TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A Randomized, Doubled-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Once-Daily, Intranasal Administration of Fluticasone Furoate Nasal Spray 55 µg and 110 µg for 4 Weeks in Chinese Pediatric Subjects Ages 2 to 12 years with Allergic Rhinitis

Compound Number: GW685698

Development Phase: IV

Effective Date: 15-JAN-2016

Protocol Amendment Number: 02

Author (s): PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2014N205225_00	2015-MAR-09	Original
2014N205225_01	2015-JUL-13	Amendment No. 1
This protocol amendment is being implemented to update inclusion/exclusion criteria, screening/baseline/run-in failures clarified and other minor protocol clarifications		
2014N205225_02	2016-JAN-15	Amendment No. 2
Protocol defined positive Skin Prick Test (SPT) as diameter of wheal which is inconsistent with some of local laboratory tests. This was affecting patient recruitment.		

Copyright 2016 the GlaxoSmithKline group of companies. All rights reserved.
Unauthorised copying or use of this information is prohibited.

SPONSOR SIGNATORY

PPD

PPD

Wim Swy
Country M
China and

15/01/2016

Date

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD				Rm. 802, Tower A, Ocean International Center no. 56, Mid 4th East Ring Rd. Beijing.100025
Secondary Medical Monitor					Rm. 802, Tower A, Ocean International Center no. 56, Mid 4th East Ring Rd. Beijing.100025
SAE group		PPD		PPD	No.1, 917 Halei Road, Zhangjiang Hi-tech Park, Pudong, Shanghai.201203

Sponsor Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
United Kingdom (UK)

Regulatory Agency Identifying Number(s): [2014B01855]

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol 201492

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:		
Investigator Address:		
Investigator Phone Number:		
Investigator Signature		Date

TABLE OF CONTENTS

PAGE

1. PROTOCOL SYNOPSIS FOR STUDY 201492

Rationale

Fluticasone Furoate is a corticosteroid with potent glucocorticoid activity. Intranasal corticosteroids are among the preferred treatments for allergic rhinitis (AR), and Fluticasone Furoate Nasal Spray has been proved as an excellent option in Chinese adult patients with AR. This study is to evaluate the efficacy and safety of Fluticasone Furoate Nasal Spray (FFNS) 55 µg and 110 µg once daily for 4 weeks in Chinese pediatric subjects ages 2 to 12 years with AR.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To establish the efficacy of FFNS 55 µg and 110 µg QD versus vehicle placebo nasal spray in pediatric subjects (ages 2 to 12 years) with AR	• Mean change from baseline over the first 2 weeks treatment period in daily, reflective total nasal symptom scores (rTNSS) in subjects ages 2 to 12 years
Secondary	
• To investigate the safety of FFNS 55 µg and 110µg QD versus vehicle placebo nasal spray in pediatric subjects (ages 2 to 12 years) with AR	**Key secondary efficacy endpoints** • Overall evaluation of response to therapy (evaluated on a 7-point categorical scale) • Mean change from baseline in intranasal finding score by anterior rhinoscopy • Mean change from baseline in reflective total ocular symptoms score (rTOSS) • Rescue loratadine use (mean rescue-free days) **Safety endpoints** • Frequency and type of clinical adverse events • Results of clinical laboratory tests • Results of physical and nasal examination • Vital signs (temperature, systolic and diastolic blood pressures, pulse rate, respiratory rate)

Overall Design

- This phase Ⅳ study will be a randomized, double-blind, placebo-controlled, multicenter parallel study. The study will be comprised of screen, run-in period (4 to 14 days), treatment period (28 days) and follow up period (3 to 7 days).

- During the study period, all investigators, subjects and GlaxoSmithKline (GSK) personnel remain blinded.

- Subjects will be assigned to randomised treatments in a 1:1:1 ratio, in accordance with a computer generated randomization schedule provided by GSK.

- The randomization will be centralized and stratified by age (≥2 to ≤6 years and >6 to ≤12 years) and by classification of AR (intermittent vs. persistent) to ensure treatment balance in age groups and AR classification groups for both safety and efficacy assessments. Subjects with 6 years old and less than 7 years old will be treated as 6 years of age; these subjects will be analysis in group of 2 to 6 years. Subjects with 12 years old and less than 13 years old will be treated as 12 years of age and will be analysis in group of 6 to 12 years.

Treatment Arms and Duration

- Eligible subjects will participate in the study which begins with a 4 to 14-day run-in period with no treatment, then subjects meeting the randomisation criteria will be randomised in a 1:1:1 ratio to the following three treatment arms:
- FFNS 110 µg once daily
- FFNS 55 µg once daily
- Vehicle placebo aqueous nasal spray
- Following the 28-day treatment period, subjects will be followed up by telephone contact within 5±2 days after the last dose.
- Subjects entering the study will participate for maximum of 50 days, including five clinical visits and a follow-up telephone contact.

Type and Number of Subjects

- Subjects with AR ages 2 to 12 years. Approximately 360 subjects will be randomized (120 subjects per arm).
- In each treatment group, there will be about 60 subjects with a diagnosis of IAR (intermittent allergy rhinitis) and about 60 subjects with a diagnosis of persistent allergy rhinitis (PER) .
- As ≥2 to ≤6 years old pediatric subjects is a subgroup of interest in this study , there will be at least 60 subjects aged ≥2 to ≤6 years per arm.

Analysis

The study is designed to provide an estimated mean treatment difference between active drug groups and placebo group in change from baseline of daily rTNSS. This is a descriptive study and no formal inference is planned. All the results from analyses model are for descriptive purpose.

The primary analysis of the primary endpoint, mean change from baseline over the first 2 weeks treatment period in daily rTNSS in subjects aged 2 to 12 years, will be the pairwise comparison of treatment groups (active drug vs. placebo) using analysis of covariance (ANCOVA) adjusting for baseline daily rTNSS, classification of AR (IAR or PER), age, gender and treatment.

All the safety endpoints will be summarized using descriptive statistics. No modeling analysis will be done for safety endpoints. All the summary and analysis will be performed for the overall population and the ≥2 to ≤6 years population.

2. INTRODUCTION

2.1. Study Rationale

Fluticasone Furoate (FF) is a corticosteroid with potent glucocorticoid activity. Intranasal corticosteroids are considered to be the most effective pharmacology treatment for Allergic Rhinitis (AR) because their anti-inflammatory properties enable control of symptoms of AR in the majority of subjects treated.

Fluticasone Furoate Nasal Spray (FFNS) has been approved in China and many other countries for treatment of AR in adult, adolescent and pediatric subjects ≥2 year of age. FFNS development program had demonstrated FFNS is an effective treatment for the symptoms of IAR and PER in pediatric subjects aged 2 years and above (55 µg and 110 µg once daily), although there is few data of FFNS for AR in Chinese pediatric subjects ages 2 to 12 years.

Accordance to requirement of CDE, this study will further establish the efficacy and safety of FFNS at dose of 55µg and 110 µg once daily in Chinese pediatric subjects (ages 2 to 12 years) with AR. The dose selected in this study follows the label approved in China.

2.2. Brief Background

Allergic Rhinitis (AR) in its seasonal and perennial form is a common allergic condition. It is clinically defined as a symptomatic disorder induced by immunoglobulin E (IgE)-mediated inflammation after allergen exposure to mucous membranes of the nose. Allergen-bound IgE on the surface of mast cells induces mast cell degranulation and release of allergic and inflammatory mediators such as histamines, leukotrienes, prostaglandin D2, tryptase and kinins.

The majority of AR sufferers report nasal (congestion, sneezing, itching and rhinorrhea) and ocular (redness, watery eyes, itching and burning) symptoms which impact quality of life and can also be associated with substantial healthcare costs (e.g. exacerbations of sinusitis and asthma, nasal polyps, hearing impairment, etc) and other economic impacts (e.g. less work productivity) if not treated properly [Schoenwetter, 2004]

Anti-inflammatory therapy is a well-accepted component of the management of AR. Intranasal corticosteroids are known to reduce vascular permeability and edema of the nasal mucosa through inhibiting activities of inflammatory cells and mediators, and are considered to be the most effective pharmacology treatment for AR [Wallace, 2008] because their anti-inflammatory properties enable efficacious control of symptoms of AR in the majority of patients treated.

Fluticasone Furoate Nasal Spray has demonstrated substantial efficacy on treatment of AR in adult subjects.

3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
• To establish the efficacy of FFNS 55 µg and 110 µg QD versus vehicle placebo nasal spray over a period of 2 weeks in pediatric subjects (ages 2 to 12 years) with AR	• Mean change from baseline over the first 2 weeks treatment period in daily, reflective total nasal symptom scores (rTNSS) in subjects aged 2 to 12 years
Secondary	
• To investigate the safety of FFNS 55 µg and 110 µg QD versus vehicle placebo nasal spray over a period of 4 weeks in pediatric subjects (ages 2 to 12 years) with AR	**Secondary efficacy endpoints** • Overall evaluation of response to therapy (evaluated on a 7-point categorical scale) after the first 2 weeks treatment (day15) • Mean change from baseline of intranasal finding score by anterior rhinoscopy at the first 2 weeks (day 15) • Mean change from baseline over the first 2 weeks treatment period in the daily, reflective total ocular symptoms score (rTOSS) • Rescue loratadine use (mean rescue-free days) over the first 2 weeks treatment period • Mean change from baseline over the 4 weeks treatment period in daily rTNSS • Overall evaluation of response to therapy after 4 weeks treatment period (day 29) • The mean change from baseline of intranasal finding score by anterior rhinoscopy at the end of treatment(day 29) • Mean change from baseline over the 4 weeks treatment period in the daily rTOSS • Rescue loratadine use (mean rescue-free days) over the entire 4 weeks treatment period **Safety endpoints** • Frequency and type of clinical adverse events • Results of clinical laboratory tests (Hematology and chemistry) • Results of physical and nasal examination • Vital signs (temperature, systolic and diastolic blood pressures, pulse rate, respiratory rate)

4. STUDY DESIGN

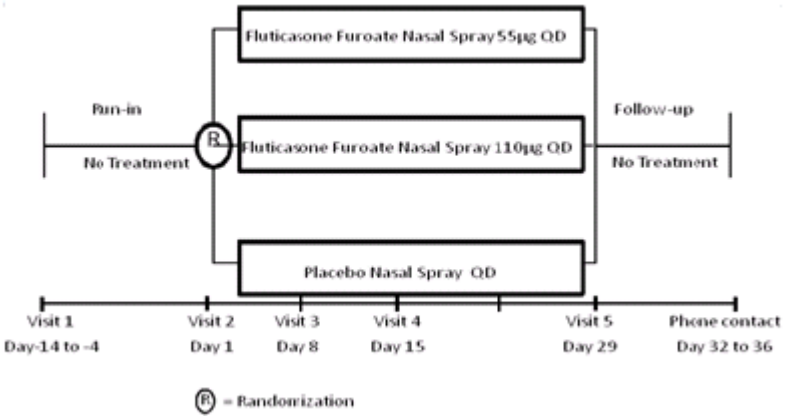
4.1. Overall Design

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table (Table 2), Section 7.1, are essential and required for study conduct.

- This phase Ⅳ study will be a randomized, double-blind, placebo-controlled, multicenter parallel study.
- Eligible subjects will participate in the study which begins with a 4 to 14-day run-in period with no treatment (Visit 1).
- After a minimum 4-day run-in period, subjects meeting the randomisation criteria will be randomised in a 1:1:1 ratio to the following three treatment arms (Visit 2):, in accordance with a computer generated randomization schedule provided by GlaxoSmithKline (GSK), via an Interactive Voice Response System (IVRS) called Registration and Medication Ordering System (RAMOS).
  - FFNS 110 µg once daily
  - FFNS 55 µg once daily
  - Vehicle placebo aqueous nasal spray
- The randomization will be centralized and stratified by age (≥2 to ≤6 years and> 6 to ≤12 years) and by classification of AR (intermittent vs. persistent) to ensure treatment balance in age groups and AR classification groups for both safety and efficacy assessments. Subjects with 6 years old and less than 7 years old will be treated as 6 years of age; these subjects will be analysis in group of 2 to 6 years. Subjects with 12 years old and less than 13 years old will be treated as 12 years of age and will be analysis in group of 6 to 12 years.
- Following the 28-day treatment period, subjects will be followed up by telephone contact within 5±2 days after the last dose. The following procedures will be performed: Adverse Event (AE)/ Serious Adverse Event (SAE) assessment. Subjects will be discharged from the study upon completion of the follow-up phone call.

In summary, this study is comprised of screen, run-in period (4 to14 days), double-blind treatment period (28 days) and follows up period (3 to7 days). Subjects entering the study will participate for maximum of 50 days, including five clinical visits and a follow-up telephone contact.

