICH E6 Guideline for GCP.
- Title 21 of the US Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312.

15.3 Informed Consent/Assent Process

The Investigator is responsible for obtaining informed consent from each subject/legally acceptable representative (LAR) participating in the study. All pertinent aspects of the study must be explained to the subject/LAR before he or she signs the ICF. 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 procedures and the administration of the first dose of the study medication. Each subject 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 before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the Sponsor and kept on file according to local procedures at the site.

The subject 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 for the subject's continuation in the study.

15.4 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, as appropriate.

These requirements for approval will in no way prevent any immediate action from being taken by the Principal Investigator in the interest 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 changes 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, may be required to send a letter to the IRB/IEC and the Regulatory Authorities notifying them of such changes.

15.5 Protocol Deviation

Any deviation from the protocol will be recorded as a protocol deviation in the CRF/eCRF and reported to the IRB per IRB policy.

16 DATA HANDLING AND RECORD KEEPING

16.1 Data Management

Data from the study will be managed by the Sponsor's Clinical Research Operations group or designee. A copy of the study results will be made available to the Clinical Investigator for review.

All data will be directly recorded on the CRFs/eCRFs. The Investigator will allow representatives of the Sponsor, regulatory agencies, and their designees to inspect all study documents (including, but not limited to, consent forms, IP accountability forms, IRB/IEC approvals) and pertinent hospital or clinic records for confirmation of data throughout and after completion of the study. Monitoring visits will be conducted as needed during the course of the study. A complete review of source documentation of key efficacy and safety data will be conducted at each monitoring visit for verification that all information recorded in the CRF/eCRF accurately reflects the data recorded in the subject's source documents.

All data verification, using hospital or clinic records, will be performed respecting subject confidentiality and will be carried out in accordance with local SOPs.

All subject data generated during the study will be recorded and transcribed in the CRF/eCRF. The Principal Investigator must approve the CRF/eCRF to confirm eligibility. The final authorization of the CRF/eCRF data is the Investigator Signature Form. This form must be approved by the Principal Investigator to signify that he/she has reviewed the CRF/eCRF, including all laboratory and safety assessments, and that all of the data therein is complete and accurate.

The data will be reviewed to ensure that the forms were completed appropriately and that all data has the correct subject identification number.

16.2 Direct Access to Source Data/Documents

Essential demographic data will be documented both within the subject’s medical record notes (source data) and within the study CRF/eCRF and be available for inspection by the Sponsor’s Clinical Study Monitor, including electronic records. Source data will also include date of consent, time of drug administration and blood sampling, together with vital signs recorded at each visit.

It is the responsibility of the Investigator(s) to maintain accurate and up to date records of all clinical study related activities, which should be entered on the source documents and CRFs/eCRFs provided. The CRFs/eCRFs should be made available to the Clinical Study Monitor on request, and in the event of a formal investigational site audit.

16.3 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 his/her colleagues and employees 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 IB, 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 prevail to the extent of such inconsistency.

16.4 Record Retention

On completion of the study, electronic copies of all CRFs/eCRFs (if generated) or the paper copies of the entire raw data generated during the study will be provided to the investigational site for safekeeping for the duration stipulated by ICH GCP (currently 15 years or last marketing authorization, whichever is later).

17 FINANCING AND INSURANCE

The Sponsor will provide 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 (e.g., 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(s) 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(s) and 60 days of receiving the manuscript(s) 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 prevail to the extent of such inconsistency.

19 DISCONTINUATION OF STUDY

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 IRB/IEC will also be informed promptly and

provided 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 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 above.

