# A PLACEBO-CONTROLLED, DOUBLE-BLIND, RANDOMIZED, PARALLEL GROUP PILOT STUDY TO EVALUATE THE EFFICACY OF DEXTROMETHORPHAN HYDROBROMIDE ON ACUTE COUGH IN A PEDIATRIC POPULATION

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|---|---|
| **Compound:** | PF-02450388 |
| **Compound Name:** | Dextromethorphan Hydrobromide |
| **United States (US) Investigational New Drug (IND) Number:** | CCI |
| **European Clinical Trials Database (EudraCT) Number:** | Not applicable |
| **Protocol Number:** | A6531002 |
| **Phase:** | 4 |

## Document History

| Document | Version Date | Summary of Changes and Rationale |
|---|---|---|
| Original protocol | 18 Nov 2015 | Not applicable (N/A) |
| Amendment #1 | 04 Feb 2016 | The following changes were made based on comments and recommendations during and after the Investigator's Meeting (15-16 Jan 2016):<br>• Typos and other minor errors were corrected.<br>• Modified the time of dosing of the single-blind liquid oral confection from before approximately 11:30 am to '*recommended to be* before 11:30 am'.<br>• Modified the time of first dose of investigational product from before approximately 3:00 pm to '*recommended to be* before 3:30 pm'.<br>• A clarification was made that, although not encouraged, to allow the parent/legally acceptable representative some flexibility regarding the timing of the second dose, the second dose may be taken as early as 4 hours post-Dose 1, but not earlier.<br>• A clarification was made that height and weight will only be assessed at Screening, and not at Visit 4; the superscripted footnote text in Table 2 was reordered accordingly.<br>• Procedures and instructions were added for an Early Termination Visit for subjects who discontinue early from the study.<br>• Lifestyle Assessments were deleted from the Post Study Follow-Up Visit (Day 18).<br>• A clarification was made that subjects vomiting after the administration of Dose 1 at the clinic will not be re-dosed. In addition, it was clarified that all the subsequent clinical procedures and subsequent dosings should be continued and performed as described in the protocol.<br>• Modified the time of first dose of investigational product from before approximately 3:00 pm to before 3:30 pm. |

| Document | Version Date | Summary of Changes and Rationale |
|---|---|---|
| | | • Inclusion Criterion #6, regarding excluded medications, was clarified as follows:<br>• Ear drop antibiotics will not be allowed; ocular antibiotics and local cream/ointment antibiotics will be allowed.<br>• Inhaled glucocorticosteroids will not be allowed.<br>• Intranasal saline sprays, inhalations or washes will be allowed.<br>• Bronchial hyperresponsiveness was added to the various exclusion criteria regarding common clinical characteristics/conditions to be excluded:<br>  • Exclusion Criterion #1;<br>  • Exclusion Criterion #3;<br>  • Exclusion Criterion #5.<br>• Exclusion Criterion #6 was modified to specify fever greater than 39ºC (102ºF oral temperature) *at the time of screening*.<br>• Exclusion Criterion #10 was clarified regarding initial and repeat blood pressure readings.<br>• Exclusion Criterion #15 was modified regarding washout periods of excluded medications:<br>  • Added a new Bullet #2, excluding ear drop antibiotics with a 5-day washout;<br>  • Added a new Bullet #4, excluding inhaled glucocorticosteroids as ever used, and with no elimination half-life;<br>  • Bullet #10 was deleted, already covered in previous Bullet #5;<br>  • Bullet #21 was rewritten to only include nasal glucocorticosteroids, since inhaled glucocorticosteroids are already covered in previous Bullet #4.<br>• Exclusion Criterion #17 was revised by deleting the word "significant" from "…*or been exposed to significant secondhand smoke…*". |