Figure 1 Study Design



4.2. Type and Number of Subjects

- Approximately 360 subjects with a diagnosis of AR will be randomised and 300 evaluable subjects for a total of 100 evaluable subjects per treatment group.
- In each treatment group, there will be about 60 subjects with diagnosis of Intermittent Allergic Rhinitis (IAR) and about 60 subjects with diagnosis of PER.
- There will enrolled at least 60 subjects ages ≥2 to ≤6 years per arm, and subjects ages ≥2 to ≤6 years will be defined as a subgroup of interest in this study.

4.3. Design Justification

- This is a Phase Ⅳ, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of FFNS 55μg and 110 μg compared with placebo Chinese pediatric subjects with AR. The approach is consistent with the requirement of China regulatory.
- Treatment duration of 2 weeks is considered adequate for assessment of symptom and intranasal score in response to intranasal FF for both IAR and PER.
- The additional 2-week treatment (D15-D28) is to evaluate the safety, meanwhile keep consistent with [Chinese Guideline for Diagnosis and Treatment of AR in Pediatrics, 2011] .
- A placebo arm is included in this study to allow for an absolute assessment of effect and safety of FFNS 55μg and 110 μg.
- Rescue loratadine will be provided for use of relief medication only as needed throughout the treatment period.

- The main analysis will be done on the overall population. As ≥2 to ≤6 years old pediatric subjects is a subgroup of interest in this study, all the summary and analysis will also be done on ≥2 to ≤6 years population.

4.4. Dose Justification

The doses evaluated for this study, 55µg and 110µg QD, follow the label for pediatric subjects age 2 to 12 years with AR, and are based on the data from phase III trials in pediatrics.

The efficacy of FFNS was evaluated in 1,112 children (633 boys and 479 girls), mean age of 8 years with IAR or PER in two controlled clinical trials (FFR10010 and FFR30008). The pediatric subjects received FFNS 55 or 110 µg once-daily for 2 to 12 weeks (n = 369 for each dose). Children treated with FFNS in these studies generally exhibited greater decreases in nasal symptoms than placebo treated patients. Efficacy results demonstrated that once daily treatment with FFNS is an effective treatment for the symptoms of IAR and PER in pediatric subjects aged 2 years and above (55 µg and 110 µg once daily).

Four clinical studies involved pediatric subjects with IAR or PER have been completed with FFNS. Based on a comprehensive assessment of safety data from the clinical development program, FFNS was well-tolerated in pediatric subjects two years of age and older with IAR and/or PER.

Across all global paediatric studies , AE incidence was similar between the FF and placebo groups and the AE profile was similar to that in adults and adolescents. Most AEs were mild or moderate in intensity.

Results involving adults, adolescents and pediatric subjects showed that FFNS 110 µg once-daily were not associated with HPA axis suppression as assessed by 24-h serum cortisol concentration and/or urinary cortisol excretion [GSK Document Number RM2004/00130/05].

4.5. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with intranasal GSK685698 can be found in the Investigator's Brochure and product label. The following section outlines the risk assessment and mitigation strategy for this protocol:

4.5.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [i.e., GW685698]		
Systemic effects of corticosteroids: cortisol suppression	Systemic effects with nasal corticosteroids including cortisol suppression have been reported, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids and may vary in individual subjects and between different corticosteroid preparations. Detailed characterisation of the effect of intranasal FF on urine and serum cortisol has been performed, including a formal HPA axis study. The proposed doses of intranasal FF in this study are unlikely to lead to any clinically significant changes.	This risk has already been characterised during the intranasal FF development programme. Review of AEs/SAEs reports. Optimised treatment duration. It's not common that HPA axis would be inhibited in 4-week treatment.
Systemic effects of corticosteroids: growth retardation	A reduction in growth velocity has been observed in children treated with fluticasone furoate 110 micrograms daily for one year. A randomised, double-blind, parallel-group, multicentre, one-year placebo-controlled clinical growth study evaluated the effect of FFNS 110 micrograms daily on growth velocity in 474 prepubescent children (5 to 7.5 years of age for girls and 5 to 8.5 years of age for boys) with stadiometry. Mean growth velocity over the 52-week treatment period was lower in the subjects receiving fluticasone furoate (5.19 cm/year) compared to placebo (5.46 cm/year). The mean treatment difference was -0.27 cm per year [95% CI -0.48 to -0.06].	This risk has already been characterised during the intranasal FF development programme. This risk had been disclosed in the label, with caution for long-term usage of intranasal FF. It's not common that administration of FFNS for 4 weeks would lead to growth retardation.
Systemic ocular effects of corticosteroids:	As with other intranasal corticosteroids, physicians should be alert to potential systemic steroid effects including ocular changes. In a two-year	This risk has already been characterised during the intranasal FF development programme.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [i.e., GW685698]		
glaucoma, cataract, raised intra-ocular pressure	study designed to assess the ocular safety of fluticasone furoate (110 micrograms once daily intranasal spray), adults and adolescents with perennial AR received either fluticasone furoate (n=367) or placebo (n=181). The primary outcomes [time to increase in posterior subcapsular opacity (≥0.3 from baseline in Lens Opacities Classification System, Version III (LOCS III grade)) and time to increase in intraocular pressure (IOP; ≥7 mmHg from baseline)] were not statistically significant between the two groups. Increases in posterior subcapsular opacity (≥0.3 from baseline) were more frequent in subjects treated with fluticasone furoate 110 micrograms [14 (4%)] versus placebo [4 (2%)] and were transient in nature for ten subjects in the fluticasone furoate group and two subjects in the placebo group. Increases in IOP (≥7 mmHg from baseline) were more frequent in subjects treated with fluticasone furoate 110 micrograms: 7 (2%) for fluticasone furoate 110 micrograms once daily and 1 (<1%) for placebo. These events were transient in nature for six subjects in the fluticasone furoate group and one placebo subject. At weeks 52 and 104, 95% of subjects in both treatment groups had posterior subcapsular opacity values within ± 0.1 of baseline values for each eye and, at week 104, ≤1% of subjects in both treatment groups had ≥0.3 increases from baseline in posterior subcapsular opacity. At weeks 52 and 104, the majority of subjects (>95%) had IOP values of within ± 5mmHg of the baseline value. Increases in posterior subcapsular opacity or IOP were not accompanied by any adverse events of cataracts or glaucoma	Review of AEs/SAEs reports.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [i.e., GW685698]		
Nasal events	A review of nasal events concluded that there was a reasonable possibility that rhinalgia, nasal discomfort (nasal burning, nasal irritation, nasal soreness) and nasal dryness were associated with the use of FFNS. Epistaxis and nasal ulceration are known class effects of intranasal corticosteroids. To complement the adverse event and nasal examination data and to characterise further effect on the nasal mucosa, GSK initiated a nasal biopsy study FFR104503. This study did not identify any new safety concerns for FFNS.	Focused nasal examinations will be conducted with grading system. Nasal examination will be one of the safety endpoints. Review AE and SAE reports.

4.5.2. Benefit Assessment

Fluticasone Furoate is an intranasal corticosteroids with potent glucocorticoid activity. It has been shown to activate the glucocorticoid response element and inhibit pro-inflammatory transcription factors. Because of the anti-inflammatory properties its efficacious control of symptoms of AR in the majority of patients treated. Anti-inflammatory therapy is a well-accepted component of the management of pediatrict AR in china. The benefit of FFNS on pediatrict with AR is control symptoms effective at relieving nasal discharge, itch, postnasal drip and watery eyes. In addition, Patients of participating in this trial will benefit from regular medical assessments and characterization of their AR, even if they are not receiving active treatment.

4.5.3. Overall Benefit: Risk Conclusion

Taking into account the measures to minimize risk to subject participating in this study, the potential risks identified in association with FFNS are justified by the anticipated benefits that may be afforded to patients with AR.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the Investigator Brochure (IB) and product label.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

5.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

[1] Informed Consent
1. Subject's parent/guardian has provided with an appropriately signed and dated informed consent.

[2] Outpatient
2. Chinese subject is treatable on an outpatient basis

[3] Gender
3. Both Male and Female

[4] Age
4. Subjects must be ≥2 to ≤12 years of age at Visit 2. Only premenarchal female subjects (of non-child bearing potential) are eligible to participate in this study.

[5] Diagnosis of AR
5. Subjects were diagnosed as IAR or PER according to the criteria for the diagnosis and classification of [Chinese Guideline for Diagnosis and Treatment of AR in Pediatrics, 2011]. Criteria for the diagnosis of AR: **1. Symptoms:** subjects must have 2 or more symptoms of AR (watery rhinorrhea, nasal obstruction, nasal itching and sneezing), which are also present consecutively or accumulatively more than 1 hour on each day prior to Visit 1, or/and concomitant ocular symptoms: ocular itching, red eyes, watery eyes etc. . **2. Physical signs:** nasal mucosa pale, oedema, nasal secretion. Allergic shiner and allergic crease in severity pediatric **3. Laboratory test:** I. **Skin Prick Test (SPT)*:** must represent a positive response using standardized allergen extract. II. **Serum-specific IgE test*:** represent a positive response using standardized allergen extract. **(***allergen must be aeroallergen**)** **Diagnosis:** subjects have nasal symptoms described above or/and associated with ocular symptoms, as well as the nasal signs and one of laboratory test positive or documents. Documents: that demonstrate SPT represented a positive response OR serum-specific IgE testing represented a positive response within 12 months prior to Visit 1. Criteria for classification of AR: • Intermittent AR, IAR: the symptoms are present <4 days a week, OR for <4 weeks. • Persistent AR, PER: the symptoms are present ≥4 days a week, OR for ≥4 weeks.

[6] Exposure
6. Subject must be willing to maintain the same environment throughout the study

[7] Ability to Comply with Procedures
7. Subject and/or subject's parent/guardian understands and is willing, able and likely to

comply with study procedures and restrictions as well as manage study drug administration

5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

[1] Concomitant Medical Conditions

1. Significant concomitant medical conditions, defined as:
   a. Historical or current evidence of clinically significant uncontrolled disease of any body system. Significant is defined as any disease that, in the opinion of the investigator or which would confound the interpretation of the study results if the disease/condition exacerbated during the study.
      - Significant renal impairment, which based on the opinion of the investigator, would preclude the subjects' participation in the study.
      - Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones or otherwise stable chronic liver disease per investigator assessment).

        NOTES:
        - Stable chronic liver disease should generally be defined by the absence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice, or cirrhosis.
        - Chronic stable hepatitis B and C (e.g., presence of hepatitis B surface antigen (HBsAg) or positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment) are acceptable if subject otherwise meets entry criteria.

   b. A severe physical obstruction of the nose(e.g., deviated septum， nasal polyp or frequent bleeding of the nose that could affect the deposition of double blind intranasal study drug
   c. Current or history of a Candida infection of the nose or oropharynx, shingles, chickenpox, measles, ocular herpes simplex.
   d. Known hypersensitivity to corticosteroids or any excipients in the product.
   e. Recent nasal septal surgery or nasal septal perforation
   f. Subjects start, discontinue or change desensitization treatment within 30 days prior to Visit 1.
   g. Bacterial or viral infection of the eyes or upper respiratory tract within two weeks of Visit 1 or during the screening period.
   h. Asthma, with the exception of mild intermittent asthma [Ruchi, 2009]
   i. Diagnosis of rhinitis medicamentosa, vasomotor AR or eosinophil rhinitis

2. Abnormal Laboratory Findings: A clinically significant laboratory abnormality

[1] Concomitant Medical Conditions
including Liver Function Tests at Visit 1 meeting the following criteria (as below and further defined in the study procedure manual): • ALT >2 x upper limit of normal (ULN) and bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%) 3. Abnormal ECG: Clinically significant abnormal ECG finding at Visit 1. Significant is defined as: QTc > 450 msec or QTc > 480 msec in subjects with Bundle Branch Block. NOTES: ○ The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method, machine-read or manually over-read. ○ The specific formula that will be used to determine eligibility and discontinuation for an individual subject should be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual subject and then the lowest QTc value used to include or discontinue the subject from the trail. ○ For purposes of data analysis, QTcB, QTcF, another QT correction formula, or a composite of available values of QTc will be used as specified in the Reporting and Analysis Plan (RAP).

[2] Concomitant Medication
1.Use of prescription or over-the-counter medication that would significantly affect the course of AR, or interact with study drug （refer to Table 1）, such as: • Chronic use of concomitant medications such as tricyclic antidepressants, that would affect assessment of the effectiveness of the study drug • Chronic use of long– acting $beta_2$-agonists (e.g., salmeterol) • Potent Cytochrome P450 3A4 inhibitors (e.g., ritonavir, ketoconazole, itraconazole, clarithromycin, etc) • Allergen immunotherapy for the treatment of allergies 2. Please refer to Section 6.9 for the list of concomitant medications permitted and prohibited during the study.