20 REFERENCES

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21 APPENDICES

21.1 Appendix 1: Schedule of Procedures and Assessments

Visits	**Screening Visit (SV) Visit 1**	**Randomization Visit (RV) Visit 2**	**Treatment Visits (TV)**									**Final Visit / Discontinuation Visit (FV/DV) Visit 12**
			TV 3	**TV4**	**TV 5**	**TV 6**	**TV 7**	**TV 8**	**TV 9**	**TV 10**	**TV 11**	
Week	**-1**	**1**	**3**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**52**
Day ± Window	**(-7 to -10)**	**1**	**22±3**	**43±3**	**85±5**	**127±7**	**169±7**	**211±7**	**253±7**	**295±7**	**337±7**	**365+10**
Activity / Observation												
Written informed consent (assent, if applicable) and HIPAA authorization	X											
Inclusion/exclusion criteria review	X											
Demographic data	X											
Medical & treatment history	X											
Concomitant medication evaluation	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X							X				X
Vital signs	X	X						X				X
Height and weight measurements	X							X				X
Clinical laboratory investigations (hematology, biochemistry, urinalysis)[a]	X							X				X

Visits	**Screening Visit (SV) Visit 1**	**Randomization Visit (RV) Visit 2**	**Treatment Visits (TV)**									**Final Visit / Discontinuation Visit (FV/DV) Visit 12**
			TV 3	**TV4**	**TV 5**	**TV 6**	**TV 7**	**TV 8**	**TV 9**	**TV 10**	**TV 11**	
Week	**-1**	**1**	**3**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**52**
Day ± Window	**(-7 to -10)**	**1**	**22±3**	**43±3**	**85±5**	**127±7**	**169±7**	**211±7**	**253±7**	**295±7**	**337±7**	**365+10**
Focused ENT and eye examination[b]	X	X	X	X	X	X	X	X	X	X	X	X
Allergen testing (skin prick test for relevant allergen, if required)[c]	X											
12-lead ECG	X											X
Urine pregnancy test (if applicable)	X	X	X	X	X	X	X	X	X	X	X	X
Review instructions and train on the proper use of the nasal spray using the GSP 301 placebo NS [redacted] bottle	X											
Review instructions and train on the proper use of the nasal spray		X	X	X	X	X	X	X	X	X	X	
Prime and dispensation and administration of single-blind GSP 301 placebo NS [redacted] at the clinic[d]	X											
Return single-blind GSP 301 placebo NS [redacted] to the clinic[e]		X										
Distribution of the AR Assessment Diary	X	X	X	X	X	X	X	X	X	X	X	

Visits	**Screening Visit (SV) Visit 1**	**Randomization Visit (RV) Visit 2**	**Treatment Visits (TV)**									**Final Visit / Discontinuation Visit (FV/DV) Visit 12**
			TV 3	**TV4**	**TV 5**	**TV 6**	**TV 7**	**TV 8**	**TV 9**	**TV 10**	**TV 11**	
Week	**-1**	**1**	**3**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**52**
Day ± Window	**(-7 to -10)**	**1**	**22±3**	**43±3**	**85±5**	**127±7**	**169±7**	**211±7**	**253±7**	**295±7**	**337±7**	**365+10**
Collection/Review of the AR Assessment Diary		X	X	X	X	X	X	X	X	X	X	X
Subject assessment of AR symptoms and recording and self-administration of placebo run-in medication[d]	X[d] →											
Subject assessment of AR symptoms and recording and self-administration of double-blind study medication[d]		X →										→
Physician assessment of nasal symptom severity		X	X	X	X	X	X	X	X	X	X	X
Review randomization criteria		X										
Randomization/treatment assignment		X										
Prime and dispensation of double-blind study medication		X	X	X	X	X	X	X	X	X	X	
Administration of double-blind study medication at the clinic[d]		X										
Return double-blind study medication to the clinic[e]			X	X	X	X	X	X	X	X	X	X
Distribution of the RQLQ(S), review instructions with the subject, and subject completion of the RQLQ(S)[f]		X		X				X				X
RCAT		X		X				X				X

