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Clinical Protocol

205684

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SUMMARY INFORMATION

Title:	A Randomized, Parallel-Group, Placebo-Controlled, Double-Blind Study to Evaluate the Efficacy and Safety of 1146A Nasal Spray in Adult Subjects with Symptoms of Common Cold
Protocol Number:	205684
Sponsor:	GlaxoSmithKline Consumer Healthcare (GSKCH) 184 Liberty Corner Road, Warren, NJ 07059 USA Tel: PPD
Product Name:	1146A (Carbopol® 980 Gel Nasal Spray)
Development Phase:	Phase II/III

Expert Advice Outside of Normal Working Hours:	Tel: PPD
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PRINCIPAL INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol and any amendments and according to the current ICH GCP guidelines.
- 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 site staff receives all appropriate information throughout the study.
- I agree to conduct this study in full conformance with the laws and regulations of the country in which the research is conducted and the Declaration of Helsinki.

Investigator Name:	
Investigator Qualifications:	
Investigator Signature:	PPD
Date of Signature/ Agreement:	PPD DD/MMM/YYYY




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PROCESS FOR AMENDING THE PROTOCOL

Protocol modifications to ongoing studies which could potentially adversely affect the safety of subjects or which alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, duration of therapy, assessment variables, the number of subjects treated, or subject selection criteria are considered major/substantial amendments and must be made only after appropriate consultation between an appropriate representative of GSKCH and the Investigator.

Details of amendments to the protocols should be recorded on the following page. Protocol modifications must be prepared by a representative of GSKCH. All changes must be justified in the Reason for Amendment section of the following Protocol Amendment Page. Approval of amendments will be made by the original protocol signatories or their appropriate designees.

All major/substantial protocol modifications must be reviewed and approved by the appropriate IRB in accordance with local requirements, before the revised edition can be implemented.

All non-substantial/ minor/ administrative amendments should be submitted to the IRB as per country specific requirements. In some countries pre-approval of a minor amendment is not required and will just be held on file by the sponsor and Investigator.

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PROTOCOL AMENDMENT PAGE


Details of all amendments should be recorded in the table below. Affected sections should be listed in the table; the actual amendment/ change should be made in the relevant section of the main protocol.

To highlight the change, the following features will be used:


To add text: Use of **CAPITAL LETTERS, BOLD AND UNDERLINE**

To delete text: Use of Strikethrough e.g. ~~striketthrough~~


Amendment No. & New Protocol Version No.	Type of Amendment	Reason for Amendment	Other Documents Requiring Amendment	Section(s) Amended	PI Amendment Agreement Signature & Date
Amendment No.: 1	Non-Substantial/Minor <input checked="" type="checkbox"/>	During application, the device should be held between the index and middle fingers, not the index and ring fingers.	Informed Consent <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No Safety Statement <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No CRF <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	Appendix 2- Subject Instructions for Use, Step 5; Section 5.2.1.	Signature: PPD
Protocol Version No.: 1.0 <u>2.0</u>	Substantial/ Major <input type="checkbox"/>				Date: PPD
Amendment No.: 2	Non-Substantial/Minor <input checked="" type="checkbox"/>	The head should be tilted forward slightly when inserting the nasal applicator into the nostril.	Informed Consent <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No Safety Statement <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No CRF <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	Appendix 2- Subject Instructions for Use, Step 5; Section 5.2.1.	Signature: PPD
Protocol Version No.: 2.0 <u>3.0</u>	Substantial/ Major <input type="checkbox"/>				Date: PPD

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Amendment No. & New Protocol Version No.	Type of Amendment	Reason for Amendment	Other Documents Requiring Amendment	Section(s) Amended	PI Amendment Agreement Signature & Date
Amendment No.: 3.0	Non-Substantial/Minor <input type="checkbox"/>	1. The eligibility criteria for common cold symptom onset was changed from 48 hours to 72 hours 2. A recent history of alcohol or other substance abuse within the past 5 years was changed to 1 year 3. Clarified how urine drug screen results would be documented in the CRF 4. Additional wording included regarding the statistical impact of subjects with common cold between >48 and ≤72 hours and that it might be reviewed 5. Date and time of symptom onset will be captured in the CRF	Informed Consent <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No Safety Statement <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No CRF <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	1. Schedule of Events, Protocol Synopsis, Section 3.1 Study Design, Section 3.3 Type and Planned Number of Subjects, Section 4.1 Inclusion Criteria-6, Section 6.1.7 Self-Assessment of Common Cold Signs & Symptoms by Subjects 2. Section 4.2. Exclusion criteria-6A 3. Section 6.1.9 Urine Drug Screening Test 4. Protocol Synopsis, 9.3.2 Primary Analysis 5. Section 6.1.7 Self-	Signature: PPD
Protocol Version No.: 4.0	Substantial/ Major <input checked="" type="checkbox"/>				Date: PPD

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				Assessment of Common Cold Signs & Symptoms by Subjects	
Amendment No.: 4	Non-Substantial/Minor <input type="checkbox"/>	1. Sample size has been lowered due to recent awareness of publications with studies employing the use of products with similar purported mechanisms of actions 2. Clarification that freezer temperatures can be below -70°C	Informed Consent <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No Safety Statement <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No CRF <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	1. Protocol Synopsis, Section 3.1 Study Design, Section 3.3 Type and Planned Number of Subjects, Section 9.1 Sample Size Determination, Section 11 References 2. Section 6.2.3 Nasal Swab Sample	Signature: PPD
Protocol Version No.: 5.0	Substantial/ Major <input checked="" type="checkbox"/>				Date: PPD

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SCHEDULE OF EVENTS


PROCEDURE	VISIT 1 (Day 1)		AT HOME PROCEDURES (Days 2-7)	VISIT 2 (Day 8) ^a
	Screening	Treatment Phase		End of study or early termination
Written informed consent	X			
Demographic data	X			
Medical history	X			
Record prior & concomitant medications and non-drug treatments/ procedures	X	X	X	X
Common cold symptom assessment ^b	X			
Vital signs ^c	X			X
Physical examination	X			X
Nasal examination	X			X
Urine drug screen	X			
Urine pregnancy test ^d	X			X
Inclusion/exclusion criteria	X			
RANDOMIZATION ^e	X			
Dispense & train subjects on e-diary		X		
Self-assessment of common cold symptoms in subject e-diary ^f		X	X	X
Nasal swab sample ^g		X		
Instruct subjects on proper use of study treatment ^h		X		
Dispense & prime 1 st study device		X		
Study treatment administration ⁱ		X	X	
Collect subject e-diary				X
SAE and AE assessment and recording ^j	X	X	X	X
Study conclusion ^k				X

- ^a Subjects who discontinue study treatment before completing the study and those who prematurely withdraw from the study for any reason should undergo end of study visit procedures in-clinic as soon as possible.
- ^b Subjects will self-evaluate and grade their common cold symptoms using a 4-point scale (See Section 6.1.7. for more details). Only subjects meeting all eligibility criteria including the following criteria will be enrolled into the study:
1. A confirmed common cold diagnosis with symptoms ~~≤48~~ ≤72 hours;
 2. TSS ≥ 9 (baseline sum of the 8 common cold symptoms described in Section 6.1.7.);
 3. Score ≥ 1 for at least one of the following symptoms: sore throat, runny nose, or blocked nose.

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The Investigator will confirm a common cold diagnosis. This will be collected in the case report form (CRF).

- c. Vitals will include blood pressure, pulse rate, respiratory rate, oral body temperature and height and weight measurements. Height and weight will only be collected during Screening.
- d. Only female subjects of childbearing potential.
- e. Site staff will stratify and randomize eligible subjects to one of the two treatment arms by contacting interactive response technology (IRT).
- f. Self-assessment of common cold symptoms using a 4-point scale (See Section 6.1.7. for more details) will be recorded in the subject e-diary immediately prior to the first dose at Baseline, immediately prior to each subsequent dose, and the morning of Day 8 upon awakening.
- g. Nasal swab sample will be obtained from each subject after randomization and self-assessment of common cold symptoms mentioned above for possible future virological analysis.
- h. Independent site personnel, who will have no other responsibilities during the study, will then instruct subjects on proper use, priming and administration technique of study treatment. Subjects will be instructed to dose for the full seven days irrespective of symptom resolution to avoid inappropriate discontinuation due to misinterpretation of reduced symptomatology as a result of the fluctuation of symptoms that occurs with a common cold. Subjects will also be instructed to change to a new study treatment device every 2 days and to prime the new device prior to the morning dose.
- i. Dosing administration is 3 actuations per nostril per dose, four times a day for 7 days. Subjects will be instructed to alternate nostrils after each actuation. First administration of study treatment will occur at the study site by independent site personnel supervision that will have no other responsibilities during the study; first dosing can occur any time prior to 13:00. Subject randomization will be stratified by dosing time on Day 1 by those study subjects receiving first dose of study treatment between the hours of 8:00-11:00 and those receiving first dose of study treatment between the hours 11:01-13:00. On Day 1, subjects dosing between 8:00-11:00 will dose every 4 hours \pm 30 minutes for 4 doses and subjects dosing between 11:01-13:00 will dose every 4 hours \pm 30 minutes for 3 doses. On Days 2-7 all subjects will administer their initial morning dose immediately following recording of their common cold symptom assessment at 07:00 \pm 2 hours and the remaining 3 doses every 4 hours \pm 30 minutes. Dosing times and number of actuations will be recorded in subject's e-diary.
- j. Any serious adverse event assessed as related to study participation that occurs subsequent to the signing of informed consent and any adverse event that occurs subsequent to the first dose will be recorded.
- k. Study conclusion will occur at the Investigator's discretion once all study procedures are complete.

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PROTOCOL SYNOPSIS FOR STUDY 205684


Brief Summary

This study, to be conducted in adult subjects with symptoms of common cold, is designed to assess if 1146A nasal spray reduces the severity of symptoms of the common cold compared to placebo. The study will also evaluate the safety of 1146A compared to placebo.

The study will be conducted at multiple sites and will be funded by GlaxoSmithKline Consumer Healthcare (GSKCH).

Objectives and Endpoints


Objectives	Endpoints
Primary	
<ul style="list-style-type: none"> To assess the efficacy of 1146A in reducing the severity of nasal symptoms on days 1-4, using the average nasal symptom score, compared to placebo in adult subjects with the common cold 	<ul style="list-style-type: none"> Average nasal symptom score Days 1-4 (ANSS₁₋₄)
Secondary	
Efficacy	
<ul style="list-style-type: none"> To assess the efficacy of 1146A in reducing the severity of nasal symptoms on days 1-7, using the average nasal symptom score, compared to placebo in adult subjects with the common cold 	<ul style="list-style-type: none"> Average nasal symptom score Days 1-7 (ANSS₁₋₇)
<ul style="list-style-type: none"> To assess the efficacy of 1146A in reducing the severity of symptoms on days 1-4 and days 1-7, using the total symptom score, compared to placebo in adult subjects with the common cold 	<ul style="list-style-type: none"> Average total symptom score Days 1-4 (ATSS₁₋₄) Average total symptom score Days 1-7 (ATSS₁₋₇)
Safety	
<ul style="list-style-type: none"> Adverse events 	<ul style="list-style-type: none"> Spontaneous and solicited adverse events and serious adverse events
Exploratory	
<ul style="list-style-type: none"> To assess the efficacy of 1146A in reducing the severity of 	<ul style="list-style-type: none"> Individual & composite total symptom scores [nasal symptom

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individual symptoms, using the individual symptom score, compared to placebo in adult subjects with the common cold	score (NSS) and total symptom score (TSS)] Days 1-7
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Study Design

<p>Overall Design</p> <p>This is a multi-center, randomized, parallel-group, double blind, 2-arm, placebo-controlled study to evaluate the efficacy and safety of 1146A (CCI carbomer 980 gel nasal spray) in adult subjects with symptomatic common cold in an outpatient setting.</p> <p>At Screening (Day 1, Visit 1), subjects with symptoms consistent with symptomatic common cold of a ≤48 <u>72</u> hour duration will provide written informed consent to be enrolled into the study. During this visit, subjects will undergo eligibility screening, which includes: assessment of common cold symptoms and diagnosis by the Investigator; review of demographics, medical and medication history; vital sign assessments (blood pressure, pulse rate, respiratory rate, oral body temperature, height and weight measurements); physical examination; Investigator-led nasal examination; urine pregnancy test (only female subjects of childbearing potential); and urine drug screen.</p> <p>Only subjects meeting all eligibility criteria including the following symptomatic common cold symptoms will be enrolled into the study:</p> <ol style="list-style-type: none"> 1. A confirmed common cold diagnosis with symptoms ≤48 <u>72</u> hours; 2. TSS ≥ 9 (baseline sum of the 8 common cold symptoms described in Section 6.1.7.); 3. Score ≥ 1 for at least one of the following symptoms: sore throat, runny nose, or blocked nose). <p>Approximately 300 <u>170</u> eligible subjects will be stratified and randomized to treatment with 1146A nasal spray or placebo (vehicle, nasal spray) in a 1:1 ratio at multiple sites. All sites should make an effort to enroll approximately equal number of males and females into the study. The study sites will stratify and randomize qualified subjects using IRT.</p> <p>Study site personnel will dispense and train subjects on the e-diary and subjects will then perform their baseline self-assessment of common cold symptoms in their e-</p>

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diary. Independent site personnel, who will have no other responsibilities during the study, will then instruct subjects on proper use, priming and administration technique of study treatment. Subjects will be instructed to dose for the full seven days irrespective of symptom resolution to avoid inappropriate discontinuation due to misinterpretation of reduced symptomatology as a result of the fluctuation of symptoms that occurs with a common cold. Subjects will also be instructed to change to a new study treatment device every 2 days and to prime the new device prior to the morning dose. The independent site personnel will then dispense the devices and demonstrate how to prime the devices by priming the first device. They will then monitor eligible subjects while the subject administers the first dose of study treatment.


Study treatment will be administered via a nasal spray device (1 dose = 3 actuations per nostril, each actuation is 140µL). Dosing administration is 3 actuations per nostril per dose, four times a day for 7 days (except for Day 1 where subjects in the 2nd strata will receive 3 doses). Subjects will be instructed to alternate nostrils after each actuation. First administration of study treatment will occur at the study site by independent site personnel supervision; first dosing can occur any time prior to 13:00.

Subject randomization will be stratified by dosing time on Day 1 by those study subjects receiving first dose of study treatment between the hours of: 8:00-11:00 and those receiving first dose of study treatment between the hours 11:01-13:00. On Day 1, subjects dosing between 8:00-11:00 will dose every 4 hours ± 30 minutes for 4 doses and subjects dosing between 11:01-13:00 will dose every 4 hours ± 30 minutes for 3 doses.