Table 1 Prohibited concomitant medications

Medications	Timeframe indicated relative to Visit 1
1. Short-acting antihistamines, including ocular preparations and antihistamines contained in anti-cold medicine, insomnia or antalgic. 2. Oral or inhaled anticholinergics 3. Oral or intranasal decongestants 4. Oral or intranasal antileukotrienes 5. Oral or inhaled long-acting beta2 agonists 6. Chinese traditional medicines that have potential effect to AR 7. Liquorice preparation 8. Medications that significantly inhibit the cytochrome P450 subfamily enzyme CYP3A4,including ritonavir and ketoconazole	5 Days
tricyclic antidepressants	9 Days
long-acting antihistamines(eg.desloratadine,fexofenadine, cetirizine and loratadine[taken as rescue medication])	10 Days
Intranasal antihistamines; or Intranasal or ocular cromolyh	16 Days
Intranasal corticosteroids	30 Days
1. Inhaled, oral, intramuscular, intravenous, ocular and/or dermatological corticosteroid (with the exception of hydrocortisone cream/ointment, 1% or less) 2. Immunosuppressive medications	60 Days
Subcutaneous omalizumab	5 months

[3] Subjects Will Travel More Than 48 Hours During the Study may Cause the Change of Allergen

[4] Investigators or Sub-investigators Consider that a Subject is Not Eligible

5.3. Randomisation Criteria

[1] At Visit 2, the Subject must continue to meet the inclusion/exclusion criteria above. In addition the subject must meet the following criteria:
a. On the morning of Visit 2, subjects must have nasal or/and ocular symptoms. b. Average of the last 8 rTNSS assessments (4 AM assessments, 4 PM assessments) over the consecutive four 24-hours periods prior to randomization must be ≥6. This includes the AM assessment on the morning of Visit 2. c. Average of the 8 reflective nasal symptom assessments for congestion (4 AM assessments, 4 PM assessments) over the consecutive four 24-hour periods prior to randomization must be ≥2. This includes the AM assessment on the morning of Visit 2.

5.4. Screening/Baseline/Run-in Failures

Subjects who fail to meet the eligibility requirements at Visit 1 are considered a screen failure. Subjects who fail to meet the eligibility requirements at Visit 2 are considered a run-in failure. Subjects who are screen or run-in failures should not be re-screened.

Data for screening/Run-in failures will be collected in source documentation at the site and will be transmitted to GSK. The following information will be collected in the case report form (CRF) for subjects who are screen/Run-in failures:

- Date of screening Visit
- Subject number
- Date of ICF signature
- Demographic information including race, age and gender
- Reason for screen/run-in failure
- SAE information

5.5. Withdrawal/Stopping Criteria

5.5.1. Withdrawal criteria

5.5.1.1. Subject Withdrawal from the Investigational Product

Premature discontinuation of the study drug will be defined as discontinuation of the study drug for more than or equal 2 consecutive days before the end of the treatment period. Subjects who discontinue administration of study drug prematurely will be withdrawn from the study.

5.5.1.2. Subject Withdrawal from the Study

A subject who takes double-blinded study drug but withdraws prior to Visit 5 will be defined as withdrawn early. Subjects who withdrew early will not be replaced.

Subject withdrew from the study was required and Early Withdrawal procedures must be performed, when:

- A subject is significantly non-compliant with the requirements of the protocol.
- A subject has an adverse event that would, in the investigator's judgment, make continued participation in the study an unacceptable risk.
- Lost to follow-up
- The treatment blind is broken for a subject (by other than GSK GCSP personnel), or
- GSK discontinues the study.
- Female subjects experience menarchal during study.

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject (or subject parents/guardian) and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records:

- Review all information recorded on diary cards, including rTNSS, rTOSS, study medication administration，rescue medication use., any medical conditions or concomitant medications
- Investigators must complete subjects' nasal examination by anterior rhinoscopy and these examined results must be recorded on patient notes.
- Conduct adverse event assessment

- Physical examination, vital signs and nasal examination
- 12-lead Electrocardiogram
- Double-blind study drug collection
- Clinical laboratory tests

These data should be recorded in the CRF, as appropriate, as they comprised an essential evaluation that should be done prior to discharging any subject from the study.

Subjects who have discontinued IP in the study should be encouraged to return to the clinic as soon as possible to complete the IP Discontinuation Visit assessments and to complete the safety follow-up contact 3 to 7 days following the subject's last dose. If a subject is prematurely discontinued during a regularly scheduled visit, that visit will become the Early Withdrawal visit.

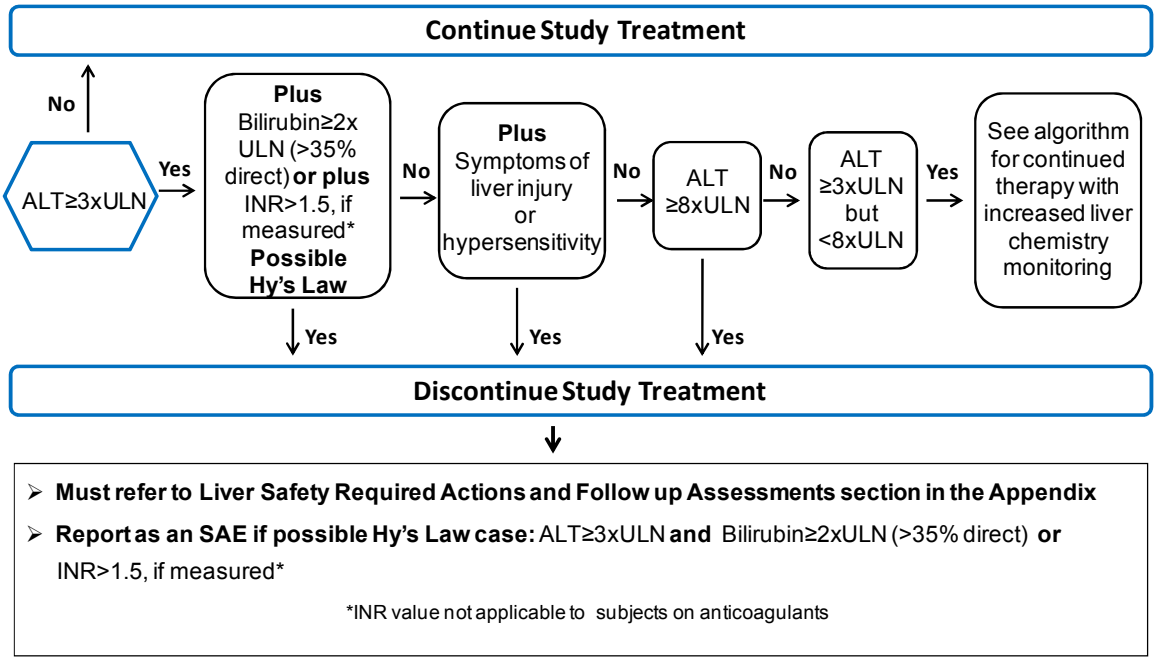
Any clinically significant adverse event, laboratory test, nasal examination, Electrocardiogram (ECG) finding, or clinically significant unfavorable change observed during the Early Withdrawal Visit necessitated that the subject be followed or treated until satisfactory resolution occurred.

In the event that a subject was prematurely discontinued from the study at any time due to an AE or SAE, the procedures stated in protocol must be followed.

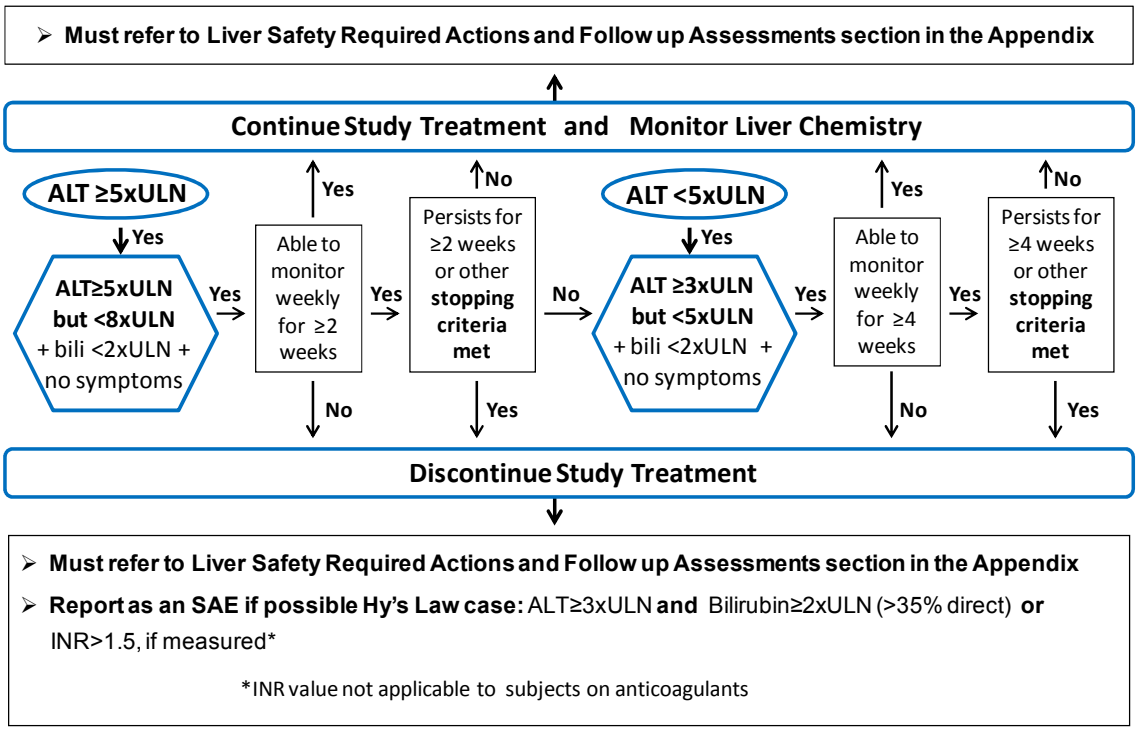
5.5.2. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for Alanine aminotransferase (ALT) ≥3x (Upper limit of normal) ULN but <8xULN



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 2

5.5.3. QTc Stopping Criteria

- The same QT correction formula must be used for each individual subject to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the subject has been enrolled.
  - For example, if a subject is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual subject as well.
  - Once the QT correction formula has been chosen for a subject's eligibility, the same formula must continue to be used for that subject for all QTc data being collected for data analysis. Safety ECGs and other non-protocol specified ECGs are an exception.
- The QTc should be based on single electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period.

  A subject who meets either of the bulleted criteria below will be withdrawn from the study:
  - QTc > 450 msec
  - QTc > 480 msec in subjects with Bundle Branch Block

5.6. Subject and Study Completion

A completed subject is one who has completed all phases of the study throughout the screening and treatment period to Visit 5 and completes the procedures for Visit 5. Any subject who withdraws prior to the completion of Visit 5 will be considered an early withdrawal. The end of the study is defined as the last subject's last visit.

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

The term 'study treatment' is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments.

6.1.1. Study Medication Review and Return

All supplies must be returned at the end of the study and returned to GSK for destruction

6.1.2. Investigational Product Malfunction

An investigational product nasal spray that fails to function properly must be identified to GSK personnel for return to GSK for testing. Details of the failure will be documented in

the CRF. The subject should return the nasal spray to the clinic as soon as possible to avoid missing any doses. The site will then call the Registration and Medication Ordering System Interactive Voice Response System (RAMOS) and obtain a new treatment pack number for this subject and dispense a new study medication kit from the site's product supply, as instructed by the RAMOS.

	Treatment Products	
Product name:	Fluticasone furoate	Placebo
Formulation description:	0.05% w/w Fluticasone furoate in an aqueous suspension preserved with EDTA (0.015% w/w) and Benzalkonium Chloride (0.015% w/w).	An aqueous suspension to match the other study treatments minus the active component(s).
Dosage form:	Intranasal aqueous microsuspension	Intranasal aqueous microsuspension
Unit dose strength(s)/Dosage level(s):	Each spray=27.5 µg	N/A
Route of Administration	Intranasal	intranasal
Dosing instructions:	Inhale one spray in each nostril from each device in the morning	Inhale one spray in each nostril from each device in the morning
Physical description:	An amber glass bottle encased within a light grey plastic casing fitted with a white plastic side lever and white plastic cap. The device is a side actuated metering atomising spray pump filled with a uniform white suspension	An amber glass bottle encased within a light grey plastic casing fitted with a white plastic side lever and white plastic cap. The device is a side actuated metering atomising spray pump filled with a uniform white suspension
Device: Only use this when a medical device is used. Note that in most cases, an inhaler (e.g. Diskus, Ellipta) is not a device	Mistpro device with VP7 pump, white cap and white side actuating lever	Mistpro device with VP7 pump, white cap and white side actuating lever
Method for individualizing dosage:	Metered atomising spray pump	Metered atomising spray pump

6.2. Treatment Assignment

Subjects will be assigned to treatments for parallel group studies in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software.