Visits	Screening Visit (SV) Visit 1	Randomization Visit (RV) Visit 2	Treatment Visits (TV)									Final Visit / Discontinuation Visit (FV/DV) Visit 12
			TV 3	TV4	TV 5	TV 6	TV 7	TV 8	TV 9	TV 10	TV 11	
Week	**-1**	**1**	**3**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**52**
Day ± Window	**(-7 to -10)**	**1**	**22±3**	**43±3**	**85±5**	**127±7**	**169±7**	**211±7**	**253±7**	**295±7**	**337±7**	**365+10**
Adverse events monitoring	X	X	X	X	X	X	X	X	X	X	X	X
Subject compliance check		X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AM = morning; AR = allergic rhinitis; ECG = electrocardiogram; ENT = ears, nose, and throat; HIPAA = Health Insurance Portability and Accountability Act; NS = nasal spray; RQLQ(S) = Rhinoconjunctivitis Quality of Life Questionnaire - Standardized Activities; RCAT = Rhinitis Control Assessment Test.

[a] Refer to Appendix 3 List of Clinical Laboratory Tests

[b] A focused ENT and eye examination will be done at all visits. Focused nasal examinations will be performed to assess signs of AR as well as known complications of intranasal corticosteroid or antihistamine use (i.e., bleeding, perforation, and ulceration). Throat examinations will be conducted to evaluate evidence of throat irritation and candidiasis. . If at any visit, clinically significant nasal ulceration, nasal mucosal erosion, and nasal septal perforation are observed, or a finding at a previous visit has worsened (as judged by the Investigator), 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 specialist 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 12.4.11). The Sponsor 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 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. A thorough eye examination will also be performed by the Investigator or medically qualified designee to assess signs of AR as well as any known complications of intranasal corticosteroid or antihistamine use. If needed, the subject should be referred to a qualified ophthalmologist for further evaluation as soon as possible.

[c] Documentation of a positive result within the last year (12 months) before the Screening Visit (Visit 1) is acceptable to meet the eligibility criteria. Intradermal and/or RAST testing will not be accepted.

[d] Generally, subjects will assess/record AR symptoms and take study medication at home. Subjects will assess their symptoms at specified clinic visits, as directed by the site personnel. The subject assessment and recording of AR symptoms will be done at the clinic at the Screening Visit (Visit 1) and study medication will be self-administered in the clinic at the Screening Visit (Visit 1) and the Randomization Visit (Visit 2). Morning doses of study medication during the run-in and treatment periods should be taken immediately following completion of the AR Assessment Diary (as applicable) except on the morning of the Screening Visit (Visit 1) and Randomization Visit (Visit 2) when the first dose of the placebo run-in medication and the double-blind study [redacted] respectively, will be self-administered in the clinic under the supervision of site personnel. [redacted] doses of study medication should be [redacted] At the Screening Visit (Visit 1), subjects should be told not to ta e study medication before coming to the cli

Randomization Visit (Visit 2). The last dose of the double-blind study medication should be the [redacted] dose on the day before the Final Visit/Discontinuation Visit (Visit 12). Subjects should be reminded not to take study medication on the morning of the Final Visit/Discontinuation Visit (Visit 12).

[e] Subjects should be instructed to bring their study medication kit to each visit after the Screening Visit (Visit 1). Site personnel will collect the kit, take the used study medication, and return the rest of the kit to the subject, as applicable.

[f] The RQLQ(S) must be the first procedure conducted at these visits.

21.2 Appendix 2: Subject Instructions for Proper Use of Nasal Spray Bottle

Subjects will administer their assigned study medication on their own (self-administration) [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); however, 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 (morning and evening).

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 1 nostril, pointing it slightly toward the outside nostril wall away from the nasal septum (the wall between the 2 nostrils), while holding your other nostril closed with 1 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 2 nostrils).
6. [redacted]

7. [redacted]
8. Replace the protective (dust) cap on the nasal spray bottle.
9. 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 if this was not done at the clinic. DO NOT prime the bottle every day. In some instances, study personnel may ask you to prime a new bottle at home prior to the 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 (morning and evening).
- After you finish administering the medication, wipe the tip with a clean dry tissue or cloth, replace the 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.

