The Procter & Gamble Company
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A 2-arm, randomised, single - (Investigator) blind, controlled, parallel design study in common cold sufferers experiencing nasal congestion to assess the speed of action of Vicks® VapoRub® (VVR)

Study Number: 2013118

Final Report
Date of Final Report: 17-Jun-2014

Name of the Test Drug/Investigational Product:	Vicks® VapoRub® (currently approved commercial product in the UK)
Study Initiation Date:	13-Feb-2014
Study Completion Date:	11-Mar-2014
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This study was designed and managed in compliance with the principles of Good Clinical Practice

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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	adverse event
ANCOVA	analysis of covariance
eCRF	electronic case report form
ERES	Electronic Records/Electronic Signatures
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITTS	Intent-to-treat Safety
P&G	Procter & Gamble
SAE	serious adverse event
TRP	transient receptor potential
VVR	Vicks® VapoRub®

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1. Ethics

1.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Before initiation of the trial, investigators submitted the protocol and all required information to their IEC/IRB for review and approval. The IEC/IRB used in this study was:

South East Wales Research Ethics Committee
Sixth Floor, Churchill House
17 Churchill Way
Cardiff CF10 2TW
Telephone: 029 2037 6823
E-mail: jagit.sidhu@wales.nhs.uk
Website: www.nres.nhs.uk

The Investigator had to inform the IEC/IRB regarding the completion of the trial and to provide the IEC/IRB with a summary of the trial's outcome and provide the regulatory authority(ies) with any required reports. The Sponsor was able to identify all documents (by date, version number, etc.) that the IEC/IRB reviewed and approved.

Clinical Trials Authorization was obtained from the Medicines and Healthcare Products Regulatory Agency prior to the start of the study in accordance with Part 3, Regulation 12 of the UK Statutory Instrument.

1.2. Ethical Conduct of the Study

This study was conducted in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guideline for Good Clinical Practice (GCP), 1997; applicable national laws and regulations; the ethical requirements of Directive 2001/20/EC; and the ethical principles that have their origin in the Declaration of Helsinki.

1.3. Subject Information and Consent

Before any study procedures were performed, all subjects were informed in detail about the test products to be administered and the nature of the clinical investigation, including the risks and discomforts that were to be expected. The consent form complied with all applicable regulations governing the protection of human subjects. The basic elements of informed consent are specified in the ICH Harmonized Tripartite Guideline for GCP E6 Section 4.8.10.

The Investigator obtained the IEC/IRB's written approval of the written informed consent form to be provided to the subjects. Prior to subject participation in the study, the Investigator or an authorized staff member informed subjects about the nature of the study. Subjects had the opportunity to inquire about details of the study and to decide whether to participate. Subjects were instructed that they were free to withdraw their participation in the study at any time without penalty or loss of benefits to which they are otherwise entitled. The Investigator agreed to inform subjects of new information that might be relevant to the subjects' willingness to

continue participation in the study and the Investigator's obligation to protect subject confidentiality.

The Investigator provided each subject with a copy of the signed and dated consent form and documented in the subject's source notes that informed consent was given.

A sample consent form is provided in Appendix 13.1.3.

2. Investigators and Study Administrative Structure

The study was conducted at the Common Cold and Nasal Research Centre, Cardiff University (Cardiff, United Kingdom). Professor R. Eccles was the study Coordinating Investigator. Moutaz Jawad, MD was the study Principal Investigator.

3. Introduction

Vicks® VapoRub® (VVR) is a pharmaceutical preparation containing a combination of levomenthol (2.75% w/w), eucalyptus oil (1.5% w/w), turpentine oil (5% w/w) and camphor (5% w/w) as active ingredients, and thymol, cedarwood oil, and white soft paraffin as excipients (http://www.medicines.org.uk/emc/medicine/20328/SPC). It is presented as a petroleum-based ointment (petrolatum) to be either applied topically to the chest, throat, and back or added to hot water and the aromatic vapours inhaled. When rubbed on the skin, the actives are evaporated by body temperature and inspired into the airways. The therapeutic effects are exerted by interaction of the vaporised essential oils with airway receptors, including members of the transient receptor potential (TRP) channel family (McKemy et al, 2002; Bautista et al, 2007).

The therapeutic effect of VVR is primarily experienced as the trigeminal and olfactory impact of the aromatics. It is hypothesised that this impact is experienced within minutes.

4. Study Objectives

The objective of the study was to investigate the speed of action of VVR and to provide data to design a pivotal study.

5. Investigational Plan

5.1. Overall Study Design and Plan

5.1.1. Description

This was a randomized, single - (Investigator) blind, controlled, 2-arm (Vicks® VapoRub® [VVR] vs. petrolatum), parallel design pilot study in 50 adult subjects with the common cold who were experiencing nasal congestion. This study was conducted at a single study site (Cardiff University, Cardiff, United Kingdom). Subjects were recruited from the study site's existing database of potential study participants and through local advertising using an initial telephone interview to establish whether they were suffering from a cold with nasal congestion that began less than 5 days previously. The subjects were asked to score their cold symptoms

(nasal congestion, runny nose, sore throat, sneezing) on a 4- point ordinal scale: 0 = not present, 1 = mild, 2 = moderate, 3 = severe.