Subjects (and subject's parent/guardian) will be educated at randomization prior to the first dose of IP regarding the use of the nasal sprays devices using a placebo demonstration device. Each subject will then be dispensed two treatment kits. Each kit will contain a nasal sprays device. One nasal spray device will be labelled Device A and the other Device B. Subjects (on their own or with assistance from parent/guardian) should administer one spray from Nasal Spray Device A into each nostril followed by one spray from Nasal Spray Device B into each nostril once a day in the AM. The first dose of study drug will be administered before 10 AM in the clinic on Visit 2.

Treatment Arm	Device A	Device A Dosing Instructions	Device B	Device B Dosing Instructions
FF 55µg QD	FFNS	Inhale one spray in each nostril from Device A in the morning	Placebo Nasal Spray	Inhale one spray in each nostril from Device B in the morning
FF 110µg QD	FFNS	Inhale one spray in each nostril from Device A in the morning	FFNS	Inhale one spray in each nostril from Device B in the morning
Placebo QD	Placebo Nasal Spray	Inhale one spray in each nostril from Device A in the morning	Placebo Nasal Spray	Inhale one spray in each nostril from Device B in the morning

Daily doses should be administered in the morning following pre-dose symptom assessment, the last dose will be administered on the morning of Visit 5. **.** Administration of the spray should be conducted according to the Patient Instruction Leaflet that will be provided to the sites by GSK. The subject Instruction Leaflets should be reviewed with the subjects (and /or subject's parent/guardian) and distributed to the subjects to take with them.

6.2.1. Assignment of Subject Number

At Visit 1, a unique **Subject Number** (CRF number) will be assigned by the site to any subject who has at least one Visit 1 procedure performed (other than informed consent) from a list of unique numbers provided by GSK. The unique subject number will be used to identify individual subjects during the course of the study.

6.2.2. Assignment of Randomisation/Treatment Pack Numbers

At Visit 2, subjects meeting the randomisation eligibility criteria will be assigned to study treatment via a telephone call to the RAMOS. During the call, the site will confirm the subject's **Subject Number** and the RAMOS will then assign two additional numbers:

1. **Treatment Kit Numbers** that identifies the double-blind medication to be dispensed to the subject from the investigators inventory; and
2. A **Randomisation Number** from the study randomisation schedule created by GSK. Once assigned, this number must not be reassigned.

6.3. Blinding

This will be a double blind study and the following will apply.

- The investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject as judged by the investigator.
- Investigators have direct access to the subject's individual study treatment.
- It is preferred (but not required) that the investigator first contacts the Medical Monitor to discuss options **before** unblinding the subject's treatment assignment.
- If GSK personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study.
- The date and reason for the unblinding must be fully documented in the CRF

A subject will be withdrawn if the subject's treatment code is unblinded by the investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the CRF.

- GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.4. Packaging and Labeling

The contents of the label will be in accordance with all applicable regulatory requirements.

6.5. Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required.

- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the SRM.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- A document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.6. Compliance with Study Treatment Administration

Subject compliance with double blind study medication will be assessed at Visit 3, 4 and Visit 5, other clinic visits as specified in the Time and Events during treatment and Early Withdrawal by assessment of subject reported use on the e-diary. To ensure protocol adherence, a subject may be re-education from the study if their compliance with study treatment is <80%. And this no-compliance will be reported as protocol deviation.

6.7. Treatment of Study Treatment Overdose

An overdose is defined as a dose greater than the total doses described above which results in clinical sign or symptoms.GSK does not recommend specific treatment for an overdose. The investigator or physician in charge of the subject at the time will use clinical judgment to treat any overdose.

6.8. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study because the indication being studied is not life threatening or seriously debilitating and/or other treatment options are available

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, whether or not GSK is providing specific post-study treatment.

6.9. Concomitant Medications and Non-Drug Therapies

The concomitant medications related to Allergy Rhinitis diseases within 30 days prior to Visit 1 will be recorded in the CRF. All concomitant medications taken during the study will be recorded in the CRF. The minimum requirement is for the reporting of the generic drug name and dates of administration.

6.9.1. Permitted Medications and Non-Drug Therapies

Loratadine syrup, an on-the-count antihistamine, will be provided as rescue medication on only an as needed basis during the treatment period of the study. At Visit 2 after randomization, subjects will be dispensed rescue medication. The subject (and/or subject's parent/guardian) will record their daily use of allergy rescue medication, not to exceed **1 teaspoon (5 mL) with weight ≤30 kg or 2 teaspoon (10 mL) with weight >30 kg** a day. The use of rescue medication should be in accordance with the instructions provided with the medication.

6.9.2. Prohibited Medications and Non-Drug Therapies

Use of prescription or over-the-counter medication would significantly affect the course of AR, or interact with study drug are prohibited. Any non-drug therapies including nasal irrigation solutions are prohibited during the screening and treatment periods. All medications of the below are prohibited throughout the study from Visit 1 to Visit 5 or withdrawal Visit.

Medications
Short-acting antihistamines, including ocular preparations and antihistamines contained in anti-cold medicine, insomnia or antalgic. Oral or inhaled anticholinergics Oral or intranasal decongestants Oral or antileukotrienes Oral or inhaled long-acting beta2 agonists Chinese traditional medicines that have potential effect to AR Liquorice preparation Medications that significantly inhibit the cytochrome P450 subfamily enzyme CYP3A4,including ritonavir and ketoconazole
long-acting antihistamines(eg.desloratadine,fexofenadine, cetirizine and loratadine[taken as rescue medication])
Intranasal antihistamines; or Intranasal or ocular cromolyh
Intranasal corticosteroids

Medications
Inhaled, oral, intramuscular, intravenous, ocular and/or dermatological corticosteroid (with the exception of hydrocortisone cream/ointment, 1% or less) Immunosuppressive medications
Subcutaneous omalizumab
Chronic use of concomitant medications such as tricyclic antidepressants

7. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section 7.1

7.1. Time and Events Table

Table 2 Time and Events Table[1]

Procedure	Visit Number					Early withdraw	Follow up
	1	2	3	4	5		
		Study Day					
Visit window (of days)	**-4 to -14**	**1**	**8±2**	**15±2**	**29±2**		**5±2 days after subject's last dose**
Informed consent[2]	X						
Subject number assignment	X						
Medical history	X						
Verification of inclusion/exclusion criteria	X	X					
Skin testing / serum-specific IgE test (if not done within 12 months of visit 1)	X						
Clinical laboratory tests[Randomisation if applicable]	X				X	X	
12-Lead electrocardiogram	X				X	X	
Verification of randomized criteria		X					
Randomization number assignment		X					
Dispense double-blind study drug		X					
Dispense rescue loratadine		X	X[3]	X[3]			
Nasal spray technique education		X	X	X			
Collect study drug					X	X	
Review screening diary[4]		X					
Review medical problem/medication diary[5]		X	X	X	X	X	
Compliance assessment			X	X	X	X	
Review treatment diary[4]			X	X	X	X	
Anterior rhinoscopy		X	X	X	X	X	
Investigator assess overall response to therapy				X	X	X	
Vital Signs	X				X	X	
Nasal examination	X	X	X	X	X	X	
Physical examination	X				X	X	

Procedure	**Visit Number**					**Early withdraw**	**Follow up**
	1	**2**	**3**	**4**	**5**		
		Study Day					
Visit window (of days)	**-4 to -14**	**1**	**8±2**	**15±2**	**29±2**		**5±2 days after subject's last dose**
AE/SAE review	X[6]	←==========→				X	X
Concomitant medication review	X	←==========→				X	X

1. Parent/ guardian will record the symptom diary instead of subjects for all ages. The involvement of the parent/guardian in assessing and rating rhinitis symptoms may vary per subject. While it may not always be possible, the preference is for a consistent level of parent/guardian involvement throughout the study.

2. Informed Consent must be obtained prior to performing any Visit 1 procedures

3. The dispense will depends on as needed

4. The diary collects rTNSS, rTOSS, rescue usage and study medication usage

5. The diary collect any medical problem (other than AR) and any medications used

6. Serious AEs will be recorded from the time the consent form is signed until the follow-up visit. All AEs will be recorded from the start of study treatment until the follow-up visit.

7.2. Diary Recorded Information

Subjects (and/or subject's parent/guardian) will be provided with 3 diaries to record their allergy symptoms:

- A **screening diary** will be used during the screening phase (from Visit 1 to Visit 2) to capture the subjects' baseline symptom scores.
- A **daily treatment diary** will be used beginning on the first day of study medication administration (approximately 12 hours after the first dose at Visit 2) and throughout the remainder of the study.
- **Medical problem/medication dairy** will be used during the study (from Visit 1 to Visit 5)

Screening diary and daily treatment diary will be used e-dairy , both of them use the same 4-point, categorical scale of 0 to 3 to assess symptoms. Throughout the study, subjects (and/or subject's parent/guardian) will rate their nasal symptoms of AR and record them on a symptom diary. Parent/ guardian will record the symptom diary instead of subjects for all ages. E-dairy will be record approximately 12 hours after dose, include morning dairy and evening dairy, record time will be on every 6 to 10 morning and evening separately. The involvement of the parent/guardian in assessing and rating rhinitis symptoms may vary per subject. While it may not always be possible, the preference is for a consistent level of parent/guardian involvement throughout the study.

Subjects (and/or subject's parent/guardian) will also document study drug compliance and loratadine rescue medication use on the daily treatment diary. Additionally, subjects (and/or subject's parent/guardian) will record any medical problem (other than AR) they experience and any medications used on medical problem/medication diary.

7.3. Screening and Critical Baseline Assessments

All demographic and baseline assessments will be completed according to the Time and Events schedule in Section 7.1. Safety parameters physical exams, vital signs, electrocardiogram (ECG) and clinical safety laboratory assessments will be define as baseline at Visit 1. Nasal exams baseline will be assessed at Visit 2.

Medical/medication history will be assessed as related to the eligibility criteria listed in Section 5. Height, weight, medical conditions will also be assessed at baseline. SAE information (see Section 12.3.2), if applicable, will also be assessed at baseline.

7.4. Efficacy

Electronic diary card will be used in this study to collect subjects (and /or subject's parent/guardian) rating efficacy endpoints, including rTNSS, rTOSS and rescue loratadine use.

7.4.1. Nasal Symptoms of AR

The nasal symptom endpoints for efficacy will be calculated from the daily subject-rated nasal scores. The four individual nasal symptoms that each subject will be assessed throughout the study are:

- Nasal Congestion
- Nasal Itching
- Rhinorrhea
- Sneezing

The total nasal symptom score (TNSS) is a composite score of the above four components with a maximum score of 12.

Rating

Subjects will use the following scale to assess the severity of each of the four symptoms above:

Rating Period

Using the 0 to 3 rating scale above, subjects will be instructed to score and document their symptoms in a reflective manner (rTNSS) using their diary.

- The reflective rating represents how the subject has been feeling over the preceding 12 hours. This assessment provides information on how effective the treatment is throughout the day and will be performed TWICE daily (AM and PM).
- The AM reflective assessment must be performed prior to administering the morning dose and assesses how the subject felt through the night.
- The PM reflective rating must be done approximately 12 hours after dosing but before bedtime and assesses how the subject felt during the day.
- The daily rTNSS is the average of the AM rTNSS and PM rTNSS assessments.

Table 3 Scoring of nasal symptoms

Severity (score) /symptom	None (0)	Mild (1)	Moderate (2)	Severe (3)
sneezing	Symptom is not present	sign/symptom is clearly present but minimal awareness; easily tolerated	definite awareness of sign/symptom that is bothersome but tolerable	sign/symptom is hard to tolerate; causes interference with activities of daily living and/or sleeping
rhinorrhea				
Nasal congestion				
Nasal itching				

7.4.2. Ocular Symptoms of AR

The ocular symptom endpoints for efficacy will be calculated from the daily subject-rated ocular symptom scores. The three individual ocular symptoms that each subject will assess throughout the study are:

- Eye Itching and Burning
- Eye Watering
- Eye Redness

The total ocular symptom score (TOSS) is a composite score of the above three components with a maximum score of 9.

Rating

Subjects will use the following scale to assess the severity of each of the three symptoms above:

Similar to the nasal symptom assessments, the subjects will be instructed to score and document their ocular symptoms in the diary in a reflective manner (rTOSS) TWICE daily at the same time as assessing their reflective nasal symptoms.