21.3 Appendix 3 List of Clinical Laboratory Tests

Safety Laboratory Test Panels

Serum Chemistry	Hematology	Urinalysis
Glucose	Hemoglobin	Urine protein
Blood urea nitrogen	Erythrocytes	pH
Creatinine	Mean corpuscular volume	Urine blood
Sodium	Platelets	Specific gravity
Potassium	Reticulocytes (absolute)	Urine ketones
Calcium	Leukocytes	Urine bilirubin
Chloride	Differential (absolute and percent):	Urine glucose
Bicarbonate	Eosinophils	Leukocytes
Bilirubin, direct bilirubin	Basophils	
Alkaline phosphatase	Neutrophils	
Aspartate aminotransferase (=SGOT)	Lymphocytes	
Alanine aminotransferase (=SGPT)	Monocytes	
Gamma glutamyl transferase	Coagulation	
Total protein	Activated partial thromboplastin time	
Albumin	Prothrombin time	
	Prothrombin time International Normalized Ratio	

21.4 Appendix 4: Rhinoconjunctivitis Quality-Of-Life Questionnaire with Standardized Activities

General Instructions:

1. This must be the first procedure performed at the visit.

2. A paper version of RQLQ(S) will be provided to subjects.

3. Subjects should be placed in a quiet room to fill out the RQLQ(S).

4. Subjects must complete the questionnaire on their own.

5. All friends/relatives/caregivers should be asked to wait in a separate room.

6. Clinical coordinators/study site personnel should never assist the subjects in answering any question on the RQLQ(S). The best approach is to repeat the question exactly as it is worded in the questionnaire, if consulted. **Under no circumstances should the question be reworded in an attempt to explain it to the subjects**.

Specific Instructions for the Clinical Coordinators/Site Personnel Prior to Subjects Completing the RQLQ(S):

The clinical staff must:
1. Tell subjects that all questions on the questionnaire (28 questions) must be answered.

2. Tell subjects that only 1 response may be given for each question.

3. Remind subjects that they are scoring limitations experienced specifically related to allergic rhinitis and not because of any other problems they may be experiencing.

4. Remind subjects that they should focus on the limitations due to allergic rhinitis that have occurred within the last week.

5. Tell subjects that they need to circle the number for each question that most closely matches how their allergy symptoms have affected their life within the past week.

After the subject has completed the RQLQ(S), the clinical coordinator/site personnel should review the completed questionnaire to ensure that all questions have been answered.

RHINOCONJUNCTIVITIS QUALITY OF LIFE QUESTIONNAIRE WITH STANDARDISED ACTIVITIES (RQLQ(S)

SELF-ADMINISTERED
(≥12 years)

For further information:

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NOVEMBER 2008

RHINOCONJUNCTIVITIS
QUALITY OF LIFE QUESTIONNAIRE (S)
SELF-ADMINISTERED ≥ 12

PATIENT ID_____

DATE_____

Please complete **all** questions by circling the number that best describes how **troubled** you have been during the **last week as a result of your nose/eye symptoms.**

ACTIVITIES

How **troubled** have you been by each of these activities during the **last week** as a result of your nose/eye symptoms?

	Not troubled	Hardly troubled at all	Somewhat troubled	Moderately troubled	Quite a bit troubled	Very troubled	Extremely troubled
1. REGULAR ACTIVITIES AT HOME AND AT WORK/ SCHOOL (tasks that you have to do regularly at work/school and around your home)	0	1	2	3	4	5	6
2. SOCIAL ACTIVITIES (*e.g.,* activities with your family and friends, playing with children and pets, sex, hobbies)	0	1	2	3	4	5	6
3. OUTDOORS ACTIVITIES (*e.g.,* gardening, mowing the lawn, sitting outdoors, sports, going for a walk)	0	1	2	3	4	5	6

SLEEP

How **troubled** have you been by each of these sleep problems during the **last week** as a result of your nose/eye symptoms?