The study included a single visit to the study site. After eligibility was confirmed, each subject was randomly assigned to 1 of 2 test products (VVR or petrolatum) and instructed regarding procedures to assess the test products. A nose clip was placed on the subject before entering a well-ventilated treatment room. The Investigator also wore a nose clip before entering the treatment room in order to maintain the treatment blind. The Investigator applied 7.5 g of the randomly assigned test product on the skin of the subject sequentially over the regions of the chest, throat, and back. A flannel cloth was placed over the treated area and secured loosely to allow the vapors to permeate the nose. The subject's nose clip was removed simultaneously with starting 2 stopclocks positioned in front of the subject. One stopclock was labeled with a sign with the following instruction: "Stop the clock immediately when you feel any sensation of nasal cooling." The other stopclock was labeled with a sign with the following instruction: "Stop the clock immediately when you feel any sensation of nasal decongestion." The subject was instructed to stop the specific clock when that particular sensation (nasal cooling or decongestion) was first experienced. Subjects continued the observation period until each clock was stopped or 15 minutes had elapsed (observational window) indicating the end of the test period. The Investigator removed his nose clip when both clocks were stopped or after 15 minutes had elapsed.

The complete schedule of study procedures is presented in tabular form in Section 11 Table 1. The study protocol can be found in Appendix 13.1.1.

5.1.2. Protocol Amendments

There were no amendments to this protocol.

5.2. Discussion of Study Design, Including the Choice of Control Groups

The sample size (25 subjects per arm) was based on advice obtained from the Coordinating Investigator, a recognized expert in the clinical effects of aromatic oils, that 25 subjects per arm ought to be sufficient.

As VVR's efficacy is inseparable from its aroma, it is not possible to ensure 100% blinding. Consequently, precautions were included to maximize blinding. Both subjects and qualified site personnel wore a nose clip prior to entering the treatment room and during application of test product. Subjects were requested to remove the nose clip immediately after the stop clocks were activated. Site personnel continued to wear the nose clips until the subject completed their assessment. The intent was to minimize any nasal sensation until the assessment time officially began.

This was a controlled study with petrolatum, the base for the VVR aromatic oils, as the control. This is not strictly a placebo in that the petrolatum smells lightly of oils but has no significant aromatic profile whereas VVR is highly aromatic. This approach has been used historically in VVR studies and is recognised as a limitation, but not a flaw, of design driven by the mode of action of the product.

5.3. Selection of Study Population

5.3.1. Inclusion Criteria

Subjects who met all of the following criteria were eligible to participate in the study:

a) generally healthy by report and review of medication/medical history;

b) at least 18 years of age;

c) report that they were suffering from a self-diagnosed common cold of no more than 5 days' duration;

d) report that they were suffering from at least mild nasal congestion (score of at least 1 on the 4-point ordinal scale);

e) willing and able to refrain from eating, drinking, smoking, and putting anything into the mouth for a period of approximately 1 hour;

f) willing and able to stay alert and awake for a period of approximately 1 hour;

g) if female and of child-bearing potential, had practiced abstinence or used an effective form of birth control (eg, intrauterine device, oral contraceptives, contraceptive implants or injections, diaphragm with spermicide, cervical cap, or consort use of condom) for at least 3 months before being enrolled in the study; and

h) read, understood, signed, and received a copy of the Informed Consent prior to initiation of the study procedures.

5.3.2. Exclusion Criteria

Subjects were excluded from the study if they met any of the following criteria:

a) had a clinically significant nasal abnormality (eg, deviated septum, ulcer, septal perforation, or polyp) discovered during the nasal examination at Screening;

b) had a history of clinically relevant anosmia;

c) had a history of allergy or hypersensitivity to the following ingredients: menthol, eucalyptus, turpentine, camphor, thymol, cedarwood;

d) had a history of airway disease or pronounced hypersensitivity of the airways/asthma;

e) had an oral body temperature > 100.5°F (38.1°C);

f) had used nasal decongestants (including but not limited to phenylephrine, oxymetazoline, or pseudoephedrine) in the past 24 hours;

g) had used inhaled, topical, or oral nedocromil or cromolyn sodium, tricyclic antidepressant medications, or MAO inhibitors for 14 days prior to screening;

h) had a history of alcohol or drug abuse within the past 2 years;

i) were currently enrolled in another clinical trial, or had received any other investigational drug within the past 30 days;

j) if female and of child-bearing potential, had a positive urine pregnancy test at screening or reported they were pregnant, trying to become pregnant, or lactating;

k) had a history of malignancy within the past 2 years, other than treated basal cell carcinoma;

l) had a condition (eg, history of clinically significant pulmonary, autoimmune, psychiatric, neurologic, hematologic/oncologic, metabolic, endocrine, gastrointestinal, hepatic or renal disease) or were taking a medication, wearing devices, utilizing medicated skin ointments or creams and aromatic body creams or solutions that the Investigator believed would interfere with the evaluation of the study, pose a safety risk, or confound the interpretation of the study results.