Table 4 Table scoring of ocular symptoms

severity (score) /symptom	None (0)	Mild (1)	Moderate (2)	Severe (3)
Eye itching/ Burning	Symptom is not present	sign/symptom is clearly present but minimal awareness; easily tolerated	definite awareness of sign/symptom that is bothersome but tolerable	sign/symptom is hard to tolerate; causes interference with activities of daily living and/or sleeping
Tearing/watering				
Eye redness				

7.4.3. Anterior rhinoscopy findings of AR

The anterior rhinoscopy change will be calculated from the subject nasal concha mucosa symptoms score. The 4 individual score that each subject will assess throughout the study are:

- swelling of inferior nasal concha mucosa
- color of inferior nasal concha mucosa
- watery secretion volume
- description of rhinorrhea

Rating

Investigator will use the following scale to assess the severity of each of the three symptoms above:

The investigator used the following 0 to 3 scale to assess the severity of each item at baseline (Visit 2) and every visit of study (Visits 3, 4, 5/Early Withdrawal).

Table 5 Table scoring of anterior rhinoscopy findings

Items	None (0)	Mild (1)	Moderate (2)	Severe (3)
Swelling of inferior nasal concha	None	To center turbinate	Between 1 and 3	Cannot observe center turbinate

Items	None (0)	Mild (1)	Moderate (2)	Severe (3)
Color of inferior nasal concha mucosa	Normal	Light red	red	pale
Watery secretion volume	None	Adhesion level	Between 1 and 3	Fullness
Description of rhinorrhea	None	purulent	Viscous	Aqueous

7.4.4. Overall evaluation of Response to therapy by investigator

The investigator will evaluate subject's overall response to therapy (improvement in the symptoms of AR) compared with Visit 2, in accordance with the Time and Event Table, using 7 point categorical scale below and record it in the CRF.

1. Significantly Improved
2. Moderately Improved
3. Mildly Improved
4. No Change
5. Mildly worse
6. Moderately worse
7. Significantly worse

7.4.5. Primary Efficacy Endpoints

The primary efficacy endpoint will be the mean change from baseline over the first 2 weeks treatment period in daily reflective total nasal symptom scores (rTNSS) in subjects ages 2 to 12 years.

7.4.6. Secondary Efficacy Endpoints

The secondary endpoints for the study will consist of the following measures:

- Overall evaluation of response to therapy (evaluated on a 7-point categorical scale) after the first 2 weeks treatment (day 15)
- The mean change from baseline of study intranasal finding score by anterior rhinoscopy at the first 2 weeks treatment (day 15)

- Mean change from baseline over the first 2 weeks treatment period in the daily, reflective total ocular symptoms score (rTOSS)
- Rescue loratadine use (mean rescue-free days) over the first 2 weeks treatment period
- Mean change from baseline over the 4 weeks treatment period in daily rTNSS
- Overall evaluation of response to therapy after 4 weeks treatment period (day 29)
- The mean change from baseline of intranasal finding score by anterior rhinoscopy at the end of treatment (day 29)
- Mean change from baseline over the 4 weeks treatment period in the daily rTOSS
- Rescue loratatine use (mean rescue-free days) over the entire 4 weeks

7.5. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1). Additional time points for safety tests (including but not limited to vital signs, physical exams and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

The safety endpoints for the study will consist of the following assessments. More detailed information is provided in Study Assessments and Procedures (Section 7.1)

- Frequency and type of clinical adverse events
- Results of clinical laboratory test (hematology and chemistry)
- Results of physical and nasal examinations
- Vital signs (temperature, systolic and diastolic blood pressures, pulse rate, respiratory rate)

7.5.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

The definitions of an AE or SAE can be found in Appendix 3.

7.5.1.1. Time period and Frequency for collecting AE and SAE information

- The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.
- Serious AEs will be recorded from the time the consent form is signed until the follow-up contact. All AEs will be recorded from the start of study treatment until the follow-up contact.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 3. Investigators will assess causality and tick the box on SAE Form in eCRF within 72 hours. If not completed in 72 hours, protocol deviation will to be entered.

- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 3

7.5.1.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- "How are you feeling?" **or** "How does your child seem to feel?"
- "Have you had any (other) medical problems since your last visit/contact?" **or** "Has your child had any (other) medical problems or seem to act differently in any way since his/her last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?" **or** "Has your child needed to take any medicines, other than those provided in this study, since his/her last visit/contact?"

7.5.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 4.5.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. Further information on follow-up procedures is given in Appendix 3.

7.5.1.4. Regulatory Reporting Requirements for SAEs/ ADRs

SAEs shall be reported to CFDA as required per regulation of *Provision for Drug Registration* and *Good Clinical Practice of Pharmaceutical Products*, ADRS shall be reported to Adverse Drug Monitoring Center as required by regulation of *Provision for Adverse Drug Reaction Reporting and Monitoring (Order 81. Of the Ministry of Health).*

Prompt notification by the investigator to GSK of SAEs is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

7.5.2. Physical Exams

- A complete physical examination will include, at a minimum, assessment of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.
- Investigators should pay special attention to clinical signs related to previous serious illnesses
- Physical examination results will be documented in the source documents only.

7.5.3. Nasal Exams

A detailed nasal examination of the mucosa, septum, secretions, nasal patency, size of any polyps and ulcers will be performed by the investigator at all visits (Visits 1 – 5 or Early Withdrawal) and the findings recorded on the nasal examination CRF page. Any unfavorable changes that are not reflective of the symptoms of AR from the Visit 1 assessment will be recorded as an adverse event, documenting the start and stop dates of the adverse event. A diagnosis of nasal candidacies should be reported as an adverse event.

7.5.4. Vital Signs

- Vital signs will be measured in semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure and pulse rate and respiratory rate.

7.5.5. Electrocardiogram (ECG)

- Single 12-lead ECGs will be obtained at each time point during the study using an ECG machine that automatically calculates the heart rate (HR) and measures PR, QRS, QT, and QTc intervals. Refer to Section 5.5 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- Continuous cardiac telemetry will be performed. Full disclosures will be reviewed in detail and the review maintained as part of the subject's source documents

7.5.6. Clinical Safety Laboratory Assessments

This study will use local laboratory except for liver event. All protocol required laboratory assessments, as defined in Table 6, must be conducted in accordance with Protocol Time and Events Schedule. Reference ranges for all safety parameters will be provided by the local laboratory responsible for the assessments.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the CRF.

Refer to the SRM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

Haematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Table 6.

Table 6 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Haematology	Platelet Count	Red blood cells (RBC) Indices:	White Blood Cells (WBC) count with Differential :	
	RBC Count	MCV	Neutrophils	
	Hemoglobin	MCH	Lymphocytes	
	Hematocrit		Monocytes	
			Eosinophils	
			Basophils	
Clinical Chemistry[1]	Blood urea nitrogen (BUN/UREA)	Potassium	AST (Serum glutamic-oxaloacetic transaminase (SGOT))	Total and direct bilirubin
	Creatinine	Sodium	ALT (Serum glutamic pyruvic transaminase (SGPT))	Total Protein
	Glucose	Calcium	Alkaline phosphatise	Albumin
Routine Urinalysis[2]	• Specific gravity • pH, glucose, protein, blood and ketones • Microscopic examination (if blood or protein is abnormal)			

NOTES :

1. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Section 5.5.2 and Appendix 2
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee.

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study or within 4 days after the last dose of study treatment should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

8. DATA MANAGEMENT

- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSK Drug.
- CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.
- For this study subject data will be collected using GSK defined case report forms and combined with data provided from other sources in a validated data system.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

The study is designed to provide an estimated mean treatment difference between active drug groups and placebo group in primary efficacy endpoint, change from baseline of daily rTNSS over the first 2 weeks treatment period. This is a descriptive study and no formal inference is planned.

The primary comparisons of interest between treatment groups are:

FF 55 µg vs Placebo

FF 110 µg vs Placebo

As a supportive comparison, the pooled active drug groups (low and high-dose) will be compared with placebo.

Although no formal inference is planned, statistical models will be used to estimate mean differences between interest comparisons. Point estimates and corresponding 95% confidence intervals (CIs) will be presented for each treatment comparison. All the results from analyses model are descriptive and no statistical conclusion will be claimed.

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

This is a descriptive study and no formal inference is planned. The planned sample size is mainly based on the feasibility and regulatory requirement (100 evaluable subjects per arm).

The study is planned for a total of 360 randomized subjects (120 subjects per each treatment group). It is assumed that 17% subjects will not be evaluable for the primary analysis. Therefore, the total of 360 randomized subjects should provide 100 evaluable subjects per arm. Among 100 evaluable subjects per arm, at least 50 subjects are ≥2 to ≤6 years old.

With a common standard deviation (SD) of 2.6 for the primary endpoint, based on previous global FF pediatric studies [FFR30008, FFR100010], a sample size of 100 subjects per treatment group ensures that the half-width of 95% CI of the treatment difference between active drug and placebo is no larger than 0.725 for the age groups ≥2 to≤12 years old and a sample size of 50 subjects per treatment group ensures the half-width of 95% CI no larger than 1.032.

It is assumed that the treatment difference between active drug and placebo in change from baseline of daily rTNSS over the first two weeks treatment period for FF 110 µg is 0.5 and FF 55 µg is 0.3 based on the pooled analysis of previous global FF pediatric studies [FFR30008, FFR100010]. With 100 subjects per treatment group for ≥2 to≤12 years old and 50 subjects per group for ≥2 to≤6 years old, the probabilities of observing a positive trend, i.e. at least one active drug is numerically superior to placebo, is calculated by means of simulation. As shown in below table, the probability of observing a positive trend in subjects aged ≥2 to≤12 years and subjects aged ≥2 to≤6 years is 95% and 90% respectively. The probability of observing a positive trend in both age groups is 88%.

Subjects aged ≥2 to≤12 years old (100 subjects per arm)	Subjects aged ≥2 to≤6 years old (50 subjects per arm)	In both age groups
95%	90%	88%

9.2.2. Sample Size Sensitivity

The assumption of a standard deviation of 2.6 for primary endpoint, change from baseline in diary rTNSS over the first two weeks treatment period, is based on the estimated from previous studies. However, the actual standard deviation in this study may deviate from 2.6. The following table presents the precision of the two sided 95% CI based on different standard deviations for a sample size of 100 subjects per treatment group aged ≥2 to≤12 years and 50 subjects per treatment group aged ≥2 to≤6

Common standard deviation	Distance from mean to limit (1/2 of the width of the 95% confidence interval)	
	Subjects aged ≥2 to≤12 years old (100 subjects per arm)	Subjects aged ≥2 to≤6 years old (50 subjects per arm)
2.4	0.669	0.953
2.5	0.697	0.992
2.6	0.725	1.032
2.7	0.753	1.072
2.8	0.781	1.111

If the assumed the treatment difference between active drugs and placebo is not exactly 0.3 for low dose and 0.5 for high dose, the probabilities of observing a positive trend calculated in Section 9.2.1 will not hold. Based on historical data, it is assumed that the treatment difference between high dose and placebo follows a normal distribution N(0.5, 0.5), and the treatment difference between low dose and placebo follows a normal distribution N(0.3, 0.5). The common SD is assumed to be 2.6. Based on the above assumptions, the probability of observing a positive trend is re-calculated as following

In ≥2 to≤12 years old subjects (100 subjects per arm)	In ≥2 to≤6 years old subjects (50 subjects per arm)	In both age groups
91%	88%	85%

9.2.3. Sample Size Re-estimation or Adjustment

Due to the uncertainties about standard deviation, the pooled SD will be monitored in blinded way. The pooled SD will be adjusted according to the assumed treatment effect. If the adjusted SD is much larger than 2.6, team will determine whether to increase sample size based on feasibility and the re-calculated probability of observing a positive trend.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

The intent-to-treat (ITT) population is defined as all randomized subjects who received at least one dose of study drug. Subjects will be assessed according to the treatment they are randomised to. This population will be the primary analysis population for efficacy analysis. Additional output(s) may be provided if subjects are mistakenly treated but not randomized to support safety tables.

The Subset ITT population (2 to 6 years old) is defined as a subset of ITT population comprising subjects aged ≥2 to ≤6 years old.

The per protocol (PP) population is defined as all randomized subjects in ITT population who do not have any full protocol deviations. This population will be used for supportive analysis of the primary efficacy endpoint only. These detailed criteria of full protocol

deviations will be defined in the Reporting and Analysis Plan (RAP). The PP population will not be analyzed if this population comprises more than 95% or less than 50% of the ITT population.

All the summary and analysis will be performedfor both ITT population and Subset ITT population (2 to 6 years old). Both the ITT, Subset ITT and PP populations will be determined prior to unblinding of the study.

9.3.2. Interim Analysis

There are no interim analyses planned for this study.

9.4. Key Elements of Analysis Plan

Where possible, data from subjects who withdraw prematurely from the study will be included in any analyses. In general, the minimum data required will be a baseline evaluation (if baseline is needed for analysis) and at least one post-baseline evaluation.

TNSS for each assessment time point is the sum of the 4 individual nasal symptom scores (rhinorrhea, nasal congestion, nasal itching and sneezing), ranging from 0 to 12, since each of the four individual symptoms will be scored on a four-point scale from 0 to 3. rTNSS is the symptom score which documented in a reflective manner (represents how the subjects has been feeling over the preceding 12 hours).