On Days 2-7 all subjects will administer their initial morning dose immediately following recording of their common cold symptom assessment at 07:00 ± 2 hours and the remaining 3 doses every 4 hours ± 30 minutes.

Dosing times and number of actuations will be recorded in the subject's e-diary. Subjects will be instructed not to take any additional cough/cold medications, including but not limited to, prescription, over-the-counter (OTC), non-drug/nutritional supplement, or procedures throughout the study. Subjects will be instructed to use acetaminophen/paracetamol over other OTC medications, but should try to avoid use if possible. See Section 3.2 and 4.2 for more detail.


Subjects will self-evaluate the severity of the following common cold signs/symptoms before each dose and record their assessment in the e-diary: headache, muscle ache, chills, sore throat, blocked nose, runny nose, cough, and sneezing. Subjects will assess symptom severity on a 4-point scale (0=none, 1=mild, 2=moderate, 3=severe) at baseline and 4 times a day (except for Day 1 where subjects

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in the 2nd strata will receive 3 doses) through Day 7 immediately prior to each dose of nasal spray and record the scores in the e-diary. Safety will be assessed by occurrence of adverse events.

Upon awakening on the morning of Day 8, subjects will complete a self-assessment of common cold symptoms in the e-diary. Subjects will be instructed to return to the study sites on Day 8 (End of study/Visit 2). An Investigator-led nasal examination, physical examination and vital signs will be repeated during this visit. A repeat urine pregnancy test will be performed on all female subjects of child bearing potential. Adverse events and the use of concomitant medications will be recorded by the subjects in e-diaries and monitored by the site personnel throughout the study.


Subjects who discontinue study treatment prior to Day 7 and those who prematurely withdraw from the study for any reason will be instructed to return to the site as soon as possible to undergo end of study assessments, and then be discharged from the study.

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Visit 1 – Screening Visit (Day 1)

The following assessments will be conducted by study site staff:

1. Obtain written informed consent from each subject.
2. Collect demographic data and medical and medication history (previous and concomitant diseases, and pre-study and ongoing concomitant medications, non-drug concomitant treatments/procedures).
3. Instruct and monitor subjects as they perform a self-assessment of common cold symptoms using a 4-point grading scale. This will be recorded in the CRF by site personnel. The Investigator will confirm the common cold diagnosis and only subjects meeting all eligibility criteria and the following criteria will be enrolled into the study (See Section 6.1.7. for more detail):
 - i. A confirmed common cold diagnosis with symptoms ~~48~~ 72 hours;
 - ii. TSS ≥ 9 (baseline sum of the 8 common cold symptoms described in Section 6.1.7.);
 - iii. Score ≥ 1 for at least one of the following symptoms: sore throat, runny nose, or blocked nose.
4. Perform physical examination (including ocular, oropharyngeal and chest examination); vital sign measurements (blood pressure, pulse, respiration rate, oral body temperature, and height and weight measurements).
5. Perform nasal examination by Investigator (for eligibility assessment). See Section 6.1.6. for details.
6. Perform urine drug screen.
7. Perform urine pregnancy test in female subjects of childbearing potential.
8. Eligibility assessment based on inclusion/exclusion criteria.
9. Stratify and randomize qualified subjects by contacting IRT (will also provide subject/kit number).
10. Monitor for serious adverse events (SAEs) and record any SAEs in CRF.

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Visit 1 – Treatment Phase Visit (Day 1)

1. Dispense and train subject on e-diary.
2. Subjects perform baseline self-assessment of common cold symptoms in e-diary.
3. A nasal swab sample will be taken for possible future virological analysis.
4. Independent site personnel, who will have no other responsibilities during the study, will instruct subjects on proper use, priming and administration technique of study treatment. Subjects will be instructed to dose for the full 7 days irrespective of symptom resolution to avoid inappropriate discontinuation due to misinterpretation of reduced symptomatology as a result of the fluctuation of symptoms that occurs with a common cold. Subjects will also be instructed to change to a new study treatment device every 2 days and to prime the new device prior to the morning dose.
5. Independent site personnel will dispense the devices and demonstrate how to prime the devices by priming the first device.
6. Eligible subject administration of the first dose of study treatment at the site by independent site personnel supervision that will have no other responsibilities during the study, and can occur any time prior to 13:00. Subject randomization will be stratified by dosing time on Day 1 by those study subjects receiving first dose of study treatment between the hours of 8:00-11:00 and those receiving first dose of study treatment between the hours 11:01-13:00. On Day 1, subjects dosing between 8:00-11:00 will dose every 4 hours \pm 30 minutes for 4 doses and subjects dosing between 11:01-13:00 will dose every 4 hours \pm 30 minutes for 3 doses. Dosing time and number of actuations will be recorded in the e-diary.
7. Monitor for SAEs/adverse events (AEs).
8. Record changes in concomitant medication or non-drug treatments/procedures in the e-diary.

Treatment Continuation and Subject Daily-Conduct (Days 2-7)

The following assessments will be conducted by study subjects every day on Days 2-7:

1. Subject self-assessment of common cold symptoms in e-diary immediately prior to dosing.
2. Subjects will administer their initial morning dose immediately following recording of their common cold symptom assessment at 07:00 \pm 2 hours and the remaining 3 doses every 4 hours \pm 30 minutes. Dosing time and number of actuations will be recorded in the e-diary.
3. Change study treatment devices every 2 days prior to the morning dose.
4. AE recording in the e-diary.
5. Record changes in concomitant medication or non-drug treatments/procedures

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in the e-diary
Visit 2 - End of Study Or Early Termination (Day 8)
<ol style="list-style-type: none"> 1. Subject self-assessment of common cold symptoms in e-diary upon awakening on the morning of Day 8. <p>The following assessments will be conducted by appropriately trained study site staff:</p> <ol style="list-style-type: none"> 2. Vital signs measurements (blood pressure, pulse, respiration rate and oral body temperature). 3. Physical examination. 4. Nasal examination by Investigator. 5. Urine pregnancy test in female subjects of childbearing potential. 6. Collection of subject e-diary. 7. Recording of any changes in concomitant medication or non-drug treatments/procedures in the CRF. 8. Monitoring and recording of any SAEs and AEs. 9. Recording of final status of subject and discharge from the study site at the Investigator's discretion once all study procedures are complete.

Type and Planned Number of Subjects

A SUFFICIENT NUMBER OF SUBJECTS WILL BE SCREENED TO ENROLL approximately ~~300~~170 eligible subjects (approximately equal number of males and females) experiencing common cold symptoms for ~~≤48~~72 hours; TSS ≥ 9 and a score ≥ 1 for at least one of the following symptoms: sore throat, runny nose, or blocked nose; and who are otherwise in good health, ~~will be stratified and randomized to ensure 274 evaluable subjects complete the entire study (approximately 137 evaluable subjects per treatment arm).~~ Subject randomization will be stratified by center and by dosing time on Day 1.


Diagnosis and Main Criteria for Inclusion

- Subjects must understand the study procedures and provide written informed consent before any assessment is performed; willing and able to complete all required assessments
- Male or female, aged 18 to 75 years
- Experiencing common cold symptoms (see Section 6.1.7. for details) for ~~≤48~~72 hours and who are otherwise in good general and mental health
- Free of concomitant treatment that could interfere with the interpretation of the study results as determined by the Investigator

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Product Information


	Test Product	Reference Product
Product Name	1146A formulation (CCI carbomer 980 gel) nasal spray	Placebo (vehicle without carbomer 980) nasal spray
Product Formulation Code (MFC)	CCI	CCI
Dose	Apply dose by alternating nostrils. 3 actuations of the 1146A nasal spray formulation per nostril per dose; each actuation is 140µL, equivalent to 140 mg.	Apply dose by alternating nostrils. 3 actuations of placebo nasal spray per nostril per dose; each actuation is 140µL.
Route of Administration	Intranasal administration	Intranasal administration
Dosing Instructions	First dosing can occur any time prior to 13:00. Subject randomization will be stratified by dosing time on Day 1 by those study subjects receiving first dose of study treatment between the hours of: 8:00-11:00 and those receiving first dose of study treatment between the hours 11:01-13:00. On Day 1, subjects dosing between 8:00-11:00 will dose every 4 hours \pm 30 minutes for 4 doses and subjects dosing between 11:01-13:00 will dose every 4 hours \pm 30 minutes for 3 doses. On Days 2-7 all subjects will administer their initial morning dose at 07:00 \pm 2 hours and the remaining 3 doses every 4 hours \pm 30 minutes. Subjects should blow their	First dosing can occur any time prior to 13:00. Subject randomization will be stratified by dosing time on Day 1 by those study subjects receiving first dose of study treatment between the hours of: 8:00-11:00 and those receiving first dose of study treatment between the hours 11:01-13:00. On Day 1, subjects dosing between 8:00-11:00 will dose every 4 hours \pm 30 minutes for 4 doses and subjects dosing between 11:01-13:00 will dose every 4 hours \pm 30 minutes for 3 doses. On Days 2-7 all subjects will administer their initial morning dose at 07:00 \pm 2 hours and the remaining 3 doses every 4 hours \pm 30 minutes. Subjects should blow their

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	nose prior to dosing and alternate actuations to each nostril. For each actuation subjects should insert the nozzle into the nostril, fully depress the pump and inhale gently. This should be repeated in the alternate nostril until 3 actuations per nostril have been completed. Refer to Appendix 2, Subject Instructions for Use for further details.	nose prior to dosing and alternate actuations to each nostril. For each actuation subjects should insert the nozzle into the nostril, fully depress the pump and inhale gently. This should be repeated in the alternate nostril until 3 actuations per nostril have been completed. Refer to Appendix 2, Subject Instructions for Use for further details.
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Statistical Methods

- Primary analysis: The nasal symptom score (NSS) for a subject and time point will be calculated as the sum score of the nasal symptoms (blocked nose, runny nose, and sneezing) at a time point. The primary efficacy endpoint is average NSS on Days 1 to 4 (ANSS₁₋₄). A subject's ANSS₁₋₄ is calculated as the mean of the 4 daily NSS across study days 1 to 4, excluding the baseline NSS on Day 1. The ANSS₁₋₄ will be summarized by means of descriptive statistics by treatment arm. For the difference of the ANSS₁₋₄ between the two treatment arms, the mean and the 95% confidence interval for the mean will be derived. The adjusted means of the ANSS₁₋₄ in both treatment arms will be compared using an analysis of covariance (at a significance level of 0.05), with factors for treatment group, center and Day 1 dosing time stratification, and the Baseline NSS as a covariate.
THE IMPACT OF SUBJECTS WITH ONSET OF SYMPTOMS OF COMMON COLD BETWEEN > 48 AND < 72 HOURS WILL BE REVIEWED IF THERE ARE MORE THAN 10% OF SUCH SUBJECTS IN THE PRIMARY ANALYSIS POPULATION. TIME OF ONSET OF SYMPTOMS OF COMMON COLD MAY BE ADJUSTED FOR IN THE MODEL AND/OR JUST A SUMMARY OF THE PRIMARY ENDPOINT WILL BE PROVIDED FOR THIS SUBSET OF SUBJECTS.
- The average nasal symptom score over Days 1 to 7 (ANSS₁₋₇) will be derived as the mean of all NSS across study Days 1 to 7 and will be summarized and analyzed in the same manner as ANSS₁₋₄.
- The average total symptom scores ATSS₁₋₄ will be derived as the mean of all TSS across study Days 1 to 4 and will be summarized and analyzed in the same manner as ANSS₁₋₄.
- The average total symptom scores ATSS₁₋₇ will be derived as the mean of all TSS across study Days 1 to 7 and will be summarized and analyzed in the same manner as ANSS₁₋₇.

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- Safety variables (incidence of adverse events, and changes in vital signs) will be summarized descriptively.
- Exploratory endpoints: Mean daily nasal symptom score (MDNSS), mean daily total symptom score (MDTSS), and mean daily individual symptom scores (MDISS) and their respective changes from baseline will be summarized by descriptive statistics by treatment arm and day.
- The course of each of the 8 common cold symptoms across the treatment period will be summarized using frequency tables by treatment arm and day.

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1. INTRODUCTION

The common cold is part of life, with most adults having 2-3 symptomatic infections per year, and children having a much higher incidence [Simasek, 2007]. Over \$3 billion are spent on over-the-counter (OTC) cough and cold remedies each year in the US [Boujaoude and Pratter, 2010]. Treatment options for the common cold focus on symptom control. For example, intranasal or oral decongestants are effective to improve nasal patency and thus relieve congestion [Sperber, 1989], first generation antihistamines reduce sneezing (Gwaltney 1997), ipratropium reduces rhinorrhea [Hayden 1996] and non-steroidal anti-inflammatory drugs (NSAIDS) may reduce fever and sore throat [Sperber, 1992]. Antitussives and mucolytics are often used to ameliorate cough and promote expectoration [Singh, 2013].

As the common cold is manifest through a plethora of symptoms, not all of which are displayed by each sufferer, there is a need for treatment options which are not specifically symptom related. Agents such as zinc, used as a preventative, given within 24 hours of symptom onset, have been shown to reduce the severity and duration of symptoms [Singh, 2013]. Various nasal sprays that do not contain pharmacologically active ingredients are available as physical barriers to prevent viruses interacting with nasal epithelium cells but little clinical data exist to support a benefit [Hull, 2007].

The pathophysiological processes that cause symptoms of the common cold continue to be explored. The fundamental premise was established in 1982 when it was proposed that these symptoms are mediated through the release of inflammatory substances by the host in response to infection and that direct viral cytopathology is of lesser importance [Turner 1982]. More recently confirmatory evidence of the role of the immune response to symptomatology has been demonstrated for rhinoviruses, which are the predominant cause of the common cold [Proud, 2008]. Once activated the humoral immune response continues irrespective of viral presence [Kennedy, 2012] so the target of minimizing the symptom complex must concentrate on containing the immune system responses while not interfering with the required antiviral activity. In addition to the barrier approach cited above [Hull, 2007], prevention of viral attachment to nasal epithelial cells via the Intercellular Adhesion Molecule 1 (ICAM-1) receptor, the mechanism by which the virus gains access to the cell to allow replication, has been explored. Tremacamara, a recombinant soluble ICAM-1, was shown to be effective in reducing the symptoms of experimental common colds [Turner, 1999]. A novel approach to minimizing an upper respiratory tract infection is to combine a barrier effect with an activity which prevents rhinovirus from binding to ICAM-1 receptors.