	Not troubled	Hardly troubled at all	Somewhat troubled	Moderately troubled	Quite a bit troubled	Very troubled	Extremely troubled
4. Difficulty getting to sleep	0	1	2	3	4	5	6
5. Wake up during night	0	1	2	3	4	5	6
6. Lack of a good night's sleep	0	1	2	3	4	5	6

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RHINOCONJUNCTIVITIS
QUALITY OF LIFE QUESTIONNAIRE (S)
SELF-ADMINISTERED ≥ 12

PATIENT ID_____

DATE_____

NON-NOSE/EYE SYMPTOMS

How **troubled** have you been during the **last week** as a result of these symptoms?

		Not troubled	Hardly troubled at all	Somewhat troubled	Moderately troubled	Quite a bit troubled	Very troubled	Extremely troubled
7.	Fatigue	0	1	2	3	4	5	6
8.	Thirst	0	1	2	3	4	5	6
9.	Reduced productivity	0	1	2	3	4	5	6
10.	Tiredness	0	1	2	3	4	5	6
11.	Poor concentration	0	1	2	3	4	5	6
12.	Headache	0	1	2	3	4	5	6
13.	Worn out	0	1	2	3	4	5	6

PRACTICAL PROBLEMS

How **troubled** have you been by each of these problems during the **last week** as a result of your nose/eye symptoms?

		Not troubled	Hardly troubled at all	Somewhat troubled	Moderately troubled	Quite a bit troubled	Very troubled	Extremely troubled
14.	Inconvenience of having to carry tissues or handkerchief	0	1	2	3	4	5	6
15.	Need to rub nose/eyes	0	1	2	3	4	5	6
16.	Need to blow nose repeatedly	0	1	2	3	4	5	6

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RHINOCONJUNCTIVITIS
QUALITY OF LIFE QUESTIONNAIRE (S)
SELF-ADMINISTERED ≥ 12

PATIENT ID_____

DATE_____

NASAL SYMPTOMS

How **troubled** have you been by each of these symptoms during the **last week**?

	Not troubled	Hardly troubled at all	Somewhat troubled	Moderately troubled	Quite a bit troubled	Very troubled	Extremely troubled
17. Stuffy/blocked	0	1	2	3	4	5	6
18. Runny	0	1	2	3	4	5	6
19. Sneezing	0	1	2	3	4	5	6
20. Post nasal drip	0	1	2	3	4	5	6

EYE SYMPTOMS

How **troubled** have you been by each of these symptoms during the **last week**?

	Not troubled	Hardly troubled at all	Somewhat troubled	Moderately troubled	Quite a bit troubled	Very troubled	Extremely troubled
21. Itchy eyes	0	1	2	3	4	5	6
22. Watery eyes	0	1	2	3	4	5	6
23. Sore eyes	0	1	2	3	4	5	6
24. Swollen eyes	0	1	2	3	4	5	6

z:\WordPerfect\Wpdocs\Qolq\Namerica\Rhinocon\Stndrhin\SRQLQS + 12.DOC

RHINOCONJUNCTIVITIS
QUALITY OF LIFE QUESTIONNAIRE (S)
SELF-ADMINISTERED ≥ 12

PATIENT ID_____

DATE_____

EMOTIONAL

How often during the **last week** have you been troubled by these emotions as a result of your nose/eye symptoms?

		None of the time	Hardly any time at all	A small part of the time	Some of the time	A good part of the time	Most of the time	All of the time
25.	Frustrated	0	1	2	3	4	5	6
26.	Impatient or restless	0	1	2	3	4	5	6
27.	Irritable	0	1	2	3	4	5	6
28.	Embarrassed by your symptoms	0	1	2	3	4	5	6

21.5 Appendix 5: Rhinitis Control Assessment Test

This questionnaire asks about your nasal and other allergy symptoms that are not related to a cold or the flu, and the control of these symptoms. For each question, please choose the response that best describes your nasal and other allergy symptoms.