The daily rTNSS will be computed as the average of the PM rTNSS and the AM rTNSS of the next day, based on the assessments prior to dosing. For example, the Day 1 rTNSS will be computed as: $[(\text{PM rTNSS})_{\text{Day1, first day of dosing}} + (\text{AM rTNSS})_{\text{Day 2, prior to second dosing}}]/2$.

If for a given subject and at a given assessment time (i.e., AM or PM) any of the four symptoms are missing, then the rTNSS will be considered missing for that assessment time. If one (but not both) of the AM and PM rTNSS is missing for a given day (e.g., a dosing interval during the treatment period), the non-missing rTNSS for that day will be used as the rTNSS for the day.

The baseline period for diary card endpoints is defined as 4 days prior to randomization, including the AM symptom assessment on the randomization (i.e., treatment initiation) date. Day 1 assessments include the PM assessment on the randomization (i.e., treatment initiation) date and the AM assessment of the day after treatment initiation. The first 2-week treatment period is defined as the first 14 dosing (24-hour) days of the treatment period. Baseline values for other endpoints will be those used as appropriate from either Visit 1 (Screening) or Visit 2 for clinic visit.

Endpoints relating to daily diary assessments will be calculated from all available data over the period of interest. The mean value over the period refers to the mean of the non-missing values of each endpoint during the period. No imputations will be performed on missing daily diary data.

Means, standard deviation, median, minimum, and maximum will be given for the summary of continuous variables and frequencies and percentages will be given for the summary of categorical variables.

In each efficacy analysis table , sample size, least square mean, standard error of the least square mean, least square mean difference, 2-sided p-values and 2-sided 95% CIs (whenever appropriate) for all pair wise comparisons will be given but no inference will be drawn. All the results from analysis modeling are for descriptive purpose.

No multiplicity adjustments are necessary since no formal hypothesis test will be done.

Appropriate graphs will be reviewed as part of the model checking process to ensure that distributional assumptions hold. In all cases, if any assumptions of the proposed method of analyses are not met, alternative methods (i.e., nonparametric methods) of analyses will be used.

9.4.1. Primary Analyses

The primary efficacy endpoint is the mean change from baseline over the first 2 weeks treatment period in daily rTNSS (rhinorrhea, nasal congestion, nasal itching and sneezing), as evaluated on a 4-point categorical scale. The minimum data required for the primary endpoint analysis will be 4 days daily rTNSS data in baseline period and at least 4 days daily rTNSS data in the first 2 week treatment period after randomisation.

The primary analysis method will be the pair wise comparison of treatment groups (active vs. placebo) using analysis of covariance (ANCOVA) adjusting for baseline daily rTNSS, classification of AR (IAR or PER), age, gender and treatment.

Mean daily rTNSS and mean change from baseline in daily rTNSS will be summarized by week (over each week) as well as over the first 2 weeks (14 days) of treatment period and over the entire treatment period (28 days) by treatment group.

The change from baseline in daily rTNSS over Week 1, Week 2, Week 3, and Week 4 will also be analyzed. The analysis results of changes over Week 1, Week 2 will be used to reinforce the robustness of the primary efficacy endpoint.

All graphs, summary and analysis tables will be provided for the ITT population (of primary interest), PP population (supportive if appropriate) and the subset ITT-≥2 to ≤6 years population (supportive).

For the modeling analysis on ITT-≥2 to ≤6 years population, if the statistical model does not converge for all the covariates, sex, age will be dropped from the model. If the model still does not converge, then classification of AR (IAR or PER) will be further dropped. The details will be included in the RAP.

Some of summary tables will also be repeated for the subgroup by classification of AR and age category.

9.4.2. Secondary Analyses

Regarding the secondary analyses for diary card endpoints (rTOSS and rTNSS over 4 weeks), the analysis method will be the same as the primary efficacy analysis..

Overall evaluation of response to therapy for subjects who are in the ITT population will be summarized, and analyzed using logistic regression adjusting for age, gender, classification of AR (IAR or PER), and treatment.

ANCOVA model adjusting for baseline nasal finding score by anterior rhinoscopy, classification of AR (IAR or PER), age, gender and treatment will be used to analyze nasal finding score by anterior rhinoscopy.

ANCOVA model adjusting for classification of AR (IAR or PER), age, gender and treatment will be used to analyze the mean rescue-free days over the first 2 weeks and over the 4 week treatment.

9.4.3. Other Analyses

Safety analysis
Safety data will be summarized and/or listed by treatment group for the ITT population.

Extent of Exposure
The extent of exposure to study drug will be summarized by treatment group.

Adverse Events (AEs)
AEs will be coded using the standard GSK dictionary, MedDRA, and grouped by body system. AEs occurring pre-treatment, during active treatment and post-treatment will be summarized separately. The number and percentage of subjects experiencing at least one AE of any type, AEs within each body system and AEs within each preferred term will be presented for each treatment group. Separate summaries will be provided for all AEs, drug related AEs, SAEs, and for AEs leading to withdrawal.

Clinical Laboratory Evaluations
Clinical laboratory evaluations, including hematological and clinical chemistry, will be summarized by treatment group for each visit. Further details will be provided in the RAP.

Nasal Examinations
Nasal examinations will be performed at each visit, and will include assessments of nostril patent, septum, mucosa, secretions, ulcers, and polyposis. Nasal examination results will be summarized by visit for each of the 6 examination parameters listed above. At all visits, frequencies of classifications (yes/no, absent/present) will be calculated. Shift from baseline (Visit 2) will be summarized for each individual nasal examination parameter. Abnormal nasal examination results will be listed.

Vital Signs Assessments
Vital signs will be summarized for each clinic visit. Further details will be provided in the RAP.

Deaths and SAEs
All SAEs will be tabulated and listed by treatment group. Deaths and SAEs will be documented in case narrative format.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Signed informed consent to be obtained for each subject before participation in the study (and for amendments as applicable)
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study

10.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.

- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents

10.4. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
- In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.

- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

11. REFERENCES

Chinese Medical Association of Otorhinolaryngology, Head and Neck Surgery, Pediatric group. Chinese Guideline for Diagnosis and Treatment of AR in Pediatrics. *Chin J Otorhinolaryngol Head Neck Surg.* 2011;46:7-8.

GSK Document Number RM2004/00130/05 Investigator's Brochure for Intranasal Fluticasone Furoate. 15-DEC-2011.

Ruchi, Gupta, Kevin B. Weiss,. The 2007 National Asthma Education and Prevention Program Asthma Guidelines: Accelerating Implementation and Facilitating Their Impact Children With Asthma. *Pediatrics.* 2009;123:S193-198.

Schoenwetter WF, Dupclay L, Appajosyula S, Botteman MF, Pashos CL. Economic impact and quality-of-life burden of allergic rhinitis. *Curr Med Res Opin.* 2004;20(3):305-317.

Wallace DV, Dykewicz MS, Bernstein DI, Blessing-Moore J, Cox L, Khan DA et al. The diagnosis and management of rhinitis: An updated practice parameter. *J Allergy Clin Immunol.* 2008;122:S1-84.

12. APPENDICES

12.1. Appendix 1 – Abbreviations and Trademarks

AE	Adverse Event
ALT	Alanine aminotransferase
AR	Allergic Rhinitis
BUN	Blood urea nitrogen
CPK	Creatinine Phosphokinase
CRF	Case Report Form
ECG	Electrocardiogram
FF	Fluticasone furoate
GCSP	Global Clinical Safety and Pharmacovigilance
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
h/hr	Hour(s)
HBsAg	Hepatitis B surface antigen
HR	Heart rate
IAR	Intermittent Allergic Rhinitis
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgE	Immunoglobulin E
INR	International Normalised ratio
IRB	Institutional Review Board
µg	Microgram
mL	Millilitre
PAR	Persistent Allergic Rhinitis
RAP	Reporting and Analysis Plan
RBC	Red blood cells
SAE	Serious Adverse Event
SD	Standard deviation
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
TOSS	Total Ocular Symptom Score
TNSS	Total Nasal Symptom Score
ULN	Upper limit of normal
UK	United Kingdom
WBC	White Blood Cells

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
MedDRA

12.2. Appendix 2: Liver Safety Required Actions and Follow up Assessments

Liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria - Liver Stopping Event	
ALT-absolute	ALT ≥ 8xULN
ALT Increase	ALT ≥ 5xULN but <8xULN persists for ≥2 weeks ALT ≥ 3xULN but <5xULN persists for ≥4 weeks
Bilirubin1, 2	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
International Normalised ratio (INR)2	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks ALT ≥ 3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks
Symptomatic3	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• Immediately discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the subject until liver chemistries resolve , stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is**	• Viral hepatitis serology[4] • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen(HBsAg)) quantitative hepatitis B DNA and hepatitis delta antibody[5]. • Blood sample for pharmacokinetic (PK) analysis, obtained within 72 hours after last dose[6] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN

granted If restart/rechallenge **not allowed or not granted**, permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessment **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	• Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]. **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)

4. Includes: Hepatitis A IgM antibody; HBsAg and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. If hepatitis delta antibody assay cannot be performed,, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].
6. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3xULN and <5xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN but <5xULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW,Hinson JA, et al. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. *Drug Metab Dispos.* 2009;37:1779-1784.

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Deny P,et al. Quantification of Hepatitis Delta Virus RNA in Serum by Consent Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. *J Clin Microbiol.* 2005;43(5):2363-2369.

12.3. Appendix 3: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.3.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: 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 a medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae). • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

Events NOT meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. • 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. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE. • Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.3.2. Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. 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.
c. 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 out-patient 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

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
from baseline is not considered an AE.
d. 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) which may interfere or prevent everyday life functions but do not constitute a substantial disruption
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. • Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse
g. Is associated with liver injury <u>and</u> impaired liver function defined as: • ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or** • ALT ≥ 3xULN and INR** > 1.5. * Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE. ** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.
• Refer to Appendix 2 for the required liver chemistry follow-up instructions

12.3.3. Recording of AEs and SAEs

AEs and SAE Recording:
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. • The investigator will then record all relevant information regarding an AE/SAE in the CRF • It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms. • Subject-completed Value Evidence and Outcomes questionnaires and the collection of AE data are independent components of the study. • Responses to each question in the Value Evidence and Outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by the scale's developer. • The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

12.3.4. Evaluating AEs and SAEs

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE. • The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals. • If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

12.3.5. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool
• Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool • If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the Medical Monitor. • Site will enter the serious adverse event data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor by telephone. • Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.4. Appendix 4: Protocol Amendment Changes

12.4.1. Protocol Amendment 1

This amendment applies to all sites participating in 201492.

Rationale

This protocol amendment is being implemented to update inclusion/exclusion criteria, screening/baseline/run-in failures clarified and other minor protocol clarifications.

The following revisions were made:

- Inclusion criteria updated: SPT laboratory test aeroallergen clarified
- Screening/Baseline/Run-in failures: screening/run-in failures clarified
- Time and Events Table: early withdraw added
- Subject's ages clarified
- Cardiovascular Events(CV) Definition deleted
- Editing errors or typo amended

List of Specific Changes

Section: Description

First: Section 1 Protocol Synopsis: Objectives and endpoints

Second: Original text:

Safety endpoints

- Frequency and type of clinical adverse events
- Results of clinical laboratory tests
- Results of physical and nasal examination
- Vital signs (systolic and diastolic blood pressures, pulse rate)

Third: Amendment text:

- Frequency and type of clinical adverse events
- Results of clinical laboratory tests
- Results of physical and nasal examination

Vital signs (temperature, systolic and diastolic blood pressures, pulse rate, respiratory rate)

First: Section 1 Protocol Synopsis: Overall design and Section 4.1 Overall design

Second: Original text:

The randomization will be centralized and stratified by age (≥2 to ≤6 years and >6 to ≤12 years) and by classification of AR (intermittent vs. persistent) to ensure treatment balance in age groups and AR classification groups for both safety and efficacy assessments.

Third: Amendment text:

- The randomization will be centralized and stratified by age (≥2 to ≤6 years and >6 to ≤12 years) and by classification of AR (intermittent vs. persistent) to ensure treatment balance in age groups and AR classification groups for both safety and efficacy assessments. Subjects with 6 years old and less than 7 years old will be treated as 6 years of age; these subjects will be analysis in group of 2 to 6 years. Subjects with 12 years old and less than 13 years old will be treated as 12 years of age and will be analysis in group of 6 to 12 years.

First: Section 4.1 Overall design

Second: Original text:

Following the 28-day treatment period, subjects will be followed up by telephone contact within 5±2 days after the last dose. The following procedures will be performed: Adverse Event (AE)/ Serious Adverse Event (SAE) assessment and register visit in RAMOS. Subjects will be discharged from the study upon completion of the follow-up phone call.