1146A contains carbomer 980, one of a series of anionic, synthetic, high molecular weight, non-linear polymers of acrylic acid [ACT, 1982]. CCI


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CCI [REDACTED] Carbomers inhibit human rhinovirus replication by a dual mode of action. First, above concentrations of 0.1% w/w carbomer 980 forms a viscous gel, which acts as a physical barrier. Second, carbomers are anionic and are believed to readily associate with the cationic binding sites on HRV which prevents viral interactions with the nasal epithelial cells via the cell surface receptors. Therefore, by preventing interaction with the cell surface receptors, the virus is prevented from entering the cell [Kennedy, 2012].

Carbomer 980 and 940 are used in ophthalmics, topicals, drugs, cosmetics, nasal moisturizing gel (Ocean Nasal Moisturizer Gel®- concentration unknown) and toothpaste [Lubrizol, 2010] and are generally regarded as safe.

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
<ul style="list-style-type: none"> To assess the efficacy of 1146A in reducing the severity of nasal symptoms on days 1-4, using the average nasal symptom score, compared to placebo in adult subjects with the common cold 	<ul style="list-style-type: none"> Average nasal symptom score Days 1-4 (ANSS₁₋₄)
Secondary	
Efficacy	
<ul style="list-style-type: none"> To assess the efficacy of 1146A in reducing the severity of nasal symptoms on days 1-7, using the average nasal symptom score, compared to placebo in adult subjects with the common cold 	<ul style="list-style-type: none"> Average nasal symptom score Days 1-7 (ANSS₁₋₇)
<ul style="list-style-type: none"> To assess the efficacy of 1146A in reducing the severity of symptoms on days 1-4 and days 1-7, using the total symptom score, compared to placebo in adult subjects with the common cold 	<ul style="list-style-type: none"> Average total symptom score Days 1-4 (ATSS₁₋₄) Average total symptom score Days 1-7 (ATSS₁₋₇)
Safety	
<ul style="list-style-type: none"> Adverse events 	<ul style="list-style-type: none"> Spontaneous and solicited adverse events and serious adverse events


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Exploratory	
<ul style="list-style-type: none"> To assess the efficacy of 1146A in reducing the severity of individual symptoms, using the individual symptom score, compared to placebo in adult subjects with the common cold 	<ul style="list-style-type: none"> Individual & composite total symptom scores (NSS and TSS) Days 1-7

3. STUDY PLAN

3.1. Study Design

Overall Design
<p>This is a multi-center, randomized, parallel-group, double blind, 2-arm, placebo-controlled study to evaluate the efficacy and safety of 1146A (CCI carbomer 980 gel nasal spray) in adult subjects with symptomatic common cold in an outpatient setting.</p> <p>At Screening (Day 1, Visit 1), subjects with symptoms consistent with symptomatic common cold of ≤48 <u>72</u> hour duration will provide written informed consent to be enrolled into the study. During this visit, subjects will undergo eligibility screening, which includes: assessment of common cold symptoms and diagnosis by the Investigator; review of demographics, medical and medication history; vital sign assessments (blood pressure, pulse rate, respiratory rate, oral body temperature, height and weight measurements); physical examination; Investigator-led nasal examination; urine pregnancy test (only female subjects of childbearing potential); and urine drug screen.</p> <p>Only subjects meeting all eligibility criteria including the following symptomatic common cold symptoms will be enrolled into the study:</p> <ol style="list-style-type: none"> 1. A confirmed common cold diagnosis with symptoms ≤48 <u>72</u> hours; 2. TSS ≥ 9 (baseline sum of the 8 common cold symptoms described in Section 6.1.7.); 3. Score ≥ 1 for at least one of the following symptoms: sore throat, runny nose, or blocked nose. <p>Approximately 300 <u>170</u> eligible subjects (approximately equal numbers of males and females) will be randomized to treatment with 1146A nasal spray or placebo (vehicle, nasal spray) in a 1:1 ratio at multiple sites. All sites should make an effort to enroll approximately equal number of males and females into the study. The study sites will</p>

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stratified and randomize eligible subjects using IRT.


Study site personnel will dispense and train subjects on the e-diary and subjects will then perform their baseline self-assessment of common cold symptoms in their e-diary. A nasal swab sample will be taken for possible future virological analysis. An independent site personnel, who will have no other responsibilities during the study, will then instruct subjects on proper use, priming and administration technique of study treatment. Subjects will be instructed to dose for the full seven days irrespective of symptom resolution to avoid inappropriate discontinuation due to misinterpretation of reduced symptomatology as a result of the fluctuation of symptoms that occurs with a common cold. Subjects will also be instructed to change to a new study treatment device every 2 days and to prime the new device prior to the morning dose. The independent site personnel will then dispense the devices and demonstrate how to prime the devices by priming the first device. They will then monitor eligible subjects while the subject administers the first dose of study treatment.

Study treatment will be administered via a nasal spray device (1 dose = 3 actuations per nostril, each actuation is 140µL). Dosing administration is 3 actuations per nostril per dose, four times a day for 7 days (except for Day 1 where subjects in the 2nd strata will receive 3 doses). Subjects will be instructed to alternate nostrils after each actuation. First administration of study treatment will occur at the study site by independent site personnel supervision that will have no other responsibilities during the study; first dosing can occur any time prior to 13:00.

Subject randomization will be stratified by dosing time on Day 1 by those study subjects receiving first dose of study treatment between the hours of: 8:00-11:00 and those receiving first dose of study treatment between the hours 11:01-13:00. On Day 1, subjects dosing between 8:00-11:00 will dose every 4 hours ± 30 minutes for 4 doses and subjects dosing between 11:01-13:00 will dose every 4 hours ± 30 minutes for 3 doses.

On Days 2-7 all subjects will administer their initial morning dose immediately following recording of their common cold symptom assessment at 07:00 ± 2 hours and the remaining 3 doses every 4 hours ± 30 minutes.


Dosing times and number of actuations will be recorded in subject's e-diary. Subjects will be instructed not to take any additional cough/cold medications, including but not limited to, prescription, OTC, non-drug/nutritional supplement, or procedures throughout the study. Subjects will be instructed to use acetaminophen/paracetamol over other OTC medications, but should try to avoid use if possible. See Section 3.2 and 4.2 for more detail.

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Subjects will self-evaluate the severity of the following common cold signs/symptoms before each dose and record their assessment in the e-diary: headache, muscle ache, chills, sore throat, blocked nose, runny nose, cough, and sneezing. Subjects will assess symptom severity on a 4-point scale (0=none, 1=mild, 2=moderate, 3=severe) at baseline and 4 times a day (except for Day 1 where subjects in the 2nd strata will receive 3 doses) through Day 7 immediately prior to each dose of nasal spray and record the scores in the e-diary. Safety will be assessed by occurrence of adverse events.

Upon awakening on the morning of Day 8, subjects will complete a self-assessment of common cold symptoms in the e-diary. Subjects will be instructed to return to the study sites on Day 8 (End of study/Visit 2). Nasal examination, physical examination and vital signs will be repeated during this visit. A repeat urine pregnancy test will be performed on all female subjects of child bearing potential. Adverse events and the use of concomitant medications will be recorded by the subjects in e-diaries and monitored by the site personnel throughout the study.


Subjects who discontinue study treatment prior to Day 7 and those who prematurely withdraw from the study for any reason will be instructed to return to the site as soon as possible to undergo all end of study assessments, and then be discharged from the study.

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Visit 1 – Screening Visit (Day 1)

The following assessments will be conducted by study site staff:

1. Obtain written informed consent from each subject.
2. Collect demographic data and medical and medication history (previous and concomitant diseases, and pre-study and ongoing concomitant medications, non-drug concomitant treatments/procedures).
3. Instruct and monitor subjects as they perform a self-assessment of common cold symptoms using a 4-point grading scale. This will be recorded in the CRF by site personnel. The Investigator will confirm the common cold diagnosis and only subjects meeting all eligibility criteria and the following criteria will be enrolled into the study (See Section 6.1.7. for more detail):
 - i. A confirmed common cold diagnosis with symptoms ~~48~~ 72 hours;
 - ii. TSS ≥ 9 (baseline sum of the 8 common cold symptoms described in Section 6.1.7.);
 - iii. Score ≥ 1 for at least one of the following symptoms: sore throat, runny nose, or blocked nose.
4. Perform physical examination (including ocular, oropharyngeal and chest examination); vital sign measurements (blood pressure, pulse, respiration rate, oral body temperature, and height and weight measurements).
5. Perform nasal examination by Investigator (for eligibility assessment). See Section 6.1.6. for details.
6. Perform urine drug screen.
7. Perform urine pregnancy test in female subjects of childbearing potential.
8. Eligibility assessment based on inclusion/exclusion criteria.
9. Stratify and randomize eligible subjects using IRT (will also provide subject/kit number).
10. Monitor for SAEs and record any SAEs in CRF.

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Visit 1 – Treatment Phase Visit (Day 1)

1. Dispense and train subject on the e-diary.
2. Subjects perform baseline self-assessment of common cold symptoms in e-diary.
3. A nasal swab sample will be taken for possible future virological analysis.
4. Independent site personnel, who will have no other responsibilities during the study, will instruct subjects on proper use, priming and administration technique of study treatment. Subjects will be instructed to dose for the full seven days irrespective of symptom resolution to avoid inappropriate discontinuation due to misinterpretation of reduced symptomatology as a result of the fluctuation of symptoms that occurs with a common cold. Subjects will also be instructed to change to a new study treatment device every 2 days and to prime the new device prior to the morning dose.
5. Independent site personnel will dispense the devices and demonstrate how to prime the devices by priming the first device.
6. Eligible subject administration of the first dose of study treatment at the site by independent site personnel supervision that will have no other responsibilities during the study, and can occur any time prior to 13:00. Subject randomization will be stratified by dosing time on Day 1 by those study subjects receiving first dose of study treatment between the hours of 8:00-11:00 and those receiving first dose of study treatment between the hours 11:01-13:00. On Day 1, subjects dosing between 8:00-11:00 will dose every 4 hours \pm 30 minutes for 4 doses and subjects dosing between 11:01-13:00 will dose every 4 hours \pm 30 minutes for 3 doses. Dosing time and number of actuations will be recorded in the e-diary.
7. Monitor for SAEs/AEs.
8. Record changes in concomitant medication or non-drug treatments/procedures in the e-diary.

Treatment Continuation and Subject Daily-Conduct (Days 2-7)

The following assessments will be conducted by study subjects every day on Days 2-7:

1. Subject self-assessment of common cold symptoms in e-diary immediately prior to dosing.
2. Subjects will administer their initial morning dose immediately following recording of their common cold symptom assessment at 07:00 \pm 2 hours and the remaining 3 doses every 4 hours \pm 30 minutes. Dosing time and number of actuations will be recorded in the e-diary.
3. Change study treatment devices every 2 days prior to the morning dose.
4. Adverse event recording in the e-diary.
5. Record changes in concomitant medication or non-drug treatments/procedures

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in the e-diary.

Visit 2 - End of Study Or Early Termination (Day 8)

1. Subject self-assessment of common cold symptoms in e-diary upon awakening on the morning of Day 8.

The following assessments will be conducted by appropriately trained study site staff:

2. Vital signs measurements (blood pressure, pulse, respiration rate and oral body temperature).
3. Physical examination.
4. Nasal examination by Investigator.
5. Urine pregnancy test in female subjects of childbearing potential).
6. Collection of subject e-diary.
7. Recording of any changes in concomitant medication or non-drug treatments/procedures in the CRF.
8. Monitoring and recording of any adverse events and serious adverse events.
9. Recording of final status of subject and discharge from the study sites at the Investigator's discretion once all study procedures are complete

3.2. Subject Restrictions


Lifestyle/ Dietary

None

Medications and Treatments

During the entire study (screening – end of study):

- A. Subjects are not permitted use of any medication other than the allocated study treatment and medications to treat chronic, controlled diseases (see Section 4.2, Number 3 for details). In addition, subjects should also refrain from non-drug concomitant treatment or procedures that may interfere with study treatment. In case subjects use any concomitant medication that could interfere with the interpretation of the study results, they will be discontinued from the study.
- B. Intranasal sprays including saline or decongestants within 24 hours.
- C. Intranasal steroids within the past 14 days.
- D. Expectorants, mucolytics, or antitussives within the past 12 hours.
- E. Cough/throat lozenges, menthol chest rub, menthol vaporizers or honey within 6 hours.

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- F. Non-steroidal anti-inflammatory drug (NSAID), or acetyl salicylic acid within the past 12 hours (immediate release) and 24 hours (sustained release). Acetaminophen/paracetamol may be used occasionally for fever or headache, but subjects should be instructed to try to avoid use if possible.
- G. Oral decongestants within 12 hours for short-acting and 24 hours for long-acting.
- H. Long acting antihistamines (cetirizine, fexofenadine, hydroxyzine, and loratadine) within 5 days.
- I. Short acting antihistamines (e.g., chlorpheniramine, brompheniramine, diphenhydramine), clemastine, long acting forms of chlorpheniramine within 2 days.
- J. Asthma medications with the exception of beta-agonists. Subject should be on a stable dose (≥ 7 days) within 24 hours.
- K. Herbal OTC medicines for cough/cold (e.g., echinacea, garlic supplements, etc.) for 24 hours.
- L. Systemic corticosteroids, immunomodulators within 3 months.
- M. Antibiotics within the past 14 days.
- N. A flu shot within the past 48 hours.
- O. Use of Tamiflu® (oseltamivir) or Relenza® (zanamivir) within the last 7 days.
- P. Other investigational drugs or devices.
- Q. Any other treatment the Investigator deems unacceptable for this study.

3.3. Type and Planned Number of Subjects

A SUFFICIENT NUMBER OF SUBJECTS WILL BE SCREEN IN ORDER TO ENROLL approximately ~~300~~**170** male and female subjects (all site will be instructed to enroll approximately equal numbers of males and females) ~~will be randomized to ensure 274 subjects (137 subjects per treatment arm) complete the study.~~ Eligible subjects will be aged 18 to 75 years, in good general health and experiencing symptomatic common cold symptoms for ~~≤ 48~~ **72** hours.

Symptomatic common cold is defined as:

- TSS ≥ 9 (baseline sum of the 8 common cold symptoms described in Section 6.1.7.) AND

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- Score ≥ 1 for at least one of the following symptoms: sore throat, runny nose, or blocked nose.

To participate, each subject must meet all study Inclusion and none of the Exclusion criteria at Screening/Baseline visit (Visit 1) prior to randomization. See Section 4.1. and 4.2. for details on Inclusion and Exclusion criteria.

