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Official Title:	An open label, multi-center study to evaluate sensory attributes of an antihistamine product
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[1] Statistical Analysis Plan is not available for this sensory study. Statistical methods are mentioned in the Study Protocol.

1. TITLE PAGE

Protocol Title:	An open label, multi-center study to evaluate sensory attributes of an antihistamine product
Protocol Number:	21048
Amendment Number:	Not applicable
Compound Number:	BAY 762211
Study Phase:	4
Sponsor Name:	Bayer HealthCare, LLC
Legal Registered Address:	100 Bayer Boulevard Whippany NJ 07981-0915, USA

Regulatory Agency Identifier Number(s): Not applicable

Approval Date: 21-Oct-2019

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Throughout this document, symbols indicating proprietary names (®, TM) may not be displayed. Hence, the appearance of product names without these symbols does not imply that these names are not protected.

The study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Sponsor Signatory

The signatory agrees to the content of the final study protocol as presented.

PPD

PPD

PPD

10/21/19

Date

2. SYNOPSIS

An open label, multi-center study to evaluate sensory attributes of an antihistamine product		
Primary Objective : • To evaluate perception of cooling sensation of a single dose of a flavored chewable antihistamine tablet		
The Test Product that will be tested is noted below.		
Product (UI # 1613932)	**Formula / Actuator Description Identifier**	**BAY 762211**
Loratadine Chewable Tablet (10 mg) (Cool Mint)	**Drug substance** Loratadine **Excipients** Anhydrous Citric Acid Aspartame Colloidal Silicon Dioxide FD&C Blue #1 Aluminum Lake Flavor, CCI [redacted] Flavor, CCI [redacted] Magnesium Stearate Mannitol Menthol Microcrystalline Cellulose Sodium Starch Glycolate Stearic Acid	
Comparator Products	Not applicable	
Diagnosis and Main Criteria for Inclusion / Exclusion	Main Inclusion Criteria: 1. Capable of understanding and providing written informed consent and confidentiality including signatures. 2. Female or male adults aged 18 to 65 years of age inclusive (recruitment to ensure that no less than approximately 40% of each gender is represented in the study population) 3. Be in good general health 4. Previous self-reported sufferers of upper respiratory allergies who at the time of the study are either asymptomatic, symptomatic but not treating and agree to use study medication or symptomatic and treating with an allergy medicine that is not an antihistamine	

	5. Agree to not use antihistamine products 24 hours before and after the treatment (see medication exclusion list, Appendix 1) 6. Willing to comply with appropriate instructions provided to complete the study 7. Willing to avoid eating food or candy (other than crackers consumed during testing), drinking any liquid other than water, gum chewing and teeth brushing one hour prior to testing 8. Willing to follow and to adhere to the testing instructions as set forth in this protocol. Main Exclusion Criteria: **Medication use** 1. Individuals who have used oral/systemic medications 24 hours before the first administration of test product as listed in the medication exclusion, Appendix 1 2. Individuals who use medications which may influence taste perception as listed in the medication exclusion, Appendix 1 3. Individuals who have received or used an investigational new drug in the last 30 days or have been an active participant in another clinical or market research study in the last 30 days. **Medical conditions and history** 4. Women who are pregnant or thinking of becoming pregnant or are nursing. 5. Participants with congestion at the time of study visit 6. Any self-reported symptoms or conditions that may interfere with the participants ability to complete the evaluation of the product on testing day 7. Any current medical condition that in the opinion of the Investigator or designee may interfere with normal taste and/or temperature perception (e.g., active common cold, sinus infection, bronchial infection, adenoids, paresthesia etc.) 8. History of alcohol or drug abuse (self-reported) 9. History of hypersensitivity or allergic reactions to any ingredients in the test product. 10. Individuals with a history of glaucoma, liver or kidney disease, respiratory conditions such as chronic bronchitis or swallowing difficulties