1. **During the past week, how often did you have nasal congestion?**

Never	Rarely	Sometimes	Often	Extremely often
☐[5]	☐[4]	☐[3]	☐[2]	☐[1]

2. **During the past week, how often did you sneeze?**

Never	Rarely	Sometimes	Often	Extremely often
☐[5]	☐[4]	☐[3]	☐[2]	☐[1]

3. **During the past week, how often did you have watery eyes?**

Never	Rarely	Sometimes	Often	Extremely often
☐[5]	☐[4]	☐[3]	☐[2]	☐[1]

4. **During the past week, to what extent did your nasal or other allergy symptoms interfere with your sleep?**

Not at all	A little	Somewhat	A lot	All the time
☐[5]	☐[4]	☐[3]	☐[2]	☐[1]

5. **During the past week, how well were your nasal or other allergy symptoms controlled?**

Completely	Very	Somewhat	A little	Not at all
☐[5]	☐[4]	☐[3]	☐[2]	☐[1]

6. <u>During the past week,</u> how often did you <u>avoid</u> any activities (for example, visiting a house with a dog or cat, gardening) because of your nasal or other allergy symptoms?

Never	Rarely	Sometimes	Often	Extremely often
☐[5]	☐[4]	☐[3]	☐[2]	☐[1]

Scoring

Responses to the questions will be scored as indicated by the number next to the response box as shown in tables below. The total RCAT score should be calculated by adding individual numbers (the simple algebraic sum of the final item scores for each RCAT item) answered for each question. The total RCAT score can range from 6 to 30.

Scoring for Questions 1, 2, 3 and 6	
Response Choices	Final Item Value
Never	5
Rarely	4
Sometimes	3
Often	2
Extremely often	1

Scoring for Question 4	
Response Choices	Final Item Value
Not at all	5
A little	4
Somewhat	3
A lot	2
All of the time	1

Scoring for Question 5	
Response Choices	Final Item Value
Completely	5
Very	4
Somewhat	3
A little	2
Not at all	1

21.6 Appendix 6: 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: + 44 1923 251137

Email: GlobalClinicalSAE@glenmarkpharma.com

Medical Monitor (CRO):

[redacted]
Novum PRS
225 W. Station Square Drive
Suite 200
Pittsburgh, PA 15219
Tel: 1-412-363-3300 x 597
[redacted]

Medical Monitor (Glenmark):

[redacted]
Vice President, Clinical Sciences-Respiratory
Glenmark Pharmaceuticals Inc.
750 Corporate Drive, Mahwah, NJ 07430, USA
Office: 1-201-684-8015
Mobile: 1-201-675-9443
[redacted]

21.7 Appendix 7: GSP 301-303 Protocol Amendment 1.0

PROTOCOL NUMBER: GPL/CT/2014/018/III

Study Number: GSP 301-303

PROTOCOL AMENDMENT 1.0

SUMMARY OF CHANGES

A Double-Blind, Randomized, Parallel-Group Study to Evaluate Long-Term Safety, Tolerability, and Efficacy of a Fixed Dose Combination GSP 301 Nasal Spray Compared with Two Placebo Nasal Spray Formulations in Subjects (Aged 12 Years and Older) with Perennial Allergic Rhinitis (PAR)

PROTOCOL HISTORY

PROTOCOL VERSION 1.0 25-Jan-2016

PROTOCOL VERSION 2.0 31-Aug-2016

Description of Changes in Protocol Version 2.0 (Amendment 1.0) dated 31-Aug-2016

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

Key:
Bold: newly added text.
~~Strikethrough~~: deleted text from the previous version of the protocol.