3.4. Study Design and Dose Justification


The target population is symptomatic subjects with the common cold. These subjects are studied in the outpatient setting and efficacy is monitored by the subjects' evaluations of specific symptoms. Safety is evaluated by subject reported adverse events.

While common cold symptoms manifest for 7-10 days, the most severe symptoms typically present within the first 4 days of symptom onset, thus the primary endpoint will focus on nasal symptoms score on Days 1 through 4.

Intranasally administered 1146A formulation containing carbomer 980 (Carbopol® 980) stabilized with buffers will be compared to placebo. The individual components of 1146A are used as excipients in pharmaceutical and cosmetic preparations. The safety of carbomers was assessed by American College of Toxicology in 1982 and reevaluated in 2002; the conclusion was that carbomers are safe for use in humans [ACT, 1982; ACT, 2002].

Tolerability and safety of the intranasal formulation has been demonstrated in rats, but no published literature was found on CCI carbomer 980 administered intranasally and used four times daily over 7 days. CCI

The concentration of carbomer selected is based on *in vitro* data (CCI carbomer 980), which has demonstrated the ability to entrap common cold viruses. The rationale for the dose and regimen is to maximize the coverage of the nasal epithelium commensurate with consumer acceptability. The maximum frequency of use and volume of application are based on the regimen for competitive products (Vick's First Defense is 2-3 sprays 4 times daily approximately 4 hours apart) [Vicks First Defence Nasal Spray, 2014].

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4. 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).

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.

4.1. Inclusion Criteria

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


1. CONSENT
Demonstrates understanding of the study procedures, restrictions and willingness to participate as evidenced by voluntary written informed consent and has received a signed and dated copy of the informed consent form.

2. AGE
Aged between 18 to 75 years inclusive.

3. GENDER
Male or female.

4. GENERAL HEALTH
Good general and mental health with, in the opinion of the Investigator or medically qualified designee no clinically significant and relevant abnormalities in medical history or upon physical and Investigator-led nasal examination.

5. CONTRACEPTION
Females of childbearing potential (refer to Section 4.4.) who are, in the opinion of the Investigator, practicing a reliable method of contraception. Adequate contraception is defined as abstinence, oral contraceptive, either combined or progestogen alone OR

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injectable progestogen OR implants of levonorgestrel OR estrogenic vaginal ring OR percutaneous contraceptive patches OR intrauterine device or intrauterine system OR double barrier method (condom or occlusive cap [diaphragm or cervical vault caps] plus spermicidal agent [foam, gel, film, cream, suppository]) OR male partner sterilization prior to the female subject's entry into the study, and this male is the sole partner for that subject.

6. STUDY SPECIFIC

Investigator confirmed diagnosis of symptomatic common cold with an onset of ≤ 48 72 hours prior to randomization. Symptomatic common cold is defined as TSS ≥ 9 AND a score ≥ 1 for at least one of the following symptoms: sore throat, runny nose, or blocked nose.

4.2. Exclusion Criteria

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

1. PREGNANCY

Women who have a positive urine pregnancy test


2. BREAST-FEEDING

Women who are breast-feeding

3. CONCURRENT MEDICATION/ MEDICAL HISTORY

During the entire study (Screening – last subject visit):

- A. Subjects who have used medications or therapies that could interfere with study evaluations and have not had the proper washout period (see Section 3.2.) from these medications or therapies or are anticipated to require any concomitant intranasal medication during that period or at any time throughout the study.
- B. Nasal disease(s) likely to affect deposition of intranasal medication, such as chronic sinusitis, rhinitis medicamentosa, clinically significant polyposis, or clinically significant nasal structural abnormalities.
- C. Nasal surgery or sinus surgery within the previous year.
- D. Any condition that prohibits the subject from actuating nasal spray devices (severe rheumatoid arthritis; deformed hands and fingers; missing fingers).

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- E. Clinically relevant abnormal physical findings which, in the opinion of the Investigator or sponsor's medical monitor, would interfere with the objectives of the study or that may preclude compliance with the study procedures.
- F. Uncontrolled cardiovascular, pulmonary, renal, hepatic, gastrointestinal, hematological, endocrine, metabolic, autoimmune, neurological, psychiatric or other diseases at screening that would interfere with the study in the opinion of the Investigator.
- G. Subjects with seasonal allergic rhinitis if randomization occurs during their expected allergy season or perennial allergic rhinitis.
- H. Severe COPD, persistent asthma, or recent COPD/asthma exacerbation.
- I. An inability to comprehend and satisfactorily use the measurement instruments as determined by the study sites staff on screening.
- J. Subjects with a fever $\geq 38^{\circ}\text{C}$ (100.4°F).
- K. Frequent uses of analgesics (i.e. have taken an analgesic for pain in headache and pain in muscle/joints for ≥ 1 doses per week on average over the past 6 months).

4. ALLERGY/ INTOLERANCE


- A. Known or suspected intolerance or hypersensitivity to any of the study treatments, excipients or investigational device material or to medications of similar chemical classes.
- B. Any history of drug hypersensitivity or other significant allergic diathesis that could affect study participation.
- C. Known or suspected contraindications, including history of allergy or photosensitivity to study treatment /s.

5. CLINICAL STUDY/ EXPERIMENTAL PRODUCT

- A. Participation in another clinical study (including cosmetic studies) or receipt of an investigational drug within 30 days of the screening visit or 5 half-lives of enrollment, whichever is longer.
- B. Previous participation in this study (i.e. subjects cannot be re-screened or randomized).

6. SUBSTANCE ABUSE

- A. Recent history (within the last 5 years) of alcohol or other substance abuse.
- B. Positive urine drug screen.

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7. PERSONNEL
<p>A. An employee of the sponsor or the study sites or members of their immediate family.</p> <p>B. Persons directly or indirectly involved in the execution of this protocol, including employees of the contract research organization (CRO) and persons related to them.</p>
8. DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
<p>A. On nasal examination by Investigator, the presence of nasal disease likely to affect deposition of intranasal treatment or any superficial or moderate nasal mucosal erosion, nasal mucosal ulceration, or nasal septum perforation at the screening visit.</p> <p>B. Subjects with difficulty in using the nasal spray applicator.</p> <p>C. "Vulnerable" individual (as defined by the IRB e.g. incarcerated person).</p> <p>D. Any condition not identified in the protocol that in the opinion of the Investigator would confound the evaluation and interpretation of the study data or may put the subject at risk.</p>


4.3. Screening/ Baseline Failures

Screen failures are defined as subjects who consent to participate in the study but are never subsequently randomized.

The following information is to be collected for screen failures:

- Screening number
- Date of screening
- Date of informed consent
- Age
- Race
- Ethnicity
- Gender
- Primary reason for screen failure
- Occurrence of Serious Adverse Events (SAE); adverse events that are not SAEs will be followed by the Investigator and collected only in the source data

Re-screening of subjects is not allowed in this study.

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4.4. Women of Childbearing Potential Definition

Female subjects of non-childbearing potential must meet at least one of the following criteria:

1. Have undergone a documented hysterectomy and/or bilateral oophorectomy;
2. Have medically confirmed ovarian failure;
3. Have undergone a documented tubal ligation;
4. Have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms).

All other female subjects (including those that do not have a documented hysterectomy, tubal ligation, bilateral oophorectomy and/or ovarian failure) will be considered to be of childbearing potential.


4.5. Withdrawal/ Stopping Criteria

A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for ethical, safety, behavioral or administrative reasons. If a subject withdraws or is withdrawn from the study, all human biological samples collected before they left will be analyzed and reported unless the subject requests otherwise. A subject may request for their human biological samples to be destroyed. In these cases, the Investigator must document this in the site study records and the samples should not be used for any further research.

The following circumstances require discontinuation of study treatment and/or premature subject withdrawal:

- Subject did not meet study criteria
- Protocol violation that may impact the outcome of the study and/or subject's safety
- Withdrawal of informed consent
- Unblinding of the subject
- Subject lost to follow-up
- Pregnancy
- Death
- Use of disallowed concomitant medications (see Section 3.2.)

If the reason for removal of a subject from the study is an AE or an abnormal laboratory test result, the principal specific event or test will be recorded on the

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electronic case report form (CRF). If a subject is withdrawn from the study because of a product limiting AE, thorough efforts should be clearly made to document the outcome. Any AEs ongoing at the final visit will be followed up until resolved, the condition stabilizes, is otherwise explained, or the subject is lost to follow-up.

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 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, at least 2 telephone calls). The contact attempt should be documented in the subject's 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".
- All subjects will not be permitted any use of disallowed concomitant medications. The subject will be discontinued from study treatment if the subject takes more than one dose of disallowed concomitant medications. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject starts study treatment must be listed in the CRF.

4.6. Subject Replacement


Subjects who withdraw from the study post-randomization will not be replaced.

4.7. Subject and Study Completion

A subject is considered completed after completion of the 7 days of dosing and the final assessments conducted on Day 8.

The study is considered completed after all randomized subjects have either completed all study procedures or have been discontinued from the study.

The end of the study is defined as the date of the last subject's last visit.


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5. PRODUCT INFORMATION

5.1. Study Product

The following study products will be supplied by the Clinical Supplies Department, GSKCH:

	Test Product	Reference Product
Product Name	1146A formulation (CCI carbomer 980 gel) nasal spray	Placebo (vehicle without carbomer 980) nasal spray
Product Formulation Code (MFC)	CCI	CCI
Dose	Apply dose by alternating nostrils. 3 actuations of the 1146A nasal spray formulation per nostril per dose; each actuation is 140µL, (equivalent to 140mg).	Apply dose by alternating nostrils. 3 actuations of placebo nasal spray per nostril per dose; each actuation is 140µL.
Route of Administration	Intranasal administration	Intranasal administration
Dosing Instructions	First dosing can occur any time prior to 13:00. Subject randomization will be stratified by dosing time on Day 1 by those study subjects receiving first dose of study treatment between the hours of: 8:00-11:00 and those receiving first dose of study treatment between the hours 11:01-13:00. On Day 1, subjects dosing between 8:00-11:00 will dose every 4 hours ± 30 minutes for 4 doses and subjects dosing between 11:01-13:00 will dose every 4 hours ± 30 minutes for 3 doses. On Days 2-7 all subjects will administer their initial	First dosing can occur any time prior to 13:00. Subject randomization will be stratified by dosing time on Day 1 by those study subjects receiving first dose of study treatment between the hours of: 8:00-11:00 and those receiving first dose of study treatment between the hours 11:01-13:00. On Day 1, subjects dosing between 8:00-11:00 will dose every 4 hours ± 30 minutes for 4 doses and subjects dosing between 11:01-13:00 will dose every 4 hours ± 30 minutes for 3 doses. On Days 2-7 all subjects will administer their initial

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	<p>morning dose at 07:00 \pm 2 hours and the remaining 3 doses every 4 hours \pm 30 minutes.</p> <p>Subjects should blow their nose prior to dosing and alternate actuations to each nostril. For each actuation subjects should insert the nozzle into the nostril, fully depress the pump and inhale gently. This should be repeated in the alternate nostril until 3 actuations per nostril have been completed. Refer to Appendix 2, Subject Instructions for Use for further details.</p>	<p>morning dose at 07:00 \pm 2 hours and the remaining 3 doses every 4 hours \pm 30 minutes.</p> <p>Subjects should blow their nose prior to dosing and alternate actuations to each nostril. For each actuation subjects should insert the nozzle into the nostril, fully depress the pump and inhale gently. This should be repeated in the alternate nostril until 3 actuations per nostril have been completed. Refer to Appendix 2, Subject Instructions for Use for further details.</p>
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Both products are filled into 10 mL amber colored glass device s fitted with an Aptar Freepod M pump. The pump is made of high-density polyethylene (HDPE), low-density polyethylene (LDPE), polypropylene and stainless steel parts and is fitted into the glass device. The pump delivers a spray of 140 mcL (equivalent to 140 mg) per actuation with a precision of \pm 15%.

5.2. Dose Schedule

5.2.1. Instructions for use of the medical device

During the 7 days of treatment each subject will receive in total 27-28 doses (depending on Day 1 dosing time strata). Therefore, a kit containing 5 devices for the 7 days of dosing (4 as treatment and 1 as a reserve device) will be allocated to the subject. Subjects will use a device for 2 days and then start a new device.

All study treatment will be administered by the subject following the instructions for use below. The first administration will take place at the study sites under supervision of an independent study personnel (who will have no other responsibilities during the study) on a one-on-one session with the subject in a private room. Prior to the first

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dose the independent study personnel will prime the device in the presence of the subject as they explain the priming instructions below.

Instructions for use (by an independent site personnel):

- On Day 1, subjects dosing between 8:00-11:00 will dose every 4 hours \pm 30 minutes for 4 doses and subjects dosing between 11:01-13:00 will dose every 4 hours \pm 30 minutes for 3 doses. All subjects will be instructed to administer 4 doses on Days 2-7.
- Dose for the full seven days irrespective of symptom resolution.
- Change to a new study treatment device every 2 days and prime the new device prior to the morning dose.
- Blow nose to clear nostrils prior to dosing.
- Subjects will be instructed to complete all 6 actuations (3 in each nostril) of study treatment within 2 minutes.
- To spray, hold the device with thumb at the base and nozzle between the index and ~~ring~~ **MIDDLE** fingers. ~~Without tilting~~ **TILT** the head **FORWARD SLIGHTLY**, insert nozzle into the nostril. Fully depress the pump rim with a firm and even stroke and inhale gently.
- Alternate actuations to each nostril
- Wipe the nozzle clean and dry after each use defined as 6 actuations.

See Appendix 2 for more details.


Priming instructions:

The device will be removed from the kit prior to using it for the first time and will be primed prior to first use as indicated below:

- Shake the device well (only prior to priming, not prior to each use).
- Point the spray tip away from you.
- Remove the protective cap and prime the pump by depressing the pump firmly 10 times. Now the pump is ready to use.

5.2.2. Dosing

Dosing administration is 3 actuations per nostril per dose, four times a day for 7 days (except for Day 1 where subjects in the 2nd strata will receive 3 doses). Subjects will be instructed to alternate nostrils after each actuation. First administration of study treatment will occur at the study site by independent site personnel supervision; first dosing can occur any time prior to 13:00.

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Subject randomization will be stratified by dosing time on Day 1 by those study subjects receiving first dose of study treatment between the hours of: 8:00-11:00 and those receiving first dose of study treatment between the hours 11:01-13:00. On Day 1, subjects dosing between 8:00-11:00 will dose every 4 hours \pm 30 minutes for 4 doses and subjects dosing between 11:01-13:00 will dose every 4 hours \pm 30 minutes for 3 doses.