5.3.3. Removal of Patients From Therapy or Assessment

Subjects could be withdrawn from the study by the Investigator or Sponsor for any of the following reasons:

- subject did not meet enrollment criteria (inclusion/exclusion criteria);
- subject has an adverse event (AE) that warranted study discontinuation;
- subject was lost to follow-up during the study or voluntary withdrawals;
- significant protocol deviation (eg, study medication noncompliance);
- withdrawal at the Investigator's discretion.

If possible, any subject who was withdrawn from the study had, at the time of withdrawal, all exit procedures performed at the visit. The reason for study withdrawal had to be documented in the subject's source documents. In all cases, the reason for early termination had to be completely documented on the appropriate CRF and all procedures described for a subject completing the study had to be performed.

5.4. Treatments

5.4.1. Treatments Administered

Subjects received the following test products: VVR (currently approved commercial product in the UK) or petrolatum (Sonneborn Refined Products BV, Parsippany, NJ, USA). Test products (7.5 g aliquots) were repackaged into 25 g empty VVR commercial containers. Test products were applied (7.5 g sequentially over the regions of the chest, throat, and back) by designated study staff after a nose clip was placed on the subject.

5.4.2. Identity of Investigational Products(s)

All study test product was labeled with a clinical study label containing the study number and all other information required to comply with regulatory requirements. All test products were supplied by Procter & Gamble (P&G). VVR was supplied as the currently approved commercial product in the UK and included a combination of levomenthol (2.75% w/w), eucalyptus oil (1.5% w/w), turpentine oil (5% w/w) and camphor (5% w/w) as active ingredients, and thymol, cedarwood oil, and white soft paraffin as excipients. The control product was commercially available petrolatum. Both test products were contained in identical packaging.

5.4.3. Method of Assigning Subjects to Test Product Sequence

Eligible subjects were stratified by baseline nasal congestion (mild versus moderate/severe) then randomly assigned to test products (VVR or petrolatum) using a block randomization. A unique randomization number (eg, 101, 102, 103, etc) was assigned to each eligible subject.

5.4.4. Selection of Doses in the Study

The dose chosen was the currently recommended amount (7.5g) for adult use as indicated in the UK product license.

5.4.5. Selection and Timing of Dose for Each Subject

All subjects received 7.5g, control or VVR. Timing was a soon as possible after entering the treatment room.

5.4.6. Blinding

This was a single - (investigator) blind study, with limited access to the randomization code. Only the Clinical Supplies Department of P&G (Bracknell, UK) and qualified study centre designee(s) responsible for handling the study medications at the site had access to the study medication sequence and codes. The study medication codes were controlled by the Clinical Supplies Department of P&G (Bracknell, UK). The designee(s) could not be involved in any other aspects related to the conduct of the study. The study medication sequence each subject received was not disclosed to the Investigator, other study centre personnel, or other Sponsor representatives.

The study medications were contained in identical packaging and were similar with regard to color. Every effort was made to keep the subject from disclosing information about any observed study medication differences to the Investigator or designee so that the Investigator remained blinded for AE assessment.

5.4.7. Prior and Concomitant Therapy

For excluded medications prior to study start and during the study, see the inclusion/exclusion criteria (Sections 5.3.1 and 5.3.2). Subjects were instructed to contact the study staff to report any changes in medication usage during the study.

5.4.8. Treatment Compliance

The prescribed study medication dosage, timing, and mode of administration could not be changed. Any departures from the intended regimen had to be recorded and evaluated for determining compliance with dosing. Test product containers were weighed before and after test product application.

5.5. Efficacy and Safety Variables

5.5.1. Efficacy Measurements Assessed

The effects of VVR versus petrolatum on efficacy parameters were assessed using 2 stopclocks as follows. A nose clip was placed on the subject before entering a well-ventilated treatment room. The Investigator also wore a nose clip before entering the treatment room in order to maintain the treatment blind. The Investigator applied 7.5 g of the randomly assigned test product on the skin of the subject sequentially over the regions of the chest, throat, and back. A flannel cloth was placed over the treated area and secured loosely to allow the vapors to permeate the nose. The subject's nose clip was removed simultaneously with starting 2 stopclocks positioned in front of the subject. One stopclock was labeled with a sign with the following instruction: "Stop the clock immediately when you feel any sensation of nasal cooling." The other stopclock was labeled with a sign with the following instruction: "Stop the clock immediately when you feel any sensation of nasal decongestion." The subject was instructed to stop the specific clock when that particular sensation (nasal cooling or decongestion) was first experienced. Subjects continued the observation period until each clock had been stopped or 15 minutes had elapsed (observational window) indicating the end of the test period. The Investigator removed his nose clip when both clocks had been stopped or after 15 minutes had elapsed.

5.5.2. Appropriateness of Measurements

The study objective was to assess how quickly VVR exerts its clinical effects. Because VVR is a highly aromatic product whose nasal aromatic nature is integral to its efficacy and administration of the product takes some time, nose clips were employed to limit nasal sensations during the administration period and to ensure that there was a clear, unambiguous start time for the assessment of speed.

5.5.3. Safety Assessments

Safety assessments included the collection of AEs reported by the subjects or observed by the investigator or study center personnel. Subjects were instructed to report whether, since the time of the last observation or visit, they had any of the following:

- experienced any changes in well-being,
- used any new medications or supplements,
- changed medication regimens (both prescription and non-prescription), or
- been hospitalized or had any accidents.

Questions were of a general nature and should not have suggested symptoms.

When an AE was suspected, all relevant evaluations were carried out and appropriate treatment provided. Additional follow-up was performed as necessary, recorded in the subject's source documents, with the results provided to the Sponsor. Subjects who experienced any clinically significant AE remained under medical supervision until the Investigator or the Sponsor's Medical Monitor deemed the AE to be resolved, stabilized, or no longer serious enough to warrant follow-up. Laboratory values that were abnormal (whether or not they were assessed as AEs) were followed at the discretion of the Investigator and the Sponsor's Medical Monitor until resolved or stabilized.

5.6. Data Quality Assurance

The following steps were taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- Study centre initiation meeting
- Routine centre monitoring
- eCRF review against source documents
- Data management quality control checks
- Statistical quality control checks
- Continuous data acquisition and cleaning
- Internal review of data
- Quality control check of the final report

In addition, a Sponsor representative conducted periodic quality assurance audits of the study processes, including, but not limited to, clinical centre visits, laboratories, vendors and contract research organizations, the clinical database, and P&G's final study report.

5.7. Statistical Methods Planned in the Protocol and Determination of Sample Size

5.7.1. Statistical and Analytical Plans

The comparisons of interest were VVR versus petrolatum for the following endpoints:

Primary Endpoint:

- time to first experiencing sensation of nasal cooling

Secondary Endpoint:

- time to first experiencing sensation of nasal decongestion

All hypothesis tests were conducted at a type I error rate of 0.05.

Adverse Events and Other Data

Adverse events, concomitant and prior medications, protocol violations and deviations, and compliance/exposure data were to be summarized in frequency tables and/or listings. Serious procedure-related AEs with an onset prior to taking the first dose of randomized study medication were to be reported separately from those with an onset subsequent to taking the first dose of randomized study medication.

Analysis Populations

The Intent-to-treat Safety (ITTS) population was comprised of all randomized subjects who applied at least 1 dose of post-baseline test product. The ITTS population was to be used for all safety analyses.

The Per Protocol population comprised all subjects in the ITTS population who, in addition, met the following criteria:

1) were generally compliant with test product usage instructions, and
2) met key Inclusion and Exclusion criteria.

The Per Protocol population was used for the efficacy analysis.

Efficacy Analysis

Subjects who had evaluable data for the given endpoint were included in the efficacy analysis provided they met the other defined Per Protocol criteria. The following hypothesis was tested separately for each endpoint:

Null Hypothesis: The survivor function for time to first experiencing desired sensation of <*insert endpoint*> is the same for VVR versus petrolatum.

Alternative Hypothesis: The survivor function for time to first experiencing desired sensation of <*insert endpoint*> is different for VVR versus petrolatum.

Each set of hypotheses was tested using the log-rank statistic where time to desired sensation was censored at X minutes (note: 15 minutes initially). The Kaplan-Meier method was used to estimate the survivor function for time to desired sensation up to 15 minutes for each treatment. If results were significant at overall timeframe (15 minutes) then timeframe was reduced by X minutes and/or seconds to arrive at the earliest timeframe in which treatment separation occurs. Once that point was obtained no additional testing occurred for that endpoint.

5.7.2. Determination of Sample Size

The sample size (25 subjects per arm) was based on advice obtained from the Coordinating Investigator, a recognized expert in the clinical effects of aromatic oils, that 25 subjects per arm ought to be sufficient.

5.8. Changes in the Conduct of the Study or Planned Analyses

There were no changes to the planned conduct or analyses of the study.

6. Study Subjects

6.1. Disposition of Subjects

A total of 52 subjects were screened, with 2 considered screening failures for meeting exclusion criteria.

A total of 50 subjects were enrolled and randomly assigned to 1 of 2 test products (VVR, 25 subjects; petrolatum, 25 subjects). All subjects completed the study. A listing of the disposition of subjects is in Appendix 13.2.1.

6.2. Protocol Deviations

There were no protocol deviations in this study.

7. Efficacy Evaluation

7.1. Data Sets Analyzed

Fifty subjects were included in the ITTS population. All subjects had data that were evaluable for efficacy and were included in the Per Protocol population.

7.2. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics were similar between the treatment groups. Summaries of demographic characteristics, baseline assessment of cold symptoms, and baseline vital signs and anthropometric measures for all subjects are shown in Table 1, Table 2, and Table 3, respectively. A listing of the demographic characteristics for each subject is in Appendix 13.2.4.