A. Details of Substantial Changes to the Protocol.
Not applicable

B. Details of Non-substantial Changes to the Protocol:

From Protocol Version 1.0 25 Jan2015	To Protocol Version 2.0 (Amendment 1.0) 31-Aug-2016	Rationale for Amendment
1. Protocol synopsis, Section 9.3 Randomization Criteria and Section 13.5 Efficacy Analyses		
3. Minimum AM subject-reported rTNSS of an average of 5 (out of a possible 12) during the last 4 days of the run-in period (last 4 consecutive AM assessments from the Day -4-AM assessment to the AM assessment on the day of randomization). 4. Has an AM subject-reported reflective nasal congestion score ≥2 during the last 4 days of the run-in period (last 4 consecutive AM assessments from the Day -4 AM assessment to the AM assessment on the day of randomization). 5. Adequate AR Assessment Diary compliance – inadequate compliance is defined as missing 1 or more of the entries on 2 or more assessment sessions (AM) during the last 4 days of the run-in period (during the last 4 consecutive AM assessments from the Day -4-AM assessment to the AM assessment on the day of randomization). Efficacy Analyses	3. Minimum AM subject-reported rTNSS of an average of 5 (out of a possible 12) during the last 4 days of the run-in period (last 4 consecutive AM assessments from the **Day -3** ~~Day -4~~ AM assessment to the AM assessment on the day of randomization). 4. Has an AM subject-reported reflective nasal congestion score ≥2 during the last 4 days of the run-in period (last 4 consecutive AM assessments from the **Day -3** ~~Day -4~~ AM assessment to the AM assessment on the day of randomization). 5. Adequate AR Assessment Diary compliance – inadequate compliance is defined as missing 1 or more of the entries on 2 or more assessment sessions (AM) during the last 4 days of the run-in period (during the last 4 consecutive AM assessments from the **Day -3** ~~Day -4~~ AM assessment to the AM assessment on the day of randomization). Efficacy Analyses	Typographical error corrected for clarification and accuracy: Changed Day -4 to Day -3.

From Protocol Version 1.0 25 Jan2015	To Protocol Version 2.0 (Amendment 1.0) 31-Aug-2016	Rationale for Amendment
Change from baseline in average AM subject-reported rTNSS and iTNSS over the first 6, 30, and 52 weeks of treatment will be analyzed using an analysis of covariance (ANCOVA) model adjusting for study treatment group, site, and baseline (defined as the average of the last 4 consecutive AM assessments during the last 4 days of the run-in period from the Day -4 AM assessment to the AM assessment on the day of randomization).	Change from baseline in average AM subject-reported rTNSS and iTNSS over the first 6, 30, and 52 weeks of treatment will be analyzed using an analysis of covariance (ANCOVA) model adjusting for study treatment group, site, and baseline (defined as the average of the last 4 consecutive AM assessments during the last 4 days of the run-in period from the **Day -3** ~~Day 4~~ AM assessment to the AM assessment on the day of randomization).	
2. Appendix 2, Subject Instructions for Proper Use of Nasal Spray Bottle		
• Release 10 sprays into the air, away from the eyes and face, by pressing down and releasing the pump 10 times. • Prime the nasal spray bottle only one time (releasing 10 sprays) prior.	• Release **6** ~~10~~ sprays into the air, away from the eyes and face, by pressing down and releasing the pump **6** ~~10~~ times. • Prime the nasal spray bottle only one time (releasing **6** ~~10~~ sprays) prior.	The number of sprays (pressing down and release) required to prime the nasal spray has been reduced from 10 to 6. Based on additional analytical data it has been determined that 6 sprays are adequate to prime the pumps for this nasal spray bottle.
3. Appendix 6, List of Contact Details		
(New appendix, not in protocol version 1.0).	The following information has been added: **SAE and Pregnancy Reporting:** **Fax: + 44 1923 251137** **Email:** **GlobalClinicalSAE@glenmarkpharma.com** **Medical Monitor (CRO)** [redacted] **Novum PRS** **225 W. Station Square Drive** **Suite 200** **Pittsburgh, PA 15219** **Tel: 1-(412) 363-3300 x 597**	The following information has been added for clarity: SAE and Pregnancy Reporting contact details CRO Medical Monitor contact details. Sponsor Medical Monitor contact details.

From Protocol Version 1.0 25 Jan2015	To Protocol Version 2.0 (Amendment 1.0) 31-Aug-2016	Rationale for Amendment
	[redacted] **Medical Monitor (Glenmark):** [redacted] **Vice President, Clinical Sciences-Respiratory** **Glenmark Pharmaceuticals Inc.** **750 Corporate Drive, Mahwah, NJ 07430, USA** **Office: 1-201-684-8015** **Mobile: 1-201-675-9443** [redacted]	