On Days 2-7 all subjects will administer their initial morning dose immediately following recording of their common cold symptom assessment at 07:00 \pm 2 hours and the remaining 3 doses every 4 hours \pm 30 minutes.

Dosing times (time that first actuation is administered) and number of actuations will be recorded in subject's e-diary.

5.3. Dose Modification

No dose modification is permitted in this study.

5.4. Product Compliance

Treatment compliance is assessed by the recording of dosing times and number of actuations in the subject e-diary.

5.5. Precautions


No special precautions are necessary provided the study is carried out in accordance with this protocol.

5.6. Overdose

An overdose is a deliberate or inadvertent administration of a product at a dose higher than specified in the protocol.

Overdose is not likely to occur in this study. Limited quantities of the product will be supplied, and closely monitored by the site for each subject.

Overdose per se is not an AE. However, any clinical sequelae of an overdose should be reported as an AE (and serious adverse event [SAE], if appropriate). For reporting, follow the AE and SAE reporting instructions provided in Section 7.4.

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5.7. Rescue Therapy

No rescue therapy is required in this study as the common cold is a self-limiting disease.

5.8. Product Assignment

A unique screening number will identify each subject screened for study participation. Screening numbers will be assigned in ascending numerical order as each subject signs their consent form. Only the assigned screening number should be entered in the field labelled "Subject ID" on the CRF. Once assigned to a subject, a screening number will not be reused.


5.8.1. Randomization

This study will use validated interactive response technology (IRT). The IRT system will be set-up, validated and administered by the CRO in accordance with the Sponsor approved protocol. The randomization schedule and treatment kit schedule will be generated under the responsibility of the CRO and uploaded into the validated IRT system. The randomization schedule will be set up using the method of randomly permuted blocks with a fixed block size.

The IRT system will randomize and stratify by site and by dosing time on Day 1. The maximum number of subjects each site can randomize will be capped at 45 (15% of the target number of randomized subjects). This is to ensure that the study population is reasonably distributed across as many sites as possible, and not dominated by one or two sites providing the majority of subjects. The IRT system will generate an initial shipment and re-supply shipments of numbered treatment kits for each treatment arm to the sites as subjects are enrolled.

All subjects that have signed an Informed Consent Form will be assigned an IRT generated subject number. The site will log into the IRT system and enter the required subject information; the IRT system will then assign a subject number, the subject will then meet the inclusion criteria and be enrolled or not meet inclusion criteria and excluded from the study. Those subjects excluded from the study will be recorded as Screen Failed in the IRT system.

Subjects who meet all inclusion criteria will be assigned by IRT to one of two treatment arms (1146A or placebo) in a 1:1 allocation ratio using the method of randomly permuted blocks with a fixed block size in accordance with the stratified randomization schedule. All site personnel will be blinded to the treatment

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allocations. Sponsor and CRO personnel who may influence study outcomes are kept blinded to the treatment allocations.

When a treatment arm is assigned to a subject, the IRT system will assign a randomization number to the subject and a treatment kit from the assigned arm that was previously allocated by the IRT system and shipped to the site. The treatment kit the IRT system assigns to the subject will then be dispensed to the subject. The site will enter the IRT generated subject number, randomization number and treatment kit number into the sites log.

If a subject fails to be randomized for any reason, the subject number and the reason for not being randomized will be entered in the sites log.

5.8.2 Blinding


The subjects, Investigator and site staff, study statistician and other employees of the Sponsor who may influence study outcomes are blinded to the product allocation of subjects until database lock. Independent site personnel will be responsible for preparing study treatment, training the subject on the proper use of study treatment and priming the first device. The independent site personnel will also monitor the subject as they administer their first dose. The independent site personnel will not be otherwise involved in the study.

5.8.3 Code Breaks

The blind must only be broken at the conclusion of the study with permission given by the Sponsor or in an emergency where it is essential to know which product a subject received in order to give the appropriate medical care. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition.

If the Investigator, or designee, feels breaking the code is required, the Sponsor should be consulted first, unless the delay would endanger the subject's health. The date, time the code was broken, and reason for breaking the code must be recorded and signed. In the event that a code break is required, the GSK Clinical Study Manager (CSM) and the monitor must be informed within 24 hours. The unblinded treatment code should not be recorded in the CRF.

It is the Investigator's responsibility to ensure that there is a procedure in place to allow access to a code break which will be provided in case of emergency through the IRT system. The Investigator will inform the subject how to contact his/her backup in cases of emergency when he/she is unavailable. Study treatments also must be

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discontinued for any subject whose treatment code has been broken inadvertently or for any emergency or non-emergency reason.

5.9. Packaging and Labelling

The contents of the label will be in accordance with all applicable regulatory requirements and will be the responsibility of the Clinical Supplies Department, GSKCH.

Clinical Supplies will be responsible for supplying kits containing 5 devices (4 as treatment and 1 as a reserve device) of test and reference products for the 7 days of dosing to be allocated to the subject. Subjects will use a device for 2 days (42-48 actuations depending on Day 1 dosing time strata) and then start a new device prior to the morning dose. All other study related items will be supplied by the CRO to the sites in their commercial packaging for dispensing by site staff as required.

Both products will be supplied in identical 10 mL amber colored glass devices fitted with an applicator pump in order to maintain the study blind. Each device will bear a study label. Each subject will receive a labelled pack containing 5 devices for the duration of the study.


Each study label will contain, but not be limited to, protocol number, storage conditions, and caution statement. Subjects will be provided with an emergency contact card with study site telephone number and contact information. Each subject carton will bear a uniquely numbered 2-part label. Immediately before dispensing study treatment to the subject, site staff will detach the outer part of the label from the packaging and affix it to the source document for that subject number.

Care should be taken with the supplied products and their labels so that they are maintained in good condition. It is important that all labels remain intact and legible for the duration of the study. Subjects should be instructed to not remove or deface any part of the study label, and to not discard any study devices.

5.9.1. Accountability of Product

All products supplied are for use only in this clinical study and should not be used for any other purpose.

Study treatments must be received by a designated person at the study sites, handled and stored safely and properly, and kept in a secured location to which only the staff have access. Upon receipt, all study treatments should be stored according to the

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instructions specified on the treatment labels. Clinical supplies are to be dispensed only in accordance with the protocol.

The Investigator or designee will maintain a full record of study product accountability. Subject Investigational Product Accountability Records must be kept current and will contain the following information:

- The identification of the subject to whom the study product was dispensed.
- The date(s) and quantity of the study product dispensed to the subject.
- The date(s) and quantity of the study product returned by the subject (if applicable).

The inventory must be available for inspection by the study monitor during the study. Monitoring of treatments accountability will be performed by the field monitor during site visits and at the completion of the trial.

At the end of the study, study product supplies will be verified by the monitor. Study product supplies will then be either collected by the study monitor or returned by the Investigator or designee to the GSKCH Clinical Supplies Department or designated vendor.


5.9.2. Storage of Product

Study product supplies must be received by a designated person at the study site, handled and stored safely and properly, stored in compliance with the label requirements in a secure location to which only designated staff have access.

6. STUDY ASSESSMENTS AND PROCEDURES

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

Adherence to the study design requirements, including all assessments and procedures are essential and required for study conduct.

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6.1. Visit 1 – Screening Visit (Day 1)

6.1.1. Informed Consent

The Investigator, or designee, must obtain written (signed and dated by the subject) informed consent from each subject participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study.

The Investigator, or designee, must also explain to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time. Appropriate forms for documenting a written consent will be provided by the Investigator. The Investigator, or designee, should sign and date the consent form to confirm that the consent process was completed correctly. The subject will be provided with a copy of their signed and dated consent form and any other written information which they should be instructed to retain.

If, during a subject's participation in the study, any new information becomes available that may affect the subject's willingness to participate in the study, each ongoing subject should receive a copy of this new information and be re-consented into the study. Subjects or should be provided with a copy of the signed and dated amended consent form. The date of consent will be recorded in the CRF.


6.1.2. Demographics

The following demographic parameters will be captured by the Investigator or designee and recorded in the CRF: age, gender, race and ethnicity.

6.1.3. Medical History and Prior Medication

Medical history will be assessed as related to the inclusion/exclusion criteria by the Investigator or medically qualified designee. Details of any relevant medical or surgical history, including allergies or drug sensitivity, will be recorded in the CRF. Wherever possible, diagnoses and not symptoms will be recorded. Any medication and non-drug therapies/procedures taken in the 90 days prior to the Screening Visit will also be recorded. Relevant history will be recorded in the CRF.

Significant findings that are present before signing informed consent form must be included in the CRF. Significant findings made after signing informed consent form which meet the definition of an SAE must be recorded on the Adverse Event CRF page. Refer Section 7.1 for information on definition of adverse event and serious adverse event.

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6.1.4. Physical Examination

A complete physical examination will be performed at Screening (Visit 1, Day 1) for eligibility. It will include examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, and extremities, vascular and neurological.

Information for all physical examination findings must be included in the source documentation at the study sites.

Any significant new findings made after signing informed consent form which meet the definition of an AE must be recorded on the Adverse Event CRF page. Refer Section 7.1 for information on definition of adverse event and serious adverse event.

6.1.5. Vital Sign Assessments


Vital signs assessments will be made which include blood pressure (BP), pulse rate, respiration rate, oral body temperature, and height and weight. Subjects will be included into the study at the Investigator's discretion.

After the subject has been sitting for approximately 5 minutes, systolic and diastolic BP will be measured three times using an automated validated device, e.g. OMRON, with an appropriately sized cuff. The repeat sitting measurements will be made at 1-2 minute intervals and the mean/average of the three measurements will be used. The results for each individual's measurements will be recorded in the CRF. If the cuff sizes available are not large enough for the subject's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

The respiration rate is the number of breaths a person takes per minute. The rate is usually measured when a person is at rest and simply involves counting the number of breaths for one minute by counting how many times the chest rises.

Reference range for vital signs are as follows: oral body temperature between 35.0 °C and 37.5 °C; systolic BP between 90 and 140 mmHg; diastolic BP between 55 and 90 mmHg; pulse rate between 50 and 100 bpm; and respiration rate between 12 and 20 breaths per minute.

For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Subjects must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight. Height in

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centimeters (cm) and body weight in kilograms (kg) (to the nearest 0.1 kilogram) will be measured.

6.1.6. Nasal Examination

Nasal examination will be performed for eligibility. The Investigator will use a nasal speculum or the end of an otoscope to perform a thorough examination of the nasal mucosal surfaces for presence of nasal diseases likely to affect deposition of intranasal treatment or any superficial or moderate nasal mucosal erosion, nasal mucosal ulceration, or nasal septum perforation.

Any clinically relevant findings will be noted in the medical history CRF page and enrollment will be based upon investigator judgement.

6.1.7. Self-Assessment of Common Cold Signs & Symptoms by Subjects

Common cold signs and symptoms will be self-evaluated by the subject at Screening before the first dosing and will be documented in the source document and recorded in the CRF.

In order to qualify each subject for eligibility, the Investigator will verbally confirm with the subject that the onset of any common cold symptoms occurred within ~~48~~ **72** hours of randomization. **THE DATE AND TIME OF SYMPTOM ONSET WILL BE CAPTURED IN THE CRF.** The investigator will also ensure that the subject has a symptomatic common cold, which is defined as TSS \geq 9 (baseline sum of the 8 common cold symptoms described below), AND a score \geq 1 for at least one of the following symptoms: sore throat, runny nose, or blocked nose.


The following are the symptoms of common cold and their severity grading:

Nasal symptoms:

- runny nose
- blocked nose
- sneezing

Other symptoms

- headache
- muscle ache
- chills
- sore throat
- cough

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Each individual sign/symptom will be scored using the following 4 point scale:

- 0 = absent symptoms (no sign/symptom evident)
- 1 = mild symptoms (sign/symptom clearly present, but minimal awareness; easily tolerated)
- 2 = moderate symptoms (definite awareness of sign/symptom that is bothersome but tolerable)
- 3 = severe symptoms (sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping)

6.1.8. Pregnancy Test


All women of childbearing potential will have a urine pregnancy test. It will be conducted at the site using a urine dipstick. A positive urine pregnancy test disqualifies a subject from the study. Results from the pregnancy test will be recorded in the CRF. See Section 7.7 for more information.

6.1.9. Urine Drug Screening Test

Urine will be collected at screening to perform urine drug test (urine dipstick). Urine will be tested for the following drugs or illicit substances: barbiturates, benzodiazepines, amphetamines, **METHAMPHETAMINES, 3,4-METHYLENEDIOXYMETHAMPHETAMINE (MDMA), cocaine, opiates, OXYCODONE, METHADONE** and cannabis. In case of a positive finding at the screening visits or any substance class, the subject must be excluded from participation in the study. Results will be recorded in the CRF. **IF THE URINE DRUG SCREEN YIELDS A POSITIVE RESULT FOR METHAMPHETAMINE, 3,4-METHYLENEDIOXYMETHAMPHETAMINE (MDMA), OR AMPHETAMINES, THE SUBJECT WILL BE CONSIDERED AS HAVING POSITIVE RESULT FOR AMPHETAMINES. IF THE URINE DRUG SCREEN YIELDS A POSITIVE RESULT FOR OPIATES, OXYCODONE, OR METHADONE, THE SUBJECT WILL BE CONSIDERED AS HAVING POSITIVE RESULT FOR OPIATES.**

6.1.10. Inclusion/Exclusion Criteria

The Investigator/delegate reviews the inclusion/exclusion criteria and various screening assessments and decides the eligibility of the subject prior to randomization. In that context, good general health (confirmed by vital signs, physical examination and nasal examination) and absence of any condition not identified in the protocol that in the opinion of the Investigator would confound the

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evaluation and interpretation of the study data or may put the subject at risk will be checked and reviewed.

6.1.11. Randomization

The study sites will contact IRT to stratify and randomize the eligible subject to one of the two treatment arms (1146A or placebo), and receive the subject randomization number and product kit number. The randomization number will be entered in the CRF. See Section 5.8.1 for details on the randomization.

6.1.12. Safety Monitoring

The occurrence of any SAEs related to study participation will be recorded, beginning at the time the subject provides written informed consent. This information should be recorded in the Investigator's source documents. SAEs must be reported to GSK. All SAEs will be treated appropriately and the action taken to treat the SAE should be recorded on the Adverse Event CRF page. See Section 7.2. for further details.

6.2. Visit 1 - Treatment Phase Visit (Day 1)

6.2.1. Dispense E-diary


The site will dispense e-diary and instruct and train subjects on completion of the e-diary.