Third: Amendment text:

Following the 28-day treatment period, subjects will be followed up by telephone contact within 5±2 days after the last dose. The following procedures will be performed: Adverse Event (AE)/ Serious Adverse Event (SAE) assessment. Subjects will be discharged from the study upon completion of the follow-up phone call.

First: Section 4.4 Dose Justification

Second: Original text:

For pediatric subjects, the most commonly reported AEs with an incidence of >3% and more common than placebo included headache, nasopharyngitis, epistaxis, pyrexia, pharyngolaryngeal pain and cough. Across all studies however, AE incidence was similar between the FF and placebo groups and the AE profile was similar to that in adults and adolescents. Most AEs were mild or moderate in intensity.

Third: Amendment text:

Across all global paediatric studies, AE incidence was similar between the FF and placebo groups and the AE profile was similar to that in adults and adolescents. Most AEs were mild or moderate in intensity.

First: Section 5.1 Inclusion Criteria

Second: Original text:

I. Laboratory test:

Skin Prick Test (SPT): must represent a positive response using standardized allergen extract

II. **Serum-specific IgE test:** represent a positive response using standardized allergen extract.

Third: Amendment text:

I. **Skin Prick Test (SPT)*:** must represent a positive response using standardized allergen extract).

A positive skin test is defined as an allergen wheal ≥3 mm, a histamine wheal ≥3mm and a negative control test represents negative for prick testing.

II. **Serum-specific IgE test*:** represent a positive response using standardized allergen extract.

(*allergen must be aeroallergen**)**

First: Section 5.4 Screening/Baseline/Run-in Failures

Second: Original text:

Data for screening failures will be collected in source documentation at the site and will be transmitted to GSK. The following information will be collected in the case report form (CRF) for subjects who are screen failures:

- Date of screening Visit
- Subject number
- Date of ICF signature
- Demographic information including race, age and gender
- Reason for screen failure
- SAE information, if applicable, only for any SAE considered as related to study participation (e.g. study treatment , protocol mandated procedures, invasive tests, or change in existing therapy) or related to GSK concomitant medication

Third: Amendment text:

Data for screening/Run-in failures will be collected in source documentation at the site and will be transmitted to GSK. The following information will be collected in the case report form (CRF) for subjects who are screen/Run-in failures:

- Date of screening Visit
- Subject number

- Date of ICF signature
- Demographic information including race, age and gender
- Reason for screen failure
- SAE information

First: Section 5.5.1.2 Subject Withdrawal from the Study

Second: Original text:

A subject who takes double-blinded study drug but withdraws prior to Visit 5 will be defined as withdrawn early. Subjects who withdrew early will not be replaced.

Subject withdrew from the study was required and Early Withdrawal procedures must be performed, when:

- A subject is significantly non-compliant with the requirements of the protocol.
- A subject has an adverse event that would, in the investigator's judgment, make continued participation in the study an unacceptable risk.
- The treatment blind is broken for a subject (by other than GSK GCSP personnel), or
- GSK discontinues the study.
- Female subjects experience menarchal during study.

A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records:

- Review all information recorded on diary card(s), including rTNSS, rTOSS, study medication administration.
- Investigators must complete subjects' nasal examination by anterior rhinoscopy and these examined results must be recorded on patient notes.
- Conduct adverse event assessment
- Physical examination, vital signs and nasal examination
- 12-lead Electrocardiogram
- Double-blind study drug collection
- Clinical laboratory tests

These data should be recorded in the CRF, as appropriate, as they comprised an essential evaluation that should be done prior to discharging any subject from the study.

Third: Amendment text:

A subject who takes double-blinded study drug but withdraws prior to Visit 5 will be defined as withdrawn early. Subjects who withdrew early will not be replaced.

Subject withdrew from the study was required and Early Withdrawal procedures must be performed, when:

- A subject is significantly non-compliant with the requirements of the protocol.
- A subject has an adverse event that would, in the investigator's judgment, make continued participation in the study an unacceptable risk.
- Lost to follow-up
- The treatment blind is broken for a subject (by other than GSK GCSP personnel), or
- GSK discontinues the study.
- The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:
- The site must attempt to contact the subject (or subject parents/guardian) and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records:

- Review all information recorded on diary card(s), including rTNSS, rTOSS, study medication administration， rescue medication use, any medical conditions or con
- Investigators must complete subjects' nasal examination by anterior rhinoscopy and these examined results must be recorded on patient notes.
- Conduct adverse event assessment
- Physical examination, vital signs and nasal examination

- 12-lead Electrocardiogram
- Double-blind study drug collection
- Clinical laboratory tests

These data should be recorded in the CRF, as appropriate, as they comprised an essential evaluation that should be done prior to discharging any subject from the study.

Subjects who have discontinued IP in the study should be encouraged to return to the clinic as soon as possible to complete the IP Discontinuation Visit assessments and to complete the safety follow-up contact 3 to 5 days following the subject's last dose. If a subject is prematurely discontinued during a regularly scheduled visit, that visit will become the Early Withdrawal visit.

First: Section 6.1.2 Investigation Product Malfunction

Second: Original text:

An investigational product nasal spray that fails to function properly must be identified to GSK personnel for return to GSK for testing. Details of the failure will be documented in the CRF. The subject should return the nasal spray to the clinic as soon as possible to avoid missing any doses. The site will then call the Registration and Medication Ordering System Interactive Voice Response System (RAMOS) and obtain a new treatment pack number for this subject and dispense a new study medication kit from the site's product supply, as instructed by the IVRS.

Third: Amendment text:

An investigational product nasal spray that fails to function properly must be identified to GSK personnel for return to GSK for testing. Details of the failure will be documented in the CRF. The subject should return the nasal spray to the clinic as soon as possible to avoid missing any doses. The site will then call the Registration and Medication Ordering System Interactive Voice Response System (RAMOS) and obtain a new treatment pack number for this subject and dispense a new study medication kit from the site's product supply, as instructed by the RAMOS.

First: Section 6.6 Compliance with Study Treatment Administration

Second: Original text:

Subject compliance with double blind study medication will be assessed at Visit 3, 4 and Visit 5, other clinic visits as specified in the Time and Events during treatment and Early Withdrawal by assessment of subject reported use on the e-diary. To ensure protocol adherence, a subject may be re-education from the study if their compliance with study treatment is <80% or >120%.

Third: Amendment text:

Subject compliance with double blind study medication will be assessed at Visit 3, 4 and Visit 5, other clinic visits as specified in the Time and Events during treatment and Early Withdrawal by assessment of subject reported use on the e-diary. To ensure protocol adherence, a subject may be re-education from the study if their compliance with study treatment is <80% or >120%. And this no-compliance will be reported as protocol deviation.

First: Section 7.1 Time and Events Table

Second: Original text:

Procedure	**Visit Number**					**Early withdraw**	**Follow up**
	1	**2**	**3**	**4**	**5**		
		Study Day					
Visit window (of days)	**-4 to -14**	**1**	**8±2**	**15±2**	**29±2**		**32 to 36**
Informed consent[2]	X						
Subject number assignment	X						
Medical history	X						
Verification of inclusion/exclusion criteria	X						
Skin testing / serum-specific IgE test (if not done within 12 months of visit 1)	X						
Clinical laboratory tests[Randomisation] if applicable	X				X	X	
12-Lead electrocardiogram	X				X	X	
Verification of randomized criteria		X					
Randomization number assignment		X					
Dispense double-blind study drug		X					
Dispense rescue loratadine		X	X	X			
Nasal spray technique education		X	X	X			
Collect study drug					X	X	
Review screening diary[3]		X					
Compliance assessment		X	X	X	X		
Review treatment diary[3]			X	X	X		
Anterior rhinoscopy		X	X	X	X		
Investigator assess overall response to therapy				X	X		

Procedure	**Visit Number**					**Early withdraw**	**Follow up**
	1	**2**	**3**	**4**	**5**		
		Study Day					
Visit window (of days)	**-4 to -14**	**1**	**8±2**	**15±2**	**29±2**		**32 to 36**
Vital Signs	X				X	X	
Nasal examination	X	X	X	X	X	X	
Physical examination	X				X	X	
AE/SAE review	X[4]	←==========→				X	X
Concomitant medication review		←==========→				X	X

1. Parent/ guardian will record the symptom diary instead of subjects for all ages. The involvement of the parent/guardian in assessing and rating rhinitis symptoms may vary per subject. While it may not always be possible, the preference is for a consistent level of parent/guardian involvement throughout the study.

2. Informed Consent must be obtained prior to performing any Visit 1 procedures

3. The diary collects rTNSS, rTOSS, rescue usage

4. Serious AEs will be recorded from the time the consent form is signed until the follow-up visit. All AEs will be recorded from the start of study treatment until the follow-up visit.

Third: Amendment text:

Procedure	**Visit Number**					**Early withdraw**	**Follow up**
	1	**2**	**3**	**4**	**5**		
		Study Day					
Visit window (of days)	**-4 to -14**	**1**	**8±2**	**15±2**	**29±2**		**5±2 days after V5 or EW**
Informed consent[2]	X						
Subject number assignment	X						
Medical history	X						
Verification of inclusion/exclusion criteria	X	X					
Skin testing / serum-specific IgE test (if not done within 12 months of visit 1)	X						
Clinical laboratory tests[Randomisation if applicable]	X				X	X	
12-Lead electrocardiogram	X				X	X	
Verification of randomized criteria		X					

Procedure	**Visit Number**					**Early withdraw**	**Follow up**
	1	**2**	**3**	**4**	**5**		
		Study Day					
Visit window (of days)	**-4 to -14**	**1**	**8±2**	**15±2**	**29±2**		**5±2 days after V5 or EW**
Randomization number assignment		X					
Dispense double-blind study drug		X					
Dispense rescue loratadine		X	X[3]	X[3]			
Nasal spray technique education		X	X	X			
Collect study drug					X	X	
Review screening diary[4]		X					
Review medical problem/medication diary[5]		X	X	X	X	X	
Compliance assessment			X	X	X	X	
Review treatment diary[4]			X	X	X	X	
Anterior rhinoscopy		X	X	X	X	X	
Investigator assess overall response to therapy				X	X	X	
Vital Signs	X				X	X	
Nasal examination	X	X	X	X	X	X	
Physical examination	X				X	X	
AE/SAE review	X[6]	←==========→				X	X
Concomitant medication review	X	←==========→				X	X

1. Parent/ guardian will record the symptom diary instead of subjects for all ages. The involvement of the parent/guardian in assessing and rating rhinitis symptoms may vary per subject. While it may not always be possible, the preference is for a consistent level of parent/guardian involvement throughout the study.

2. Informed Consent must be obtained prior to performing any Visit 1 procedures

3. The dispense will depends on as needed

4. The diary collects rTNSS, rTOSS, rescue usage and study medication usage

5. The diary collect any medical problem (other than AR) and any medications used

6. Serious AEs will be recorded from the time the consent form is signed until the follow-up visit. All AEs will be recorded from the start of study treatment until the follow-up visit.

First: Section 7.2 Diary Recorded Information

Second: Original text:

Subjects (and/or subject's parent/guardian) will be provided with 2 diaries to record their allergy symptoms:

- A **screening diary** will be used during the screening phase (from Visit 1 to Visit 2) to capture the subjects' baseline symptom scores.
- A **daily treatment diary** will be used beginning on the first day of study medication administration (approximately 12 hours after the first dose at Visit 2) and throughout the remainder of the study.

use the same 4-point, categorical scale of 0 to 3 to assess symptoms. Throughout the study, subjects (and/or subject's parent/guardian) will rate their nasal symptoms of AR and record them on a symptom diary. Parent/ guardian will record the symptom diary instead of subjects for all ages. The involvement of the parent/guardian in assessing and rating rhinitis symptoms may vary per subject. While it may not always be possible, the preference is for a consistent level of parent/guardian involvement throughout the study.

Subjects (and/or subject's parent/guardian) will also document study drug compliance and loratadine rescue medication use on the daily treatment diary. Additionally, subjects (and/or subject's parent/guardian) will record any medical problem (other than AR) they experience and any medications used diary.

Third: Amendment text:

Subjects (and/or subject's parent/guardian) will be provided with 3 diaries to record their allergy symptoms:

- A **screening diary** will be used during the screening phase (from Visit 1 to Visit 2) to capture the subjects' baseline symptom scores.
- A **daily treatment diary** will be used beginning on the first day of study medication administration (approximately 12 hours after the first dose at Visit 2) and throughout the remainder of the study.
- **Medical problem/medication dairy** will be used during the study (from Visit 1 to Visit 5)

Screening diary and daily treatment diary will be used e-dairy , both of them use the same 4-point, categorical scale of 0 to 3 to assess symptoms. Throughout the study, subjects (and/or subject's parent/guardian) will rate their nasal symptoms of AR and record them on a symptom diary. Parent/ guardian will record the symptom diary instead of subjects for all ages. E-dairy will be record approximately 12 hours after dose, include morning dairy and evening dairy, record time will be on every 6 to 10 morning and evening separately. The involvement of the parent/guardian in assessing and rating rhinitis symptoms may vary per subject. While it may not always be possible, the preference is for a consistent level of parent/guardian involvement throughout the study.