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| | | • Exclusion Criterion #18 regarding consumption of alcohol was deleted.<br>• A new Exclusion Criterion #19 was added to exclude siblings from participating in the study contemporaneously.<br>• The randomization criteria were numbered, as opposed to a bulleted list.<br>• Section 5.3 Subject compliance, simplified the language regarding the assessment subject's compliance with investigational product.<br>• Deleted all references to 'oz' and 'teaspoons' throughout the protocol, using mL instead:<br>• Section 5.7 Investigational Product Accountability was modified:<br>• Clarified that subject diary dosing entries will also be reviewed as part of subject compliance.<br>• Added simplified language regarding the assessment investigational product accountability.<br>• The following modifications were made to Section 8.4, Medication Errors:<br>  • Bullet describing mediation errors was modified to include acetaminophen (APAP) provided by the sponsor as a permitted concomitant medication if required for headache, fever and/or body aches and pains associated with the common cold.<br>  • Non-templated language describing overdoses was deleted.<br>• Changed "*parent/legal guardian*" to "*parent/legally acceptable representative*" throughout the document.<br>• Added pictures to Appendix 4 and 5. |

| Document | Version Date | Summary of Changes and Rationale |
|---|---|---|
| Amendment #2 | 23 Mar 2016 | The following changes were made to the protocol based on FDA recommendation, and additional revisions were requested from investigative sites for increased study flexibility without affecting the integrity of the study. In addition, the dosing time windows for evening and morning dosing are shortened from 2 hours to 30 minutes before bedtime or after waking, respectively.<br>• The primary endpoint is 24-hour cough count, and the key secondary endpoint is cough count during the first dosing interval on Day 1.<br>• A justification was added to support the safety of DXM should the 15 mg dosage be administered with a 4-hour interval between doses 1 and 2 on Day 1.<br>• The Day 18 phone call to assess for subject safety was extended to Day 18 + up to 3 days.<br>• Subject bronchodilator or inhaled glucocorticoid use is prohibited for a 6-month period prior to screening.<br>• Bronchial hyperresponsiveness was removed as an exclusion criterion for this protocol. Prohibited bronchodilator and inhaled glucocorticoid use serves as a surrogate for the measurement of bronchial hyperresponsiveness.<br>The following change was made to the dose time windows:<br>• The allowed dosing time window for the evening of Day 1 and the morning of Day 2 was shortened from 2 hours to 30 minutes before bedtime or after waking, respectively, because the dose times are being used as a surrogate for sleep and wake times. These dose times, with the shortened time windows from actual sleep and wake times, will more closely reflect sleep time for cough counting calculations, necessary information for determining and evaluating nighttime and daytime cough counts (secondary endpoints). To maintain consistency for subject-reported endpoints on Days 2 through 4, the allowed time windows for dosing on |

| Document | Version Date | Summary of Changes and Rationale |
|---|---|---|
| | | Days 3 and 4 are also shortened from 2 hours to 30 minutes before bedtime for the evening doses, and from 2 hours to 30 minutes after waking for the morning doses.<br><br>Additional changes were made to inclusion/exclusion criteria:<br><br>• Ocular antibiotics were added as an exclusion.<br><br>• Oral glucocorticoid use was added as an exclusion (along with inhaled glucocorticoid use).<br><br>• The inactive ingredient list for acetaminophen (APAP) was added to the exclusion criterion concerning hypersensitivity or allergy.<br><br>• Inclusion #4 (regarding the subject having a URTI, and the URTI being within 3 days of onset of symptoms at the screening visit) was segmented into 2 bullets for database categorization purposes.<br><br>The procedures conducted at an early termination visit were made consistent or corrected as appropriate.<br><br>Subject enrollment will be actively monitored with the goal of attaining at least 40% population in the younger group (6-8 years).<br><br>Requirements for investigational product compliance and accountability checks were clarified.<br><br>The procedures conducted at an early termination visit were made consistent across the protocol.<br><br>The regulatory status and reference for the VitaloJAK device were corrected.<br><br>CCI [redacted] safety analysis was added.<br><br>In addition, minor grammatical changes or clarifications were made throughout the protocol. |