6.2.2. Self-Assessment of Common Cold Symptoms

Subjects will perform a self-assessment of common cold symptoms prior to dosing (see Section 6.2.5.) and record it in the e-diary. See Section 6.1.7 for details on Common Cold Symptoms and the severity grading.

6.2.3. Nasal Swab Sample

A nasal swab sample will be taken for possible future virological analysis. Experienced site staff will collect a posterior nasopharyngeal sample by inserting a Copan FLOQSwab (Copan Diagnostics, Corona, CA) into one nostril. The swab will be inserted posteriorly approximately equidistant from the subject's nose to the ear and held in place for 10 seconds to allow absorption of secretions. Gently rotate swab 2-3 times and then gently remove swab and place in labeled vials containing Universal Transport Media (Copan Diagnostics, Corona, CA). Ensure the swab is placed all the way to the bottom of the tube, break swab applicator shaft at the specified molded breakpoint, replace cap and screw on securely. Sample vials will be stored at **OR BELOW** -70°C and shipped on dry ice to a diagnostic laboratory for possible future analysis.

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6.2.4. Study Treatment Dispensation, Priming of 1st Device, and Instructions for Use

Independent site personnel, who will have no other responsibilities during the study, will dispense study treatment according to IRT randomization and instruct the subject on proper use of study treatment. Subjects will be instructed to dose for the full seven days irrespective of symptom resolution to avoid inappropriate discontinuation due to misinterpretation of reduced symptomatology as a result of the fluctuation of symptoms that occurs with a common cold.

Subjects will be instructed to change to a new study treatment device every 2 days (48 actuations) on Days 3, 5 and 7, and to prime the new device prior to the morning dose. The independent site personnel will then dispense the devices and demonstrate how to prime the devices by priming the first device. See Section 5.2. for details on Dose Schedule.

6.2.5. First Administration of Study Treatment


The first dose of study treatment will be administered by the subject at the site with independent site personnel supervision and can occur any time prior to 13:00. Subject randomization will be stratified by dosing time on Day 1 by those study subjects receiving first dose of study treatment between the hours of: 8:00-11:00 and those receiving first dose of study treatment between the hours 11:01-13:00. On Day 1, subjects dosing between 8:00-11:00 will dose every 4 hours \pm 30 minutes for 4 doses and subjects dosing between 11:01-13:00 will dose every 4 hours \pm 30 minutes for 3 doses. The time of dosing and the number of actuations will be recorded in the subject's e-diary by site personnel. Refer to Section 5.1. or Appendix 2 for further details.

6.2.6. Safety Monitoring

The occurrence of any SAEs related to study participation will be recorded beginning at the time the subject provides written informed consent. AEs and SAEs will be collected from the start of the investigational product. This information should be recorded in the Investigator's source documents or in the subject's e-diary if they are not at the study site. If the AE meets the criteria of an SAE, it must be reported to GSK. All adverse events will be treated appropriately and the action taken to treat the AE should be recorded on the Adverse Event CRF page. See Section 7.2. for further details.

6.2.7. Concomitant Medication

Any changes in concomitant medication or non-drug treatments/procedures will be recorded in subject's e-diary and will also be captured in the CRF. There will be a

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specific question asking about acetaminophen/paracetamol and all other concomitant medication usage prior to each dose of study treatment.

6.2.8. Instructions for Treatment Continuation at Home

The independent site personnel will instruct subjects on proper use and continuation of study treatment, change of devices, completion of e-diary, reporting of incidence of AEs to site, and self-assessment of common cold symptoms to be followed until Day 7.

6.3. Treatment Continuation and at Home Procedures (Days 2-7)

6.3.1. Self-Assessment of Common Cold Symptoms by Subjects

Subjects will perform self-assessment of common cold symptoms immediately prior to each dosing and record it in the e-diary. See Section 6.1.7 for details on Common Cold Symptoms and the severity grading.

6.3.2. Administration of Study Treatment


Subjects will be instructed to continue dosing of study treatment at home. Doses will be administered four times a day. Subjects will administer initial morning dose immediately following recording of their common cold symptom assessment at 07:00 \pm 2 hours and the remaining 3 doses every 4 hours \pm 30 minutes. The time of dosing and the number of actuations will be recorded in their e-diary. Refer to Section 5.1 or Appendix 2 for further details.

6.3.3. Safety Monitoring

The occurrence of any SAEs related to study participation will be recorded beginning at the time the subject provides written informed consent. AEs and SAEs will be collected from the start of the investigational product. This information should be recorded in the Investigator's source documents or in the subject's e-diary if they are not at the study site. If the AE meets the criteria of an SAE, it must be reported to GSK. All adverse events will be treated appropriately and the action taken to treat the AE should be recorded on the Adverse Event CRF page. See Section 7.2 for further details.

6.3.4. Concomitant Medication

Any changes in concomitant medication or non-drug treatments/procedures will be recorded in subject's e-diary and will also be captured in the CRF. There will be a specific question asking about acetaminophen/paracetamol and all other concomitant medication usage prior to each dose of study treatment.

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6.4. Visit 2 – End of Study /Early Termination (Day 8)

6.4.1. Self-Assessment of Common Cold Symptoms

Upon awakening on Day 8, subjects will perform a self-assessment of common cold symptoms and record it in the e-diary. See Section 6.1.7. for details on Common Cold Symptoms and the severity grading.

6.4.2. Physical Examination

A complete physical examination will be performed (Visit 2, Day 8). Refer to Section 6.1.4. above for details on physical examination. Information for all physical examination findings must be included in the source documentation at the study sites.

Any significant new findings made after signing informed consent form which meet the definition of an Adverse Event (AE) must be recorded on the Adverse Event CRF page. Refer Section 7.1. for information on definition of adverse event and serious adverse event.

6.4.3. Vital Sign Assessments

Vital signs assessments will be made which include blood pressure (BP), pulse, respiration rate and oral body temperature. The results for each individual's measurements will be recorded in the CRF. See Section 6.1.5. above for further details.

6.4.4. Nasal Examination


Nasal examination will be performed (Visit 2, Day 8). The Investigator will perform a thorough examination of the nasal mucosal surfaces for presence of nasal diseases likely to affect deposition of intranasal treatment or any superficial or moderate nasal mucosal erosion, nasal mucosal ulceration, or nasal septum perforation. Any clinically relevant (new or worsening) findings will be noted in the adverse event CRF page.

6.4.5. Pregnancy Test

All women of childbearing potential will have a urine pregnancy test. It will be conducted at the site using a urine dipstick. Results from the pregnancy test will be recorded in the CRF. See Section 7.7. for more information.

6.4.6. Return of Study Treatment Devices and Subject E-diary

The site personnel will collect the subject e-diary and all used and unused study treatment from the subjects. Comments related to breakage, replacement of devices and treatment compliance (visual verification) will be recorded in the CRF.

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6.4.7. Concomitant Medication

Any changes in concomitant medication or non-drug treatments/procedures will be recorded in the CRF.

6.4.8. Safety Monitoring

The occurrence of any SAEs related to study participation will be recorded beginning at the time the subject provides written informed consent. AEs and SAEs will be collected from the start of the investigational product. This information should be recorded in the Investigator's source documents or in the subject's e-diary if they are not at the study site. If the AE meets the criteria of an SAE, it must be reported to GSK. All adverse events will be treated appropriately and the action taken to treat the AE should be recorded on the Adverse Event CRF page. See Section 7.2. for further details.

6.4.9. Early Termination/ Premature Subject Withdrawal


Subjects may voluntarily discontinue study treatment for any reason at any time. Study treatments also must be discontinued for any subject whose treatment code has been broken inadvertently or for any emergency or non-emergency reason. If premature withdrawal occurs for any reason, the Investigator must determine the primary reason for a subject's premature withdrawal from the study and record this information in the CRF. Subjects, who discontinue study treatment before completing the study and those who prematurely withdraw from the study for any reason, should undergo final visit procedures (Visit 2, Day 8) as soon as possible.

6.4.10. Study Conclusion

Subjects will be evaluated to determine if they completed all study procedures or if they were discontinued from the study early. If the subject discontinued at any point during the study, the primary reason for withdrawal should be recorded in the CRF by selecting one of the options below.

- Subject did not meet study criteria
- Protocol violation
- Withdrawal of informed consent
- Unblinding of the subject
- Subject lost to follow-up
- Pregnancy
- Death
- Other

The site personnel will contact IRT to close out of the subject. Subject will be discharged.

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7. SAFETY ASSESSMENTS

7.1. Definitions of an Adverse Event and Serious Adverse Event

7.1.1. Adverse Events

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

Adverse Event Definition:


- An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of an investigational or washout product, whether or not considered related to the investigational or washout 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 an investigational or washout product.

Events meeting AE definition include:

- Any abnormal laboratory test results (if applicable) or other safety assessments, including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgment 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 condition(s) detected or diagnosed after study product 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 product or a concomitant medication (overdose per se will not be reported as an AE/SAE).

Events NOT meeting definition of an AE include:

- Any clinically significant abnormal laboratory findings (if applicable) 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/ condition being studied or expected progression, signs,

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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.

7.1.2. Serious Adverse Events

Serious Adverse Event 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 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

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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 or reports of spontaneous abortion.

7.2. Recording Adverse Events and Serious Adverse Events


Recording of adverse events and serious adverse events:

- The Investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE. The Investigator or site staff will then record all relevant information regarding an AE/SAE in the CRF.
- 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 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. Clinical AEs will be described by diagnosis and not by symptoms when possible (e.g., upper respiratory tract infection, seasonal allergy, etc. instead of runny nose).
- AEs will be collected from the start of the investigational product and until 5 days following last administration of the study product.
- SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed as **related** to study participation (e.g., investigational product, protocol mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- Medical conditions reported prior to the time period for reporting AEs/SAEs should be recorded as part of the subject's medical history.

7.3. Evaluating Adverse Events and Serious Adverse Events

Assessment of Intensity:

The Investigator or designee will make an assessment of intensity for each AE and

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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.

Note: 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 product 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 product 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 (source document) or CRF 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.

7.4. Reporting Adverse Events and Serious Adverse Events

AE Reporting to GSKCH:

- AEs will be recorded in the AE section of the CRF.
- Medical conditions recorded by the subject on a diary card or similar

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document that meet the definition of an AE must also be recorded in the AE section of the CRF, if not previously well-characterized by the Investigator in the subject's medical history.

- AEs elicited by the Investigator in a standard manner at the study visits should also be recorded in the AE section of the CRF. The Investigator or designee must ask the subject the following question during each visit including any follow-up visits: *"Have you felt unwell, experienced any symptoms or taken any medication (since your last visit) (today) (since your last dose) (since the last session)?"*
- The medically qualified Investigator should review adverse events in a timely manner; this review should be documented in writing in the source document or in the CRF.
- After the study is completed at a given site, and the site has received their study data on Compact Discs (CDs), the electronic data collection tool will be removed from the internet to prevent the entry of new data or changes to existing data.

SAE Reporting to GSKCH:

A paper copy of the SAE form provided in the Investigator study master file should be completed as fully as possible.

It is essential to enter the following information:

- Protocol and subject identifiers
- Subject's demography
- Description of events, with diagnosis if available
- Investigator opinion of relationship to study product (see Section 8.3.)
- Criterion for seriousness.

The following are desirable and are of particular relevance for Investigator and GSKCH assessment of the SAE report:


- Date of onset of AE
- Date AE stopped, if relevant
- Study product start date
- Study product end date if relevant
- Action taken on study product
- Outcome if known

The SAE form, completed as fully as possible, must be faxed to PPD within 24 hours of awareness at the following fax number:

SAE Contact Information

PPD Hotline: PPD

PPD Fax: PPD

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PPD will then email the SAE form to the Case Management Group, Global Clinical Safety and Pharmacovigilance at GSK, with copy to the appropriate GSKCH Study Manager as soon as possible, **but not later than 1 business day** after study site personnel learn of the event. The GSKCH Study Manager will be responsible for forwarding the SAE form to the Medical Director responsible for the study and other GSKCH personnel as appropriate via email.

The initial report will be followed up with more information as relevant, or as requested by the GSKCH study manager.

7.5. Follow-up of Adverse Events and Serious Adverse Events

Follow-up of AEs and SAEs:

- After the initial report, the Investigator is required to proactively follow up with each subject and provide further information on the subject's condition.
- All AEs/SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.
- 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.
- Investigators are not obliged to actively seek AEs or SAEs in former subjects. However, if the Investigator learns of any SAE, including the death, at any time after a subject has been discharged from the study, and considers the event reasonably related to the investigational product or study participation, the Investigator will promptly notify GSKCH.
- The Investigator will submit any updated SAE data to GSK within the designated reporting time frames.

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Regulatory and ethics reporting requirements for SAEs:


- The Investigator will promptly report all SAEs to GSKCH within the designated reporting timeframes (within 24 hours of learning of the event). GSKCH has a legal responsibility to notify, as appropriate, the local regulatory authority and other regulatory authorities about the safety of a product under clinical investigation. Prompt notification of SAEs by the Investigator to GSKCH is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.
- GSKCH will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB and Investigators.
- Investigator safety reports are prepared according to GSKCH policy and are forwarded to Investigators as necessary. An Investigator safety report is prepared for a SAE(s) that is both attributable to investigational product and unexpected. The purpose of the report is to fulfill specific regulatory and GCP requirements, regarding the product under investigation.
- An Investigator who receives an Investigator safety report describing a SAE(s) or other specific safety information (e.g., summary of listing of SAEs) from GSKCH will file it with the Investigator Brochure (or safety statement) and will notify the IRB, if appropriate according to local requirements.

7.6. Collection of Pregnancy Information

7.6.1. Time Period for Collecting of Pregnancy Information

Collection of Pregnancy Information:

- Pregnancy information will be collected on all pregnancies reported following administration of any investigational product. Information on pregnancy identified during the screening phase and prior to investigational product administration does not need to be collected.

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7.6.2. Action to be Taken if Pregnancy Occurs

Action to be Taken:


- The investigator will collect pregnancy information on any subject who becomes pregnant while participating in the study after administration of the investigational product. The investigator will record pregnancy information on the appropriate form and submit it to PPD within 2 weeks of learning of the subject becoming pregnant. The subject will be followed to determine the outcome of the pregnancy. Information on the status of the mother and infant / neonate (including concomitant medications taken by the mother during the pregnancy) will be forwarded to PPD. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported. Like with SAE and Incident Forms, PPD will then email the pregnancy form to the Case Management Group, Global Clinical Safety and Pharmacovigilance at GSK.
- While pregnancy itself is not considered to be an AE, any pregnancy complication or elective termination for medical reasons will be recorded as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such. An SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject completed the study and considered by the investigator as possibly related to the investigational product, must be promptly forwarded to GSK.
- While the investigator is not obliged to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- If the subject becomes pregnant during the study they should be withdrawn from the study and this should be recorded in the appropriate section of the CRF.