	11. Individuals who are currently wearing any kind of dental braces or with dental work or have cavities and associated pain that may affect their ability to chew a tablet **Other exclusion criteria** 12. Currently working for a market research, flavor house, expert sensorial evaluator, or consumer product company; OR Close affiliation with the investigational site; e.g. a close relative of the investigator, dependent person (e.g. employee or student of the investigational site) or Bayer employee or affiliate; OR They or someone else in the household work for a market research company, an advertising agency, a public relations firm, a pharmaceutical company, as a healthcare professional, or as part of a health care practice.
Study Design	This study is an open label, multi-center study assessing the cooling attribute of a flavored antihistamine chewable tablet. The study will consist of one site visit where a single dose (10 mg loratadine chewable tablet) of study product will be administered.
Methodology	**Pre-Screening Phase (Electronic or Telephone pre-screening)** The test site will recruit participants via an IRB approved screener. Potentially eligible participants will be given an appointment time to visit the site. This Process will be 1 to 30 days prior to study start. **Note:** No recruiting will be performed unless IRB approval has been obtained. **Screening Phase (On-site screening for verification of eligibility)** • The study staff will screen potential participants to verify they meet the study's eligibility criteria. Not all participants may fulfill the inclusion/exclusion criteria, so a higher number of participants than needed will be asked to participate in the screening examinations. • After obtaining the participant's signature on the consent form, screening procedures will be performed and qualifying participants will be enrolled. • If the screening procedures start on the same day the participant signs the informed consent form (ICF), the time of the participant's signature must be recorded in the participant's file **Assessment Phase** Adequate and appropriate training will be conducted to ensure participants understand the study tasks and how to use the study scales. A nurse practitioner will be on site during the entire dosing period. **Visit 1, Day 1 (Assessment Phase)** • One test product will be provided in a dosing cup to the participant and will be asked to chew completely before swallowing. Participants cannot drink water until end of visit. • Study staff initiates timer as soon as the study medication is administered

	• Participant will be asked to indicate if he/she perceives a cooling sensation in each of the locations (mouth, nose and throat) at 10 seconds, 30 seconds and 1 minutes post ingestion of study product • After the 1 minute time point, participants will be asked to complete a brief questionnaire on the sensory attributes of the test product. Participants will be allowed four (4) minutes to complete the questionnaire. • Following the completion of the questionnaire, participants will continue to evaluate perception of cooling sensation in the mouth, nose and throat starting at the 5 minute time point and at 5 minute intervals for 60 minutes • Following completion of all study assessments, participants will be asked open ended questions which will be used for learning purposes • The study visit will last approximately 60-75 minutes. • Adverse events, if applicable, will be recorded • Participants will be reminded to report any unusual or unexpected medical changes within the 24 hour period following administration of the study product to site personnel **Follow Up Phase** • At the End of Study, if a participant has an ongoing adverse event, the adverse event will be monitored and recorded and the participant will be contacted during the following week after discharge from the study site.
Number of Participants	Approximately 400 adults (100 per location: North East, South, Midwest and West regions within the United States of America)
Primary Variable	• Agreement (strongly agree or somewhat agree) of perception of cooling sensation based on a 5 point agreement scale
Plan for Statistical Analysis	**Sensory attributes questionnaire:** The percentage of selection of the top 2 choices (strongly agree and somewhat agree) will be determined for each question. This percentage and its 95% confidence interval will be calculated, if the lower bound of the confidence interval is greater than 50%, the statistical majority of agreement will be claimed. **Time to perception of cooling and duration of cooling**: variables will be analyzed descriptively (Mean, Standard deviation, Median, Mode and Range). The mean time point at which cooling is initially perceived will be claimed as the onset of cooling. The mean time point at which cooling is perceived to last will be claimed as the duration of cooling. Participants who never reach "Yes" in the perception of cooling will be (1) imputed by the maximum study time (60 minutes), and (2) treated as censored and used Kaplan-Meyer to estimate the median time to perception of cooling.

Table of Contents

Table 1 List of Abbreviations

AE	Adverse Event
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRO	Contract Research Organization
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
OTC	Over the Counter
SAE	Serious Adverse Event
SoA	Schedule of Activities
SP	Study Protocol
SUSAR	suspected unexpected serious adverse reactions

3. INTRODUCTION

Second generation antihistamines like loratadine are used for the temporary relief of symptoms associated with upper respiratory allergies.[1] Several anti-histaminergic drugs are available as over-the-counter (OTC) drugs around the world. In general, these medications are safe and effective when used as directed. Availability as OTC allows consumers to effectively manage their symptoms by following labeled instructions without needing to consult a health care provider.[2]

In addition to efficacy benefits of an over-the-counter product, sensorial benefits may also be of importance for consumer acceptance.[3] Bayer Consumer Health has a currently approved, flavored chewable tablet that contains the antihistamine, loratadine. Participants will be recruited to participate in this study that requires taking the product and evaluating sensory attributes of the product.

