GlaxoSmithKline Consumer Healthcare

Protocol #: 205684

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

03AUG2017

Statistical Analysis Plan

Version 2.0

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Upon review of this document, including table, listing, and figure shells, the undersigned approves the statistical analysis plan. The analysis methods and data presentation are acceptable, and the table, listing, and figure production can begin.

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List of 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
°C	Degrees Celsius
CRF	Case report form
GSKCH	GlaxoSmithKline Consumer Healthcare
IBHRVs	Human rhinoviruses
ICAM-1	Intercellular adhesion molecule 1
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IRT	Interactive response technology
ITT	Intention to treat
LOCF	Last observation carried forward
MDISS	Mean daily individual symptom score
MDNSS	Mean daily nasal symptom score
MDTSS	Mean daily total symptom score
mITT	Modified Intention to treat
NSAID	Non-steroidal anti-inflammatory
NSS	Nasal symptom score
OTC	Over-the-counter
PP	Per protocol
PRO	Patient reported outcome
SAE	Serious adverse event
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

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]. 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 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. 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]. 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 [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

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.

2.1 Primary Objective

- 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

2.2 Secondary Objectives

- Efficacy:
    - 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
    - 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
- Safety:
    - Adverse events

2.3 Exploratory Objectives

- 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

3. Investigational Plan

3.1. Overall Study Design and Plan

This is a multi-center, randomized, parallel-group, double blind, 2-group, placebo-controlled study to evaluate the efficacy and safety of 1146A formulation CCI carbomer 980 gel nasal spray) in adult subjects with symptomatic common cold in an outpatient setting.

At Screening (Day 1, Visit 1), subjects with symptoms consistent with symptomatic common cold of a ≤ 72 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.

Eight common cold symptoms are defined as follows:

Nasal symptoms:

- runny nose
- blocked nose
- sneezing

Other symptoms

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

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)

Only subjects meeting all eligibility criteria including the following symptomatic common cold symptoms will be enrolled into the study:

1. A confirmed common cold diagnosis with symptoms $\leq$72 hours;
2. Total Symptom Score (TSS) $\geq$ 9 (baseline sum of the 8 common cold symptoms);
3. Score $\geq$1 for at least one of the following symptoms: sore throat, runny nose, or blocked nose.

Approximately 170 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 Interactive Response Technology (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.

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.

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). 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.

3.2. Study Endpoints

3.2.1. Efficacy Endpoint

3.2.1.1 Primary Efficacy Endpoint

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 across Days 1 to 4 ($ANSS_{1-4}$).

3.2.1.2 Secondary Efficacy Endpoint

The secondary efficacy endpoints are as follows:

- average nasal symptom score Days 1-7 ($ANSS_{1-7}$), derived as the mean of the daily NSS across study Days 1 to 7.
- average total symptom score Days 1-4 ($ATSS_{1-4}$), derived as the mean of the daily TSS across study Days 1 to 4.
- average total symptom score Days 1-7 ($ATSS_{1-7}$), derived as the mean of the daily TSS across study Days 1 to 7.

3.2.2. Exploratory Efficacy Endpoints

- Individual & composite total symptom scores (NSS and TSS) Days 1-7

3.2.3. Safety Endpoints

- Spontaneous and solicited adverse events and serious adverse events

3.3. Treatments

The study treatment is called 1146A formulation (CCI carbomer 980 gel) nasal spray. The control is called placebo (vehicle without carbomer 980) nasal spray. Subjects will apply the dose by alternating nostrils. Both treatments 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).

3.4. Dose Adjustment/Modifications

No dose modification is permitted in this study.

4. General Statistical Considerations

Continuous data will be summarized by descriptive statistics showing the number of subjects (N), the mean, standard deviation (SD), median and minimum and maximum. Categorical data will be summarized by frequency tables showing the number and percentage of subjects falling into each category. When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. The denominator for all percentages will be the number of subjects in that treatment within the analysis set of interest, unless otherwise specified.

For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean and median will be displayed to one level of precision greater than the data collected. Standard deviation will be displayed to two levels of precision greater than the data collected. P-values will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as "<0.001." If a p-value is greater than 0.999 it will be reported as ">0.999." Data will be displayed in all listings sorted by treatment group.

Unless otherwise specified, baseline will be defined as the last non-missing evaluation prior to or on the date that the first dose of treatment is taken. The study day will be calculated as assessment date - first dose date of double-blind study drug + 1.

All analyses will be conducted using SAS Version 9.3 or higher.

A two-sided test for primary analysis of the primary efficacy endpoint will be used at a Type I error rate of 0.05 for comparison between active group (i.e., 1146A formulation) and control group. The p-values reported for sensitivity analyses of the primary efficacy

endpoint and statistical analyses of the secondary efficacy endpoints and the exploratory efficacy endpoints will not be adjusted for multiplicity and will be considered nominal.

4.1. Definition of Baseline and Study Day

Baseline is defined as the latest assessment prior to the first dose of treatment on Day 1, i.e., Day 1 Assessment 1. If a baseline measurement is missing or the subject receives the first dose prior to Day 1 Assessment 1, and a Screening value is available, the Screening value is utilized as the baseline. For assessments on or after Day 1, the study day will be calculated as assessment date – date of treatment (Day 1) + 1. For assessment prior to Day 1, the study day will be calculated as assessment date – date of treatment (Day 1).

4.2. Sample Size

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.

4.3. Randomization, Stratification, and Blinding

Subjects will be assigned to one of two treatment groups (1146A or placebo) using the method of randomly permuted blocks with a fixed block size in accordance with the stratified randomization schedule. The sites will not receive the randomization schedule, but will be assigned blocks of randomization numbers generated from the IRT system. All site personnel will be blinded to the treatment allocations. GSK and PPD personnel who may influence study outcomes are kept blinded to the treatment allocations.

Subjects who meet all inclusion and exclusion criteria will be randomized to one of the two treatment groups (1146A or placebo) in a 1:1 allocation ratio. 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 26 (15% of the target number of randomised 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.

4.4. Analysis Population

The following analysis populations are defined:

4.4.1. Intent-to-Treat (ITT) Population

Intent-to-Treat (ITT) population will consist of all randomized subjects.

In the event there is a discrepancy between treatment received and randomized treatment, all subjects in the ITT set will be analyzed according to the treatment they were randomized to receive and not according to what they actually received.

4.4.2. Modified Intent-to-Treat (mITT) Population

The mITT population includes subjects who received at least one dose of study medication and have at least one post-baseline efficacy assessment. The mITT will be used for all primary, secondary and exploratory efficacy analyses.

In the event there is a discrepancy between treatment received and randomized treatment, all subjects in the mITT population will be analyzed according to the treatment they were randomized to receive and not according to what they actually received.

4.4.3. Safety (SAF) Population

The SAF population will include all randomized subjects who received at least one dose of study medication.

All subjects in the SAF population will be analyzed according to the treatment actually received and not according to the treatment they were randomized to receive, in the event there is a discrepancy. The SAF population is used to tabulate all of the safety endpoints.

4.4.4. Per Protocol (PP) Population

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.

Any randomized subjects who violated the following inclusion or exclusion criteria will be reviewed on a case by case basis to determine whether they should be excluded from the PP population.

In addition, any subjects who violated the following criteria will be excluded from the PP population.

a. Subjects who complete less than 80% or more than 120% of their target number of actuations over Days 1 to 4
b. Subjects who miss 2 or more doses on any one day during Days 1 to 4
c. Subjects who miss a total of 4 or more of their doses during Days 1 to 4

d. Subjects who miss more than 1 nasal assessment on any one day during Days 1 to 4.

e. Dosing outside of allowable time window (2 or more times on any day during Days 1-4)

f. Use of prohibited medications during Days 1 to 4 as listed in the protocol

g. Dosing more than 5 minutes prior to self-assessments of symptoms using the eDiary device at home. This is because dosing time is entered manually and can only allow entrance in the increments of 5 minutes. The manual time to be entered has to be in the past. Since the time for dosing has to be in the past and only in 5 minute increments, subjects may have entered a time for dosing that is earlier than automatic time for symptoms assessments.

Analysis on the PP population will be used as a supplement to the mITT analysis and will be performed for the primary efficacy endpoint average nasal symptom score Days 1-4 ($ANSS_{1-4}$) and the secondary efficacy endpoint average total symptom score Days 1-4 ($ATSS_{1-4}$).

5. Subject Disposition

5.1. Disposition

Subject disposition will be summarized for the population of all screened subjects by treatment group and overall. A disposition of subjects includes the number and percentage of subjects for the following categories: subjects randomized, subjects who completed the study, subjects who discontinued from the study, subjects in the ITT population, subjects in mITT population, subjects in the SAF population, and subjects in the PP population. All percentages will be based on the number of subjects randomized.

The number and percentage of subjects' study completion/termination status and the categories of study completion/termination status will be displayed in the order they are displayed in the CRF as follows:

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

- Adverse event
- Other

Subject disposition data will also be presented in a listing. A listing of screen fail subjects will be also provided. Screen failures are defined as subjects who did not meet one or more criteria required for participation in a trial.

5.2. Protocol Deviations

Protocol deviation is defined as non-compliance with the protocol/ICH-GCP which may impact subject rights, safety or well-being, or the integrity of the data:

- Significant Deviation: Non-compliance with the protocol/ICH-GCP which significantly impacts subject rights, safety or well-being, or the integrity of the data.
- Non-Significant Deviation - Non-compliance with the protocol/ICH-GCP which does not significantly impact subject rights, safety or well-being, or the integrity of the data.

The significant protocol deviations are defined in Appendix C by the study team and will be finalized before database lock.

All protocol deviations including protocol deviations leading to exclusion from the Per Protocol population will be presented in a listing. The subject data listing will be sorted by site, subject number, and treatment group. Potentially important protocol deviations will be summarized in the clinical study report.

6. Demographics and Baseline Characteristics

6.1. Demographics

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

Age (years) will be summarized using descriptive statistics. The number and percentage of subjects by age category (<65 vs. ≥ 65), gender (Male, Female), race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, other), and ethnicity (Hispanic or Latino, Not Hispanic or Latino) will also be reported.

Demographic characteristics will be summarized descriptively by treatment group and overall for the Safety population. The demographic characteristics will also be summarized

by center as a subgroup. Percentages will be based on the total number of subjects in the Safety population. Subject demographic data will also be presented in a listing.

6.2. Baseline Disease Characteristics

Baseline characteristics will be summarized descriptively by treatment group and overall for the Safety population. Baseline characteristics will also be summarized by center as a subgroup. Baseline characteristics include the following:

- Total Symptom Score (TSS)
- Severity grading of the symptoms common cold as follows:

  Nasal symptoms:
  - runny nose
  - blocked nose
  - sneezing

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

Subject baseline disease characteristics will be presented in a listing.

6.3. Medical History

Medical history will be listed.

6.4. Inclusion and Exclusion Criteria

The subjects who fail to meet the inclusion/exclusion criteria will be listed. Please refer to Protocol Sections 4.1 and 4.2 for details of with inclusion/exclusion.

7. Treatments and Medications

7.1. Prior and Concomitant Medications

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 therapy taken in the 90 days

prior to the Screening Visit will also be recorded. Relevant history will be recorded in the CRF.

For purposes of analysis, prior medications are defined as any medication with a stop date that is prior to the initial study drug dosing date and concomitant medications are defined as any medications with a start date on or after the initial study drug dosing date, but prior to the last study drug dosing or any medications with a start date prior to the initial study drug dosing date and a stop date after the initial study dosing date.

For medications with partial start or stop dates, the partial dates will be imputed according to Table 1 and then will be categorized as prior medication or concomitant medication according to the definitions, Medications with completely missing dates will be included in the concomitant medication summary.

Imputation rules for the start or stop date of missing or incomplete medications are presented in Table 1.

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 in the e-diary asking about acetaminophen/paracetamol and all other concomitant medication usage prior to each dose of study treatment.

The number and percentage of subjects receiving prior and concomitant medications will be displayed by medication classes (levels 1 and 2) of the Anatomical Therapeutic Chemical (ATC) classification system and by treatment group using Safety set. A listing of all medications taken by subjects, including those are only prior, will be produced.

Table 1. Imputation rules for the start or stop date of missing or incomplete medications

	Missing	Imputation	Exception
Start date (concomitant medication)	Day	01	Default to Study Day 1 if an event starts the same year and month as Day 1 and the stop date contains a full date and the stop date is later than Day 1; Otherwise If the stop date is prior to Day 1, default to 1 day prior to the stop date
	Day/Month	01Jan	Default to Study Day 1 if an event started the same year as Day1 and the stop date contains a full date and the stop date is later than Day 1; Otherwise If the stop date is prior to Day 1, default to 1 day prior to the stop date
	Day/Month/Year	No imputation	Assume start prior to study entry.
Stop date (concomitant medication)	Day	Last day of the month	Default to the End of Study Date if the concomitant medication stopped the same year and month as the End of Study Date.
	Day/Month	31DEC	Default to the End of Study Date if the concomitant medication stopped the same year as the End of Study Date.
	Day/Month/Year	No imputation	Assume stops after study end.

7.2. Study Treatments

Subjects will receive either 1146A formulation (CCI carbomer 980 gel) or placebo. Study medication 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. Subjects will be instructed to alternate nostrils after each actuation.

First administration of study medication will occur at the study site by independent site personnel supervision; first dosing can occur any time prior to 13:00. 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.

7.2.1. Extent of Exposure

Study medication exposure will be summarized descriptively by treatment group for the Safety population, including the following summaries:

- Number and percentages of subjects who took study medication by study day
- Total number of and percentages of administrations
    - Days 1 to 4
        - For subjects dosing between 8:00-11:00 on Day 1, the target number of medication administration is 96 actuations.
        - For subjects dosing between 11:01-13:00 on Day 1, the target number of medication administration is 90 actuations.
    - Days 1 to 7
        - For subjects dosing between 8:00-11:00 on Day 1, the target number of medication administration is 168 actuations.
        - For subjects dosing between 11:01-13:00 on Day 1, the target number of medication administration is 162 actuations.
- Total dose and average daily dose received
    - Days 1 to 4
        - For subjects dosing between 8:00-11:00 on Day 1, the target number of doses is 13,440 mg and the target average daily dose is 3,360 mg.
        - For subjects dosing between 11:01-13:00 on Day 1, the target number of doses is 12,560 mg and the target average daily dose is 2,520 mg for Day 1 and 3,360 mg for Days 2-4.
    - Days 1 to 7
        - For subjects dosing between 8:00-11:00 on Day 1, the target number of doses is 23,520 mg and the target average daily dose is 3,360 mg.
        - For subjects dosing between 11:01-13:00 on Day 1, the target number of doses is 22,680 mg and the target average daily dose is 2,520 mg for Day 1 and 3,360 mg for Days 2-7.

7.2.2. Treatment Compliance

Treatment compliance is assessed by the recording of dosing times and number of actuations in the subject e-diary. Treatment compliance for Days 1-4 and Days 1-7 will be

summarized descriptively (number of subjects and percentage) for <80% Compliance, 80-120% Compliance, >120% Compliance and by treatment group for the Safety population.

8. Efficacy Analysis

Efficacy analyses will be performed on both the mITT population and PP population. The primary endpoint average nasal symptom score Days 1-4 ($ANSS_{1-4}$) and secondary efficacy endpoint total symptom score Days 1-4 ($ATSS_{1-4}$) will be analyzed using the mITT population and PP population, all the other secondary and exploratory efficacy endpoints will be analyzed using the mITT population. The mITT analyses will be considered primary; the PP analyses will be considered supportive of the primary analyses on the mITT population.

8.1. Primary Efficacy Endpoint

The primary efficacy endpoint is average nasal symptom score on Days 1 to 4 ($ANSS_{1-4}$). 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 $ANSS_{1-4}$ is calculated as the mean of these daily NSS across study Days 1 to 4.

8.1.1. Primary Analysis

The primary efficacy analysis of the $ANSS_{1-4}$ in each treatment group will be performed on the mITT population. An analysis of covariance (ANCOVA) 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, will be used to test the following hypothesis:

H_0: $ANSS_{1-4}$ active group = $ANSS_{1-4}$ control group

vs.

H_1: $ANSS_{1-4}$ active group $\neq$ $ANSS_{1-4}$ control group

When assumption of normality in ANCOVA model is violated, nonparametric methods, e.g., Wilcoxon rank sum test stratified by center and dosing time strata (i.e., van Elteren test) can be used.

The $ANSS_{1-4}$ values for each treatment group will be descriptively summarized. For the difference of the $ANSS_{1-4}$ between the two treatment groups, the mean and the 95%

confidence interval for the mean based on the Wald statistic will also be presented. The two-sided p-value based on the Wald statistic Chi-Square will be calculated.

The descriptive statistics will also be broken down by center, gender, and Day 1 dosing time stratification.

If there are more than 10% of subjects, who are enrolled after Protocol Amendment 3 and in the mITT population, with onset of symptoms of common cold between >48 and $\leq$72 hours from onset date and time and randomization date and time, time of onset of symptoms of common cold will be factored in the analysis of covariance described above for this subset of subjects. The descriptive statistics will also be provided for this subset of subjects.

8.1.2. Data Imputation

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 with the imputed mean rounded up to the next whole number.. Assessment date and time of the imputed common cold symptom scores will not imputed.

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.

8.1.3. Sensitivity Analysis for Primary Endpoint

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 for primary endpoint will be performed using the following methods:

a. Last observation carried forward (LOCF). If a subject has no further cold assessments after taking an alternative cough/cold medication (including acetaminophen/paracetamol), for subjects in the active group, subsequent symptom scores will be imputed with LOCF+1 (as per the additional sensitivity analysis described below).

b. Control-based pattern imputation (Ratitch and O'Kelly 2011). The control-based pattern imputation will impute missing scores using available data from placebo subjects for each study day.

Additional sensitivity analyses will be performed whereby cold symptom assessments made within 4 hours after the use of any other cough/cold medication (including acetaminophen/paracetamol) are set to missing and the following imputation algorithm applied:

For subjects in the placebo group, individual symptom scores will be replaced using LOCF; for subjects in the active group, individual symptom scores will be replaced with LOCF+1. If the previous score for an individual symptom is 3 (maximum possible score), then LOCF will be used, as LOCF+1 would result in a value of 4, which is not possible. This imputation algorithm reflects 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 it is designed to ensure the imputed values do not introduce a bias in favor of the test product.

The sensitivity analyses will be performed based on the mITT population. Details of sensitivity analyses are provided in Appendix D.

8.1.4. Secondary Analysis for Primary Endpoint

If more than 20% of the symptom scores in the calculation of the $ANSS_{1-4}$ for an analysis population are missing, the summaries and analyses described for the $ANSS_{1-4}$ in Section 8.1.1 will be repeated for that analysis population on the $ANSS_{1-4}$ calculated without imputation of missing symptom scores (i.e. observed case analysis). The secondary analyses will be performed based on the mITT population.

In addition, the analysis described in Section 8.1.1 will be repeated for the PP population.

8.1.5. Adjustment of Covariates

All efficacy models will be adjusted by center and Day 1 dosing time stratification, and Baseline values.

8.2. Secondary Efficacy Endpoint

The secondary efficacy endpoints are (1) average nasal symptom score over Days 1 to 7 ($ANSS_{1-7}$), (2) average total symptom scores over Days 1 to 4 ($ATSS_{1-4}$), and (3) average total symptom scores over Days 1 to 7 ($ATSS_{1-7}$).

The $ANSS_{1-7}$, $ATSS_{1-4}$, and $ATSS_{1-7}$ will be summarized and analyzed in the same manner as $ANSS_{1-4}$. The $ATSS_{1-4}$, and $ATSS_{1-7}$, will also be analyzed using ANCOVA with a term included for treatment, treatment by Day 1 dosing time interaction, center and Day 1 dosing time stratification, and Baseline TSS (Day 1 prior to the first dose) as covariates. From this model, estimates of $ATSS_{1-4}$, and $ATSS_{1-7}$ for each dosing time strata will be obtained.

8.3. Other Efficacy Endpoints

8.3.1. Exploratory Analysis

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 group and day. NSS and MDNSS will be displayed graphically as line graphs showing the mean +/- SE within each treatment group 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 group and day. TSS and MDTSS will be displayed graphically as line graphs showing the mean +/- SE within each treatment group 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 group and day. Individual symptom scores and MDISS will be displayed graphically as line graphs showing the mean +/- SE within each treatment group over time.

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

9. Safety Analysis

Safety analyses will be summarized for the Safety population. All tables will be presented by treatment group.

9.1. Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a subject enrolled into this study regardless of its causal relationship to study treatment. Subjects will be instructed to contact the investigator at any time after randomization if any symptoms develop.
AE analysis tables, namely overall AE tables and summary of all AE events tables, will be summarized. One listing of AE information will be presented, including treatment emergent and non-treatment emergent AEs.

For AEs with missing date, please refer to Table 1 for imputation rules.

9.1.1. Incidence of Adverse Events

Treatment-emergent adverse events (TEAE) , i.e. AEs that start or worsen during the treatment period (on or after first study medication 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 (PT)). At each level of subject summarization, a subject is counted once if the subject reported one or more events. Percentages will be calculated out of the number of subjects in the Safety population. The number of events will also be presented in the table.

The summary of TEAEs will be presented in descending order from the SOC with the highest total incidence (that is, summed across all treatment groups) to the SOC with the lowest total incidence. If the total incidence for any two or more SOC is equal, the SOC will be presented in alphabetical order. Within each SOC, the PTs will be presented in descending order, in the same manner as SOC.

The incidence of TEAE between treatment groups is compared using a frequency table for Safety population.

9.1.2. Relationship of Adverse Events to Study Treatment

Summaries of TEAEs which are related to study treatment will be presented by number of subjects. The investigator will provide an assessment of the relationship of the event to the study treatment. A treatment related AE is an event that is related to study medication assessed “Possible” or “Probable” or “Definite” to the question of “Relationship to the study treatment” as reported on an AE CRF page for any subject who had taken one dose of the study medication. TEAEs that are missing a relationship will be presented in the

summary table as “Related” but will be presented in the data listing with a missing relationship. Percentages will be calculated based on the number of subjects in the Safety population.

The TEAE data will be categorized and presented by SOC and PT in a manner similar to that described in Section 9.1.1.

9.1.3. Severity of Adverse Event

A summary of AEs by treatment and severity will be presented in a table. In the AE severity table, if a subject reported multiple occurrences of the same AE, only the most severe AE will be presented. AEs with missing severity will be included in the summary table as severe, but will be presented in the data listing with a missing severity. Percentages will be calculated out of the number of subjects in the Safety population.

9.1.4. Serious Adverse Events

A SAE is defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation, results in significant disability/incapacity, is a congenital anomaly/birth defect, is an important medical events that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above. SAEs will be collected through the end of the study.

All SAEs, regardless of their treatment-emergent status will be summarized by system organ class (SOC) and PT. Percentages will be calculated out of the number of subjects in the Safety population.

All SAEs will be presented in a listing.

9.1.5. Adverse Events Leading to Study Discontinuation

All subjects who have an AE where the answer to “Did the subject withdraw from study as a result of AE?” is “Yes” will be presented in a listing.

9.1.6. Death

All deaths will be presented in a listing.

9.2. Clinical Laboratory Evaluations

9.2.1. Urine Drug Screen and Pregnancy 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, cocaine, opiates, 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.

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.

Number of subjects in each substance will be summarized and all laboratory data will be presented in a listing. Urine drug and pregnancy test for women will also be presented in listings.

9.3. Vital Sign Measurements

Vital sign data will be collected, including

- sitting systolic blood pressure (mmHg) which is the average of 3 measurements,
- sitting diastolic blood pressure (mmHg) which is the average of 3 measurements,
- pulse rate (beats per minute),
- respiration rate (breath per min),
- oral body temperature (ºC)
- height (cm)
- weight (kg)

Summary table for change from baseline will be presented for the collected data by treatment group for subjects in the Safety population. Baseline height and weight will be summarized with other demographic parameters.

All vital sign data by subject will also be presented in a listing.

9.4. 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.

All physical examination by subject in the Safety population will be presented in a listing.

9.5. Nasal Examination

Nasal examination will be performed for eligibility at Screening (Visit 1, Day 1)

All nasal examination by subject will be presented in a listing.

10. References

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11. Appendices

Appendix A. Schedule of Events

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 1st 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.

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 ± 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.

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.

Appendix B - Medications and Treatments

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
2. 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.

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.

Appendix C. Protocol Deviations

DESCRIPTION OF RULE	SIGNIFICANCE
Subjects are not within the age of 18 to 75 years old.	Significant
Patient is not in good general and mental health with, in the opinion of the Investigator or medically qualified designee clinically significant or relevant abnormalities in medical history or upon physical and Investigator-led nasal examination.	Significant
Females of childbearing potential (refer to Section 4.4. of protocol) who are not practicing a reliable method of contraception.	Significant
Investigator has not confirmed diagnosis of symptomatic common cold with an onset of < 72 hours prior to randomization.	Significant
The total symptom score (TSS) is not > 9 AND there is not a score >1 for at least one of the following symptoms: sore throat, runny nose, or blocked nose.	Significant
PREGNANCY: Women who have a positive urine pregnancy test.	Significant
BREAST-FEEDING: Women who are breast-feeding.	Significant
CONCURRENT MEDICATION/MEDICAL HISTORY: Defined in protocol Exclusion criteria 3.	Significant
ALLERGY/INTOLERANCE: Defined in protocol Exclusion criteria 5.	Significant
CLINICAL STUDY/ EXPERIMENTAL PRODUCT: Defined in protocol Exclusion criteria 5.	Significant
SUBSTANCE ABUSE: Defined in protocol Exclusion criteria 6.	Significant
PERSONNEL: Defined in protocol Exclusion criteria 7.	Significant
DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA: Defined in protocol Exclusion criteria 8.	Significant
Wrong dosing time (2 or more times on any day during Days 1-7)	Not Significant
Missed doses (<80% of target number of actuations over Days 1-7)	Not Significant
Additional doses (>120% of target number of actuations over Days 1-7)	Not Significant
Subjects who miss 2 or more doses on any day during Days 1-7	Not Significant
Subject who miss a total of 6 or more of their doses during Days 1-7	Not Significant
Wrong dosing time (2 or more times on any day during Days 1-4)	Significant
Missed doses (<80% of target number of actuations over Days 1-4)	Significant
Additional doses (>120% of target number of actuations over Days 1-4)	Significant
Subjects who miss 2 or more doses on any day during Days 1-4	Significant
Subject who miss a total of 4 or more of their doses during Days 1-4	Significant
Use of prohibited medications as listed in protocol	Significant
Nasal swab sample not collected at screening	Not Significant
Urine drug screen not completed at screening	Significant

DESCRIPTION OF RULE	SIGNIFICANCE
Urine pregnancy testing not completed	Significant
Subject who misses 2 or more of their nasal symptom assessments on any day during Days 1-7	Not Significant
Any subject who misses a total of 6 or more of their nasal symptom assessments during Days 1-7	Not Significant
Subject who misses 2 or more of their nasal symptom assessments on any day during Days 1-4	Significant
Any subject who misses a total of 4 or more of their nasal symptom assessments during Days 1-4	Significant
Screening procedures not completed	Significant
Subject not enrolled within 72 hours of symptom onset	Significant
Subject randomized out of sequence (IWRS problem)	Significant
Received incorrect treatment, not according to randomization schedule	Significant
Subject randomized prior to the completion of ICF	Significant
SAE not reported by site to PPD at all or not within 24 hours of awareness	Significant
SAE not reported by PPD to GSKCH at all or not within 1 business day of awareness	Significant
Pregnancy not reported by site to PPD within 2 weeks of learning of subject becoming pregnant	Significant
Site did not follow up to obtain required information for SAE reporting	Significant
AE not included on AE section of the eCRF	Not Significant
Failure to discontinue subjects that meet defined discontinuation criteria	Significant
Subject did not sign ICF	Significant
ICF signed by subject prior to IRB approval	Significant
ICF signed by subject but not approved by IRB	Significant
Original ICF signed and dated after screen/enroll date	Significant
ICF was lost, no copy available	Significant
ICF was lost, copy available	Significant
Subject signed consent but did not date it, but there is other sufficient information to confirm the date	Significant
Subject forgot to sign the ICF but gave verbal consent	Significant
Investigator and/or witness did not sign or date the ICF and there isn't any supporting documentation to confirm that the consent process was performed appropriately	Significant
Version date not recorded on ICF	Significant
Subject signed a superseded/outdated version of the ICF (and never signed correct version)	Significant

DESCRIPTION OF RULE	SIGNIFICANCE
Revised ICF not signed; subject visit has occurred & not remediated at a subsequent visit	Significant
Blood Pressure Repeat Assessments not completed in 1-2 minute intervals per protocol.	Significant
Early Termination procedures not completed	Significant
ICF Section "AGREEMENT TO BE IN THE STUDY" was not completed by the subject	Significant
Incorrect actuations according to StudyWorks Smart Reports	Significant
Out of Window Visit	Not Significant
Site personnel did not enter Dose time into eDiary	Not Significant
Subject dosed IP on Day 8	Significant
Subject's first dose after 13:00 on Day 1	Significant
Subject missed 1 nasal assessment on any day between Days 1-8	Not Significant
Subject who miss a total of 5 or less of their doses during Days 1-7	Not Significant
Subject who missed 1 IP dose on any one day during Days 1-7	Not Significant
IP not returned	Significant
Subject who missed completing self-assessments in the eDiary	Significant
Self-assessment of common cold symptoms using a 4-point scale was not recorded in the subject e-diary immediately prior to the first dose at Baseline	Significant
Any subject who misses a total of 5 or less of their nasal symptom assessments during Days 1-7	Not Significant
Temperature Excursions for -70 Freezer: Nasal Swab Sample	Not Significant
Subject initialed and dated every page of the ICF and added the printed name on the signature page but did not add signature on the signature page	Significant
IP Storage Temperature Excursion	Not Significant
Subject discontinued at Day 2. No doses or self-assessments completed after Day 1.	Not Significant
ICH/GCP Deviation: Delegation of Authority Log Tasks Not Delegated or Not Delegated Correctly	Not Significant
Urine Drug Screen Test not read at 5 mins but was read at 3 mins.	Not Significant
Subject did not add initials and date on page 16 of ICF	Not Significant
Urine Temperature Not Captured on urine Drug Screen Requisition	Not Significant

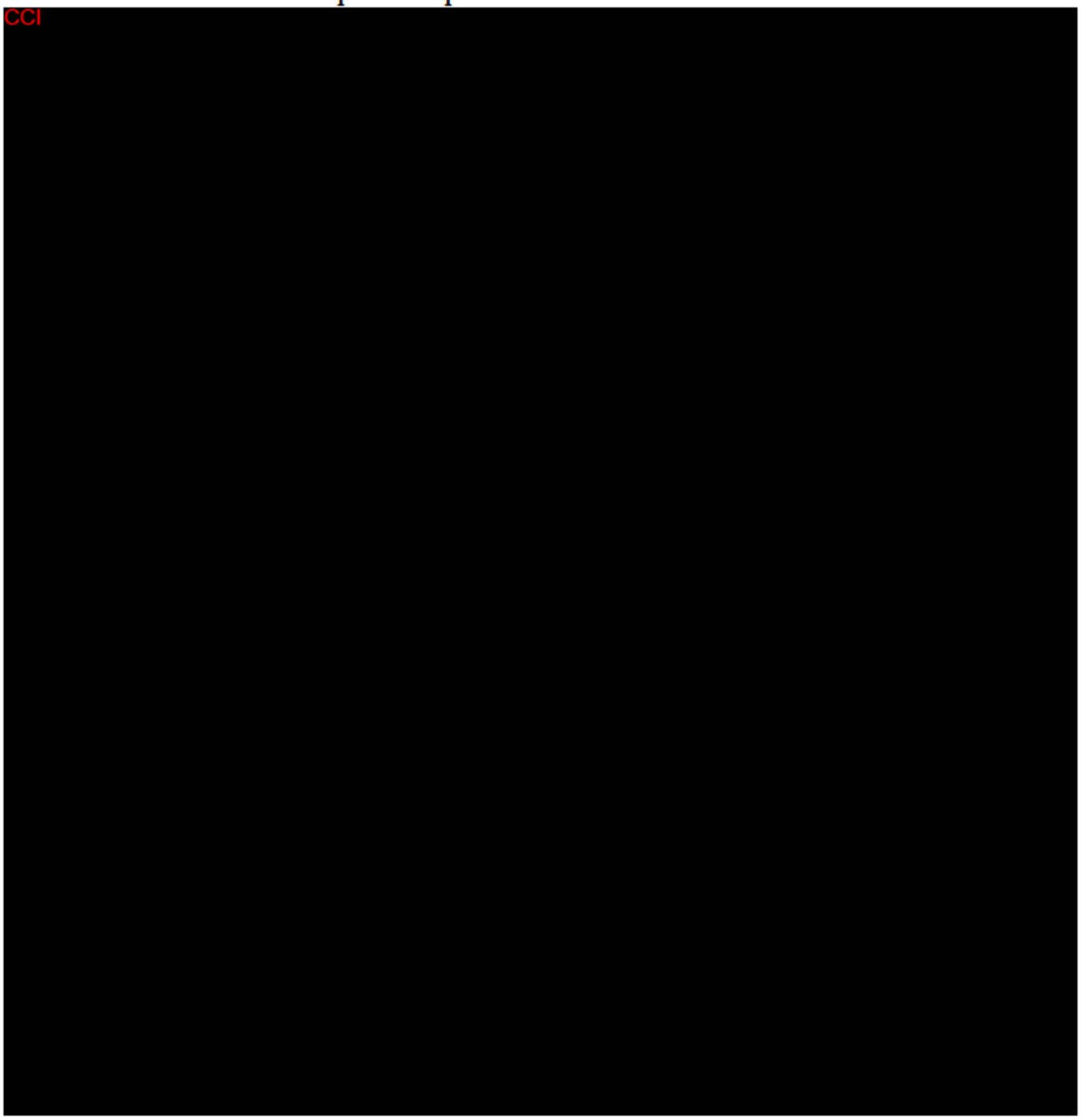
Appendix D – Details of Sensitivity Analyses

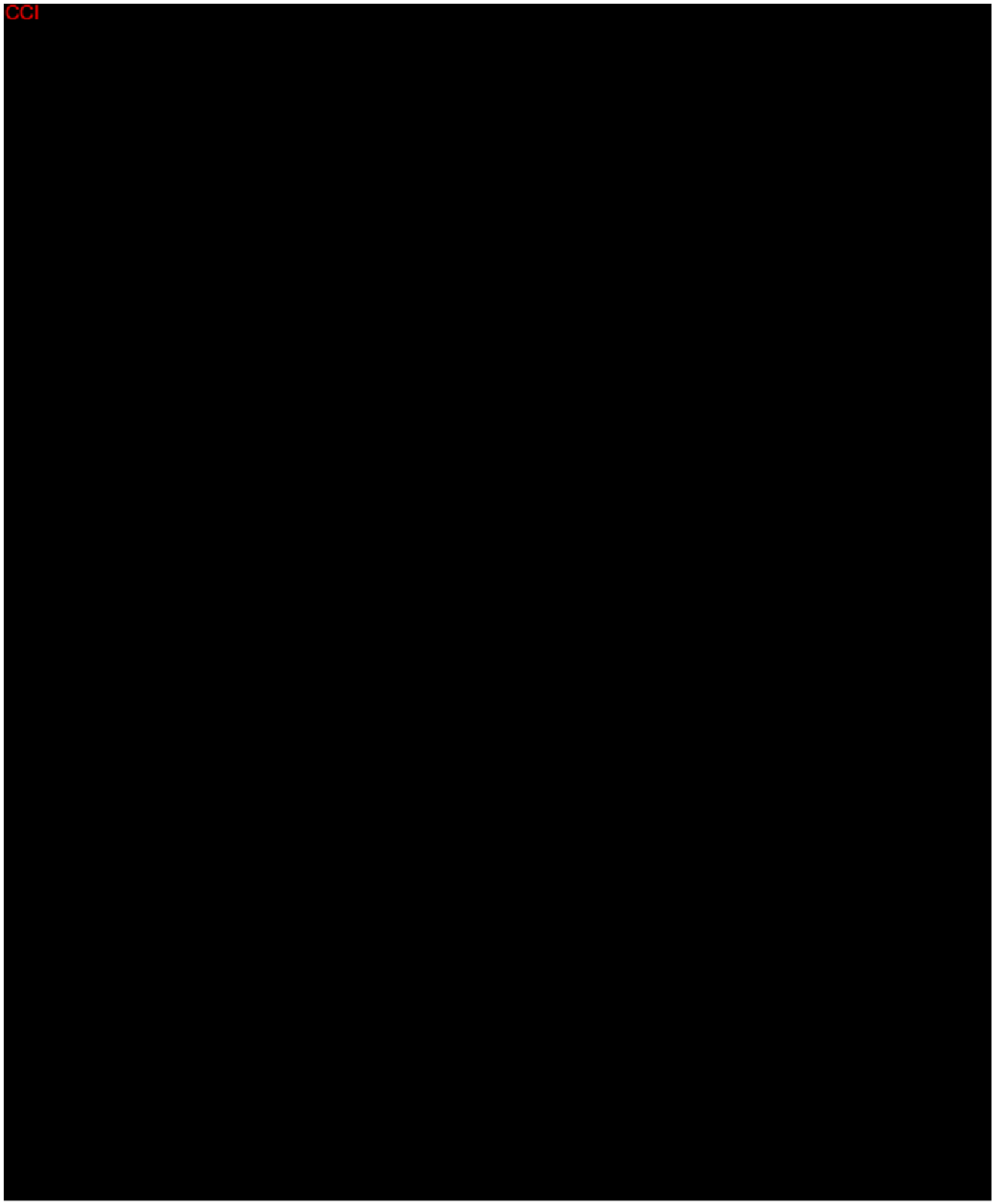
A. Sensitivity analysis whereby cold symptom assessments made within 4 hours after the use of any other cough/cold medication (including acetaminophen/paracetamol) will be performed for the primary endpoint $ANSS_{1-4}$ using last observation carried forward LOCF as follows:
    a. The nasal symptom scores (blocked nose, runny nose, and sneezing) recorded within 4 hours after the use of any other cough/cold medication (including acetaminophen/paracetamol) are set to missing.
    b. The missing scores from step a. are imputed,
        i. for subjects in the Placebo group, using the score from the latest non-missing score before the medication was taken, or
        ii. for subjects in the Active group, using the score from the latest non-missing score + 1 before the medication was taken if the score is less than or equal 2, or using the score from the latest non-missing score before the medication was taken if the score is equal to 3.
    c. Missing nasal symptom scores between two non-missing nasal symptom scores are not imputed for this sensitivity analysis.

B. 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 for the primary endpoint $ANSS_{1-4}$ will be performed using the following methods:

1. last observation carried forward (LOCF)
    a. The missing scores will be imputed using the score of the latest non-missing score before the drop-out.
    b. If the latest non-missing score before drop-out was made within 4 hours after the use of any other cough/cold medication (including acetaminophen/paracetamol), the score will be set to missing and imputed as described in Section A.

2. Controlled-based pattern imputation.

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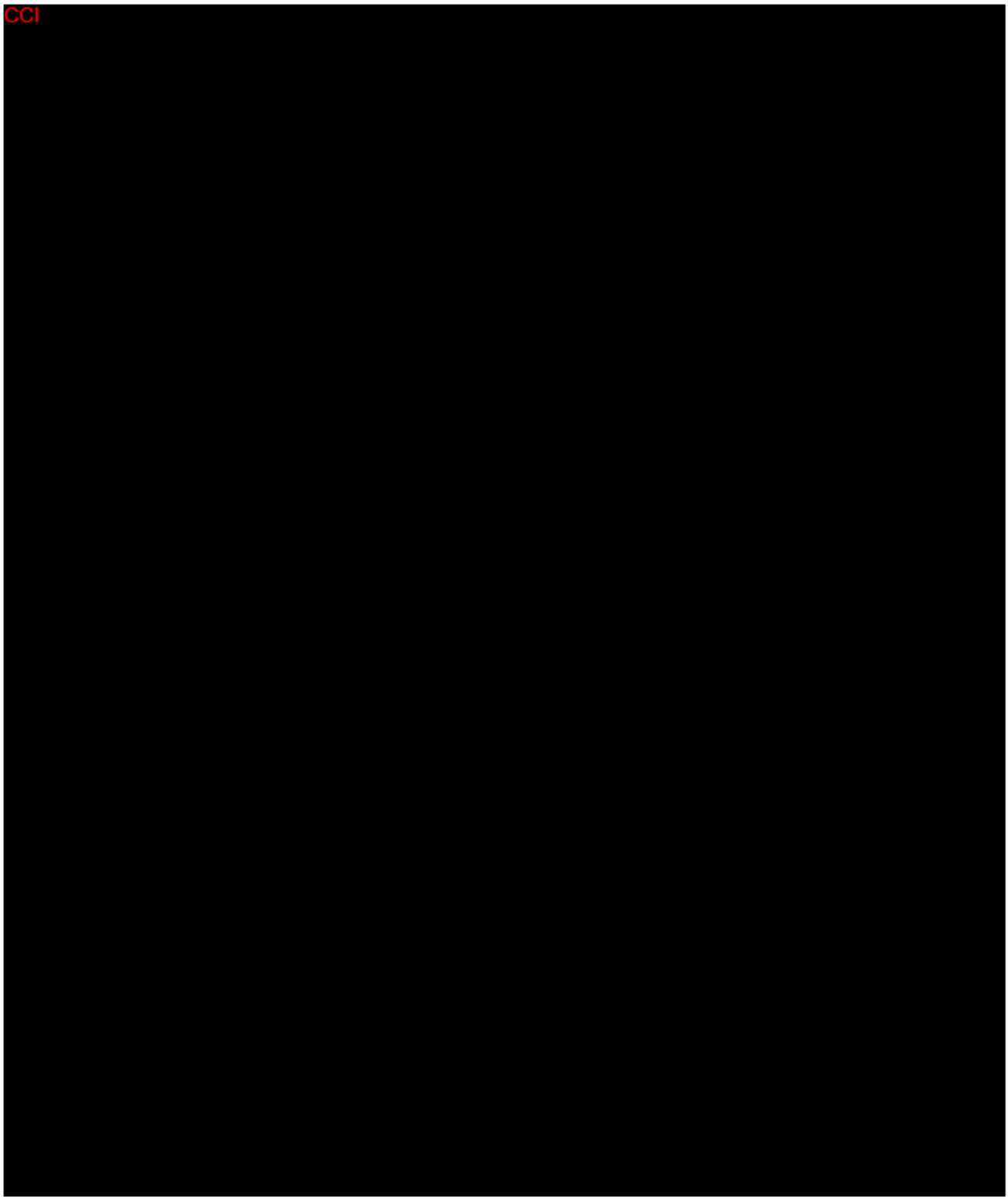
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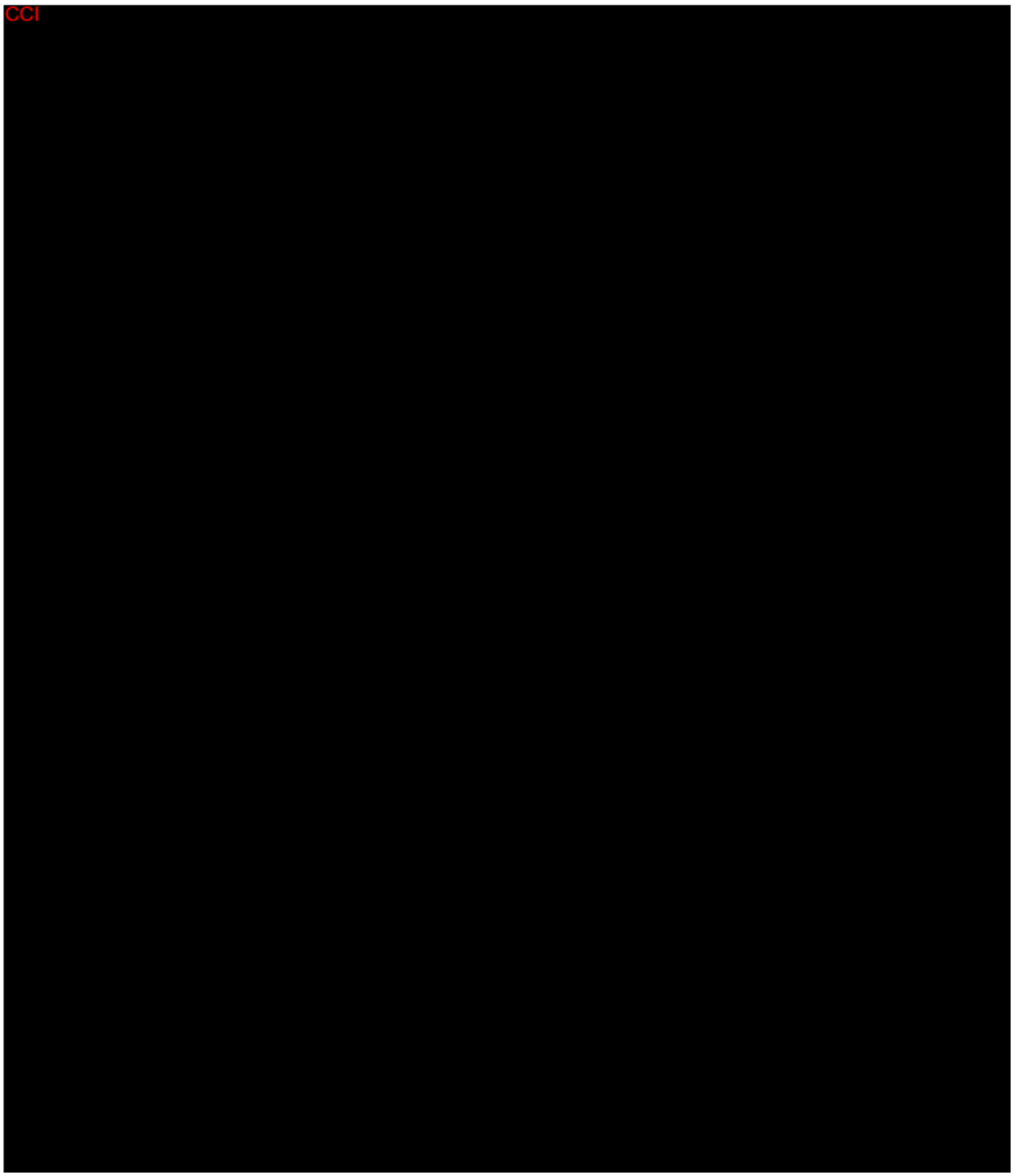
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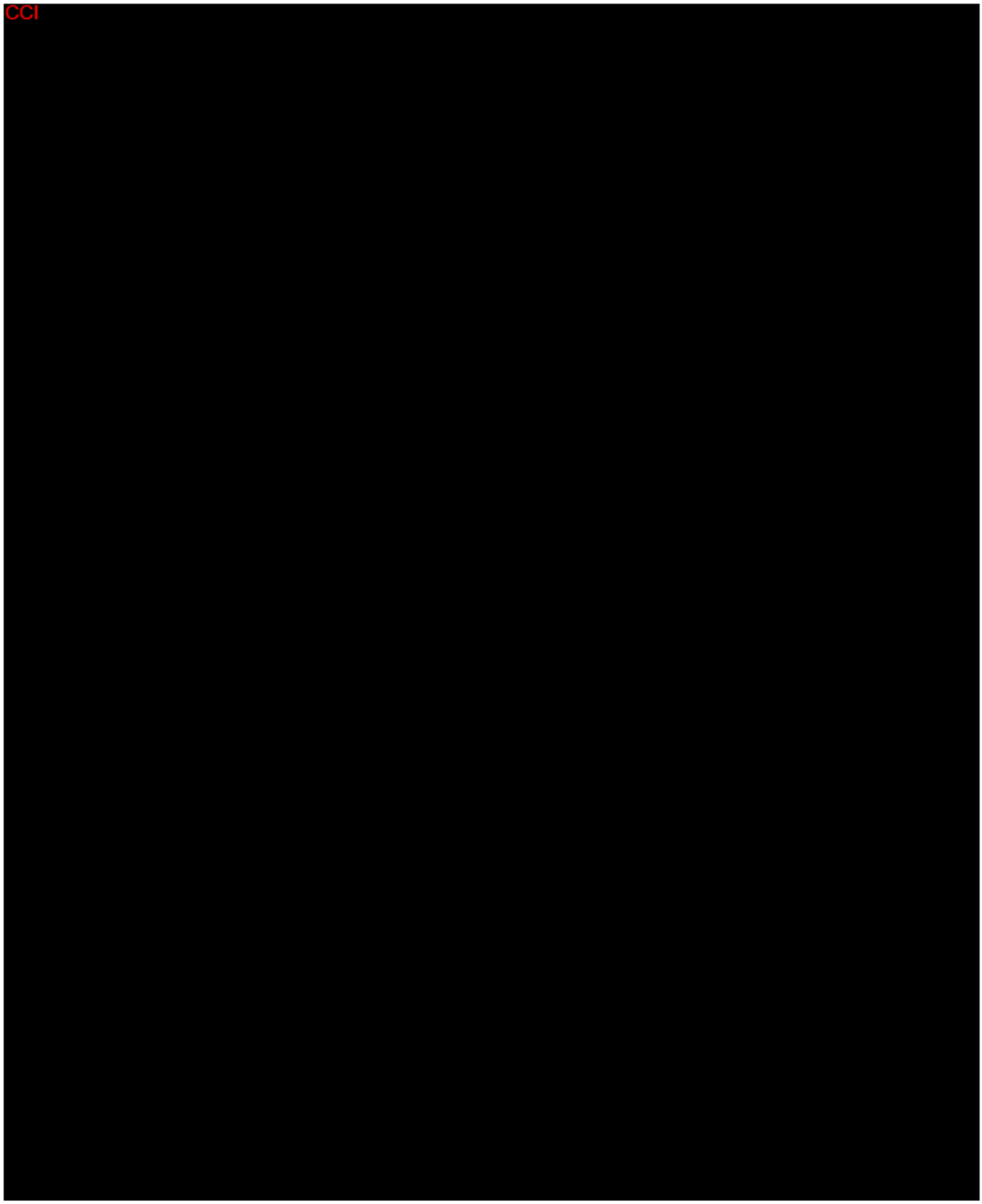
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