8. DATA MANAGEMENT

For this study subject data will be entered into an electronic case report form, using a CRO's validated data system.

8.1. Source Documents/ Data

The source documents (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files and records kept at the pharmacy, at the laboratory and at the medico-technical departments involved in the

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clinical study) which contain the source of data recorded in the CRF should be specified. In some cases the e-diary can be used as a source document.

Each subject will be assigned and identified by a unique Screening Number. Any reference made to an individual subject within the study must be done using the unique Screening Number.

8.2. Electronic Case Report Form

A CRF is a printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

For each subject who has given informed consent and has been screened, CRF must be completed and signed by the Principal Investigator (or authorized designee) to certify that the data are complete and correct.

Management of clinical data will be performed in accordance with applicable CRO standards and data cleaning procedures to ensure the integrity of the data e.g. removing errors and inconsistencies in the data.

In order to protect the privacy of subjects, no Personally Identifiable Information (PII) (including the subject's name or initials or birth date) is to be recorded in the CRF or as part of the query text.


Adverse events and concomitant medications terms (if applicable) will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSK Drug respectively.

All CRF pages must be completed during a subject assessment when the CRF has been designated as the source. Data that is sourced elsewhere should be entered into the CRF in an agreed upon timeframe between the Investigator and Sponsor.

At completion of the study report, all CRF data (including queries, query responses and audit trails) will be transmitted in an agreed upon format to GSKCH via secured web portal or CD/DVD via mail carrier with tracking capabilities.

8.3. Data Handling

Documentation of all data management activities should allow step-by-step retrospective assessment of data quality and study performance. Any changes or corrections to data will be performed in the Electronic Data Capture (EDC) System,

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and it will include rationale for changes. The EDC system has an audit trail, which will provide a complete record of the changes and corrections endorsed by the Investigator.

8.3.1. Data Queries

Programmed edit checks will be generated automatically, as the data is being entered into the system. Data Management will also run reports and listings on the CRF data, in addition to the queries already programmed and generated by the system, to raise manual queries as needed for site clarification or correction. The Clinical Dictionary Development and Management Group will raise queries as needed on safety data to code the terms (Adverse Events and Drugs) are reported appropriately.

The study monitor at the study sites will review the CRFs in accordance with the monitoring plan, and any queries will be generated in the EDC System to the Investigator or designee, enabling the errors to be addressed in parallel with Data Management review. Monitor can also run reports and listings on the CRFs, to raise manual queries as needed for site clarification or correction.

8.4. Processing Patient Reported Outcomes


Patient reported outcome (PRO) data will be collected directly into an electronic diary (e-diaries). AEs and concomitant medications entered into the e-diary will be transcribed into the eCRF. Data from the e-diaries will be extracted and loaded in a secured web portal, for the CRO handling Data Management to perform necessary reconciliation with the study data in the Clinical Data Management system. The process for reconciliation will be handled the same way as external data below. The e-diary data will eventually be merged with the Study Data sets.

8.5. External Data

External Data are subject data obtained externally to the CRF. These data are generated from laboratory instruments, computers, e-diaries or other sources and then transcribed into a file and format agreed upon by CRO to identify the subject and time point referenced in the CRF and/or protocol.

An agreed upon quality control process is performed against the transcribed data to the source to ensure the accuracy of the transcription.

Proper reconciliation will be performed between the transcribed data and the clinical database to ensure subject and time point referenced in the Clinical Database match before Clinical Database Freeze (locking of the database) can occur.

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9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES


This section provides the key features of the planned data analysis. The data analysis will be performed in accordance with the ICH E9 Guidelines.

9.1 Sample Size Determination

There is no previous experience and data with 1146A in the common cold setting and literature on products similar to 1146A and their efficacy on common cold symptoms is sparse. ~~However, one paper was considered useful to be taken as basis for the sample size estimation. In a previous study (Hull et al, 2007), a nasal irrigation spray, designed to deliver a low pH gel to the nasal cavity was compared to placebo. That study had a comparable scenario in terms of the form (spray) of the study product and regarding the endpoint as the current study. That study measured the cold severity for the 7 days of dosing, defined as the mean of the average of total symptom severity scores at 9:00 across the 7 days of dosing and of average of total symptom severity scores at 21:00 across the 7 days of dosing. The total symptom severity score was calculated per assessment by summing the severity scores across the 5 symptoms sore/scratchy throat, runny nose, blocked nose, cough, and tired/run down feeling (each scored using a 4 point scale 0 = absent, 1 = mild, 2 = moderate, and 3 = severe). The mean score of the average of the total symptom severity score reported for placebo was 0.8 with a standard deviation of 0.4 (n=85). Although the endpoint used in the Hull study differs slightly from the endpoint(s) in the current study and it was calculated over a longer time period (7 days as opposed to 4 days in the current study), it is assumed that the placebo result and the variability reported in the Hull study are indicative for the severity of cold symptoms in such setting and for comparable severity endpoints.~~

UPON REVIEW OF THE MOST RECENT LITERATURE (FAZEKAS ET AL 2012, LUDWIG ET AL 2013 AND ECCLES ET AL 2015), SIMILAR STUDIES EMPLOYING THE USE OF NASAL SPRAY PRODUCTS WITH A SIMILAR PURPORTED MECHANISM OF ACTION HAD SAMPLE SIZES BETWEEN 153 AND 211. THEREFORE, AN APPROXIMATE SAMPLE SIZE OF 170 (85 SUBJECTS IN EACH TREATMENT GROUP) IS CONSIDERED SUFFICIENT FOR THIS STUDY.

A SUFFICIENT NUMBER OF SUBJECTS WILL BE SCREENED TO ENROLL APPROXIMATELY 170 SUBJECTS.

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~~A sample size of 274 subjects (137 subjects per arm) will achieve 80% power to reject the null hypothesis of equal means in both arms for the average nasal symptom score when the mean difference is 17% (e.g. 0.136 when the placebo mean score result is 0.8) with a common standard deviation of 0.40 and with a significance level (alpha) of 0.05 using a two-sided two-sample equal variance t test. Considering a dropout rate of approximately 10%, 300 subjects will have to be recruited to have 274 evaluable subjects.~~

~~NQuery Advisor 7.0 Software was used to calculate the sample size.~~


9.2. General Considerations

9.2.1. Definition of Analysis Populations

The following analysis populations are defined:

- The Intent-to-Treat (ITT) population will consist of all randomized subjects.
- A modified ITT population will consist of subjects who
 - received at least one dose of study treatment
 - have at least one post-baseline efficacy assessment
- The Safety population (SAF) will include all randomized subjects who received at least one dose of study treatment.
- The Per-Protocol (PP) population will be determined from compliance during days 1 to 4, since this is the period of the primary efficacy evaluation. Protocol deviations leading to the exclusion of subjects from the PP population will include:
 - subjects who complete less than 80% or more than 120% of their target number of actuations over Days 1 to 4
 - subjects who miss 2 or more doses on any one day during Days 1 to 4
 - subjects who miss a total of 4 or more of their doses during Days 1 to 4
 - subjects who miss more than 1 nasal assessment on any one day during Days 1 to 4.
- Other reasons for exclusion from the PP population will be detailed in the statistical analysis plan (SAP).

9.2.2. Exclusion of Data from Analysis

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Exclusion of any data from the analyses will be determined during a Blind Data Review Meeting prior to database lock. Any reasons for exclusion from an analysis population will be listed, if applicable.

9.2.3. Criteria for Assessing Efficacy

The primary efficacy criterion is the difference in the mean of the average nasal symptom score of the two treatments arms on Days 1 to 4. At each assessment, the individual nasal symptom scores (blocked nose, runny nose, and sneezing) will be summed to provide the NSS. On each day, the NSS scores at each assessment (excluding the baseline NSS on Day 1) will be averaged (mean) to provide a daily NSS. A subject's average nasal symptom score on Days 1 to 4 (ANSS₁₋₄) is calculated as the mean of these daily sum scores for the nasal symptoms across the Days 1 to 4.

The investigational product will be considered effective if the mean ANSS₁₋₄ in the active treatment arm is at least 17% lower than in the placebo arm.

9.2.4. Criteria for Assessing Safety

Safety is assessed by comparing the incidence of adverse events between treatment arms.


It is expected that the findings in both treatment arms are comparable.

9.2.5. Handling of Dropouts and Missing Data

Dropouts will not be replaced and for the primary analysis, missing data after dropout will not be imputed.

For data that is missing at intermediate assessments from subjects who still continue in the study, the fact that these subjects remain in the study and provide data at subsequent assessments supports the assumption that the mechanism for the missing data at these intermediate assessments is unlikely to be related to either their randomized treatment or the condition under study. Therefore, missing common cold symptom scores between two non-missing symptom scores will be imputed by the mean of the last available and the next available symptom score.

In the event that more than 10% of subjects do not complete the first 4 days of treatment (i.e. the period over which the primary endpoint is evaluated) or if there is a differential drop-out rate between the treatment groups, sensitivity analyses using

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different imputation methods for data that is missing post-discontinuation will be performed. These sensitivity analyses will be detailed in the SAP.

Subjects will be instructed not to take any additional cough/cold medications, including but not limited to, prescription, OTC, non-drug/nutritional supplement, or procedures throughout the study. Subjects will be instructed to use acetaminophen/paracetamol over other OTC medications, but should try to avoid use if possible. In the event that a subject uses any additional cough/cold medication (including acetaminophen/paracetamol), its usage (time and reason for use) will be recorded in the e-diary. The primary analysis (modified ITT) will use the recorded cold symptom scores, irrespective of other cough/cold medication usage. The number of subjects using other cough/cold medications and frequency of use will be summarized by treatment group. Additional sensitivity analyses will be performed whereby cold symptom assessments made within 4 hours after the use of any other cough/cold medication are set to missing and various methods used to impute these values. The imputation methods used will (a) reflect the fact that the true cold symptom score, had alternative medication not been used, would have been at least as severe as the cold symptom score prior to the use of the alternative medication, and (b) to ensure the imputed values do not introduce a bias in favor of the test product. Missing data imputations will be applied throughout the assessment period (day 1 to day 8). Further details of the imputation methods will be provided in the SAP.

9.2.6. Other Issues


None

9.3. Statistical Methods and Analytical Plan

Additional details of the proposed statistical analysis will be documented in the SAP, which will be written following finalization of the protocol and prior to study unblinding.

A review of the study data will be conducted before the study is unblinded, and any decisions made at that meeting leading to changes in the statistical analyses, e.g., additional outcomes and analysis populations, exclusion of subjects or data from analysis, will be documented in the SAP. Any changes in the statistical analysis that must be made after the study is unblinded will be documented separately and described in clinical study report.

Continuous data will be summarized by descriptive statistics showing the number of subjects (N), the mean, standard deviation (SD), median and minimum and

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maximum. Categorical data will be summarized by frequency tables showing the number and percentage of subjects falling into each category. All study data will be listed.

Unless stated otherwise, for a parameter the Baseline value is the value of the last valid measurement/assessment prior to the first dose of study treatment.

9.3.1. Demographic and Baseline Characteristics

Demographic and other baseline data will be summarized descriptively overall and by treatment arm and by gender (and overall) for the Safety population.


9.3.2. Primary Analysis

The nasal symptom score (NSS) for a subject and time point will be calculated as the sum score of the nasal symptoms (blocked nose, runny nose, and sneezing) at that time point.

The primary efficacy endpoint is average nasal symptom score on Days 1 to 4 (ANSS₁₋₄). At each assessment, the individual nasal symptom scores will be summed to provide the NSS. On each day, the NSS scores at each assessment (excluding the baseline NSS on Day 1) will be averaged (mean) to provide a daily NSS. A subject's ANSS₁₋₄ is calculated as the mean of these daily NSS across study Days 1 to 4.

The ANSS₁₋₄ will be summarized by means of descriptive statistics by treatment arm. For the difference of the ANSS₁₋₄ between the two treatment arms, the mean and the 95% confidence interval for the mean will be derived. If deemed appropriate, descriptive statistics might be further broken down by center, gender and/or Day 1 dosing time stratification. The means of the ANSS₁₋₄ in both treatment arms will be compared using an analysis of covariance (at a significance level of 0.05), with factors for treatment, center and Day 1 dosing time stratification, and Baseline NSS (Day 1 prior to the first dose) as a covariate. The primary analysis will be done for the modified ITT population.

THE IMPACT OF SUBJECTS WITH ONSET OF SYMPTOMS OF COMMON COLD BETWEEN > 48 AND ≤ 72 HOURS WILL BE REVIEWED IF THERE ARE MORE THAN 10% OF SUCH SUBJECTS IN THE PRIMARY ANALYSIS POPULATION. TIME OF ONSET OF SYMPTOMS OF COMMON COLD MAY BE ADJUSTED FOR IN THE MODEL AND/OR JUST A SUMMARY OF THE PRIMARY ENDPOINT WILL BE PROVIDED FOR THIS SUBSET OF SUBJECTS.

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9.3.3. Secondary Analyses

If more than 20% of the symptom scores in the calculation of the ANSS₁₋₄ for an analysis population are missing, the summaries and analyses described for the ANSS₁₋₄ in Section 9.3.2 will be repeated for that analysis population on the ANSS₁₋₄ calculated without imputation of missing symptom scores (i.e. observed case analysis). In addition, the analysis described in Section 9.3.2 will be repeated for the PP population. Depending on the amount of missing data, further sensitivity analyses deemed necessary upon blind review of study data may be performed, and these will be detailed in the SAP.

Likewise, average nasal symptom score over Days 1 to 7 (ANSS₁₋₇) will be derived as the mean of the daily NSS across study Days 1 to 7, average total symptom scores ATSS₁₋₄ will be derived as the mean of the daily TSS across study Days 1 to 4, and average total symptom scores ATSS₁₋₇ will be derived as the mean of the daily TSS across study Days 1 to 7. The ANSS₁₋₇, ATSS₁₋₄, and ATSS₁₋₇ will be summarized and analyzed in the same manner as ANSS₁₋₄.


9.3.4. Safety Analyses

Safety variables (incidence of adverse events, and vital signs) will be summarized for the Safety population. All tables will be presented by treatment arm.