| Document | Version Date | Summary of Changes and Rationale |
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| Amendment #3 | 07 Nov 2016 | Under Protocol Summary/Study Design and Section 3.0 Study Design, the bullet outlining what is collected on the subject diary will include mention of the time and date of APAP dosing if applicable, for completeness.<br><br>Exclusion criterion #5 (Protocol Section 4.2) will be edited to read as follows:<br><br>5. Pneumonia (active or with a symptom-free period of <30 days), asthma (active or with a symptom-free period of <1 year) or other significant pulmonary diseases.<br><br>Principal investigators/physicians for this study have reported that in some instances, children in the past may have had a wheezing episode and had a diagnosis of asthma applied to their patient chart/record, but these children are neither currently asthmatic nor receiving corticosteroids or bronchodilators. Such children would be appropriate for enrollment in this study.<br><br>Section 6.6 Subject Discontinuation:<br><br>Fever greater than 39°C (102°F) oral temperature will be removed as a reason for subject discontinuation.<br><br>Principal investigators/physicians for this study have reported that in some instances, children may report with a fever greater than 39°C (102°F), and still have an uncomplicated common cold/upper respiratory tract infection. Removing this discontinuation criterion is not a safety concern, as acetaminophen is allowed (and provided) as part of the study.<br><br>Table 5. Concomitant Medication, Acetaminophen, has product numbers WH-0001-0568-001 (originally provided at study start) and WH-0001-0568-002 (provided as re-supply during study conduct).<br><br>Section 15.1, all references to subjects should be changed to patients.<br><br>Spelling error(s) as noted were corrected. |

| Document | Version Date | Summary of Changes and Rationale |
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| Amendment #4 | July 18, 2018 | The following changes were made primarily to support the interim analysis planned after at least 50% of subjects have completed or discontinued early:<br>• Language was added documenting and supporting a planned interim analysis.<br>• Language was modified for the analysis of primary endpoint and an additional analysis was added for the primary endpoint:<br>  • The treatment effect for dextromethorphan hydrobromide vs placebo from the primary negative binomial model was rephrased using a ratio of rates instead of an odds ratio.<br>  • A linear model will be used based on the log-transformed primary endpoint, including treatment, study site, log-transformed baseline average cough count per hour (based on the Baseline Run-in Period), and age group terms in the model.<br>  • Clarification was made for the primary endpoint analysis and the main effect model is defined as primary.<br>• Additional secondary endpoint variables were added:<br>  • Total cough count collected by the cough recording device over the first dosing interval on Day 1 (Dose 1 to Dose 2) and the first dosing interval on Day 2 (Dose 3 to Dose 4).<br>  • Time accumulated over a 24-hour period when cough events occurred.<br>• The analysis model for the other endpoint variables was revised.<br>• The inclusion criterion (#4) was revised slightly for clarity as follows: An onset of symptoms within 3 days of Visit 1, as determined by the subject or parent/legally acceptable representative (ie, Visit 1 should not occur later than on Day 3 of symptoms). |

| Document | Version Date | Summary of Changes and Rationale |
|---|---|---|
| | | • WH numbers were described more generically to account for multiple lots of investigational product supplied throughout the study.<br><br>• APAP will no longer be included in the study kit, but supplied separately from the study kit.<br><br>• A correction was made to the protocol for consistency, that subjects will be stratified by age group (6-8 years and 9-11 years).<br><br>• Several statements from the US. Pharmacopeia (USP) were added to the 5.6 Investigational Product Storage section.<br><br>• The safety section of the protocol was updated to reflect current standardized safety language.<br><br>• Updated information about the planned interim analysis and the Internal Review Committee (IRC) for reviewing the unblinded data has been added to this amendment.<br><br>• Several minor formatting inconsistencies or other corrections were made across the document.<br><br>• Several references were added to the References section of the protocol. |

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.