4. STUDY OBJECTIVES

Primary Objective

- To evaluate perception of cooling sensation of a single dose flavored chewable antihistamine tablet

5. STUDY DESIGN

5.1 Design Overview

This study is an open label (participants blinded to brand), multi-center study assessing the sensory attributes of a flavored antihistamine chewable tablet.

The study will consist of one site visit where a single dose of study product will be administered.

Approximately 520 subjects will be screened across 4 sites in the North East, South, Midwest and West regions within the United States of America. With approximately 400 adults completing; 100 per location.

Visit 1: participants will present for an onsite screening for inclusion and exclusion criteria prior to the beginning of any product evaluation. Upon qualification and prior to participation in the study, participants will sign an informed consent form.
Qualifying participants will be instructed to chew completely before swallowing, one full dose (10 mg loratadine chewable tablet) during this visit. The study visit will last approximately 60-75 minutes.

A detailed description of study procedures and tabular schedule of evaluations will be found in Section 9.

5.2 End of study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA) (Section 9.1), including follow up if required.

Primary completion

The primary completion is defined as the date of completion of all assessments at visit 1.

6. STUDY POPULATION

6.1 Inclusion Criteria

Only participants who meet all of the following eligibility criteria will be eligible for the study:

1. Capable of understanding and providing written informed consent and confidentiality including signatures.
2. Female or male adults aged 18 to 65 years of age inclusive (recruitment to ensure that no less than approximately 40% of each gender is represented in the study population)

3. Be in good general health
4. Previous sufferers of self-reported upper respiratory allergies who at the time of the study are either asymptomatic, symptomatic but not treating and agree to use study medication or symptomatic and treating with an allergy medicine that is not an antihistamine
5. Agree to not use antihistamine products 24 hours before and after the treatment (see medication exclusion list, Appendix 1)
6. Willing to comply with appropriate instructions provided to complete the study
7. Willing to avoid eating food or candy (other than crackers consumed during testing), drinking any liquid other than water, gum chewing and teeth brushing one hour prior to testing
8. Willing to follow and to adhere to the testing instructions as set forth in this protocol.

6.2 Exclusion Criteria

Participants presenting with any of the following will not be eligible for the study:

Medication use

1. Individuals who have used oral/systemic medication (prescription or non-prescription) 24 hours before the first administration of test product, as listed in the medication exclusion Appendix 1.
2. Individuals who use medications which may influence taste perception as listed in the medication exclusion, Appendix 1
3. Individuals who have received or used an investigational new drug in the last 30 days or have been an active participant in another clinical or market research study in the last 30 days.

Medical conditions and history

4. Women who are pregnant or thinking of becoming pregnant or are nursing.
5. Participants with congestion at the time of study visit
6. Any self-reported symptoms or conditions that may interfere with the participants ability to complete the evaluation of the product on testing day
7. Any current medical condition that in the opinion of the Investigator or designee may interfere with normal taste and/or temperature perception (e.g., active common cold, sinus infection, bronchial infection, adenoids, paresthesia etc.)
8. History of alcohol or drug abuse (self-reported)
9. History of hypersensitivity or allergic reactions to any ingredients in the test product.
10. Individuals with a history of glaucoma, liver or kidney disease, respiratory conditions such as chronic bronchitis or swallowing difficulties
11. Individuals who are currently wearing any kind of dental braces or with dental work or have cavities and associated pain that may affect their ability to chew a tablet

Other exclusion criteria

12. Currently working for a market research, flavor house, expert sensorial evaluator, or consumer product company; OR Close affiliation with the investigational site; e.g. a

close relative of the investigator, dependent person (e.g. employee or student of the investigational site) or Bayer employee or affiliate; OR They or someone else in the household work for a market research company, an advertising agency, a public relations firm, a pharmaceutical company, as a healthcare professional, or as part of a health care practice.

Justification of selection criteria
The selection criteria were chosen to ensure that participants with specific risks for administration of the study drug and/or participants with conditions that may have an impact on the aims of the study are excluded.

6.3 Lifestyle/Dietary Restrictions

Participants will be restricted from eating food or candy (other than crackers consumed during testing), drinking any liquid other than water, gum chewing and teeth brushing one hour prior to testing. During testing, participants cannot drink any liquid including water, chew gum or brush their teeth until the end of the visit; otherwise, there are no lifestyle restrictions.

6.4 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

6.4.1 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to study intervention/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

A participant who, for any reason – e.g., failure to satisfy the selection criteria – terminates the study before the time point used for the definition of "dropout" is regarded a "screening failure". A participant who discontinues study participation prematurely for any reason is defined as a "dropout" if the participant has already been administered at least one dose of the study medication.

Individuals who do not meet the criteria for participation in this study (screen failure) may/may not be rescreened, with the following exceptions:

- The participant had successfully passed the screening procedures, but could not start subsequent treatment on schedule.
- Initial screening occurred too early to complete the required washout period after prior therapy.
- The inclusion/exclusion criteria preventing the participant's initial attempt to participate have been changed (via protocol amendment).

In any case, the investigator has to ensure that the repeated screening procedures do not expose the participant to an unjustifiable health risk. Also, for re-screening, the participant has to re-sign the

informed consent form, even if it was not changed after the participant's previous screening. Rescreened participants should be assigned a new participant number.

6.4.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or at the request of their legally acceptable representative, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- A participant may be withdrawn from the study at the specific request of the sponsor and in liaison with the investigator (e.g. obvious non-compliance, safety concerns).
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the Schedule of Activities (SoA). See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

6.4.3 Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered lost to follow up.

6.5 Replacement

Participants who drop out will be replaced by another participant who will qualify on inclusion and exclusion criteria.

6.6 Participant Identification

Each participant is identified by the study site's unique participant identification (SID) code. After informed consent/assent procedure every participant is given a screening number (SNR). Following assessment of inclusion and exclusion criteria, participants who meet the entry criteria will be sequentially assigned to a three-digit number in ascending order.

At the beginning of screening every participant is given a participant number (9 digit number consisting of: Digits 1 to 2 = Country code *(Code 14 is the U.S. country code)*

Digits 3 to 5 = Center number within the country *(Code 001 for first center, 002 for second center and so on)*

Digits 1 to 5 = Trial unit (*For the first site, the center/trial number is 14001 which consists of the country code and the center number.)*

Digits 6 to 9 = Current patient/Participant number within the center (*Participant numbers are the last four digits of the nine digit participant identification. First participant number at the first center is 160010001; second participant number is 160010002 and so on, which includes the country code, center number, and participant number. Participant numbers and screening numbers are the same number.*

7. TEST PRODUCTS

Test Products to be Administered/Tested

There is one test product to be administered/tested in this study:

Table 2: Test Product

Product (UI Number: 1613932)	**Strength**	**Dosage Form or Quantity**	**Route of Administration**
Loratadine Chewable Tablet	10 mg	1 Chewable Tablet*	Oral
*Each tablet to be chewed completely before swallowing. Participants are not allowed to drink water until the end of the visit			
Excipients (identification of potentially allergenic compounds may have to be considered)			
Anhydrous Citric Acid Aspartame Colloidal Silicon Dioxide FD&C Blue #1 Aluminum Lake Flavor, CCI [redacted] Flavor, CCI [redacted] Magnesium Stearate Mannitol Menthol Microcrystalline Cellulose Sodium Starch Glycolate Stearic Acid			

7.1 Identity of Test Product

All test products will be labeled according to the requirements of local law and legislation. Label text will be approved according to the sponsor's agreed procedures, and a copy of the labels will be made available to the study site upon request.

All study drugs will be stored at the investigational site in accordance with GCP and GMP requirements and the instructions given by the clinical supplies department of the sponsor (or its affiliate/CRO), and will be inaccessible to unauthorized personnel. Special storage conditions and a complete record of batch numbers and expiry dates can be found in the Sponsor's study file; the site-relevant elements of this information will be available in the investigator site file. On the day of receipt, the responsible site personnel will confirm receipt of study investigational products in writing. The personnel will use the study investigational products only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, return and destruction (if any) of the study drug must be properly documented according to the sponsor's agreed and specified procedures.

7.2 Test Product Assignment

The sample will be evaluated in a single monadic way (single product is rated by respondents), in a non-randomized fashion. The test produce to be evaluated will be blinded to the participants but not the site staff.

7.3 Administration

Regarding amount, route / mode of administration, formulation(s) and duration of testing, refer to Section 7

Each qualified participant will assess one (1) chewable tablet during each of his/her visit. Each participant will be at the site for approximately 60-75 minutes.

7.4 Blinding

As this is a single monadic study, the study will be performed in an open label design because the site technician will dispense the chewable tablets in dosing cups and then provide to test participants. The participants will have a chance to visually inspect the product prior to administration and will be blinded to brand.