Treatment emergent adverse events, i.e. AEs that start or worsen during the treatment period (on or after first study treatment administration), will be summarized by presenting the number and percentage of subjects having any AE, any AE in each MedDRA System Organ Class (SOC) and having each individual AE (using MedDRA preferred term). The subset of AEs suspected of a relationship to study treatment will be presented similarly. All treatment-emergent AEs will also be tabulated by severity. Any other information collected (e.g. action taken, duration, outcome) will be listed.

For the summary by severity, subjects who have multiple occurrences of the same AE will be classified according to the worst reported severity of the AE. Similarly, for the summary by treatment relationship, the AE will be classified according to the closest relationship.

Vital signs (blood pressure, pulse, respiration rate, and body temperature) and their change from baseline will be summarized with descriptive statistics.

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9.3.5. Other Analyses

9.3.5.1. Treatment Exposure and Treatment Compliance

Study treatment exposure and treatment compliance will be summarized descriptively by treatment arm for the Safety population, including the following summaries:

- Number of subjects who took study treatment by study day (frequency table)
- Total number of administrations (frequency table)
- Total dose and average daily dose received
- Treatment compliance (frequency table)

9.3.5.2. Use of Concomitant Medication

Use of concomitant medication will be summarized by medication classes (levels 1 and 2) of the Anatomical Therapeutic Chemical (ATC) classification system and by treatment arm.

9.3.5.3. Exploratory Analysis


All exploratory analysis below will be done for the modified ITT population.

The mean daily NSS (MDNSS) per study day will be derived as the mean of a subject's NSS scores per study day. The MDNSS and its change from baseline will be summarized by descriptive statistics by treatment arm and day. NSS and MDNSS will be displayed graphically as line graphs showing the mean \pm SE within each treatment arm over time.

Likewise, the mean daily total symptom score (MDTSS) per day will be calculated. The MDTSS and its change from baseline will be summarized by descriptive statistics by treatment arm and day. TSS and MDTSS will be displayed graphically as line graphs showing the mean \pm SE within each treatment arm over time.

Finally, for each symptom, the mean daily individual symptom scores (MDISS) per day will be calculated. The MDISS and change from baseline will be summarized by descriptive statistics by treatment arm and day. Individual symptom scores and MDISS will be displayed graphically as line graphs showing the mean \pm SE within each treatment arm over time.

The course of each of the 8 common cold symptoms across the treatment period will be summarized using frequency tables by treatment arm and day.

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10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trials 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


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 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:

- Before initiating a trial, the Investigator/institution should have written and dated approval/favorable opinion from the IRB for the trial protocol (including amendments), written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), Investigator brochure/ safety statement (including any updates) and any other written information to be provided to subjects. A letter or certificate of approval will be sent by the Investigator to the sponsor prior to initiation of the study, and also when subsequent amendments to the protocol are made.
- 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)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.

10.3. Quality Control (Study Monitoring)

In accordance with applicable regulations including GCP, and GSK procedures, GSK or designee (i.e. third party vendor) 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.

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

GSK or designee 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 extent and nature of monitoring will be described in a written monitoring plan on file at PPD. The Investigator (or designee) agrees to allow the monitor direct access to all relevant documents and agrees to co-operate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

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.

The sponsor will be available to help Investigators prepare for an inspection.

10.5. Conditions for Terminating the Study

Upon completion or premature discontinuation of the study, the GSKCH monitor will conduct site closure activities with the Investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSKCH Standard Operating Procedures.

Both GSKCH and the Investigator reserve the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited

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to, safety or ethical issues or severe non-compliance. For multicenter studies (if applicable), this can occur at one or more or at all sites.

If the trial is prematurely terminated or suspended for any reason, the Investigator site should promptly inform the trial subjects and should assure appropriate therapy/ follow-up for the subjects. Where required by the applicable regulatory requirements, GSKCH should inform the regulatory authority(ies).

In addition:

- If the Investigator terminates or suspends a trial without prior agreement of GSKCH, the Investigator site should promptly inform the sponsor and the IRB, and should provide the sponsor and the IRB a detailed written explanation of the termination or suspension.
- If the GSKCH terminates or suspends a trial, the Investigator should promptly inform the IRB and provide the IRB a detailed written explanation of the termination or suspension.
- If the IRB terminates or suspends its approval/favorable opinion of a trial, the Investigator should promptly notify the GSKCH and provide GSKCH with a detailed written explanation of the termination or suspension.


10.6. Records Retention

Following closure of the study, the Investigator 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 (study/ site master file) 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.

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The Investigator must assure that the subject's anonymity will be maintained. On CRFs or other documents submitted to GSKCH, subjects should not be identified by their names or initials, but by an identification code. The Investigator should keep a separate log of subjects' codes, names and addresses. Documents not for submission to GSKCH, e.g. subjects' written consent forms, should be maintained by the Investigator in strict confidence.

GSK will inform the Investigator of the time period for retaining these records to comply with all applicable regulatory requirements (GSKCH recommends that documents be kept for 10 years). The Investigator is also required to keep subject identification codes on file for at least 15 years after completion or discontinuation of the study. 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.


No study document should be destroyed without a prior written agreement between GSKCH and the Investigator. 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 Publicly 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.

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.


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


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12. APPENDICES

12.1. Appendix 1 - Abbreviations


AE	Adverse event
ATC	Anatomical therapeutic chemical
ANSS 1-7	Average nasal symptom score days 1-7
ANSS 1-4	Average nasal symptom score days 1-4
ATSS 1-7	Average total symptom scores over days 1-7
ATSS 1-4	Average total symptom scores over days 1-4
BP	Blood pressure
°C	Degrees Celsius
CD	Compact Disc
COPD	Chronic obstructive pulmonary disease
CRF	Case report form
CRO	Contract research organization
CSM	Clinical study manager
EDC	Electronic data capture
GCP	Good clinical practice
GSKCH	GlaxoSmithKline Consumer Healthcare
HDPE	High-density polyethylene
HRVs	Human rhinoviruses
IB	Investigator brochure
ICAM-1	Intercellular adhesion molecule 1
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IRB	Institutional review board
IRT	Interactive response technology
ITT	Intention to treat
LDPE	Low-density polyethylene
MDISS	Mean daily individual symptom score
MDNSS	Mean daily nasal symptom score
MDTSS	Mean daily total symptom score
NSAID	Non-steroidal anti-inflammatory
NSS	Nasal symptom score
OTC	Over-the-counter
PII	Personally identifiable information
PP	Per protocol
PRO	Patient reported outcome
SAE	Serious adverse event

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SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SOC	System organ class
TSS 1-7	Total symptom score days 1-7
TSS 1-4	Total symptom score days 1-4

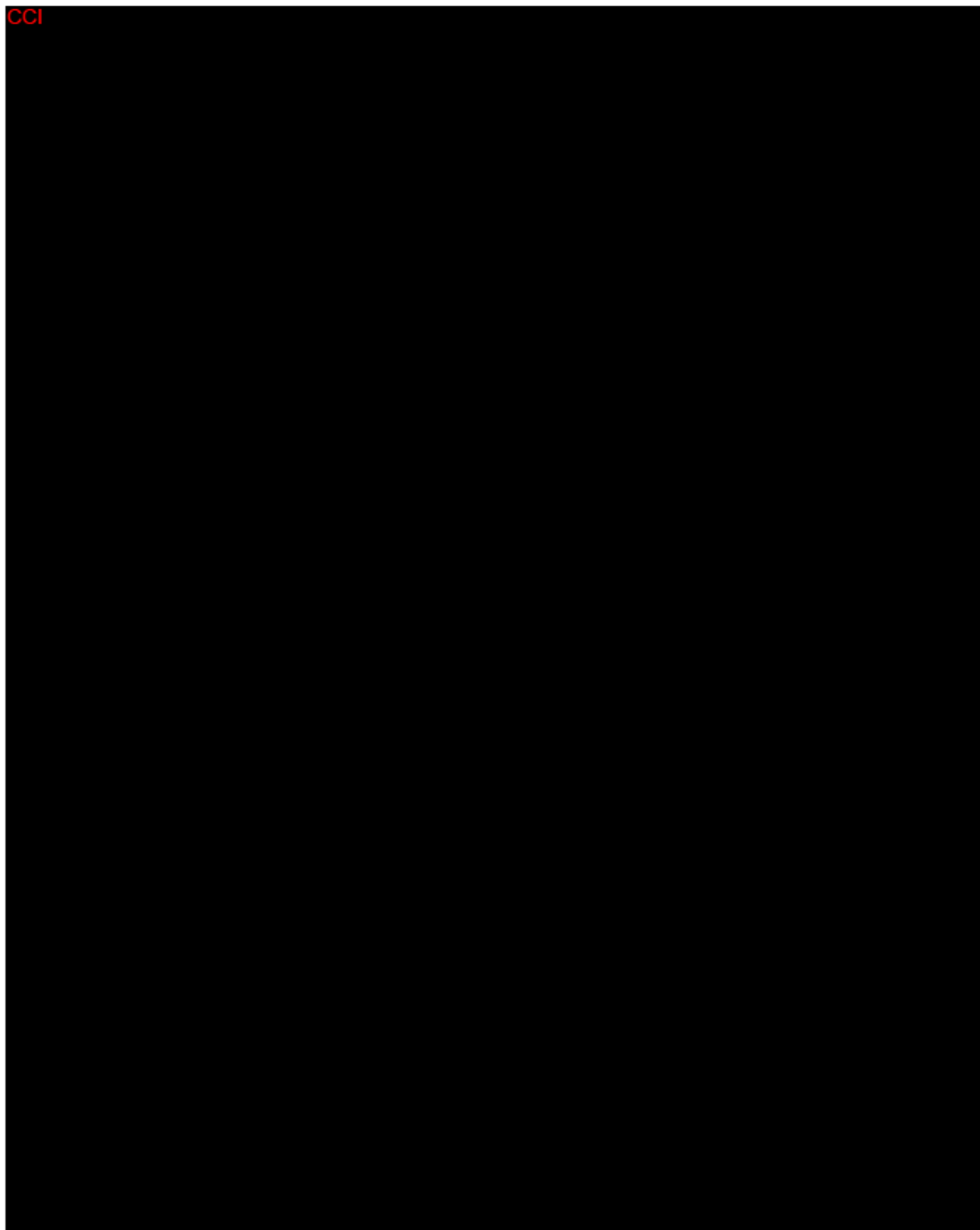
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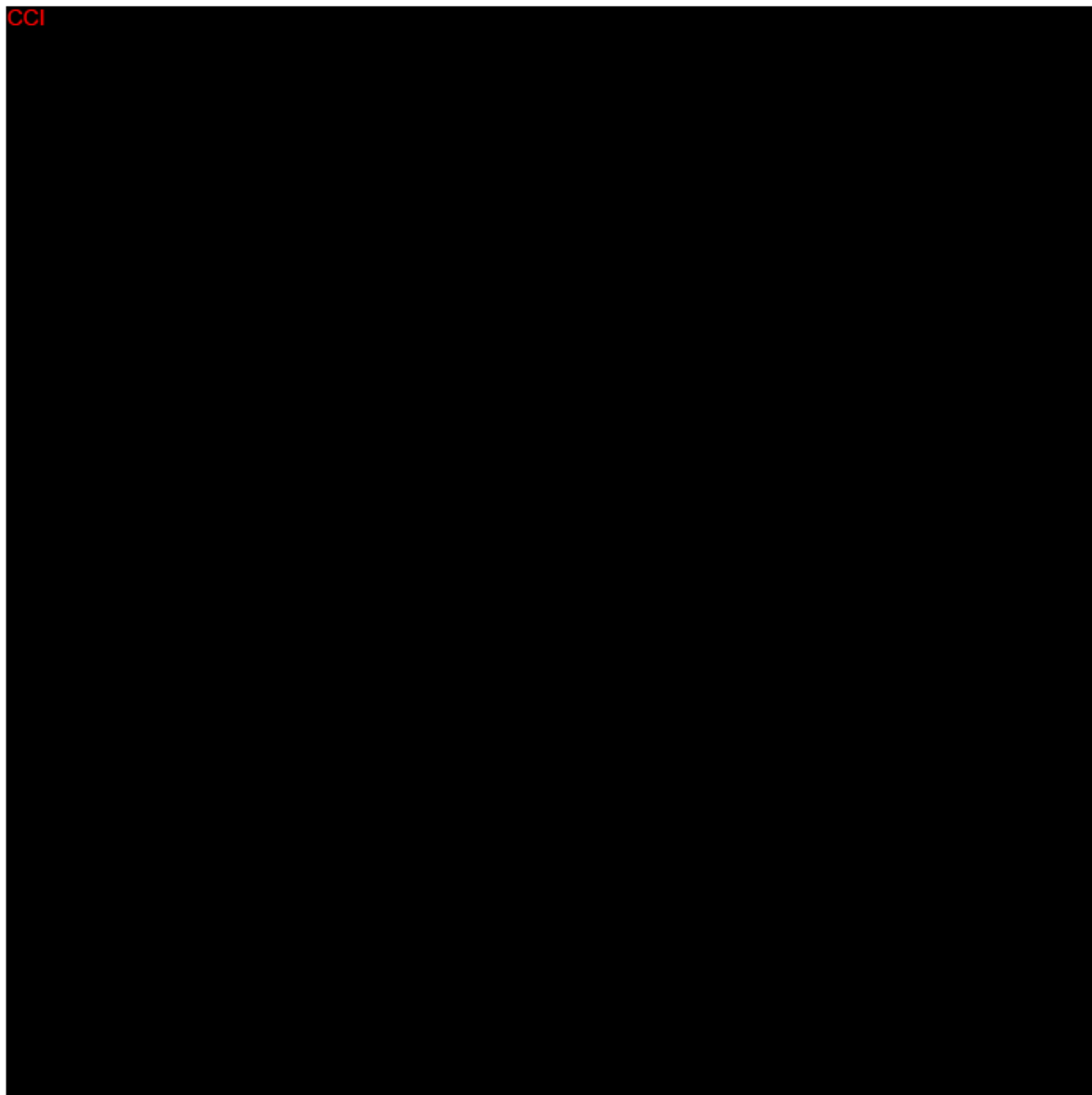
12.2. Appendix 2 - Subject Instructions for Use


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Date	Signed By
19-May-2017 04:39:52	PPD
Justification	Biostatistics Approval

Date	Signed By
19-May-2017 07:38:28	PPD
Justification	Clinical Operations Approval

Date	Signed By
19-May-2017 09:57:53	PPD
Justification	Approved

Date	Signed By
Justification	

Date	Signed By
Justification	

Date	Signed By
Justification	