Table 1
Summary of Demographic Characteristics

Parameter Statistic/Category	VapoRub (N=25)	Petrolatum (N=25)
Age		
n	25	25
Min-Max	18.0-24.0	18.0-24.0
Mean (SD)	20.4 (1.83)	20.1 (1.69)
Median	20	20
Sex		
Female	18 (72%)	18 (72%)
Male	7 (28%)	7 (28%)
Race		
Asian Oriental	1 (4%)	0 (0%)
Caucasian	22 (88%)	24 (96%)
Asian Indian	1 (4%)	1 (4%)
Multi-Racial	1 (4%)	0 (0%)
Ethnicity		
Hispanic or Latino	1 (4%)	0 (0%)
Not Hispanic or Latino	24 (96%)	25 (100%)

N = number of subjects within specified treatment.
n(%) = number and percentage of subjects within specified Parameter, treatment, and category.

Table 2
Summary of Baseline Assessment of Cold Symptoms

Parameter Category	VapoRub (N=25) n (%)	Petrolatum (N=25) n (%)
NASAL CONGESTION		
1-Mild	7 (28%)	7 (28%)
2-Moderate	14 (56%)	15 (60%)
3-Severe	4 (16%)	3 (12%)
RUNNY NOSE		
1-Mild	5 (20%)	7 (28%)
2-Moderate	14 (56%)	10 (40%)
3-Severe	6 (24%)	8 (32%)
SORE THROAT		
0-Not Present	6 (24%)	5 (20%)
1-Mild	7 (28%)	13 (52%)
2-Moderate	3 (12%)	5 (20%)
3-Severe	9 (36%)	2 (8%)
SNEEZING		
0-Not Present	1 (4%)	2 (8%)
1-Mild	7 (28%)	12 (48%)
2-Moderate	11 (44%)	11 (44%)
3-Severe	6 (24%)	0 (0%)

N = number of subjects within specified treatment.
n(%) = number and percentage of subjects within specified Parameter, treatment, and Category.

Table 3
Descriptive Statistics for Baseline Vital Signs and Anthropometric Measures by Treatment

Parameter Statistic	VapoRub (N=25)	Petrolatum (N=25)
Systolic Blood Pressure (mmHg)		
n	25	25
Min-Max	101.0-153.0	102.0-147.0
Mean (SD)	125.1 (13.25)	123.5 (11.59)
Median	124	122
Diastolic Blood Pressure (mmHg)		
n	25	25
Min-Max	57.0-83.0	54.0-90.0
Mean (SD)	72.4 (6.59)	70.2 (9.27)
Median	74	70
Pulse (bpm)		
n	25	25
Min-Max	54.0-90.0	48.0-98.0
Mean (SD)	69.5 (8.88)	73.9 (12.96)
Median	68	74
Respiratory Rate (rpm)		
n	25	25
Min-Max	14.0-18.0	14.0-20.0
Mean (SD)	16.0 (1.37)	16.7 (1.49)
Median	16	17
Temperature (C)		
n	25	25
Min-Max	35.5-37.2	35.5-37.4
Mean (SD)	36.3 (0.43)	36.3 (0.45)
Median	36	36
Height (cm)		
n	25	25
Min-Max	151.6-184.7	157.6-184.3
Mean (SD)	169.6 (8.44)	168.5 (8.42)
Median	169	166
Weight (kg)		
n	25	25
Min-Max	46.6-160.1	49.3-155.4
Mean (SD)	74.3 (21.40)	73.3 (22.59)
Median	69	65

7.3. Measurements of Treatment Compliance

Amount of test product applied was similar between the treatment groups (Table 4). A listing by subject of test product compliance is in Appendix 13.2.5.1.

Table 4
Summary of Dosing Amount by Treatment

Parameter Statistic	VapoRub (N=25)	Petrolatum (N=25)
Amount of Test Product Applied (grams)		
n	25	25
Min-Max	5.9-7.5	6.8-7.4
Mean (SD)	7.0 (0.32)	7.1 (0.15)
Median	7	7

N = number of subjects within specified treatment.

7.4. Efficacy Results and Tabulations of Individual Patient Data

7.4.1. Analysis of Efficacy

A listing of individual subject efficacy response data is in Appendix 13.2.6.

Primary Efficacy Assessment

The time to first experience of a sensation of nasal cooling was significantly ($p<0.001$) faster for subjects who received VVR compared to petrolatum, with median times of 23 and 99 seconds, respectively (Figure 1 and Figure 2; Table 5). VVR delivered a statistically significant sensation of nasal cooling at all times from 12 seconds to 15 minutes after application of product. The hazard ratio indicates that at any time point subjects who received VVR were approximately 4.4 times more likely to experience their first sensation of nasal cooling before subjects who received petrolatum (95% CI: 2.180, 8.728).

Figure 1
Time to First Experiencing a Sensation of Nasal Cooling

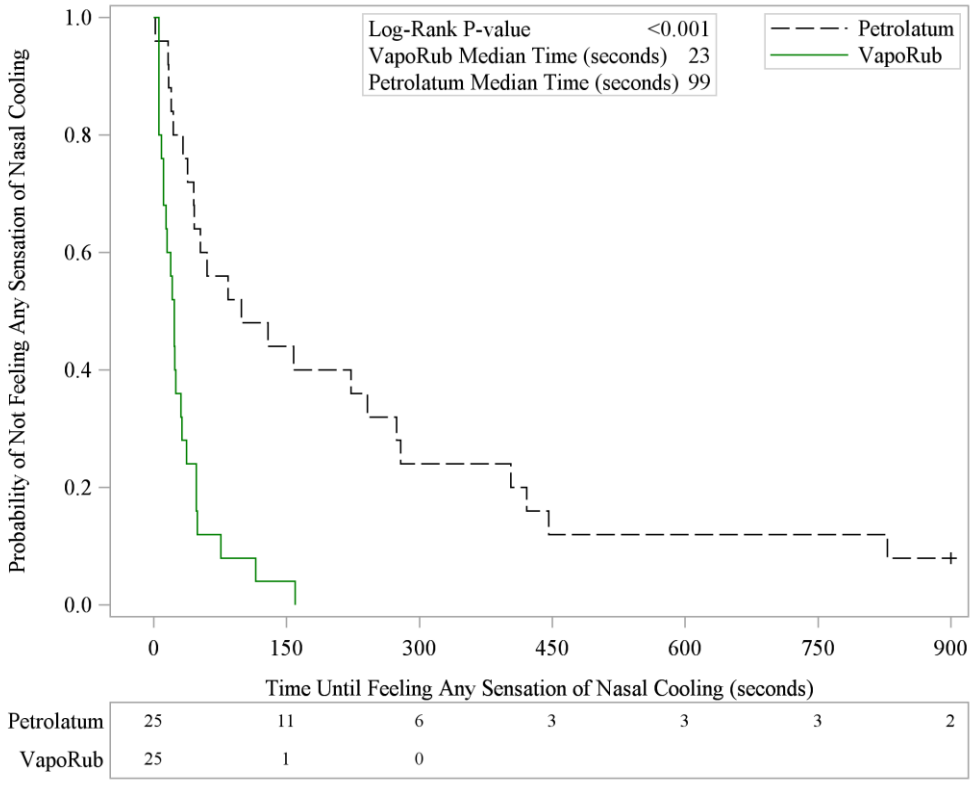


Figure 2
Median Time to First Experiencing Sensations of Nasal Cooling and Nasal Decongestion

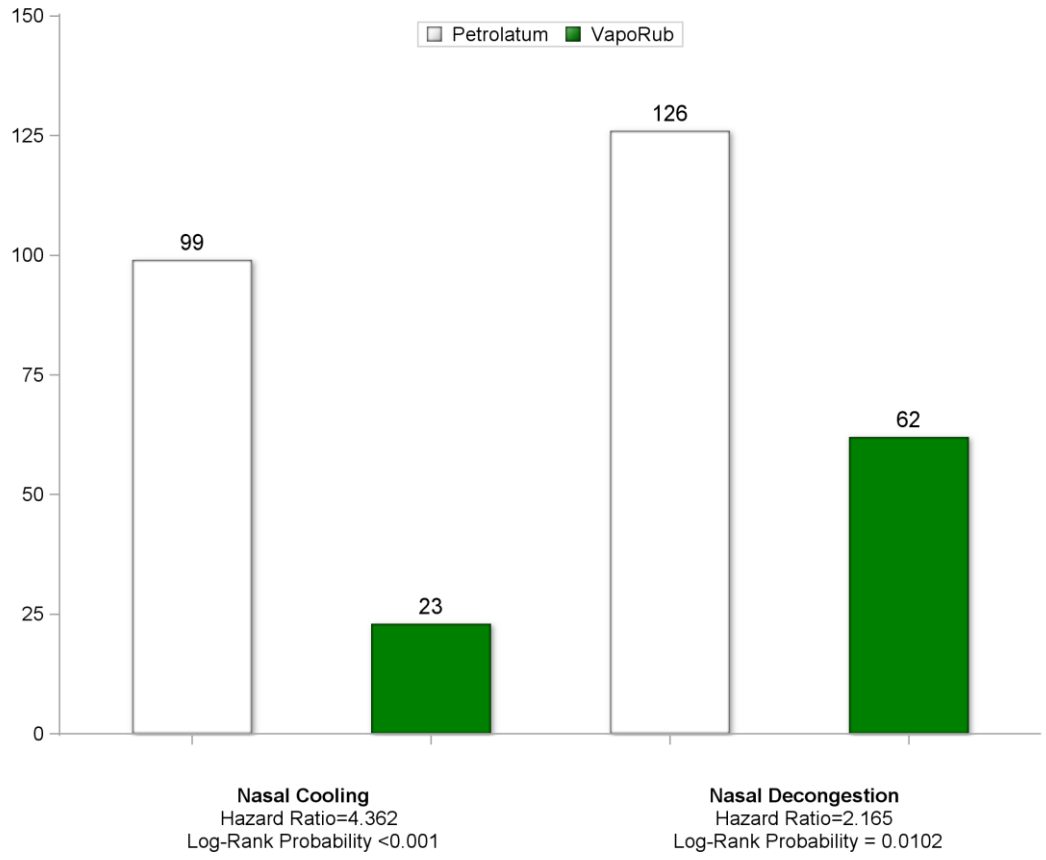


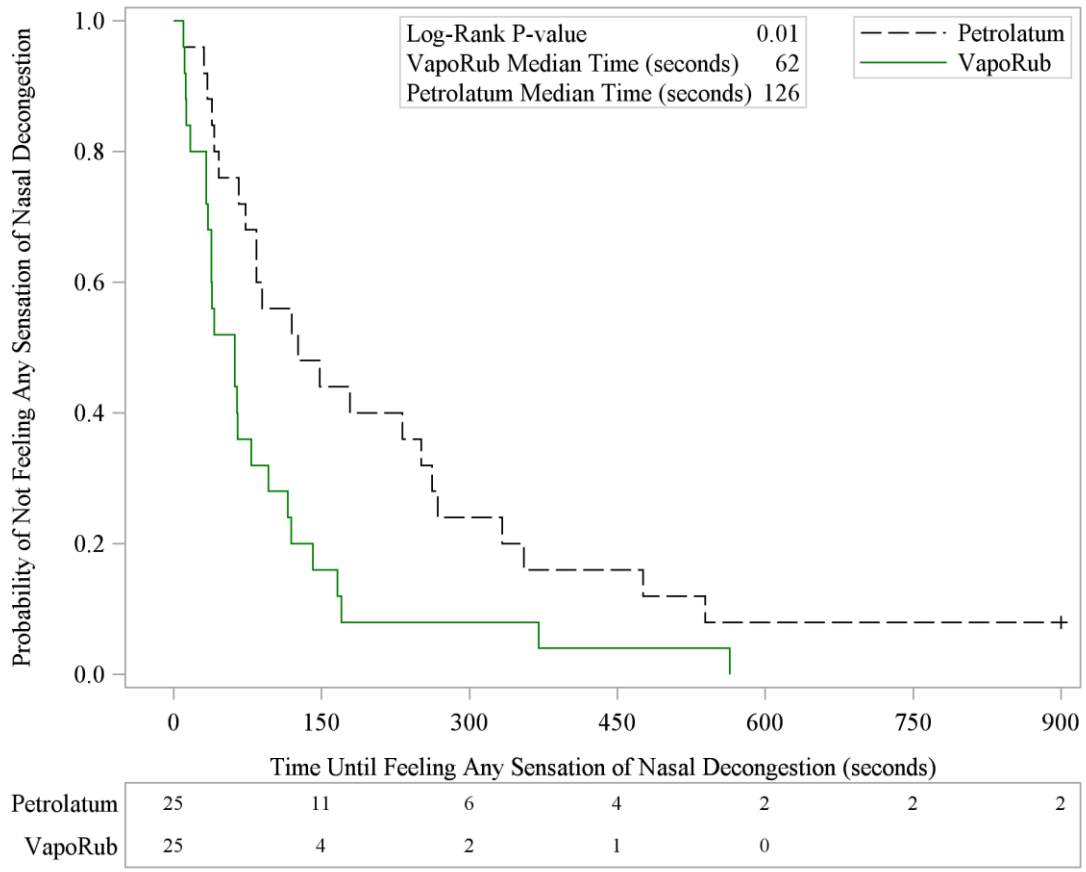
Table 5
Survival Analysis Results: Nasal Cooling and Nasal Decongestion are Censored at 15 Minutes

				Life Test		Cox Regression	
Symptom	**Treatment**	**Events**	**Censored**	**Median**	**Log-Rank P-value**	**Hazard Ratio**	**95% CI**
Nasal Cooling	VapoRub	25	0	23	<.0001	4.362	(2.180, 8.728)
	Petrolatum	23	2	99			
Nasal Decongestion	VapoRub	25	0	62	0.0102	2.165	(1.210, 3.877)
	Petrolatum	23	2	126			

Secondary Efficacy Assessment

The time to first experience of a sensation of nasal decongestion was significantly (p=0.0102) faster for subjects who received VVR compared to petrolatum, with median times of 62 and 126 seconds, respectively (Figure 2 and Figure 3; Table 5). VVR delivered a statistically significant sensation of nasal decongestion at all times from 62 seconds to 15 minutes after application of product. The hazard ratio indicates that at any time point subjects who received VVR were approximately 2.2 times more likely to experience their first sensation of nasal decongestion before subjects who received petrolatum (95% CI: 1.210, 3.877).

Figure 3
Time to First Experiencing a Sensation of Nasal Decongestion



7.4.2. Efficacy Conclusions

The time to first experience of a sensation of nasal cooling was significantly (p<0.001) faster for subjects who received VVR compared to petrolatum, with median times of 23 and 99 seconds, respectively. The time to first experience of a sensation of nasal decongestion was significantly (p=0.0102) faster for subjects who received VVR compared to petrolatum, with median times of 62 and 126 seconds, respectively.

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8. Pharmacokinetics and/or Pharmacodynamics

This section is not applicable to this study.

9. Safety Evaluation

9.1. Extent of Exposure

Amount of test product applied was similar between the treatment groups (see Section 7.3).

9.2. Adverse Events

No adverse events were reported in this study.

9.3. Clinical Laboratory Evaluation

Not applicable to this final report.

9.4. Vital Signs, Physical Findings, and Other Observations Related to Safety

Listings for medication history by subject can be found in Appendix 13.2.9.

9.5. Safety Conclusions

VVR was shown to be safe and well-tolerated in this study. No adverse events were reported.

10. Discussion and Overall Conclusions

In a population of otherwise healthy adults suffering from a self-diagnosed symptomatic common cold of no more than 5 days duration who reported at least mild nasal congestion, the speed of action of VVR was significantly faster than petrolatum with regard to time to first experience of sensations of nasal cooling and nasal decongestion. VVR was shown to be safe and well-tolerated in this study.

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11. Tables, Figures, and Graphs Referred to but not Included in the Text

11.1. Demographic Data Summary Figures and Tables

Section 11 Table 1 Schedule of Procedures		
	Visit Day	
Study Procedures	**Screening/ Baseline**	**Test Period**
Informed consent	X	
Demographic data	X	
Assessment of cold symptom severity	X	
Medical history	X	
Medication history	X	
Brief physical examination	X	
Vital signs (blood pressure, pulse, respiration rate, temperature) and height and weight	X	
Pregnancy test	X	
Inclusion/exclusion criteria	X	
Randomly assign test product		X
Weigh test product container before and after test product application		X
Apply test product and assess the speed of action of the test product		X
Test product accountability		X
Collect adverse events[a]		X
Subject accountability		X

[a] Prior to taking the first dose of study medication, **only** serious, procedure-related AEs were to be captured on source documents and the eCRF. If reported events were not serious and procedure-related, they were to be documented in the medical history. All treatment-emergent AEs (serious and non-serious) were to be captured on source documents and the eCRF.

11.2. Efficacy Data Summary Figures and Tables

Efficacy summary figures and tables are provided in Section 7.4.

11.3. Safety Data Summary Figures and Tables

This section is not applicable.

11.4. Displays of Adverse Events

There were no AEs reported in this study.

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11.5. Listings of Deaths, Other Serious and Significant Adverse Events

There were no deaths, other serious, or significant AEs reported in this study.

11.6. Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

This section is not applicable.

11.7. Abnormal Laboratory Value Listing (each patient)

This section is not applicable for this study.

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12. Reference List

Bautista DM, Siemens J, Glazer JM, Tsuruda PR, Basbaum AI, Stucky CL, et al. The menthol receptor TRPM8 is the principal detector of environmental cold. *Nature* 2007;448:204-8.

McKemy DD, Meuhausser WM, Julius D. Identification of a cold receptor reveals a general role for TRP channels in thermosensation. *Nature* 2002;416:52-8.

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13. Appendices

Appendix		Description
13.1		**Study Information**
13.1.1		Protocol and protocol amendments
13.1.2		Sample case report form
13.1.3		List of IEC's or IRB's and representative written information for patient and sample consent forms
13.1.4	§	List and description of investigators and other important participants in the study
13.1.5		Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer
13.1.6	†	Listing of patients receiving test drug(s)/investigational product(s) from specific batches, where more than one batch was used.
13.1.7		Randomization scheme and codes
13.1.8	†	Audit certificates
13.1.9	§	Documentation of statistical methods.
13.1.10	†	Documentation of inter-laboratory standardization methods and quality assurance procedures if used.
13.1.11	†	Publications based on the study.
13.1.12	†	Important publications referenced in the report.
13.2		**Subject Data Listings**
13.2.1		Discontinued subjects
13.2.2	§	Protocol deviations
13.2.3	§	Subjects excluded from the efficacy analysis
13.2.4		Demographic data
13.2.5		Compliance and/or drug concentration data
13.2.5.1		Compliance and Exposure
13.2.5.2	†	Pharmacokinetic Data
13.2.5.3	†	Bioanalytical Reports
13.2.6		Individual efficacy response data
13.2.7	†	Adverse event listings
13.2.8	†	Individual laboratory measurements by patient
13.2.9		Other Safety Listings
13.3		**Case Report Forms**
13.3.1	†	CRF's for deaths, other serious adverse events, and withdrawals for adverse events
13.3.2	†	Other CRF's submitted
13.4		**Individual Patient Data Listings**
13.4.1	†	Patient Narratives
13.5	*	**Archival Individual Patient Data Listings**

* This appendix is available upon request.
† Not applicable to this final report.
§ Incorporated in Clinical Report text.