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## PROTOCOL SUMMARY

### Background and Rationale

Dextromethorphan (DXM) is the most commonly used oral antitussive ingredient in both adult and pediatric non-prescription medications (Dicpinigaitis, 2004),[3] and is "*Generally Recognized as Safe and Effective*" (GRASE) under the over-the-counter (OTC) Monograph system (21 US Code of Federal Regulations (CFR) 341.14). The product is intended for use in adults and children 2 years of age and over, with the indication:

Temporarily relieves cough due to minor throat and bronchial irritation as may occur with a cold (21 CFR 341.74(b)(1)). Under 21 CFR 341.74(d)(iii), DXM can be formulated as syrups and as solid oral dosage forms, with age-dependent dosing as follows:

- Adults and children 12 years of age and older: 10 to 20 mg every 4 hours up to 6 doses/day or 30 mg every 6-8 hours up to 4 doses/day, not to exceed 120 mg/day;
- Children 6 to under 12 years of age: 5 to 10 mg every 4 hours up to 6 doses/day or 15 mg every 6-8 hours up to 4 doses/day, not to exceed 60 mg/day;
- Children 2 to under 6 years of age: 2.5 to 5 mg every 4 hours or 7.5 mg every 6 to 8 hours; not to exceed 30 mg/day.

The safety and efficacy of DXM in adults at the United States monograph-approved dose of 30 mg has been established in a variety of studies (Pavesi et al., 2001).[13] Efficacy in children is less well established and results have been equivocal (Shadkam et al, 2010; Paul, 2004a; Paul, 2004b; Yoder, 2006).[14,11,12,19] The difficulty in establishing efficacy in children is at least partially due to the lack of a standardized methodology and a validated device to evaluate objective antitussive effects (ie, a reduction in cough count), in the natural environment.

The leading pharmaceutical manufacturers of over-the-counter (OTC) pediatric cough and cold products, via the Consumer Healthcare Products Association (CHPA), and in consultation with the Food and Drug Administration (FDA), announced in 2008 that they are transitioning product labeling as it relates to children aged less than 4 years of age. The product labeling now states *"Do not use in children under four years of age."* The safety of the ingredients in these products was not in question; it was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children (CHPA, 2008).[2]

This pilot study is being conducted to identify the appropriate endpoints and sample size for a subsequent definitive pediatric cough study that will evaluate the efficacy of dextromethorphan hydrobromide (DXM HBr) at the approved monograph dose in children aged 6 to 11 years. This current pilot study will utilize -the 510(k) status cough recording device (VitaloJAK™, Vitalograph Ltd, Ennis, Ireland), which has been validated for use in adults (McGuiness, 2012) [7] and has recently been validated in children (Elghamoudi, 2015).[5] A subject-completed patient-reported outcome (PRO) self-assessment of cough symptoms will also be included as a secondary endpoint, to provide another endpoint for evaluation.

## Objective

The objective of this pilot study is to evaluate the endpoints and analyses that may be most appropriate to evaluate the efficacy of dextromethorphan hydrobromide (DXM HBr) 15 mg/10 mL versus placebo in children ages 6 to 11 years in a future study.

## Endpoints

The primary endpoint of this study is the total cough count collected by the cough recording device in an ambulatory setting over a 24-hour period post-first dose on Day 1 after randomization to DXM HBr or placebo.

Secondary endpoints are the total cough count collected in the dosing intervals of interest during the 24-hour interval:

- Total cough count collected by the cough recording device during the first dosing interval (Dose 1 to Dose 2) on Day 1;
- Total cough count collected by the cough recording device over the dosing interval from evening dose (Dose 2) on Day 1 to morning dose (Dose 3) on Day 2 (ie, night time cough count);
- Total cough count collected by the cough recording device over the first dosing interval on Day 2 (interval between morning dose and afternoon dose on Day 2, ie, Dose 3 to Dose 4);
- Total cough count collected by the cough recording device over the first dosing interval on Day 1 (Dose 1 to Dose 2) and the first dosing interval on Day 2 (Dose 3 to Dose 4). These 2 dose intervals approximately represent the daytime cough count.

Time accumulated over a 24-hour period when cough events occurred. Other endpoints as assessed by patient reported outcomes (PROs) include:

- Change from screening evaluation (assessed in the morning) in morning cough frequency (“from when you woke up this morning until now, how much have you been coughing”), cough severity (“how bad is your cough this morning”), and impact on sleep (“last night in bed, how much did your cough keep you awake”), assessed by subject;
- Change from baseline evaluation (assessed at afternoon) in afternoon cough frequency (“how much have you been coughing this afternoon”) and severity (“how bad is your cough this afternoon”) in the afternoon of Days 2-4, assessed by subject;
- Change from baseline evaluation (assessed at afternoon) in daily assessment of the cold in the Child Global Question (“how bad is your cold today”), assessed by subject;

- Subject and parent/legally acceptable representative global assessment of satisfaction with study medication at the end of the study.

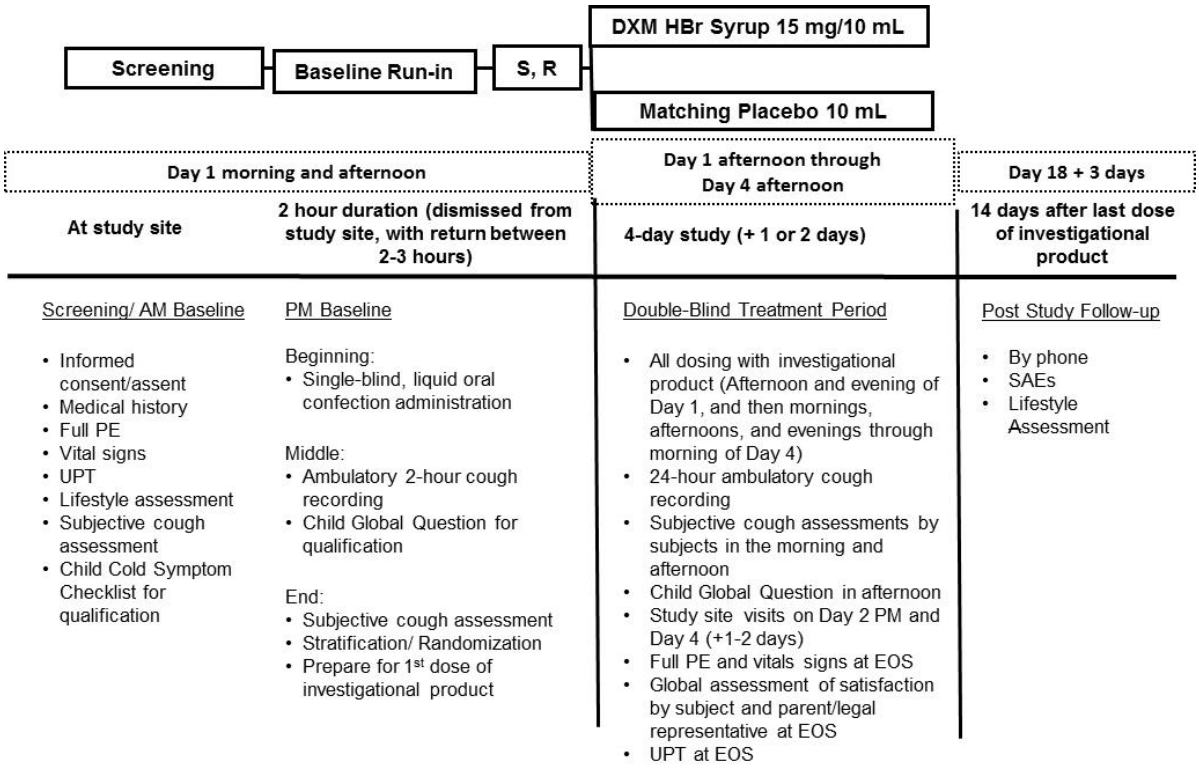
CCI [redacted] Protocol Amendment #4 introduced an interim analysis to assess whether or not the study would be continued. The rationale is based upon the vulnerable subject population (pediatrics) being studied and in association with the extended recruitment period and challenging enrollment for the trial. The main focus of this interim analysis is the primary endpoint and the first secondary endpoint (cough count during the first dosing interval), but other secondary CCI [redacted] endpoints may also be considered by the independent committee established to review the information as detailed in the committee charter and described in Section 9.4. The interim analysis will be conducted after at least 50% subjects complete the study or discontinue early.

Adverse Events (AEs) will be collected to assess the safety of DXM HBr and placebo during the study period.

**Study Design**

This is a randomized, stratified by age group (6-8 years and 9-11 years), parallel, double-blind, placebo-controlled, multicenter, pilot study in approximately 150 males and females aged 6 to 11 years, inclusive, who exhibit cough associated with a common cold or acute upper respiratory tract infection (URTI) but are otherwise healthy. Prior to performing any study-related activities and after having been informed of the study by the investigator or authorized designee, the parent/legally acceptable representative will provide informed consent, and the subject will provide informed assent to participate. The study design is shown in Figure 1 below. The dosing schedule is shown in Table 1 below. The schedule of activities is shown in Table 2 below.

## Figure 1. Study Design Schematic




DXM = dextromethorphan; HBr = hydrobromide; PE = physical examination; R = randomization; S = stratification; UPT = urine pregnancy test for post-menarchal females; EOS = end of study

**Table 1. Dosing Schedule**

| DAY | TIME OF ADMINISTRATION | | |
|---|---|---|---|
| | MORNING | AFTERNOON | EVENING |
| 1 | Single-Blind, Liquid Oral Confection (In the morning, recommended to be before 11:30 am, at the study site) | Dose 1[a,b] (Recommended to be before 3:30 pm, at the study site) | Dose 2[a,c] (Prior to bedtime [within 30 minutes], 6-8 hours after Dose 1) |
| 2 | Dose 3[a] (In the morning, within 30 minutes of waking up) | Dose 4[a] (6-8 hours after morning dose and at least 24 hours after Dose 1; administered at the study site) | Dose 5[a] (Prior to bedtime [within 30 minutes], 6-8 hours after afternoon dose) |
| 3 | Dose 6[a] (In the morning, within 30 minutes of waking up) | Dose 7[a] (6-8 hours after morning dose) | Dose 8[a] (Prior to bedtime [within 30 minutes], 6-8 hours after afternoon dose) |
| 4 | Dose 9[a] (In the morning, within 30 minutes of waking up) | | |

[a] Double-blind randomized investigational product.
[b] Subjects vomiting after the administration of Dose 1 at the clinic will not be re-dosed. In addition, all the subsequent clinical procedures and dosings should be continued and performed as described in the protocol.
[c] Although not encouraged, but to ensure there is a second dose administered on Day 1, and to allow the parent/legally acceptable representative some flexibility regarding the timing of that second dose, the second dose may be taken as early as 4 hours post-Dose 1, but not earlier.

Subjects who meet screening criteria, including sufficient cough and acute URTI or common cold symptoms, will be enrolled in a 2-hour Baseline Run-in Period and follow the procedures below:

- The subject will be fitted with the VitaloJAK™ device at the study site for at least 2 hours of ambulatory cough count monitoring;

- The parent/legally acceptable representative will be advised that the VitaloJAK™ is a sound recording device, and therefore may inadvertently capture confidential information from casual speech within its range; and that Vitalograph has standard operation procedures and measures in place to ensure that any such information is kept confidential, including removing such speech to a certain extent. While wearing the device, the subject should also avoid overly noisy locations;

- The subject will be given a single-blind (to the parent/legally acceptable representative and subject), inactive (non-medicinal) liquid oral confection at the study site, recommended to be before 11:30 am. The 2-hour recording will begin immediately (+5 minutes) after the confection is administered;

- The subject and parent/legally acceptable representative will be released from the study site during the 2-hour ambulatory cough count monitoring and instructed to engage in normal activities. Alternatively, they may stay at the study site, if convenient. The study site staff will capture in the case report form (CRF) whether or not the subject leaves the study site;

- The subject and parent/legally acceptable representative will return to the study site after at least 2 hours and preferably before 2:30 pm. The VitaloJAK™ device will be removed. The subject will complete the afternoon subjective cough assessments and Child Global Question, and if qualified, will be enrolled in the 4-day Treatment Period.