Subjects (and/or subject's parent/guardian) will also document study drug compliance and loratadine rescue medication use on the daily treatment diary. Additionally, subjects

(and/or subject's parent/guardian) will record any medical problem (other than AR) they experience and any medications used on medical problem/medication diary.

First: Section 7.3 Screening and Critical Baseline Assessments

Second: Original text:

All demographic and baseline assessments will be completed according to the Time and Events schedule in Section 7.1.Safety parameters will be assessed at Visit 1.

Medical/medication history will be assessed as related to the eligibility criteria listed in Section 5. Cardiovascular medical history/risk factors including height, weight, blood pressure, smoking history, medical conditions will also be assessed at baseline. SAE information (see Section 12.3.2), if applicable, will also be assessed at baseline

Third: Amendment text:

All demographic and baseline assessments will be completed according to the Time and Events schedule in Section 7.1.Safety parameters physical exams, vital signs, electrocardiogram (ECG) and clinical safety laboratory assessments will be define as baseline at Visit 1. Nasal exams baseline will be assessed at Visit 2.

Medical/medication history will be assessed as related to the eligibility criteria listed in Section 5. Height, weight, medical conditions will also be assessed at baseline. SAE information (see Section 12.3.2), if applicable, will also be assessed at baseline

First: 7.4.2 Ocular Symptoms of AR

Second: Original text:

The total ocular symptom score (TOSS) is a composite score of the above three components with a maximum score of 9.Scores for both eyes will be averaged.

Similar to the nasal symptom assessments, the subjects will be instructed to score and document their ocular symptoms in the diary in a reflective manner (rTOSS) TWICE daily at the same time as assessing their instantaneous and reflective nasal symptoms.

Third: Amendment text:

Similar to the nasal symptom assessments, the subjects will be instructed to score and document their ocular symptoms in the diary in a reflective manner (rTOSS) TWICE daily at the same time as assessing their reflective nasal symptoms.

The total ocular symptom score (TOSS) is a composite score of the above three components with a maximum score of 9.

First: Section 7.5.1.1 Time period and Frequency for collection AE and SAE information

Second: Original text:

All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 3.

Third: Amendment text:

- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 3. Investigators will assess causality and tick the box on SAE Form in eCRF within 72 hours. If not completed in 72 hours, protocol deviation will to be entered.

First: full protocol applicable

Second: Original text:

2 to ≤6 years, 6-≤12 years

Third: Amendment text:

≥2 to ≤6 years, >6-≤12 years

First: Section 12.3.2 Definition of Cardiovascular Events

Second: Original text:

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

Third: Amendment text:

Delete.

12.4.2. Protocol Amendment 2

This amendment applies to all sites participating in 201492.

Rationale

This protocol amendment is being implemented to clarify SPT laboratory test, update safety laboratory assessment and other minor protocol clarifications.

The following revisions were made:

- Inclusion criteria updated: SPT laboratory test
- Safety laboratory assessment table updated
- Treatment assignment
- Compliance with study treatment administration
- Time and event table
- Editing errors or typo amended

List of Specific Changes

Section: Description

First: Section 5.1: Inclusion Criteria

Second: Original text: Diagnosis of AR

I. **Skin Prick Test (SPT)*:** must represent a positive response using standardized allergen extract).
A positive skin test is defined as allergen wheal ≥3 mm, a histamine wheal ≥3mm and a negative control test represents negative for prick testing.

Third: Amendment text:

I. **Skin Prick Test (SPT)*:** must represent a positive response using standardized allergen extract.

First: Section 5.4: Screening/Baseline/Run-in Failures
Second: Original text:
Data for screening/Run-in failures will be collected in source documentation at the site and will be transmitted to GSK. The following information will be collected in the case report form (CRF) for subjects who are screen/Run-in failures:

- Date of screening Visit
- Subject number
- Date of ICF signature
- Demographic information including race, age and gender
- Reason for screen failure
- SAE information

Third: Amendment text:

Data for screening/Run-in failures will be collected in source documentation at the site and will be transmitted to GSK. The following information will be collected in the case report form (CRF) for subjects who are screen/Run-in failures:

- Date of screening Visit
- Subject number
- Date of ICF signature
- Demographic information including race, age and gender
- Reason for screen/run-in failure
- SAE information

First: Section 5.5.1.2: Subject Withdrawal from the Study
Second: Original text:
Subjects who have discontinued IP in the study should be encouraged to return to the clinic as soon as possible to complete the IP Discontinuation Visit assessments and to complete the safety follow-up contact 3 to 5 days following the subjects last dose. If a subject is prematurely discontinued during a regularly scheduled visit, that visit will become the Early Withdrawal visit.

Third: Amendment text:

Subjects who have discontinued IP in the study should be encouraged to return to the clinic as soon as possible to complete the IP Discontinuation Visit assessments and to complete the safety follow-up contact 3 to 7 days following the subjects last dose. If a

subject is prematurely discontinued during a regularly scheduled visit, that visit will become the Early Withdrawal visit.

First: Section 6.2: Treatment Assignment
Second: Original text:
Daily doses should be administered in the morning following pre-dose symptom assessment **except on the morning of Visit 5, where the last dose will be administered in the clinic.** Administration of the spray should be conducted according to the Patient Instruction Leaflet that will be provided to the sites by GSK. The subject Instruction Leaflets should be reviewed with the subjects (and /or subject's parent/guardian) and distributed to the subjects to take with them.
Third: Amendment text:

Daily doses should be administered in the morning following pre-dose symptom assessment, the last dose will be administered on the morning of Visit 5. Administration of the spray should be conducted according to the Patient Instruction Leaflet that will be provided to the sites by GSK. The subject Instruction Leaflets should be reviewed with the subjects (and /or subject's parent/guardian) and distributed to the subjects to take with them.
First: Section 6.2.2: Assignment of Randomisation/Treatment Pack Numbers
Second: Original text:

At Visit 2, subjects meeting the randomisation eligibility criteria will be assigned to study treatment via a telephone call to the IVRS. During the call, the site will confirm the subject's **Subject Number** and the IVRS will then assign two additional numbers:

Third: Amendment text:

At Visit 2, subjects meeting the randomisation eligibility criteria will be assigned to study treatment via a telephone call to the RAMOS. During the call, the site will confirm the subject's **Subject Number** and the RAMOS will then assign two additional numbers:

First: Section 6.6: Compliance with Study Treatment Administration
Second: Original text:
To ensure protocol adherence, a subject may be re-education from the study if their compliance with study treatment is <80% or >120%. And this no-compliance will be reported as protocol deviation.
Third: Amendment text:

To ensure protocol adherence, a subject may be re-education from the study if their compliance with study treatment is <80%. And this no-compliance will be reported as protocol deviation.

First: Section 6.9: Concomitant Medications and Non-Drug Therapies
Second: Original text:
All concomitant medications taken during the study will be recorded in the CRF. The minimum requirement is for the reporting of the generic drug name and dates of administration.
Third: Amendment text:

The concomitant medications related to Allergy Rhinitis diseases within 30 days prior to Visit 1 will be recorded in the CRF. All concomitant medications taken during the study will be recorded in the CRF. The minimum requirement is for the reporting of the generic drug name and dates of administration.

First: Section 7.1 Time and Events Table
Second: Original text

Procedure	**Visit Number**					**Early withdraw**	**Follow up**
	1	**2**	**3**	**4**	**5**		
		Study Day					
Visit window (of days)	**-4 to -14**	**1**	**8±2**	**15±2**	**29±2**		**5±2 days after V5 or EW**
Informed consent[2]	X						
Subject number assignment	X						
Medical history	X						
Verification of inclusion/exclusion criteria	X	X					
Skin testing / serum-specific IgE test (if not done within 12 months of visit 1)	X						
Clinical laboratory tests[Randomisation] if applicable	X				X	X	
12-Lead electrocardiogram	X				X	X	
Verification of randomized criteria		X					
Randomization number assignment		X					
Dispense double-blind study drug		X					
Dispense rescue loratadine		X	X[3]	X[3]			
Nasal spray technique education		X	X	X			
Collect study drug					X	X	
Review screening diary[4]		X					

Procedure	**Visit Number**					**Early withdraw**	**Follow up**
	1	**2**	**3**	**4**	**5**		
		Study Day					
Visit window (of days)	**-4 to -14**	**1**	**8±2**	**15±2**	**29±2**		**5±2 days after V5 or EW**
Review medical problem/medication dairy[5]		X	X	X	X	X	
Compliance assessment			X	X	X	X	
Review treatment diary[4]			X	X	X	X	
Anterior rhinoscopy		X	X	X	X	X	
Investigator assess overall response to therapy				X	X	X	
Vital Signs	X				X	X	
Nasal examination	X	X	X	X	X	X	
Physical examination	X				X	X	
AE/SAE review	X[6]	←==========→				X	X
Concomitant medication review	X	←==========→				X	X

Third: Amendment text:

Procedure	**Visit Number**					**Early withdraw**	**Follow up**
	1	**2**	**3**	**4**	**5**		
		Study Day					
Visit window (of days)	**-4 to -14**	**1**	**8±2**	**15±2**	**29±2**		**5±2 days after subjects last dose**
Informed consent[2]	X						
Subject number assignment	X						
Medical history	X						
Verification of inclusion/exclusion criteria	X	X					
Skin testing / serum-specific IgE test (if not done within 12 months of visit 1)	X						
Clinical laboratory tests[Randomisation] if applicable	X				X	X	
12-Lead electrocardiogram	X				X	X	

Procedure	**Visit Number**					**Early withdraw**	**Follow up**
	1	**2**	**3**	**4**	**5**		
		Study Day					
Visit window (of days)	**-4 to -14**	**1**	**8±2**	**15±2**	**29±2**		**5±2 days after subjects last dose**
Verification of randomized criteria		X					
Randomization number assignment		X					
Dispense double-blind study drug		X					
Dispense rescue loratadine		X	X[3]	X[3]			
Nasal spray technique education		X	X	X			
Collect study drug					X	X	
Review screening diary[4]		X					
Review medical problem/medication dairy[5]		X	X	X	X	X	
Compliance assessment			X	X	X	X	
Review treatment diary[4]			X	X	X	X	
Anterior rhinoscopy		X	X	X	X	X	
Investigator assess overall response to therapy				X	X	X	
Vital Signs	X				X	X	
Nasal examination	X	X	X	X	X	X	
Physical examination	X				X	X	
AE/SAE review	X[6]	←==========→				X	X
Concomitant medication review	X	←==========→				X	X

First: Section 7.5.6: Clinical Safety Laboratory Assessments
Second: Original text:

Laboratory Assessments	**Parameters**		
Haematology	Platelet Count	Red blood cells (RBC) Indices:	White Blood Cells (WBC) count with Differential :
	RBC Count	MCV	Neutrophils
	Hemoglobin	MCH	Lymphocytes
	Hematocrit		Monocytes
			Eosinophils

Laboratory Assessments	**Parameters**			
			Basophils	
Clinical Chemistry [1]	Blood urea nitrogen (BUN)	Potassium	AST (Serum glutamic-oxaloacetic transaminase (SGOT))	Total and direct bilirubin
	Creatinine	Sodium	ALT (Serum glutamic pyruvic transaminase (SGPT))	Total Protein
	Glucose	Calcium	Alkaline phosphatise	Albumin
Routine Urinalysis[2]	• Specific gravity • pH, glucose, protein, blood and ketones • Microscopic examination (if blood or protein is abnormal)			

NOTES :

1. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Section 5.5.2 and Appendix 2
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee.

Third: Amendment text:

Laboratory Assessments	**Parameters**			
Haematology	Platelet Count	Red blood cells (RBC) Indices:	White Blood Cells (WBC) count with Differential :	
	RBC Count	MCV	Neutrophils	
	Hemoglobin	MCH	Lymphocytes	
	Hematocrit		Monocytes	
			Eosinophils	
			Basophils	
Clinical Chemistry[1]	Blood urea nitrogen (BUN/UREA)	Potassium	AST (Serum glutamic-oxaloacetic transaminase (SGOT))	Total and direct bilirubin

Laboratory Assessments	**Parameters**			
	Creatinine	Sodium	ALT (Serum glutamic pyruvic transaminase (SGPT))	Total Protein
	Glucose	Calcium	Alkaline phosphatise	Albumin
Routine Urinalysis[2]	• Specific gravity • pH, glucose, protein, blood and ketones • Microscopic examination (if blood or protein is abnormal)			

NOTES :

1. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Section 5.5.2 and Appendix 2
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee.