CO-170302131230-URCT

RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, STUDY OF THE EFFICACY OF PHENYLEPHRINE HCL [redacted] 30 MG AND PHENYLEPHRINE HCL [redacted] 12 MG CAPSULES IN SUBJECTS WITH NASAL CONGESTION DUE TO THE COMMON COLD

Investigational Product Name:	Phenylephrine HCl Equivalent, [redacted] 30 mg
Protocol Number:	CO-170302131230-URCT
IND / EudraCT number:	
Phase:	2
Version (Draft, Final, Amendment) Date	**Amendment 3: 14 Jun 2018** **Amendment 2: 30 Jan 2018** **Amendment 1: 11 Oct 2017** **FINAL: 31 May 2017**

1. SYNOPSIS

Name of Sponsor/Company: Johnson & Johnson Consumer Inc., Fort Washington, PA 19034
Active Ingredient(s): Phenylephrine HCl Equivalent, [redacted] 30 mg
Title of Study: Randomized, Double-Blind, Placebo-Controlled, Study of the Efficacy of Phenylephrine HCl [redacted] 30 mg and Phenylephrine HCl [redacted] 12 mg Capsules in Subjects with Nasal Congestion Due to the Common Cold
Countries: Canada
Investigators: Multicenter study.
Phase of development: 2
Objective: To investigate the potential for efficacy of an [redacted] equivalent to Phenylephrine HCl 30 mg twice daily and Phenylephrine HCl [redacted] 12 mg Capsules four times daily and placebo, administered orally, in subjects with nasal congestion due to the common cold.
Methodology: This will be a randomized, double-blind, placebo controlled, parallel-group Phase 2 study to evaluate the efficacy of an [redacted] oral tablet equivalent to phenylephrine HCl 30 mg taken twice daily and an [redacted] oral capsule of phenylephrine HCl 12 mg taken four times daily for relief of nasal congestion in subjects with naturally occurring cold symptoms. The trial will have a double dummy design so all subjects will take investigational product four times a day. Subjects randomized to the phenylephrine [redacted] group will take active dose morning and evening, with a period of 12 hours between the doses, with placebo given in the interim doses. Subjects randomized to the phenylephrine HCl [redacted] group will take all four doses of active product. The morning dose will be administered between 7:00AM and noon at the site, the next dose will be administered 4 hours (+10 minutes) later at the site and the last two doses will be given to the subjects to take 4 hours and 8 hours later. Approximately 450 subjects (150 per treatment group), ages 18 years and older, will be enrolled. Potential subjects will be identified through advertising and unsolicited presentation at the study site for complaint of common cold symptoms. Eligible subjects will have an onset of cold symptoms (per subject self-report) within approximately 72 hours (3 days) before study entry, consisting of cold symptoms per the following: • At Visit 1, at least moderate severity (score ≥ 5, on a scale from 0 = none to 7 = severe) for

stuffy/congested nose, and

- At visit 1, at least mild (score ≥ 3, on a scale from 0 = none to 7 = severe) for sinus pressure/tenderness, and

- Within approximately 72 hours of enrollment, two or more of the following symptoms: runny nose, sneezing, sore or scratchy throat, headache, malaise, or cough.

Subjects who qualify per inclusion and exclusion criteria during onsite screening will be randomly assigned to one of three blinded treatments: [redacted] equivalent to 30 mg phenylephrine HCl, [redacted] phenylephrine HCl 12 mg, or placebo. Treatment will be for a twelve-hour period (Day 1).

On Day 1, subjects will complete subjective assessments of symptoms at baseline, within approximately 30 minutes prior to dosing. Dosing should occur within 72 hours of onset of cold symptoms. Study staff will administer the first dose between approximately 7:00 and noon (0 hour). Subjects will remain at the site for 4 hours following the first dose, and they will complete symptom assessments at 2 hours and 4 hours (±10 minutes) post-dose. The 4-hour assessment will be conducted before administration of the next due dose. At 4 hours (+10 minutes) post first dose, subjects will be given the second dose. Vital signs will be measured at Visit 1 (pre-dose). Vital signs will also be measured at approximately 2 and 4 hours post initial dose, immediately following completion of efficacy assessments. Subjects will be discharged from the site after the 4 hour procedures with instructions to complete subjective assessments using a diary at approximately 6, 8, 10 and 12 hours after the first dose of medication on Day 1 and to take the next two doses at 8 and 12 hours after the first dose was administered at the site. At the 8 and 12 hour timepoints, the diaries should be completed prior to the medication being taken.

One third of the eligible subjects will be assigned to the pharmacokinetic cohort at a limited number of sites. They will have 3-mL blood samples collected by direct venipuncture. Two samples will be collected; one at approximately 1 (±10 minutes) and another at 4 hrs (±20 minutes) after the initial dose. These subjects will have provided written consent to the collection of blood samples. After the pharmacokinetic cohort has been completed, subsequent enrolling subjects will not be asked to consent to the collection of blood samples.

Subjects will be instructed to complete the final assessments in their diary the next morning on Day 2, 24 hours (+/- 30 mins) after they took the first dose. Subjects will return to the study site for a Follow-up Visit on Day 2 (+1 day) for reconciliation of drug and reporting of any adverse events or concomitant medications. The 24-hour assessments can also be completed during the follow-up visit if it falls within the window. Vital signs will be obtained and the subject will be discharged from the study.

No other cough, cold, allergy, or analgesic/antipyretic medicines (nonprescription or prescription) or herbal/dietary supplements will be permitted during the study. Adverse events will be collected during the study to evaluate safety.

Number of subjects (planned):
Approximately 450 (150 per treatment group)

Diagnosis and main criteria for inclusion:

Subjects 18 years or older who meet the inclusion and exclusion criteria, which includes cold symptoms due to an acute upper respiratory tract infection, will be eligible for the study.

Eligible subjects will have experienced cold symptoms for no longer than 72 hours (3 days) prior to enrollment at Visit 1. These will consist of cold symptoms including a) at Visit 1, at least moderate severity (score ≥ 5) for stuffy/congested nose, and b) at Visit 1, at least mild (score ≥ 3) for sinus pressure/tenderness, and c) within the past 72 hours, two or more of the following symptoms: runny nose, sore or scratchy throat, sneezing, headache, malaise, or cough.

Study product, dosage and mode of administration:

Phenylephrine HCl [redacted] 30 mg; one tablet taken orally twice daily (every 12 hours)

Phenylephrine HCl, [redacted] 12 mg; one capsule by mouth four times a day (every 4 hours)

Reference therapy (comparator or placebo control), dosage and mode of administration:

Matching placebo for [redacted] phenylephrine HCl, 30 mg and phenylephrine HCl [redacted] capsules, 12 mg.

Duration of treatment:

Twelve hours of treatment.

Data for evaluation:

Endpoints:

Primary

The primary efficacy endpoint is the change from baseline in the nasal congestion severity score (NCSS) averaged over assessments at 2, 4, 6, 8, 10, and 12 hours on Day 1. The baseline nasal congestion score will be measured within approximately 30 minutes before the first dose.

Secondary

The secondary efficacy endpoints include

- Change from baseline in the NCSS averaged over assessments at 8, 10, and 12 hours.
- Change from baseline in the NCSS at 2, 4, 6, 8, 10, and 12 hours and in the morning of Day 2 (24 hours), respectively.
- Change from baseline in Sinus Pressure/Tenderness Scores averaged over assessments at 2, 4, 6, 8, 10, and 12 hours.
- Change from baseline in Sinus Pressure/Tenderness Scores at 2, 4, 6, 8, 10, and 12 hours and in the morning of Day 2 (24 hours), respectively.

Exploratory

The exploratory efficacy endpoints include

- Change from baseline in Head Congestion Scores averaged over assessments at 2, 4, 6, 8,

10, and 12 hours.

- Change from baseline in Head Congestion Scores at 2, 4, 6, 8, 10, and 12 hours and in the morning of Day 2 (24 hours), respectively.
- Change from baseline in Reflected Impact of Nasal / Sinus Congestion on Clear Thinking (reflected for the previous 12 hours) at 12 hour assessment
- Reflected Change in Nasal Congestion Symptoms (reflected over 12 hours after the first dose).
- Reflected Nasal Functioning (reflected over 12 hours after the first dose).
- Change from baseline in Reflected Congestion Severity (reflected for the previous 12 hours) at 12 hour assessment
- Assessment of cold severity using Wisconsin Upper Respiratory Symptom Survey-21 (reflected over 24 hours) at baseline and in the morning of Day 2 (24 hours).

Efficacy Assessments:

The decongestant effect of the phenylephrine [redacted] formulation will be evaluated with the following subjective assessment questions and verbal rating scales (VRS) completed by the subject at the designated time points:

- Assessment of Nasal Congestion (stuffy/congested nose), instantaneous, on an 8-point scale, at baseline, at 2, 4, 6, 8, 10 and 12 hours after the first dose on Day 1 and in the morning of Day 2 (24 hours).
- Assessment of Sinus Pressure/Tenderness, instantaneous, on an 8-point scale, at baseline, at 2, 4, 6, 8, 10 and 12 hours after the first dose on Day 1, and in the morning of Day 2 (24 hours)
- Assessment of Head Congestion, instantaneous, on an 8-point scale, at baseline, at 2, 4, 6, 8, 10 and 12 hours after the first dose on Day 1, and in the morning of Day 2 (24 hours).
- Assessment of Reflected Impact of Nasal / Sinus Congestion on Clear Thinking, reflective, on a 5-point scale, at baseline and at 12 hours after the first dose on Day 1.
- Assessments of Reflected Change in Nasal Congestion Symptoms, reflective, on a 7-point scale, at 12 hours after the first dose on Day 1.
- Assessments of Reflected Nasal Functioning (clear breathing), reflective, on an 8-point scale, at 12 hours after the first dose of treatment on Day 1.
- Assessment of Reflected Congestion Severity, reflective, on a 5-point scale, at baseline and at 12 hours after the first dose on Day 1.
- Assessment of cold severity using the Wisconsin Upper Respiratory Symptom Survey (WURSS-21) at baseline and in the morning of Day 2 (24 hours).

Pharmacokinetic Assessments:

Plasma concentration-time data will be subjected to population pharmacokinetic analysis and reported separately, however, blood plasma levels will be summarized descriptively by treatment

and assessment time points.

Safety Assessments:

Safety assessments will consist of the monitoring of AEs collected throughout the study, and review of blood pressure and heart rate measured at baseline (before drug) and at 2 and 4 hours after the morning dose on Day 1, and at the End of Study visit that will occur the next day (+ one day).

Statistical Methods:

Statistical Analysis of Primary Efficacy Endpoint

For the efficacy analyses, the Full Analysis Set will include all randomized subjects who provide a valid baseline assessment of nasal congestion severity.

This is a Phase II, POC study and therefore the inferential statistical procedures are focused on point and interval estimation of pairwise treatment differences in the efficacy endpoints. However, to further aid interpretation of findings, p-values from 2-sided tests of the null hypotheses of no treatment (mean) difference will be provided in each case.

The primary analysis of the primary endpoint, which is the change from baseline in the Nasal Congestion Score (score for stuffy/congested nose averaged over assessments at 2, 4, 6, 8, 10, and 12 hours on Day 1), will be based on all randomized subjects who provide at least an assessment of nasal congestion at baseline and receive study treatment. The primary endpoint will be analyzed by an ANOVA model with treatment group, study center, and baseline nasal congestion score as factors. For subjects who dropout, their last reported congestion score before the dropout will be carried forward to the remaining assessment time points.

Safety Analysis

The safety analysis will be based on all randomized subjects who took at least one dose of investigational product. The safety data will be summarized using standard procedures.

2. STUDY FLOW CHART AND SCHEDULE OF ACTIVITIES

Protocol Activities	Screening/ Day 1 (site)[a]	Day 1 (offsite)	Day 2 (offsite)	Follow-up Day 2 (+1 day) (site)
Informed consent	X			
Significant Medical History	X			
Demography	X			
Height, weight, body mass index	X			
Blood pressure and heart rate	Pre-dose, 2,4 hrs[b]			X
Respiratory rate and oral body temperature	X			X
Urine Pregnancy Test	X[c]			
Urine Drug Screen	X			
Inclusion/Exclusion criteria	X			
Subject Cold Symptoms Assessment	X			
Randomization	X			
Subject Questionnaire (Diary) • Nasal Congestion • Sinus pressure / tenderness • Head Congestion	BL[d],2,4 hrs	6,8,10,12 hrs	X[e]	
Subject Questionnaire (Diary) • Reflected Impact of Nasal / Sinus Congestion on Clear Thinking • Reflected Congestion Severity	BL[d]	12 hrs		
Subject Questionnaire (Diary) at hour 12 • Reflected Change in Nasal Congestion Symptoms • Reflected Nasal Function		X		
Wisconsin Upper Respiratory Symptom Survey	BL[d]		X[e]	
Administer Investigational Product (IP) at site at 0 and 4 hours	X			
Pharmacokinetic blood samples[f]	X			
Dispense IP and instruct on diary completion	X			
IP Dosing 8 & 12 hrs post dose		X		
Collect diary				X
Assess compliance of returned IP				X
Adverse Event Assessment	X	X		X
Prior and Concomitant Therapies	X	X		X

Protocol Activities	Screening/ Day 1 (site)[a]	Day 1 (offsite)	Day 2 (offsite)	Follow-up Day 2 (+1 day) (site)
Subject Disposition				X

a. Within approximately 72 hours after the onset of cold symptoms.
b: After assessments are completed at the 2 and 4 hour timepoints.
c: Females of childbearing potential only.
d: Within approximately 30 minutes before the first dose of IP.
e. 24 hours after the first dose of IP (either offsite or onsite during the follow-up visit)
f. The first 150 subjects randomized into the study who have consented for PK. Blood samples for the pharmacokinetic cohort population will be collected at approximately 1 (±10 mins) and 4 hours (±20 mins) post dose

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

LIST OF TABLES

LIST OF FIGURES

No table of figures entries found.

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse Event
ANCOVA	Analysis of Covariance
CRF	Case Report Form
CMH	Cochran Mantel Haenszel
EIU	Exposure in utero
GCP	Good Clinical Practice
HCl	Hydrogen Chloride
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
IxRS	Interactive Web or Voice Response System
J&J	Johnson & Johnson
MAOI	Monoamine Oxidase Inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
NCSS	Nasal Congestion Severity Scale
OTC	Over the Counter
PI	Principal Investigator
PQC	Product Quality Complaint
SAE	Serious Adverse Event
t½	Half life
VRS	Verbal Rating Scales
WURSS-21	Wisconsin Upper Respiratory Symptom Survey 21 Point

4. ETHICS

4.1. Institutional Review Board (IRB) / Independent Ethics Committee (IEC)

It is the responsibility of the Investigator to have prospective approval of the study protocol, protocol amendments, informed consent forms, and other relevant documents, e.g., advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File (Site Master File). Copies of IRB/IEC approvals should be forwarded to the Sponsor.

The only circumstance in which a protocol amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the Investigator must notify the IRB/IEC and the Sponsor in writing within 5 working days after implementation.

4.2. Ethical Conduct of the Study

The study will be performed in accordance with the protocol, International Conference on Harmonisation Good Clinical Practice guidelines (ICH E6) and applicable local regulatory requirements and laws.

4.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or subject initials on any forms, reports, publications, or in any other disclosures. Each subject will be assigned a study number that is used in the Case Report Form (CRF) in lieu of the subject's name. In case of data transfer, the Sponsor will maintain high standards of confidentiality and protection of subject personal data.

The informed consent form must be agreed to by the Sponsor and the IRB/IEC and must be in compliance with current ICH E6, GCP, local regulatory requirements, and legal requirements and be in a language that the subject can read and understand.

The Investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation. The Investigator, or a person designated by the Investigator, will obtain written informed consent from each subject before any study-specific activity is performed (except review of Drug Facts Label). The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB and the Sponsor before use. The Investigator will retain the original of each subject's signed consent form. A copy of the signed and dated consent form will be provided to subjects.

Only subjects who provide informed consent will enter in the study.

5. STUDY ADMINISTRATIVE STRUCTURE

Details on the administrative structure of the study (e.g., Principal Investigator (PI)/study site personnel, the Sponsor's study team, and the external service providers/clinical research organizations) will be included in the study contact list. The study contact list will also include contact information for the Sponsor, Investigator(s), Monitor(s), Clinical and Bioanalytical Laboratories, and IRB(s), as well as the names and titles of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor. This list will be maintained in the trial and site master files throughout the study.

6. INTRODUCTION

6.1. Background

Phenylephrine HCl is used as a nasal decongestant in over-the-counter adult and pediatric cough and cold medicines. It is indicated for use for the temporary relief of nasal and sinus congestion and sinus pressure due to the common cold, hay fever, or other upper respiratory allergies. Phenylephrine HCl is commercially available in many countries worldwide as [redacted] single ingredient and combination products for oral administration. The dosing regimen for adults and children 12 years of age and older is one dose of phenylephrine HCl 10 mg every four hours over a 24-hour period or 12 mg up to four times daily [1].

Phenylephrine is rapidly absorbed between 15 and 60 minutes following oral administration and undergoes high first-pass metabolism in the intestinal wall [2]. The bioavailability of phenylephrine after an oral dose is approximately 38% [3]. When phenylephrine HCl is administered after a high-fat meal, the absorption rate is decreased, lowering maximum plasma concentrations about 50% [2]. However, total extent of absorption is not affected by food. Both maximum and total drug exposures increase more than proportionally with increasing single doses from 5 to 30 mg phenylephrine HCl, although the disproportional increase is relatively modest. The terminal elimination t½ of phenylephrine is short, approximately 1 to 2 hours [2,4,5].

[redacted]

6.2. Rationale

Phenylephrine HCl is available in a variety of [redacted] single ingredient and combination products. However, given its short elimination half-life, [redacted] phenylephrine HCl requires frequent dosing every, i.e., 4-6 hours, for optimal symptom relief. [redacted]

7. STUDY OBJECTIVES AND ENDPOINTS

To investigate the potential for efficacy of [redacted] phenylephrine HCl 30 mg twice daily and to compare with phenylephrine HCl [redacted] 12 mg capsules four times a day and placebo, administered orally, in subjects with nasal congestion due to the common cold.

7.1. Primary Endpoint

The primary efficacy endpoint is the change from baseline in the nasal congestion severity score (NCSS) averaged over assessments at 2, 4, 6, 8, 10, and 12 hours on Day 1. The baseline nasal congestion score will be measured within approximately 30 minutes before the first dose.

7.2. Secondary Endpoints

The secondary efficacy endpoints include

- Change from baseline in the NCSS averaged over assessments at 8, 10, and 12 hours.
- Change from baseline in the NCSS at 2, 4, 6, 8, 10, and 12 hours and in the morning of Day 2 (24 hours), respectively.
- Change from baseline in Sinus Pressure/Tenderness Scores averaged over assessments at 2, 4, 6, 8, 10, and 12 hours.
- Change from baseline in Sinus Pressure/Tenderness Scores at 2, 4, 6, 8, 10, and 12 hours and in the morning of Day 2 (24 hours), respectively.

7.3. Exploratory Endpoints

The exploratory efficacy endpoints include

- Change from baseline in Head Congestion Scores averaged over assessments at 2, 4, 6, 8, 10, and 12 hours.
- Change from baseline in Head Congestion Scores at 2, 4, 6, 8, 10, and 12 hours and in the morning of Day 2 (24 hours), respectively.
- Change from baseline in Reflected Impact of Nasal / Sinus Congestion on Clear Thinking (reflected for the previous 12 hours) at 12 hour assessment
- Reflected Change in Nasal Congestion Symptoms (reflected over 12 hours after the first dose).
- Reflected Nasal Functioning (reflected over 12 hours after the first dose).
- Change from baseline in Reflected Congestion Severity (reflected for the previous 12 hours) at 12 hour assessment
- Assessment of cold severity using Wisconsin Upper Respiratory Symptom Survey-21 (reflected over 24 hours) at baseline and in the morning of Day 2 (24 hours).

8. INVESTIGATIONAL PLAN

8.1. Overall Study Design and Plan

This will be a randomized, double-blind, placebo controlled, parallel-group Phase 2 study to evaluate the efficacy of an [redacted] oral tablet equivalent to phenylephrine HCl 30 mg taken twice daily and an [redacted] oral capsule of phenylephrine HCl 12 mg taken four times daily for relief of nasal congestion in subjects with naturally occurring cold symptoms. The trial will have a double dummy design so all subjects will take investigational product four times a day. Subjects randomized to the phenylephrine HCl [redacted] group will take active dose morning and evening, with a period of 12 hours between the doses, with placebo given in the interim doses. Subjects randomized to the phenylephrine HCl [redacted] group will take all four doses of active product. The morning dose will be administered between 7:00AM and noon at the site, the next dose will be administered 4 hours (+10 minutes) later at the site and the last two doses given to the subjects to take 4 hours and 8 hours later. Approximately 450 subjects (150 per treatment group), ages 18 years and older, will be enrolled.

Potential subjects will be identified through advertising and unsolicited presentation at the study site for complaint of common cold symptoms. Eligible subjects will have an onset of cold symptoms (per subject self-report) within approximately 72 hours (3 days) before study entry, consisting of cold symptoms per the following:

- At Visit 1, at least moderate severity (score $\geq$ 5, on a scale from 0 = none to 7 = severe) for stuffy/congested nose, and
- At Visit 1, at least mild (score $\geq$ 3, on a scale from 0 = none to 7 = severe) for sinus pressure/tenderness, and
- Within the past 72 hours, two or more of the following symptoms: runny nose, sore or scratchy throat, sneezing, headache, malaise, or cough

Subjects who qualify per inclusion and exclusion criteria during onsite screening will be randomly assigned via IWRS to one of three blinded treatments: [redacted] tablet equivalent to phenylephrine HCl 30 mg, [redacted] phenylephrine HCl 12 mg, or placebo. Treatment will be for a twelve-hour period (Day 1).

On Day 1, subjects will complete subjective assessments of symptoms at baseline, within approximately 30 minutes prior to dosing. Study staff will then administer the first dose between approximately 7:00 and noon (0 hour). Subjects will remain at the site for 4 hours following the first dose, and they will complete symptom assessments at 2 hours and 4 hours (±10 minutes) post first dose. The 4 hour assessment will be conducted before administration of the next due dose. At 4 hours (+ 10 minutes) post initial dose, subjects will be given the second dose. Vital signs will be obtained at Visit 1 (pre-dose). Vital signs will also be measured at approximately 2 and 4 hours post initial dose, immediately following completion of efficacy assessments. Subjects will be discharged from the site after the 4 hour procedures with instructions to complete subjective assessments using a diary at approximately 6, 8, 10

and 12 hours after the first dose of medication on Day 1 and to take the next two doses at 8 and 12 hours after the first dose was administered at the site. At the 8 and 12 hour time points, the diaries should be completed prior to the medication being taken.

One third of eligible subjects will be assigned to the pharmacokinetic cohort. They will have 3-mL blood samples collected by direct venipuncture. Two samples will be collected; one at approximately 1 (±10 minutes) and another at 4 hrs (±20 minutes) after the initial dose. These subjects will have provided written consent to the collection of blood samples. After the pharmacokinetic cohort has been completed, subsequent enrolling subjects will not be asked to consent to the collection of blood samples.

Subjects will be instructed to complete the final assessments in their diary the next morning on Day 2, 24 hours after the first dose was administered. The 24-hour assessments can also be completed during the follow-up visit if it falls within the window. Subjects will return to the study site for a Follow-up Visit on Day 2 (+1 day) for reconciliation of drug and reporting of any adverse events or concomitant medications. Vital signs will be obtained and the subject will be discharged from the study.

No other cough, cold, allergy, or analgesic/antipyretic medicines (nonprescription or prescription) or herbal/dietary supplements will be permitted during the study. Adverse events will be collected during the study to evaluate safety.

8.2. Subject Inclusion Criteria

This clinical study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject. No waivers to inclusion or exclusion criteria will be permitted.

Subjects must meet all of the following inclusion criteria (and none of the exclusion criteria) to be eligible for enrollment into the study:

1. Provide a signed and dated informed consent form before any study-related procedures.
2. Men or non-pregnant, non-lactating women, aged 18 years or older, who have cold symptoms due to an acute upper respiratory tract infection but are otherwise healthy
3. Have experienced onset of common cold symptoms (per subject report) within 72 hours before study entry consisting of cold symptoms per the following:
    a. At Visit 1, at least moderate severity (score ≥ 5, on a scale from 0 = none to 7 = severe) for stuffy/congested nose, and
    b. At Visit 1, at least mild (score ≥ 3, on a scale from 0 = none to 7 = severe) for sinus pressure/tenderness, and
    c. Within the past 72 hours, two or more of the following symptoms: runny nose, sore or scratchy throat, sneezing, headache, malaise, or cough.

4. Are normotensive and have no clinically significant abnormalities identified by medical history or vital sign measurement (except as consistent with the diagnosis of the common cold) as determined by the Investigator at screening.
    - Blood pressure must be within the following limits after sitting for approximately 5 minutes: > 90 and <140 mm Hg systolic, and >50 and <90 mm Hg diastolic, at screening
    - Pulse rate >50 and <90 beats/minute at screening;
    - Body Mass Index (BMI) of 18 to 34 kg/m^2 (inclusive);
5. Willing to use only the study treatment for cold symptom relief during the course of the study and avoid the use of treatments that may affect nasal / cold symptomatology; no other cough, cold, allergy, or analgesic/antipyretic medicines (non-prescription or prescription) or herbal/dietary supplements will be permitted during the study
6. Females of childbearing potential must have used an effective form of birth control for three months before Screening and a negative urine pregnancy test at the Screening visit.
7. Female and male subjects must agree to the contraceptive requirement use during the study and for at least 30 days after the last dose (for females) (See Section 10.4.3).
8. Willing and able to comply with the study procedures and visit schedule, which includes remaining at the study site for at least 4 hours after the first dose of study medicine on Day 1.
9. Able to read and understand English and/or French;

8.3. Subject Exclusion Criteria

Subjects presenting with any of the following will not be included in the study:

1. Currently experiencing nasal congestion due to allergic rhinitis or chronic respiratory disease.
2. Any ear, nose, throat, or respiratory tract disease, other than the common cold, identified by signs and symptoms reported by the subject, or by medical history or medication history
3. Presence of asthma.
4. History of rhinitis medicamentosa, anatomical nasal obstruction or deformity, nasal reconstructive surgery, or chronic sleep apnea.
5. Fever of ≥ 101.0 °F (38.3 °C).
6. Heart disease, controlled or uncontrolled hypertension, thyroid disease, diabetes, glaucoma, prostatic hypertrophy, or presence of a disease, which in the opinion of the investigator, would preclude the use of phenylephrine.

7. Are currently taking, or have taken within two weeks of screening, a monoamine oxidase inhibitor (MAOI).
8. Have the need to use medications which may impact nasal symptomatology i.e. systemic, inhaled (oral or nasal) corticosteroids, and the following drugs with significant anticholinergic properties: tricyclic antidepressants, paroxetine, medicines used to treat overactive bladder, antipsychotic medication, skeletal muscle relaxants, antiparkinsonian medication, the anticonvulsants carbamazepine and oxcarbazepine, and dicycloverine (dicyclomine), dimenhydrinate, propantheline, atropine, hyoscyamine, belladonna, prochlorperazine and promethazine.
9. Have a bacterial sinus infection within 2 weeks prior to screening.
10. Use of systemic antibiotics within the past 7 days prior to screening.
11. Known or suspected alcohol or substance abuse (e.g., amphetamines, benzodiazepines, cocaine, marijuana, opiates).
12. Use of marijuana containing substances within the 10 days prior to screening and throughout the study.
13. Positive Urine Drug Screen.
14. Use of alcohol throughout the study.
15. History of smoking tobacco products or use of nicotine-containing substances within the previous three months as determined by subject's medical history or subject's verbal report.
16. Known sensitivity to the investigational product or any excipients of the drug product.
17. Before the first dose of study medicine, use of
    a. oral or intranasal cold, cough, allergy, or analgesic/antipyretic medicines within approximately 12 hours;
    b. menthol products, medicated lozenge, humidifier, nasal saline spray or throat spray within approximately 6 hours;
    c. herbal/dietary supplements within approximately 12 hours.
18. Have difficulty swallowing tablets/capsules or are unable to swallow whole without crushing, chewing, splitting, or dissolving.
19. Subjects who were previously randomized and received the IP.
20. Significant unstable or uncontrolled medical condition that may interfere with a subject's participation in the study.
21. Other severe, acute or chronic, medical or psychiatric condition(s) or laboratory abnormality that may increase the risk associated with study participation or IP administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

22. Currently participating in another clinical trial or has done so in the past 30 days.
23. Subjects who are related to those persons involved directly or indirectly with the conduct of this study (i.e., principal investigator, sub-investigators, study coordinators, other site personnel, employees of Johnson & Johnson (J&J) subsidiaries, contractors of J&J, and the families of each).

8.4. Subject Withdrawal Criteria

Subjects have the right to withdraw from the study at any time for any reason without compromising their rights to receive further treatment. The Investigator and/or the Sponsor may terminate a subject from investigational treatment and/or study follow-up in the event of any of the following:

- Medical reasons considered significant by the subject, Investigator and/or the Sponsor, which may include, an AE, intercurrent illness or medical reasons unrelated to the study
- Non-medical reasons (e.g., subject request or non-compliance with the treatment procedure as determined by the investigator, the Sponsor and/or subject)
- Pregnancy
- Serious eligibility or on-study violation of the protocol
- Administrative or other reasons

Should a subject decide to withdraw from the study at any point, all efforts should be made to complete all End of Study assessments (if subject cannot come to study site, a telephone call to collect information could be performed). In case of questions surrounding the circumstances that a subject needs to be withdrawn from the study (e.g., protocol deviation), the Sponsor or the Sponsor representative should be consulted. The reason for withdrawal should be documented in the subject's source document and in the Subject Disposition CRF.

9. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

9.1. Investigational Product

Subjects who qualify for study entry per inclusion and exclusion criteria during onsite screening will be randomly assigned to one of three blinded treatments: [redacted] tablet equivalent to phenylephrine HCl 30 mg 2 times daily, [redacted] phenylephrine 12 mg 4 times daily or placebo 4 times a day, for one day.

Study staff will administer the first dose between approximately 07:00 and 12:00 hours (0 hour) on Day 1 and the second dose 4 hours later. Subjects will be discharged from the site after the second dose and will be instructed to continue taking the IP as directed for the rest of the day.

9.2. Description of Investigational Product

Table 2: Investigational Product

Investigational Product:	Phenylephrine HCl equivalent	Phenylephrine HCl equivalent	Matching Placebo	Matching Placebo
Dosage Form:	[redacted]	[redacted]	Tablet	Capsule
Unit Dose	30 mg	12 mg	NA	NA
Route of Administration	Oral	Oral	Oral	Oral
Physical Description	White film-coated oval shaped tablet.	Yellow capsule	White film-coated oval shaped tablet	Yellow capsule
Manufacturer	McNeil Fort Washington Pilot Plant	McNeil Products Ltd. Maidenhead, Bershire. SL6 3UG, UK	McNeil Fort Washington Pilot Plant	Almac Clinical Services

9.3. Investigational Product Packaging and Labeling

Phenylephrine HCl equivalent [redacted] 30 mg tablets and phenylephrine HCl [redacted] capsules and matching placebo tablets and capsules will be packaged in blister cards. Each card will have a sufficient supply for the duration of the study for one subject. The Sponsor will label the blister cards for use per the standard operating procedures. The card will have a two-part, three-panel label with a perforation between Panels I and II. Panels I and II will provide study related information, instructions for use, storage conditions, and randomization number. In addition, Panel III will include a concealed scratch off sticker containing the treatment assignment for each subject. Part II of the label should be removed at the perforation line (entire section of the label which includes the Panel III scratch off sticker) and attached to the source document prior to dispensing the kit to the

subject. The scratch off sticker should not be removed from the label and the integrity of the scratch off surface should be preserved.

9.4. Blinding and Unblinding

Breaking the blind during the study is restricted to medical emergencies and should only be done under circumstances where knowledge of a subject's treatment is necessary for reasons of subject safety. In such cases, the investigator may in an emergency determine the identity of the treatment by accessing the Interactive Web Response System (IWRS). The decision to unblind a subject can be made by the PI. Where possible, the Sponsor should be informed before breaking the blind. However, if an emergency condition exists and there is not sufficient time to consult with the Sponsor, the PI alone can request the unblinding of a subject. The Sponsor must be informed within 24 hours after the unblinding. Telephone contact with the Sponsor or its designee will be available 24 hours per day, 7 days per week. The rationale, date, time, and contact attempts for breaking the blind for a subject in a trial should be documented in the subject's file and in the appropriate section of the CRF. The reason for un-blinding is not captured through the IWRS.

The study site should take necessary measures to maintain the study treatment blind and prevent any unintended or premature unblinding. If unblinding is performed, the occurrence will be reported by the PI to the Clinical Research Organization and the Sponsor as soon as possible and will be entered into the subject's record, but the group assignment will not be divulged. The subject whose treatment blind has been broken will be immediately discontinued from the IP and will be discontinued from the study and followed-up by the study staff until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator (see Adverse Events section).

The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner (e.g., secure e-mail, fax, sealed envelope) so as not to un-blind the treatment assignment to the study site or Sponsor personnel. The investigator is also advised not to reveal the study treatment assignment to the study site (except as necessary for the clinical management of the subject) or Sponsor personnel.

9.5. Method of Assigning Subjects to Treatment Groups

The randomization schedule will be generated by the Sponsor. Subjects will be randomized via an IWRS to receive one of three treatments (phenylephrine [redacted] phenylephrine [redacted] or placebo, 1:1:1 ratio).

Table 3: Investigational Product

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

9.6. Study Product Storage and Accountability

Temperature monitors will be included with the IP that is shipped to the sites. These monitors will indicate if the temperature has varied (either too hot or too cold) beyond what is appropriate for the product. Sites will store product in accordance with Sponsor's requirements and will report temperature variations as appropriate. The Investigator or a designated study staff member will ensure that IP is stored at the correct temperature upon arrival at the site.

The Investigator, or a designated study staff, will ensure that all IP are stored in a secured area, under recommended room temperature storage conditions between 68 °F to 77 °F (20 °C to 25 °C) with excursions allowed as permissible and in accordance with applicable regulatory requirements.

The Investigator must maintain adequate records documenting the receipt, use, loss, or other disposition of the IP on the IP Accountability Log. The log must identify the IP and account for its disposition on a subject-by-subject basis, including specific dates and quantities dispensed and returned. The log must be signed by the individual who dispensed/retrieved the IP, and copies must be provided to the Sponsor for the Trial Master File.

At the end of the study, the Sponsor will provide instructions on the disposition of any unused IP. If the Sponsor authorizes destruction at the study site, the Investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by the Sponsor. Destruction must be adequately documented.

9.7. Administration of the Investigational Product

The first and second dose of the IP will be administered by the investigational study staff at the site. Subjects will be given 2 doses to dose the rest of the day.

9.8. Product Quality Complaints

A Product Quality Complaint (PQC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability or safety of a product, including its labeling, delivery system or packaging integrity. This does not include effectiveness, preference or performance measures, which will be reviewed in aggregate at appropriate intervals.

Any PQC discovered during the initial inventory of study supplies should follow the instructions provided on the receipt letter; no PQC form should be filed for issues identified when opening or unpacking a shipment. Subsequently, any observation of a PQC requires immediate notification to the Sponsor or designee via a completed PQC form and telephone call. The PI or designee should complete, sign and forward a copy of the PQC form, via an agreed upon secure exchange, to the Sponsor or designee.

In addition, PQC information must be included on the IP Dispensing and Accountability Log or equivalent in the "Comments" field. The Sponsor or designee listed can assist the site or answer questions related to this process. To aid in the initial conversation and understanding

of a PQC, the site staff may be asked to photograph the issue and send it to the Sponsor or designee.

When enrolling subjects into this study it is the site's responsibility to instruct subjects not to use the product if they have a concern related to the product such as an issue with the labeling, IP or package integrity and to immediately report it using the instruction on the Informed Consent or product label.

10. STUDY PROCEDURES

10.1. Overview

Collection of AEs and concomitant therapies will start after the study-specific informed consent document has been signed and continue until completion of the follow-up procedures. The Schedule of Activities/Study Flow Chart (Table 1) summarizes dose administration and the timing and frequency of safety and efficacy procedures and measurements. In the event of abnormal safety findings during the conduct of the study, the attending physician may request additional safety evaluations, either immediately or subsequently at a frequency considered appropriate.

10.2. Screening / Day 1 Visit (including up to morning of Day 2)

Informed consent must be obtained from the subjects before any study related assessments are conducted. If subjects did not qualify per Inclusion Criteria 3 they may be re-screened one other time with a different episode of Upper Respiratory Tract Infection (URTI). For subjects who are being re-screened, all inclusion/exclusion criteria must be re-evaluated.

Procedures to be performed at this visit are:

- Informed Consent (Informed Consent can be performed the day prior to Visit 1 as long as the Day 1 visit is within the 72 hour window of onset of cold symptoms).
- Inclusion and exclusion criteria
- Demography
- Height, weight and body mass index assessment
- Significant medical history (e.g., drug allergy, major medical conditions as noted in the Exclusion criteria, previous heavy drinking and/or smoking history)
- Collect Adverse Events if subject reports an event beginning after medical history has been taken (i.e. if screening and baseline are separate days.)
- Prior and concomitant medication and other therapies (within 14 days)
- Vital signs: respiratory rate, oral body temperature
- Vital signs: Resting blood pressure and heart rate at baseline (pre-dose) and at 2 and 4 hours post-dose, immediately following completion of subject assessments at 2 and 4 hours post dose (baseline vital signs can be performed either before or after baseline assessments.
- Urine pregnancy test for all female subjects of childbearing potential
- Urine Drug Screen
- Allocating treatment assignment via IWRS

- Administer the first dose of IP between 7:00 and noon and a second dose 4 hours (+10 minutes) later.
- PK blood draws at 1 hour (±10 minutes) and 4 hours (±20 minutes) post dose for those subjects who have consented to the PK portion of the study. The 4 hour PK sample should be performed after the 4 hour vital signs have been collected.
- Subjects will remain at the site until after the second dose administration.
  - While subjects are at the site, all lifestyle guidelines outlined in the protocol must be followed.
- Subject Assessments/Questionnaires
  - Subject Cold Symptoms Assessment - at baseline
  - Nasal Congestion Severity Rating - at baseline (within approximately 30 minutes prior to administration of IP), at 2 and 4 hours (±10 minutes) post-dose
  - Sinus Pressure Severity Rating - at baseline (within approximately 30 minutes prior to administration of IP), at 2 and 4 hours (±10 minutes) post-dose
  - Head Congestion Severity Rating - at baseline (within approximately 30 minutes prior to administration of IP), at 2 and 4 hours (±10 minutes) post-dose
  - Reflected Impact of Nasal / Sinus Congestion on Clear Thinking – at baseline (within approximately 30 minutes prior to administration of IP)
  - Reflected Congestion Severity Rating – at baseline (within approximately 30 minutes prior to administration of IP)
  - Wisconsin Upper Respiratory Symptom Survey (WURSS-21) cold severity rating – at baseline (within approximately 30 minutes prior to administration of IP)
- Dispense IP and instruct subjects on the completion of subject questionnaires using diaries.

Subjects will be discharged from the site with instructions to complete the subject questionnaires using the Diary as follows:

- Nasal Congestion Severity Rating - at 6, 8, 10 and 12 hours post-dose and morning of Day 2 (24 hours).
- Sinus Pressure Severity Rating - at 6, 8, 10 and 12 hours post-dose and morning of Day 2 (24 hours).
- Head Congestion Severity Rating - at 6, 8, 10 and 12 hours post-dose and morning of Day 2 (24 hours).

- Reflected Impact of Nasal / Sinus Congestion on Clear Thinking – at Hour 12 post-dose
- Reflected Congestion Severity Rating – at Hour 12 post-dose
- Reflected Change in Nasal Congestion Symptoms, reflective over the day – at Hour 12 post-dose.
- Reflected Nasal Functioning (clear breathing) Rating, reflective over the day – at Hour 12 post-dose.
- Wisconsin Upper Respiratory Symptom Survey (WURSS-21) cold severity rating – morning of Day 2 (24 hours).

10.3. End of Study Procedures

End of Study Procedures are to be performed at the Follow-up visit on Day 2 (+1 day) when the subject returns to the site.

The following information will be collected during this visit:

- Vital signs: blood pressure, heart rate, respiratory rate, oral body temperature
- Adverse Events
- Concomitant medications/therapies
- If the 24 hour assessment window falls during the follow-up visit, this assessment can be completed at the site.
- Return of diary (if paper)
- Return of IP and check compliance.
- Subject Disposition

10.4. Lifestyle Guidelines

Usual methods for relieving nasal congestion and other cold symptoms, including steam humidifier, nasal saline spray, menthol lozenges, menthol gum, menthol shower gels and vapor rubs should be strictly avoided until after the final efficacy assessments are completed on Day 2.

10.4.1. Meals and Dietary Restrictions

While subjects are at the site and offsite on Day 1, all snacks, drinks, and meals during the efficacy assessment period should not be consumed within 30 minutes prior to the next subjective assessments.

Warm drinks, including caffeine-containing drinks or hot soup, should not be consumed either onsite or offsite until after the efficacy assessments are completed. A study has shown a significant improvement in subjective symptoms scores after consuming these fluids when compared with drinks at room temperature [8].

10.4.2. Alcohol, Caffeine and Tobacco Consumption / Restrictions

Subjects will abstain from

- drinking alcohol during the study until all End of Study procedures are completed;
- the use of tobacco- or nicotine-containing products until all End of Study procedures are completed;
- smoking marijuana or the use of marijuana-containing products until all End of Study procedures are completed;
- drinking caffeine-containing products (e.g., soda, tea, and coffee) during the study until the Day 2 assessment is completed.

10.4.3. Contraception

Female subjects are considered not of childbearing potential if they meet at least one of the following criteria:

- Had a hysterectomy and/or bilateral oophorectomy at least 6 months prior to product administration.
- Had sterilization surgery (for hysteroscopic sterilization/tubal implants) at least 6 months prior to screening and has been confirmed effective by medical assessment as reported by the subject.
- Are post-menopausal (e.g., amenorrhoeic for at least 12 consecutive months, without an alternative medical cause, prior to Day 1).

Medically acceptable forms of birth control that may be used by the subject and/or his/her partner include:

- Established use of hormonal methods of contraception (oral, injected, implanted, patch or vaginal ring).
- Barrier methods of contraception with spermicide: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/ film/ cream/ suppository.
- Intrauterine device or intrauterine system.
- Surgical sterilization (e.g., vasectomy that has been confirmed effective by sperm count check, tubal occlusion, hysterectomy, bilateral salpingectomy).
- Abstinence from heterosexual intercourse, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Male and female subjects with reproductive potential must agree to practice a medically acceptable form of birth control throughout the study and for at least 30 days after the last dose (for females).

10.5. Treatment Compliance

On Day 1, investigational site staff will instruct the subjects on the importance of being compliant with the IP and completing the Diary at the specified timepoints. At the End of Study visit, subject's compliance to IP will be checked by the number of doses of IP returned compared with the number of doses the subject was supposed to have taken with consideration of what was entered in the Diary by the subject.

10.6. Previous and Concomitant Therapies

Female subjects who are using hormonal contraceptives will continue to take them during the study and this concomitant medication will be recorded on the CRF. Other medications or non-drug therapies used 14 days before the Screening visit and during the study will be recorded in the source document and CRF.

Any medications taken before the first dose of IP will be considered as prior medications. Any medications taken after the first dose of IP until the End of Study will be considered as concomitant medications.

Subjects will abstain from using prescription or non-prescription drugs and dietary and herbal supplements in accordance with the inclusion/exclusion criteria. All subjects will be questioned about concomitant medication at each visit.

11. ASSESSMENTS

11.1. Efficacy Assessments

The decongestant effect of phenylephrine [redacted] will be evaluated with the following subjective assessment questions and Verbal Rating Scales (VRS) at the designated time points using the Diary:

- Assessment of Nasal Congestion (stuffy/congested nose), instantaneous, on an 8-point scale, at baseline, at 2, 4, 6, 8, 10 and 12 hours after the first dose on Day 1, and on the morning of Day 2 (24 hours)
- Assessment of Sinus Pressure/Tenderness, instantaneous, on an 8-point scale, at baseline, at 2, 4, 6, 8, 10 and 12 hours after the first dose on Day 1, and on the morning of Day 2 (24 hours)
- Assessment of Head Congestion, instantaneous, on an 8-point scale, at baseline, at 2, 4, 6, 8, 10 and 12 hours after the first dose on Day 1, and on the morning of Day 2 (24 hours)
- Assessment of Reflected Impact of Nasal / Sinus Congestion on Clear Thinking, on a 5-point scale, at baseline and at 12 hours after the first dose on Day 1.
- Assessments of Reflected Change in Nasal Congestion Symptoms reflective, on a 7-point scale, at 12 hours after the morning dose on Day 1.
- Assessments of Reflected Nasal Functioning (clear breathing), reflective, on an 8-point scale, at 12 hours after the morning dose on Day 1.
- Assessment of Reflected Congestion Severity, reflective, on a 5-point scale, at baseline and at 12 hours after the morning dose on Day 1.
- Assessment of cold severity using the Wisconsin Upper Respiratory Symptom Survey (WURSS-21) at baseline and on the morning of Day 2 (24 hours).

11.1.1. Nasal Congestion, Sinus Pressure and Head Congestion

Rate the severity of each symptom at this point in time	None	Very Mild		Mild		Moderate		Severe
	0	1	2	3	4	5	6	7
Stuffy / congested nose	☐	☐	☐	☐	☐	☐	☐	☐
Sinus pressure / tenderness	☐	☐	☐	☐	☐	☐	☐	☐
Congested Head	☐	☐	☐	☐	☐	☐	☐	☐

11.1.2. Reflected Impact of Nasal / Sinus Congestion on Clear Thinking

To what extent has your nasal/sinus congestion affected your ability to think clearly over the past 12 hours?	No effect on clear thinking	Very mild	Mild	Moderate	Severe
	☐	☐	☐	☐	☐

11.1.3. Reflected Change in Nasal Congestion Symptoms

How are your nasal congestion symptoms now, compared to just before you were given the first dose of study medication at the start of the study?	Much worse	Worse	A little worse	No change	A little better	Better	Much better
	0	1	2	3	4	5	6
	☐	☐	☐	☐	☐	☐	☐

11.1.4. Reflected Nasal Functioning

When breathing, how clear has your nose felt over the whole day since the first dose of study medication?	Clear	Mostly clear		Partly clear		A little clear		Not clear at all
	0	1	2	3	4	5	6	7
	☐	☐	☐	☐	☐	☐	☐	☐

11.1.5. Reflected Congestion Severity

Rate the average severity of your stuffy nose over the past 12 hours?	No stuffy nose	Very mild	Mild	Moderate	Severe
	☐	☐	☐	☐	☐

11.1.6. Wisconsin Upper Respiratory Symptom Survey 21

Wisconsin Upper Respiratory Symptom Survey – 21 --- *Daily Symptom Report*

Day:	*Date:*	*Time:*	*ID:*

Please fill in one circle for each of the following items:

	Not sick	Very mildly		Mildly		Moderately		Severely
	0	1	2	3	4	5	6	7
How sick do you feel today?	o	o	o	o	o	o	o	o

Please rate the **average severity of your cold symptoms over the last 24 hours** for each symptom:

	Do not have this symptom	Very mild		Mild		Moderate		Severe
	0	1	2	3	4	5	6	7
Runny nose	o	o	o	o	o	o	o	o
Plugged nose	o	o	o	o	o	o	o	o
Sneezing	o	o	o	o	o	o	o	o
Sore throat	o	o	o	o	o	o	o	o
Scratchy throat	o	o	o	o	o	o	o	o
Cough	o	o	o	o	o	o	o	o
Hoarseness	o	o	o	o	o	o	o	o
Head congestion	o	o	o	o	o	o	o	o
Chest congestion	o	o	o	o	o	o	o	o
Feeling tired	o	o	o	o	o	o	o	o

Over the last 24 hours, how much has your cold interfered with your ability to:

	Not at all	Very mildly		Mildly		Moderately		Severely
	0	1	2	3	4	5	6	7
Think clearly	o	o	o	o	o	o	o	o
Sleep well	o	o	o	o	o	o	o	o
Breathe easily	o	o	o	o	o	o	o	o
Walk, climb stairs, exercise	o	o	o	o	o	o	o	o
Accomplish daily activities	o	o	o	o	o	o	o	o
Work outside the home	o	o	o	o	o	o	o	o
Work inside the home	o	o	o	o	o	o	o	o
Interact with others	o	o	o	o	o	o	o	o
Live your personal life	o	o	o	o	o	o	o	o

Compared to yesterday, I feel that my cold is…

Very much better	Somewhat better	A little better	The same	A little worse	Somewhat worse	Very much worse
o	o	o	o	o	o	o

WURSS -21© (Wisconsin Upper Respiratory Symptom Survey) 2004
Created by Bruce Barrett MD PhD et al., UW Department of Family Medicine, 777 S. Mills St. Madison, WI 53715, USA

11.2. Pharmacokinetic Assessments

11.2.1. Blood collection

From a pharmacokinetic cohort of approximately 150 subjects, two blood samples (3 mL) will be collected by venipuncture into appropriately labeled K3 EDTA tubes at 1 hour (±10 minutes) and 4 hours (±20 minutes) after the first dose. The 4 hour PK sample should be performed after the 4 hour vital signs have been collected. These samples will be collected at the nominal time relative to dosing. The exact time of the sample collection will be noted on the source document and CRF. Samples will be assayed for either phenylephrine using validated analytical methods.

11.2.2. Blood sample processing

After collection of pharmacokinetic blood samples into appropriately labeled K3 EDTA tubes, the tubes will be gently mixed approximately eight times and immediately placed on ice or cryoblocks for transportation to the centrifuge. The tubes will be centrifuged at approximately 2700 to 3000 (high-speed) rpm for about 10 minutes within 60 minutes of collection. Following centrifugation, the plasma will be immediately returned to an ice bath while samples are divided into two identically labeled screw-capped polypropylene tubes. They will be frozen at nominally -20ºC or -70ºC within a fluctuation range of ±15ºC at the clinic. The time from sample collection to the freeze time should not exceed 60 minutes. Frozen samples will be stored at nominally -70ºC at the bioanalytical laboratories. The blood and plasma tubes will be labeled with the following information at a minimum: subject identification number, sampling time, date of collection, and unique study code (i.e., protocol number).

11.2.3. Shipment of Pharmacokinetic Samples

Pharmacokinetic plasma samples will be shipped at times specified by the Sponsor. Further information regarding handling, shipment (e.g., addresses and laboratory contacts), and labeling of biological samples will be provided as separate documents to the clinical site.

11.2.4. Analytical Procedures

Plasma samples will be sorted by assigned staff at the laboratory such that those samples having active treatment will be assayed for phenylephrine concentrations. After quantification of phenylephrine, remaining plasma will be retained until destruction is approved by the Sponsor.

11.2.5. Population Pharmacokinetic Modeling

Plasma concentration-time data for phenylephrine will be evaluated in a population pharmacokinetic analysis with potential simulations to evaluate and optimize future clinical study designs. The results will be reported separately from the efficacy and safety results.

11.3. Safety Assessments

Safety assessments will consist of the monitoring of AEs collected throughout the study, and review of blood pressure and heart rate measured at baseline (before drug) and at 2 and 4 hours after the morning dose on Day 1, and at the End of Study Visit which will occur on Day 2.

11.3.1. Vital Signs

As shown in the Study Flow Chart and Schedule of Activities, the following vital signs will be assessed at Visit 1: respiratory rate, oral body temperature, and resting blood pressure and heart rate at baseline (pre-dose). Resting blood pressure and heart rate will also be assessed at 2 and 4 hours post-dose, immediately following completion of subject assessments. At the Follow-up visit on Day 2 (+1 day), resting blood pressure and heart rate, respiratory rate, and oral body temperature will be assessed. Sitting blood pressure will be obtained after the subject has been sitting with feet flat for approximately 5 minutes. At screening, blood pressure must be within the following limits after sitting for approximately 5 minutes: > 90 and <140 mm Hg systolic, and >50 and <90 mm Hg diastolic, to be randomized into the study.

Blood pressure can be repeated up to three times and recorded in the source document, but only the qualifying measurement will be entered in the eCRF. According to the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure in adults ages 18 and older, hypertension is defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. This classification is based on the average of two or more properly measured seated blood pressure readings on each of two or more office visits.

12. ADVERSE EVENT REPORTING

12.1. Introduction

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the IP(s) will be reported as described in the following sections. For all AEs, the Investigator or medically qualified individual must pursue and obtain adequate information both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a Serious Adverse Event (SAE) requiring immediate notification (within 24 hours) to the Sponsor or its designated representative. For all AEs, sufficient information should be obtained by the Investigator or medically qualified individual to try to determine causality. The Investigator is required to assess causality. For AEs with a suspected causal relationship to the IP, follow-up by the Investigator or medically qualified individual is required until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator, and the Sponsor concurs with that assessment.

12.2. Reporting Period

All AEs for randomized subjects, whether serious or non-serious will be recorded on the CRF in the AE section beginning from the time the informed consent is signed and dated. If a screen failed subject has an AE, the AE will be recorded in the CRF along with the subject's demographic data. Once, non-serious AE changed to Serious, the subsequent notification and completed SAE form should be completed and sent to Sponsor or designated representative within the timeline established for SAE reporting. Informed consent is considered the point at which the subject is participating in the clinical study and all events are captured even if it is prior to undergoing any study-related procedure and/or receiving IP. Non-serious AEs will be reported through the subject's last study visit (or termination if the subject terminates early from the study for any reason). Spontaneous reports of SAEs will be collected through and including 30 calendar days after administration of the subject's last dose or exposure to IP.

SAEs require immediate notification to the Sponsor or its designated representative. Any SAE occurring any time after the reporting period must be promptly reported if a causal relationship to the IP is suspected.

12.3. Definition of an Adverse Event

An AE is any untoward medical occurrence that occurs in a subject after they have signed an informed consent for a trial involving an IP. Any AE that occurs after the informed consent has been signed, until first usage of IP, will be considered non-treatment emergent and cannot (by virtue of time of occurrence) have a causal relationship with the IP.

The event does not need to have a suspected causal relationship with the IP. Therefore, an AE can be any unfavorable and unintended sign, symptom, disease or injury temporally associated with the use of an IP, whether or not related to the IP. Examples of AEs include, but are not limited to:

- Abnormal test findings,
- Clinically important signs and symptoms,
- Changes in physical examination findings,
- Hypersensitivity, and
- Progression/worsening of underlying disease.

Additionally, they may include the signs or symptoms resulting from:

- Overdose,
- Withdrawal,
- Abuse,
- Drug misuse,
- Drug interactions,
- Medication errors,
- Product dependency,
- Exposure *in utero*, and
- Study related procedure.

12.4. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a discontinuation from the study, significant additional concomitant treatment, or other therapy, and/or
- Test result is considered to be an AE by the Investigator or the Sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

12.5. Serious Adverse Events (SAE) for Drugs

An AE or suspected adverse reaction is considered "serious" for a drug study if, in the view of either the Investigator (physician) or the Sponsor, it results in any of the following outcomes:

- Results in death,

- Is life-threatening (immediate risk of death),
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- Results in congenital anomaly/birth defect,
- Is considered medically significant (medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not result in death, be life-threatening or require hospitalization but may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the other outcomes listed above). Examples of such medical events include allergic bronchospasm requiring intensive treatment in an Emergency Room or at home, blood dyscrasia, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse, or malignancy), or,
- Is a suspected transmission of any infectious agent via a medical product (medically significant) and should be reported as an SAE in the category 'Other medically important conditions.'

12.6. Hospitalization

AEs reported from clinical studies associated with hospitalization or prolonging hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). Hospitalization does not include the following:

- Rehabilitation facilities,
- Hospice facilities,
- Respite care (e.g., caregiver relief),
- Skilled nursing facilities,
- Nursing homes,
- Emergency room visits (unless the reason for the emergency room visit meets one of the other outcomes in the definition of serious), and/or
- Same day surgeries (as outpatient/same day/ambulatory procedures)

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality),
- Social admission (e.g., subject has no place to sleep),
- Administrative admission (e.g., for yearly physical exam),
- Protocol-specified admission during a clinical study (e.g., for a procedure required by the study protocol),
- Optional admission not associated with a precipitating clinical AE (e.g., or elective cosmetic surgery),

Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

- Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE and the resulting appendectomy should be recorded as treatment of the AE.

12.7. Resolution

The Investigator will be required to assess the outcome of the AE for IP as one of the following:

- Resolved,
- Not Resolved,
- Fatal,
- Resolved with sequelae,
- Resolving, or
- Unknown.

Any causally-related AEs unresolved upon completion of the last study visit will be followed up by the study staff until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator and recorded on the CRF. An event that is assessed as resolved with sequelae or resolving indicates that the subject has stabilized to a level acceptable to the Investigator and has concurrence by the Sponsor.

12.8. Severity Assessment

The Investigator or medically qualified individual (physician) will assess the severity of AEs using the following general categorical descriptors:

MILD:	Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with subject's usual function or normal everyday activities
MODERATE:	Sufficient discomfort is present to cause interference to some extent with subject's usual function or normal everyday activity
SEVERE:	Extreme distress, causing significant impairment of functioning or incapacitation; interferes significantly with subject's usual function; prevents normal everyday activities

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

12.9. Causality Assessment

The Investigator or medically qualified individual (physician) will assess causality to IP (i.e., relationship to IP) for all serious and non-serious AEs. An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the IP caused or contributed to an AE.

- Not Related - An AE that is not related to the use of the drug
- Doubtful - An AE for which an alternative explanation is more likely, e.g., concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship to IP is unlikely.
- Possible - An AE that might be due to the use of the drug. An alternative explanation, e.g., concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship to IP cannot be excluded.
- Probable - An AE that might be due to the use of the drug. The relationship in time is suggestive (e.g., confirmed by dechallenge) and an alternative explanation is less likely, e.g., concomitant drug(s), concomitant disease(s).
- Very Likely - An AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g., it is confirmed by dechallenge and rechallenge) for a causal relationship to the drug.

If the Investigator determines an SAE is associated with study procedures, the Investigator must record this suspected causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

12.10. Exposure In Utero

For IPs within clinical studies and for marketed products, an exposure *in utero* (EIU) occurs if:

1. A woman is exposed to the IP at any time between her last menses prior to conception through the delivery of the baby.
2. There is a possibility of intrauterine exposure to drug via semen from the male partner who is taking the IP at the time of conception, thereby possibly exposing the fetus to the product.

If any study subject or study subject's partner becomes or is found to be pregnant during the study subject's participation, the Investigator must report the pregnancy to the Sponsor on a Pregnancy Notification Form (to be provided by the Sponsor when applicable). In addition, the Investigator must submit information regarding environmental exposure to a Sponsor product in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the Pregnancy Notification Form. This must be done irrespective of whether an AE has occurred and notification must occur within 24 hours of awareness of the pregnancy. Initial notification via telephone to the Sponsor's study team contact must occur immediately upon the investigational site's awareness of the pregnancy. The Pregnancy Notification Form must then be sent to the Sponsor within 24 hours of the site's awareness. The information submitted should include the anticipated date of delivery (see below for information related to induced termination of pregnancy).

Follow-up is conducted to obtain pregnancy outcome information on all EIU reports. The Investigator will follow the pregnancy until completion or until pregnancy termination (i.e., induced abortion) and then notify the Sponsor of the outcome. The Investigator will provide this information as a follow-up to the initial Drug Exposure During Pregnancy Collection Form A and/or End of Pregnancy Collection Form B (provided by the Sponsor when applicable). The reason(s) for an induced abortion should be specified. An EIU report is not created when an ectopic pregnancy report is received since this pregnancy is not usually viable. Rather, an SAE case is created with the event of ectopic pregnancy.

The Investigator should follow the procedures for reporting SAEs if the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus, stillbirth, or neonatal death]). In the case of a live birth, the "normality" of the newborn can be assessed at the time of birth (i.e., no minimum follow-up period of a presumably normal infant is required before an End of Pregnancy Collection Form B can be completed). The "normality" of an aborted fetus can be assessed by gross visual inspection, unless pre-abortion test findings are suggestive of a congenital anomaly.

Additional pregnancy outcomes that are classified as SAEs and should be reported as such include:

- "Spontaneous abortion" includes miscarriage and missed abortion.

- All neonatal deaths that occur within 1 month of birth, without regard to causality.
- Any infant death after 1 month that the Investigator assesses as possibly related to *in utero* exposure to the IP.

12.11. Withdrawal Due to Adverse Events

When a subject withdraws due to an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

12.12. Eliciting Adverse Event Information

The Investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs.

12.13. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for an SAE. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

All AEs will be reported on the AE page(s) of the CRF. A Clinical SAE Report Form must also be completed if the event is considered to be serious. It should be noted that this Clinical SAE Report Form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

12.13.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, the Sponsor is to be initially notified by telephone immediately upon awareness of the event by the Investigational site. Completed SAE Report form should always indicate the causality assessment by Investigator. Follow-up SAE form should re-state the causality assessment based on new/additional information. Within 24 hours of the investigational site's awareness of the event, the study site must send the Sponsor the Clinical SAE Report Form. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of EIU cases. In the rare event that the Investigational site does not become aware of the occurrence of an SAE immediately (e.g., if an outpatient study subject initially seeks treatment elsewhere), the Investigational site is to report the event immediately after learning of it as described and document the time of the investigational site's first awareness of the SAE.

For all SAEs, the Investigator is obligated to pursue and provide information to the Sponsor in accordance to the timeframes for reporting as specified above. In addition, an Investigator may be requested by the Sponsor to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a

complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject's death, a summary of autopsy findings (if available) and death certificate should be collected if permission is obtained from the subject's family. For a hospitalization, a copy of the hospital discharge summary should be requested. If obtained, these documents (with subject's personal identifiers redacted) should be forwarded to the Sponsor or its designated representative as soon as possible.

Appropriate SAE forms will be provided to the investigational site at the initiation of the study. Upon notification of an SAE at the investigational site, the Investigator or designated study site staff should call and speak to their Sponsor's study team contact immediately to initially notify them of the SAE.

Within 24 hours of awareness of the event, the Investigator or designated study site staff:

- Complete the Clinical SAE Report Form that has been provided by the Sponsor or designee with as much information as possible, however at a minimum, the subject identification number, name of the IP, SAE, and name of the reporter;
- Ensures the Investigator signs the Clinical SAE Report Form **prior to** sending it to the Sponsor;
- Scans and send the Clinical SAE Report Form to the Sponsor contacts (See Contact List or SAE Pregnancy Flow Diagram provided by the Sponsor separately) securely.

12.14. Special Situations

Special Situations (SS): Safety events that may not meet the definition of an AE; however, are required to be collected to meet Health Authority requirements. Examples include:

- Overdose of a J&J medicinal product.
- Pregnancy exposure (maternal and paternal) to a J&J medicinal product.
- Exposure to a J&J product from breastfeeding.
- Suspected abuse/misuse of a J&J medicinal product.
- Inadvertent or accidental exposure to a J&J medicinal product (including occupational exposure).
- Unexpected therapeutic or clinical benefit from use of a J&J product.
- Medication error involving a J&J medicinal product with or without patient/consumer exposure to the J&J product, (e.g., product name confusion) OR that caused an unintended effect or could cause an intended effect (e.g. adult medicine given to a young child).
- Suspected transmission of an infectious agent via a J&J product.

13. STATISTICS

The Sponsor will be responsible for the statistical analysis of study data. Detailed methodology for the statistical analysis of the data will be documented in a Statistical Analysis Plan finalized and approved prior to database lock and release of randomization codes.

13.1. Sample Size Determination

The study sample size is based on a requirement to achieve appropriate precision of estimated treatment mean differences with respect to mean change from baseline in the Nasal Congestion Severity Score (NCSS) assessed at 2, 4, 6, 8, 10, and 12 hours on Day 1. From available data on the primary endpoint [redacted] it is reasonable to assume a common standard deviation of 1.5 scale units for the three study treatments.

With this assumption, 138 completed study subjects in both compared arms implies a 90% probability that the length of a 95% confidence interval for a treatment mean difference with respect to the primary endpoint will be at most 0.75 scale units. With an assumed 9% dropout rate, 150 subjects will be enrolled in each treatment arm.

13.2. Analysis Sets

For the efficacy analyses, the Full Analysis Set will include all randomized subjects who provide a valid baseline assessment of nasal congestion severity. The safety analyses will be based on all randomized subjects who take at least one dose of treatment.

13.2.1. Secondary Endpoints

The secondary efficacy endpoints include

- Change from baseline in the NCSS averaged over assessments at 8, 10, and 12 hours.
- Change from baseline in the NCSS at 2, 4, 6, 8, 10, and 12 hours and in the morning of Day 2 (24 hours), respectively.
- Change from baseline in Sinus Pressure/Tenderness Scores averaged over assessments at 2, 4, 6, 8, 10, and 12 hours.
- Change from baseline in Sinus Pressure/Tenderness Scores at 2, 4, 6, 8, 10, and 12 hours and in the morning of Day 2 (24 hours), respectively.

13.2.2. Baseline and Demographics

Baseline and demographic characteristics will be presented by treatment group. For continuous variables, descriptive summaries will include number of subjects, mean, standard deviation, median and range (min, max). For categorical variables, the number and percent of subjects in each response category will be presented.

13.3. Efficacy Analysis

13.3.1. Primary Endpoint

The primary efficacy endpoint is the change from baseline in the nasal congestion severity score (NCSS) averaged over assessments at 2, 4, 6, 8, 10, and 12 hours on Day 1. The baseline nasal congestion score will be measured within approximately 30 minutes before the first dose.

13.3.2. Exploratory Endpoints

- Change from baseline in Head Congestion Scores averaged over assessments at 2, 4, 6, 8, 10, and 12 hours.
- Change from baseline in Head Congestion Scores at 2, 4, 6, 8, 10, and 12 hours and in the morning of Day 2 (24 hours), respectively.
- Change from baseline in Reflected Impact of Nasal / Sinus Congestion on Clear Thinking (reflected for the previous 12 hours) at 12 hour assessment
- Reflected Change in Nasal Congestion Symptoms (reflected over 12 hours after the first dose).
- Reflected Nasal Functioning (reflected over 12 hours after the first dose).
- Change from baseline in Reflected Congestion Severity (reflected for the previous 12 hours) at 12 hour assessment
- Assessment of cold severity using Wisconsin Upper Respiratory Symptom Survey-21 (reflected over 24 hours) at baseline and in the morning of Day 2 (24 hours).

13.3.3. Pharmacokinetics

Plasma concentration-time data will be subjected to a population pharmacokinetic analysis and reported separately; however, blood plasma levels will be summarized descriptively by treatment and assessment time points.

13.3.4. Psychometric Analyses

In addition to the analyses described here, the data collected in this study will also be used to evaluate the psychometric properties of the primary and secondary outcome assessments in this context of use and to perform analyses to estimate the level of change in scores that can be considered meaningful and important. Those analyses will be performed using data pooled across treatment and placebo groups. These analyses will be described in a specific psychometric analysis plan which will be finalized prior to database lock and will be reported separately.

13.3.5. Statistical Analyses

This is a Phase II, POC study and therefore the inferential statistical procedures are focused on point and interval estimation of pairwise treatment differences in the primary and secondary efficacy endpoints. However, to further aid interpretation of findings, p-values from 2-sided tests of the null hypotheses of no treatment (mean) difference will be provided in each case.

The primary analysis of the primary endpoint, which is the change from baseline in the Nasal Congestion Score (score for stuffy/congested nose averaged over assessments at 2, 4, 6, 8, 10, and 12 hours on Day 1), will be based on all randomized subjects who provides at least an assessment of nasal congestion at baseline and receives study treatment. The primary endpoint will be analyzed by an ANOVA model with treatment group, study center, and baseline nasal congestion score as factors. For subjects who dropout, their last reported congestion score before the dropout will be imputed for the remaining assessment time points.

In addition, a secondary analysis of the primary endpoint will be restricted to randomized subjects who complete all assessments of congestion for Day 1. The same statistical model will be used as in the primary analysis.

Analysis of all other secondary endpoints involving instantaneous nasal congestion scores will be performed using an ANOVA model with treatment group, study center, and baseline nasal congestion score as factors.

Analysis of secondary endpoints involving Sinus Pressure/Tenderness Scores will be performed using an ANCOVA model with treatment group and study center as factors, and baseline Sinus Pressure/Tenderness Score as a covariate.

Analysis of endpoints involving Head Congestion Scores will be performed using an ANCOVA model with treatment group and study center as factors, and baseline Head Congestion Score as a covariate.

Pairwise treatment differences in the distributions of Reflected Change in Nasal Congestion Symptoms and Reflected Nasal Functioning scores, both reflected over 12 hours after the first dose, will be analyzed using the van Elteren test stratified by center.

Pairwise treatment differences in the distributions of Change from baseline in Reflected Impact of Nasal / Sinus Congestion on Clear Thinking and Change from baseline in Reflected Congestion Severity (reflected for the previous 12 hours), will be analyzed using the van Elteren test stratified by center.

All efficacy endpoints, including the assessments of cold severity using the Wisconsin Upper Respiratory Symptom Survey (WURSS-21) at baseline and in the morning of Day 2 (24 hours), will be described by summary statistics.

Presented confidence intervals will be two-sided and have confidence level 95%. To guide interpretation p-values from 2-sided tests of the null hypotheses of either no treatment (mean) difference or no distributional difference between treatments will be provided in each case.

This is an exploratory Phase 2 POC study. Additional post-hoc analyses may be performed.

13.4. Safety Analysis

The safety analyses will be based on all randomized subjects who take at least one dose of treatment.

13.4.1. Adverse Events

The number and percentage of subjects experiencing AEs will be tabulated by treatment using the MedDRA coding dictionary. Subjects experiencing SAEs, treatment-related AEs, and who discontinued from the study due to an AE will also be presented. Treatment-related AEs will include events marked as being at least possibly related to study treatment. AEs will be presented by severity and by relation to treatment. Subjects will be counted only once for each system organ class and preferred term by selecting the most severe event.

13.4.2. Clinical Laboratory Tests

Not applicable.

13.4.3. Vital Signs

Descriptive statistics of oral body temperature, respiratory rate, heart rate, and blood pressure (systolic and diastolic) will be summarized by treatment and assessment time point, as applicable.

13.5. Interim Analysis

13.5.1. Rationale for Interim Analysis

Planned enrollment was not achieved during the 2017-2018 cold season as previously planned, necessitating continued enrollment into subsequent cold season(s) to complete the study's planned enrollment. In order to avoid exposing patients to unnecessary clinical research, an interim futility analysis will occur to assess the likelihood of a study result that would lead to an acceptable Phase III sample size estimate.

The potential acceptability of the future Phase III study will be directly proportional to the sample size/sponsor resourcing required for the study. The sponsor has not defined an acceptable sample size/resourcing limit. Therefore, the interim analysis will include three sample size thresholds.

13.5.2. Communication and Logistics

The statistical analysis of interim study data will be performed by an independent third party statistician and programmer. They will be the only people who will have access to both the subject data and the treatment assignments.

Detailed methodology for the interim statistical analysis will be documented in an Interim Statistical Analysis Plan finalized and approved prior to release of randomization codes to the independent third party.

Study data for the interim analysis will be stored in a version-controlled environment, and will not include treatment assignments. Treatment/randomization codes will be provided by the JNJ randomization administrator directly to the independent third party statistician and independent programmer who will be performing the analysis. Treatment/randomization codes will be stored in a secure area only accessible to the independent statistician and independent programmer, according to the third party SOPs.

Upon completion of the analysis, the independent third party statistician will communicate results directly and restricted (via secure email exchange) to key stakeholders within the sponsor organization, that is, the Vice President of Over-the-Counter Research & Development and the Vice President of Global Medical Affairs. These individuals may provide the results to the Chief Technology Officer of Consumer and the President of Global Franchise Organization, Worldwide Over-the-Counter Marketing. Results will not include identification of subject treatment assignments.

13.5.3. Scope

The interim statistical analysis will be an analysis of futility based exclusively on interim data on the primary endpoint, that is, the change from baseline (score improvement) in the nasal congestion severity score (NCSS) averaged over assessments at 2, 4, 6, 8, 10, and 12 hours on Day 1.

For the interim statistical analysis of the primary study endpoint, the Full Analysis Set (FAS) will include all randomized subjects who provide a valid baseline assessment of nasal congestion severity.

13.5.4. Handling of missing data and assessment time deviations

In the interim futility analysis of the primary endpoint, subjects who were withdrawn any time after the baseline NCSS assessment, will have their last reported NCSS before the dropout imputed for the remaining assessment time points during Day 1. For example, any subjects without post-baseline assessments will have their baseline values carried forward. Any intermittent missing assessments will be imputed using linear interpolation between adjacent assessments.

For time deviations in post-baseline assessment time points exceeding 10 minutes in either direction relative to target, the corresponding assessment values at the target time points will be estimated using linear interpolation. If the actual 12 hour assessment is made more than 10 minutes before the target time point, the assessment value at 12 hours will be estimated using extrapolation based on the last two assessments preceding 12 hours. The interpolated and extrapolated assessment values will be used in the statistical interim analysis.

13.5.5. Statistical methodology

The interim futility analysis will be based on an adaptation of the methodology described in [10] to the current Phase II study and its objective to serve as a basis for the planning of a confirmatory Phase III non-inferiority study involving the same three treatment groups. The adaptation will be based on the following definition of a successful outcome of a completed

Phase II study in the originally targeted 450 subjects (with 150 subjects in each treatment group):

Definition of a Successful Outcome of a completed Phase II POC (SPOC) study:

A completed Phase II study, with 450 randomized subjects enrolled in total from the two study phases, will provide estimates of the population mean differences for the primary study endpoint, [redacted] *respectively, of magnitudes such that a sample size calculation for a Phase III non-inferiority study, based on the data from the completed Phase II study, will suggest a confirmatory Phase III study of total sample size at most N, assuming an equal number of subjects allocated to the three treatment arms,* [redacted] *respectively.*

The interim analysis will evaluate futility for three (3) different suggested maximum sample sizes, N, of a confirmatory Phase III non-inferiority study: N= 1800, 2700, and 3600, respectively.

For each fixed choice of N, two conditional probabilities of a SPOC, defined above, will be calculated given interim data, corresponding to two, somewhat different, approaches to determine the size of a Phase III non-inferiority study:

a. Based on a pre-set non-inferiority margin derived from an interval estimate of half the population difference in means between [redacted] and Placebo (using data from the completed POC study), while assuming the effects of [redacted] to be the same and a required statistical power of 90%. This approach assesses the reference product effect and the resulting margin.
b. Based on a requirement to show, with 90% statistical power, that the population difference in means between [redacted] is at least as large as minus half the population difference in means between [redacted] Placebo (using data from the completed POC study). This approach assesses the effect of the test product vs. placebo and the reference.

The first preparatory step of the calculation of the conditional probability of a SPOC corresponding to A is to determine a minimal value of the pre-set margin, Δ say, that will correspond to a suggested total Phase III study sample size of at most N subjects under an assumption of a common standard deviation between the three treatment groups and a one-sided significance level of 2.5%. The common standard deviation will be estimated from a pooled variance estimate based on all evaluable interim data. Using normal approximation in the derivation,

$$\Delta = \Delta(N) = \sqrt{6} \times \sigma^* \times (z_{0.025} + z_{0.10})/\sqrt{N},$$

where σ^* is the pooled standard deviation estimate and z_α is a percentile of the standard normal distribution defined by $1 - \Phi(z_\alpha) = \alpha$.

The second approach (B) does not use a pre-set margin but is instead based on a Phase III non-inferiority evaluation in which one compares the difference in means between [redacted] to minus half the difference in means between [redacted] Placebo. In this case the sample size derivation does not assume the effects of [redacted] to be the same. With [redacted] and

$\mu_{PLACEBO}$ denoting the population primary endpoint means corresponding to the three treatments, the first preparatory step of the calculation of the corresponding conditional probability of a SPOC is to determine the minimal (population) value of [redacted] $\mu_{PLACEBO})/2$, Δ' say, for which the power to reject the null hypothesis H_0: [redacted] $\mu_{PLACEBO})/2 \leq 0$ is at least 90% with a study in at most N subjects, again under an assumption of a common standard deviation between the three treatment groups and using a one-sided significance level of 2.5%. The common standard deviation will be estimated from a pooled variance estimate based on all evaluable interim data, that is the same estimate as in the first approach will be applied. Using normal approximation in the derivation,

$$\Delta' = \Delta'(N) = 3 \times \sigma^* \times (z_{0.025} + z_{0.10}) / \sqrt{(2N)},$$

where again σ^* is the pooled standard deviation estimate and z_α is a percentile of the standard normal distribution defined by $1 - \Phi(z_\alpha) = \alpha$.

Based on the methodology outlined in [10], for a fixed maximum total sample size N, the calculations of the two conditional probabilities of a successful outcome of a completed POC study, as defined above and corresponding to A and B, are similar. With δ^* denoting the estimate from interim data of half the mean difference between [redacted] Placebo, the first conditional probability of a SPOC, corresponding to A, is given by

$$1 - \Phi((z_{0.65} - Z)/\sqrt{f})$$

with $Z = [2\times(\delta^* - \Delta)\times\sqrt{300}] / [\sigma^*\times\sqrt{(2 + i/j + j/i)}]$ and where i is the number of evaluable subjects in the Placebo arm at interim, j is the number of evaluable subjects in the [redacted] arm at interim, $f = 1 - (i+j)/300$, $\Phi(.)$ is the standard normal distribution function, z_α is the percentile defined by $1 - \Phi(z_\alpha) = \alpha$, and σ^* is a pooled standard deviation estimate based on all evaluable interim data. The use of $z_{0.65}$ in the above formula for the conditional probability corresponds to using the lower bound of a one-sided 65% confidence interval, based on the completed POC study, as an estimate for the margin in a Phase III non-inferiority study sample size calculation according to A.

Similarly for step B, with δ'^* denoting the estimate from interim data of [redacted] $\mu_{PLACEBO})/2$, the second conditional probability is given by

$$1 - \Phi((z_{0.50} - Z')/\sqrt{f'})$$

where $Z' = [(\delta'^* - \Delta')\times\sqrt{450}] / [\sigma^*\times\sqrt{(1.5 + (i+j)/k + (j+k)/4i + (i+k)/4j)}]$ with notation as above extended to: k the number of evaluable subjects in the [redacted] at interim and $f' = 1 - (i+j+k)/450$. The use of $z_{0.50} = 0$ in the above formula corresponds to using the observed point estimate of [redacted] + [redacted] $\mu_{PLACEBO})/2$, based on the completed POC study, in a Phase III non-inferiority study sample size calculation according to B.

Based on the interim data, the estimates σ^*, δ^* and δ'^* will, with obvious notation, be derived according to

$$\sigma^* = \sqrt{([(i-1) \times s^2_{Placebo} + (j-1) \times [redacted] + (k-1) \times [redacted] / (i+j+k-3))};$$

$$\delta^* = [redacted] \bar{x}_{Placebo})/2;$$

$\delta'^{*} =$ [redacted] $\bar{x}_{Placebo})/2 =$ [redacted] $_{Placebo})/2.$

13.5.6. Statistical decision rules

For each choice of N, a recommendation to stop the study for futility will be given, based on the outcome of the interim statistical analysis, if at least one of the two conditional probabilities of a successful, completed POC study is below 0.2. The only information disseminated to sponsor (see Section 0) will be in the form of a 'Yes/No' answer to the question

'Does the interim analysis outcome suggest that the current study should be stopped for futility based on the probability of a maximum tolerable Phase III non-inferiority sample size of, in total, N subjects?'.

This interim analysis is a futility analysis. To limit the risk of introducing bias in estimates based on a potential completion of the Phase II study in 450 subjects, the cut-off probability for futility used for evaluation of the conditional probabilities corresponding to the two steps, A and B, have been pre-set to a reasonably low value = 0.2. There will be no other stopping rules applied.

13.6. Data Monitoring Committee

Not applicable.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Before an investigational site can enter a subject into the study, a representative of J&J will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities the site's responsibility with regard to protocol adherence as well as the study and monitoring responsibilities of J&J or its representatives. These responsibilities will be documented in a Clinical Study Agreement between J&J and the investigator.

During the study, a monitor from J&J or representative will have regular contacts with the investigational site, for the following:

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

The monitor will be available between visits if the Investigator(s) or other staff needs information or study-related direction.

14.2. Audits and Inspections

Authorized representatives of J&J, a regulatory authority, IRB/IEC may visit the site to perform audits or inspections, including source data verification. The purpose of a J&J audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP) guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The investigator should contact their study contacts immediately if contacted by a regulatory agency about an inspection.

14.3. Institutional Review Board / Independent Ethics Committee (IRB/IEC)

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

15. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCP and all applicable regulatory requirements, J&J may conduct a quality assurance audit. Please see Section 14.2 for more details regarding the audit process.

16. DATA HANDLING AND RECORDKEEPING

16.1. Case Report Forms / Electronic Data Capture

As used in this protocol, the term CRF should be understood to refer to the EDC system.

All data will be collected on source documents by site staff first, and then recorded in an EDC system, except for the subject-completed cold symptom questionnaires. The responses to these questionnaires will be directly entered into the diary by the subject, then transcribed by the site staff into the EDC.

The EDC system is the database where pertinent study data are collected such as demography, subject randomization, efficacy assessments, AEs, and subject disposition. EDC should be completed for each enrolled subject. The completed pages of the EDC system are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of the Sponsor or appropriate regulatory authorities, without written permission from the Sponsor.

It is the PI's responsibility to ensure completion and to review and approve all information captured in the EDC. The subject's data in the EDC system must be electronically signed by the PI. These signatures serve to attest that the information contained in the EDC system is true. At all times, the PI has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered in the EDC. Subject source documents are the Investigator's/physician's subject records maintained at the study site. In cases where the source documents are the hospital or the physician's chart, the information collected in the EDC must match those charts. All final data recorded in EDC system will be copied onto files and kept by the Sponsor. A copy of these files will also be kept at the clinical site. All data recorded on source documents will be kept at the clinical site.

It is recommended that the author of an entry in the source documents be identifiable. At a minimum, the type and level of detail of source data available for a study subject should be consistent with that commonly recorded at the site. Specific details required as source data for the study will be reviewed with the PI before the study and will be described in the monitoring guidelines (or other equivalent document).

16.2. Inspection of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator agrees to keep records including the identity of all participating subjects (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

16.3. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 25 years. If it becomes necessary for J&J or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor. The Investigator must obtain Sponsor's written permission before disposing of any records, even if retention requirements have been met.

17. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this clinical study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of the Sponsor. In addition, the Sponsor retains the right to discontinue development of the study at any time.

If a study is prematurely terminated or discontinued, the Sponsor will promptly notify the Investigator. After notification, the Investigator must contact all participating subjects within two weeks. All study materials must be collected and all CRFs completed to the greatest extent possible.

18. PUBLICATION POLICY

Publication of study results by the Investigator is discussed in the Clinical Study Agreement, as appropriate. Results from this study may be published in the form of oral or written presentations at scientific meetings or as one or more peer-reviewed journal articles. In these cases, no information on individual subjects will be revealed.

19. LIST OF REFERENCES

1. Martindale - The Complete Drug Reference, accessed via Micromedex 28 March 2017
2. [redacted]
3. Hengstmann JH, Goronzy J. Pharmacokinetics of 3H-phenylephrine in man. Eur J Clin Pharmacol 1982;21:335-341.
4. [redacted]
5. Gelotte K, Zimmerman BA. Pharmacokinetics, Safety, and Cardiovascular Tolerability of Phenylephrine HCl 10, 20, and 30 mg After a Single Oral Administration in Healthy Volunteers. Clin Drug Investig 2015; 35: 547-558
6. [redacted]
7. [redacted]
8. Sanu A, Eccles R. The effects of a hot drink on nasal airflow and symptoms of common cold and flu. Rhinol 2008;46:271-275.
9. [redacted]
10. K.K. Gordon Lan and Janet Wittes: *The B-value: A Tool for Monitoring Data*. Biometrics, Vol. 44, No. 2, 1988 (pp. 579-585).

20. APPENDICES

Not applicable