7.5 Test Product Logistics and Accountability

All test products will be stored at the investigational site as per labeling requirements and the instructions given by the trial supplies department of the sponsor (or its affiliate/CRO), and will be inaccessible to unauthorized personnel. On the day of receipt, the responsible site personnel will confirm receipt of test product in writing. The personnel will use the test product only within the framework of this study and in accordance with this protocol. Receipt, distribution, return and destruction (if any) of the test product must be properly documented according to the sponsor's agreed and specified procedures.

7.6 Test Product Compliance

A member of the investigator's team will monitor the administration of the study product. This person(s) will ascertain and document that the participant receives the test product as planned.

8. NON-STUDY THERAPY

At the screening, potential participants will be asked questions from the health eligibility case report form (CRF) that verifies each participant meets the inclusion/exclusion criteria and qualifies for the study.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Participants should not use antihistamine products 24 hours before and after the treatment

9. PROCEDURES AND VARIABLES

9.1 Tabular Schedule of Evaluations

	Pre- Study (-30 Day to -1 Day)	Visit 1 (Day 1)										
		Baseline	10 s.	30 s.	1 min.	(4 min interval)	5 min.	10 min.	15 min.	…*	60 min.	End of Study and Follow-up
Pre-Screening	X											
Informed Consent		X										
Medical/Medication History		X										
Demographics		X										
Verification of Inclusion & Exclusion Criteria		X										
Allergy Profile Questionnaire		X										
Test Product Administration		X										
Cooling Time Point Assessment			X	X	X		X	X	X	X	X	
Sensory Attributes Questionnaire						X						
Open Ended Questions												X
Adverse Event Monitoring		X	X	X	X	X	X	X	X	X	X	X‡

(…)* Time points are at 5-minute intervals up to the last time point.

‡At the End of Study, if a participant has an ongoing adverse event, the adverse event will be monitored and recorded and the participant will be contacted during the following week after discharge from the study site.

s= seconds, min= minutes

9.2 Visit Description

9.2.1 Screening

Pre-Screening Phase

In this study, the test site will recruit participants via an IRB approved screener. Potentially eligible participants will be given an appointment time to visit the site. This process will be 1 to 30 days prior to study start.

Screening Phase

Note: No screening procedures may be performed unless written informed consent has been obtained. During the screening period, the study staff will screen potential participants to verify they meet the study's eligibility criteria. Not all participants may fulfill the inclusion / exclusion criteria, so a higher number of participants than needed will be asked to participate in the screening examinations. If the (first) screening procedures start on the same day the participant signs the informed consent form/assent (ICF), the time of the participant's signature must be recorded in the participant's file.

After obtaining the participant's signature on the consent form, the below listed screening procedures will be performed and the respective results will be assessed on the day of the first study drug administration:

- allocation of participant identification (see Section 6.6)
- demographic data
- review eligibility
- questioning for special behavior (e.g., eating food or candy, chewing gum, or brushing teeth within one (1) hour prior to enrollment on testing day and not willing to abstain from this at least 1 hour prior to testing)
- participation in previous research studies

No participant will be assigned a participant number unless adherence to all selection criteria as given in Section 6.1 and Section 6.2 is established.

9.2.2 Pre-dose (relative time: Day 1)

Participants will arrive at the study site for their scheduled study visit at the designated time preceding study drug administration. The following measures / actions will be carried out:

- Informed consent
- Review of inclusion- / exclusion criteria
- Allergy Profile Questionnaire

9.2.3 Randomization

No randomization schedule will be used.

9.2.4 Treatment

Treatment / Assessment Phase

Prior to each assessment, adequate and appropriate training will be conducted to ensure participants understand the task and how to use the study scales. An appropriate nurse practitioner will be on site during the entire dosing period.

Visit 1 (Day 1)

- One test product will be provided in a dosing cup to each participant who will then be asked to completely chew completely before swallowing. Participants cannot drink water until end of visit.
- Study staff initiates timer as soon as the study medication is administered
- Participant will be asked to indicate on the case report form (CRF) if he/she perceives a cooling sensation in the mouth, nose and throat at 10 seconds, 30 seconds and 1 minutes post ingestion of test product
- After the 1-minute time point, participants will be asked to complete a brief questionnaire on the sensory attributes of the test product. Participants will be allowed four (4) minutes to complete the questionnaire.
- Following the completion of the questionnaire, participants will continue to evaluate perception of cooling sensation in the mouth, nose and throat at 5 minute intervals, starting at the 5 minute time point for 60 minutes
- Following completion of all study assessments, participants will be asked open ended questions which will be used for learning purposes
- Adverse events, if applicable, will be recorded
- Participants will be reminded to report any unusual or unexpected medical changes within the 24 hour period following administration of the study medication to site personnel

Follow- Up

At the End of Visit 1, if a participant has an ongoing adverse event, he/she will be contacted during the following week after discharge from the study site.

9.3 Population Characteristics

9.3.1 Demographics

The following information will be collected for the Demographics

- Year of birth
- Sex

- Race/ethnicity

9.3.2 Medical History

Medical history findings (i.e. previous diagnoses, diseases or surgeries) meeting all criteria listed below will be collected as available to the investigator:

- Start before signing of the informed consent
- Considered relevant for the participant's study eligibility.

Detailed instructions on the differentiation between (i) medical history and (ii) adverse events can be found in Section 9.5.1.

9.3.3 Allergy Profile Questionnaire

The following questionnaire will be completed by subjects prior to dosing.

Allergy Profile Questionnaire

1. What type of allergies have you experienced in the last 12 months? (Select all that apply)

   a. Seasonal allergies

   b. Dust or dust mite allergies

   c. Pet/ animal allergies

   d. Mold

   e. Other _____

2. CCI [redacted]

3. CCI [redacted]

9.4 Study Assessment

The following study specific assessments will be performed by the participants during this study.

9.4.1 Cooling Time Point Assessment

Participants will be instructed to complete as follows:

“Please indicate at each time point whether you perceive a cooling sensation in the mouth (1), nose (2), throat (3) or (4) No Sensation Felt.

Time	Cooling in the mouth (1)	Cooling in the nose (2)	Cooling in the throat (3)	No Sensation Felt (4)
Immediate (10 seconds)				
30 seconds				
1 minute				
Complete the sensory attributes questionnaire (see questionnaire below)				
5 minutes				
10 minutes				
15 minutes				
20 minutes				
25 minutes				
30 minutes				
35 minutes				
40 minutes				
45 minutes				
50 minutes				
55 minutes				
60 minutes				

9.4.2 Sensory Attributes Questionnaire

Participants will be instructed to complete the questionnaire as following:

“Please indicate to what level you agree or disagree with the corresponding statement:”

Question	**Strongly agree (5)**	**Somewhat agree (4)**	**Neither agree nor disagree (3)**	**Somewhat disagree (2)**	**Strongly disagree (1)**
The product provides a cooling sensation					
The product provides a cooling sensation in the mouth					
The product provides a cooling sensation in the nose					
The product provides a cooling sensation in the throat					
The product provides a refreshing sensation					
The product provides a refreshing sensation in the mouth					
The product provides a refreshing sensation in the nose					
The product provides a refreshing sensation in the throat					
The product tastes great					
The product experience was enjoyable					

I like the flavor sensation of the product					
The product feels soothing on the throat					
The sensory experience is unique for an allergy medicine					
The cooling sensation is refreshing					

9.4.3 CCI [redacted]

9.5 Adverse Events

9.5.1 Definition if AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, “lack of efficacy” or “failure of expected pharmacological action” also constitutes an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant’s condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition.

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

9.5.2 Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

- The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

9.5.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is not acceptable for the investigator to send photocopies of the participant's medical records in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

- The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:
- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. • The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment. • For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission** of the SAE data. • The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.
Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to sponsor contact within 24 hours of receipt of the information.

9.5.4 Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the signing of the informed consent form (ICF) OR until the follow-up visit at the time points specified in the SoA.

All AE will be collected from the signing of the ICF until at the time points specified in the SoA .

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstances should this exceed 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

9.5.5 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.

9.5.6 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met. See section 9.5.4 for reporting time periods. Investigator should notify the sponsor by sending the completed SAE forms to:

PPD or Fax: PPD

- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators, as applicable.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigational Product information and will notify the IRB/IEC, if appropriate according to local requirements.

9.5.7 Pregnancy

The investigator must report to the sponsor any pregnancy occurring in a female study participant during her participation in this study. The outcome of the pregnancy should be followed up carefully, and any outcome of the mother and the child at delivery should be reported.

For all reports, the forms provided are to be used. The investigator should submit them within the same timelines as an SAE. Send the completed SAE forms to:

PPD or Fax: PPD

9.5.8 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

The following events are common in participants with upper respiratory allergies

- Runny nose
- Sneezing
- Itchy, watery eyes
- Itching of the nose or throat
- Nasal congestion

Although the study drug contains an active ingredient approved for all the above listed symptoms (except nasal congestion), onset of relief of symptoms may or may not be achieved prior to the conclusion of the study assessment. Given that this study is not designed to assess efficacy and because these events are typically associated with the condition under study, they do not qualify as an AE.

10. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

10.1 General Considerations

All statistical analyses will be conducted using SAS. Missing data will not be imputed.

10.2 Analysis Sets

All participants who have an evaluation data for study medication will be included into the statistical analysis of the primary parameter.

Safety Population
Any participant who receives the study medication will be included for the analyses of adverse events.

10.3 Variables and Planned Statistical Analyses

Variables

Primary Variable

- Agreement (strongly agree or somewhat agree) of perception of cooling sensation based on a 5 point agreement scale

Adverse events will be collected and assessed by the investigator.

Statistical and Analytical Plans

Questionnaire: The primary variable of interest will be analyzed by determining the percentage of selection of the top 2 choices (strongly agree and somewhat agree). This percentage and its 95% confidence interval will be calculated, if the lower bound of the confidence interval is greater than 50%, the statistical majority of agreement will be claimed. Other secondary variables of interests from the questionnaire will be analyzed in the same manner as the primary variable.

Time to perception of cooling and duration of cooling: These secondary variables will be analyzed descriptively (Mean, Standard deviation, Median, Mode and Range). The mean time point at which cooling is initially perceived will be claimed as the onset of cooling. The mean time point at which cooling is perceived to last will be claimed as the duration of cooling.

Participants who never reach “Yes” in the perception of cooling will be (1) imputed by the maximum study time (60 minutes), and (2) treated as censored and used Kaplan-Meyer to estimate the median time to perception of cooling.

10.4 Determination of Sample Size

The sample size of 400 participants was based on accepted industry standards for sensory studies.

11. DATA HANDLING AND QUALITY ASSURANCE

11.1 Data Recording

The data collection tool for this study will be questionnaires.

Source Documentation

The site must implement processes to ensure availability of all required source documentation.

It is the expectation of the sponsor that all data entered into the CRF has source documentation available at the site.

It is the expectation of the sponsor that all data entered into the CRF has source documentation available at the site except for the data listed below which will be entered directly into the CRF; thus, these CRF data will be the source and no additional source documentation will be available.

11.2 Data Quality Assurance

- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors may perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 10 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

11.3 Monitoring

In accordance with applicable regulations, and sponsor's/CRO's procedures, monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and sponsor's requirements. When reviewing data collection procedures, the discussion will also include identification and documentation of source data items.

The sponsor/designee will monitor the site activity to verify that the:

- Data are authentic, accurate and complete.
  Supporting data may be requested (example: blood glucose readings to support a diagnosis of diabetes).
- Safety and rights of participants are being protected
- Study is conducted in accordance with the currently approved protocol
  (including test product being used in accordance with the protocol)
- Any other study agreements and all applicable regulatory requirements are met.

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

11.4 Data Processing

Data will be collected as described in Section 11.1. Data management will be performed in accordance with applicable sponsor's/CRO's standards and data cleaning procedures.

As applicable for data coding (e.g. AEs, medication), internationally recognized and accepted dictionaries will be used.

11.5 Missing Data

Any missing data will be left as such.

11.6 Audit and Inspection

To ensure compliance with regulatory requirements, a member of the sponsor's (or a designated CRO's) quality assurance unit may arrange to conduct an audit to assess the performance of the study at the study site and of the study documents originating there. The investigator/institution will be informed of the audit outcome.

In addition, inspections by regulatory health authority representatives and IEC(s)/IRB(s) are possible. The investigator should notify the sponsor immediately of any such inspection.

The investigator/institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any issues. Audits and inspections may occur at any time during or after completion of the study.

12. PREMATURE TERMINATION OF THE STUDY

The sponsor has the right to close this study at any time. The investigator has the right to close his/her center at any time.

If the study is to be closed for any reason, the following applies:

- Closures should occur only after consultation between involved parties. Final decision on the closure must be in writing.
- All affected institutions (e.g. IEC(s)/IRB(s); competent authority(ies); study center; head of study center) must be informed as applicable according to local law.
- All study materials (except documentation that has to remain stored at site) must be returned to the sponsor. The investigator will retain all other documents until notification is given by the sponsor for destruction.
- In the event of a partial study closure, ongoing participants, including those in post study follow-up, must be taken care of in an ethical manner.

Details for individual participant's withdrawal can be found in Section 6.4.2

13. ETHICAL AND LEGAL ASPECTS

13.1 Investigator(s) and Other Study Personnel

Sponsor's Study Medical Expert

PPD
Bayer HealthCare Consumer Care
100 Bayer Boulevard
Whippany, NJ 07981
Email: PPD
Phone: PPD

PPD
Bayer HealthCare Consumer Care
100 Bayer Boulevard
Whippany, NJ 07981
Email: PPD
Phone: PPD

All other study personnel not included in this section are identified in a separate personnel list (not part of this study protocol) as appropriate. This list will be updated as needed; an abbreviated version with personnel relevant for the centers will be available in each center's investigator site file.

Whenever the term 'investigator' is noted in the protocol text, it may refer to either the principal investigator at the site, or an appropriately qualified, trained and delegated individual of the investigational site.

The principal investigator of each center must sign the protocol signature page and must receive all required external approvals (e.g. health authority, ethics committee, sponsor) before participant recruitment may start at the respective center. Likewise, all amendments to the protocol must be signed by the principal investigator and must have received all required external approvals before coming into effect at the respective center.

13.2 Funding

Funding

This study will be funded by its sponsor.

13.3 Ethical and Legal Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by:

- The guiding principles detailed in the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines,
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable local law(s) and regulation(s).

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties. Any deviations from the protocol must be explained and documented by the investigator.

The protocol, protocol amendments, ICF, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/IEC and all other applicable local regulations.

Details on discontinuation of the entire study or parts thereof can be found in Section 0.

13.4 Participant Information and Consent

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative. .

Participants who are rescreened are required to sign a new ICF.

13.5 Data Protection

- Participants will be assigned a unique identifier. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

13.6 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

13.7 Compensation for Health Damage of Participants / Insurance

The sponsor maintains product liability insurance, if required, for this study in accordance with the laws and regulations of the country in which the study is performed.

14. APPENDIX: MEDICATION EXCLUSION LIST

Individuals who have used the following medications 24 hours before the first administration of test product should be excluded

- Amiodarone (Cordarone, Pacerone)
- Carbamazepine (Tegretol, Tegretol-XR, Epitol, Equetro)
- Cimetidine (Tagamet)
- Ketoconazole (Nizoral)
- Pitolisant (Wakix)
- Potassium Citrate (Urocit-K)

To be included in the study, subjects must agree not to use any antihistamine products 24 hours before and after treatment. The following are examples of commonly used antihistamine containing products:

Single ingredient oral antihistamine medications

- Diphenhydramine (Benadryl, Benadryl Allergy)
- Chlorpheniramine (Chlor-Trimeton)
- Doxylamine (Unisom)
- Cetirizine (Zyrtec)
- Fexofenadine (Allegra Allergy)
- Loratadine (Claritin, Alavert)
- Levocetirizine (Xyzal)
- Clemastine (Tavist Allergy)

Antihistamine containing oral combination medications

- Chlorpheniramine/pseudoephedrine
- Loratadine/pseudoephedrine (Claritin D)
- Cetirizine/pseudoephedrine (Zyrtec D)
- Fexofenadine/pseudoephedrine (Allegra D)

Antihistamine nasal sprays

- Azelastine (Astelin, Astepro)
- Olapatadine (Patanase)

Antihistamine containing oral cough and cold combination medications

- Note: Several cough and cold combination medications are available on the market, some, which contain antihistamines, and some, which do not. A review of the Drug Facts Label will be required to determine which products contains an antihistamine.

Individuals who use any of the following medications which may influence taste perception are excluded from the study:

- Acetazolamide (Diamox Sequels)
- Cisplatin (Platinol-AQ)
- Eszopiclone (Lunesta)
- Topiramate (Topamax, Topiragen, Trokendi XR, Quedexy XR)
- Captopril (Capoten)
- Lithium (Eskalith, Eskalith-CR, Lithobid)
- Procainamide (Procanbid, Pronestyl, Pronestyl-SR)
- Terbenafine (Lamisil, Lamisil AT, Terbinex)
- Amiodarone (Cordarone, Pacerone)

15. REFERENCE LIST

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3. Liu, Fang et al. “Patient-centred pharmaceutical design to improve acceptability of medicines: similarities and differences in paediatric and geriatric populations.” Drugs vol. 74,16 (2014): 1871-1889.