Activities for the Treatment Period are as follows:

- The study site staff will set-up the VitaloJAK™ device for 24 hours of ambulatory cough count recording;

- The subject will be stratified based on the subject's age (6-8 years or 9-11 years) and randomized to investigational product;

- The subject will receive the first dose of investigational product at the study site, recommended to be before 3:30 pm. Subjects vomiting after the administration of Dose 1 at the clinic will not be re-dosed, and all the subsequent clinical procedures and dosings should be continued and performed as described in the protocol;

- The subject and parent/legally acceptable representative will receive investigational product, permitted acetaminophen (APAP) as concomitant medication, and subject diary. In addition, the subject will be wearing the VitaloJAK™ device and will receive instructions regarding its use;

- After receiving instructions for diary completion and investigational product administration for the remaining days, the subject and parent/legally acceptable representative will be allowed to leave the study site during the 24-hour ambulatory cough count monitoring to engage in normal activities;

- The subject will receive investigational product in the evenings of Days 1-3 prior to bedtime, on the mornings of Days 2-4, and in the afternoons of Days 2-3 (Table 1);

- The subject will complete subjective cough assessments in the mornings and afternoons of Days 2-4, immediately prior to the morning and afternoon dosing with the investigational product (as applicable);

- The subject will complete the Child Global Question in the afternoons of Days 2-4;

- A subject diary will be used to record the time and date of investigational product dosing; the time and date of APAP dosing if applicable; and the time, date, and entries for the subjective cough assessments/Child Global Question. The subject diary will be used from the afternoon of Day 1 through the afternoon of Day 4. The parent/legally acceptable representative may assist or complete diary entries for dates and times, but the subject must choose the responses for the subjective cough assessments and child global question without assistance;

- The subject and parent/legally acceptable representative will return to the study site in the afternoon of Day 2 for Visit 3, at least 24 hours after recording began on Day 1, for removal of the VitaloJAK™ device, for assessment of compliance with the investigational product and diary completion, and evaluation of concomitant treatments and adverse events;

- The subject and parent/legally acceptable representative will return to the study site for an End of Study visit on Day 4 (+1 to 2 days for scheduling flexibility). A global assessment of product satisfaction should be completed by the subject, and subsequently by the parent/legally acceptable representative, at this visit. The afternoon subjective cough assessments and Child Global Question should be completed on the afternoon of Day 4 even if the End of Study visit occurs on Day 5 or 6. Compliance with the investigational product and diary completion, and evaluation of concomitant treatments and adverse events, will be assessed at this visit. All study materials should be returned at this visit;

- A post-study follow-up phone visit will occur 14 (+ up to 3 days for scheduling flexibility) days after the last dose of investigational product (ie, Day 18). The study site staff will call the subject and parent/legally acceptable representative to inquire about any serious adverse events (SAEs) that may have occurred.

**Study Treatments**

The double-blind investigational product assessed for efficacy and safety in this pediatric population are:

- DXM HBr 15 mg/10 mL, administered as 10 mL per dose;

- Placebo, administered as 10 mL per dose.

Subjects will be randomized to treatment in a 1:1 ratio.

A single-blind (to the parent/legally acceptable representative and subject), inactive (non-medicinal), liquid oral confection will be given to all subjects during the Baseline Run-in Period.

During the Treatment Period, APAP will be provided by the sponsor as a permitted concomitant medication if required for headache, fever and/or body aches and pains associated with the common cold. Dosing will be as directed per the product label, based on weight or age. If requested by parent/legally acceptable representative, use of ibuprofen (IBU) will be permitted after consultation with the investigator or designee. IBU will not be supplied by the sponsor.

### Statistical Methods

Statistically significant treatment differences will be declared if the probability of random occurrence among or between the treatment groups (p) is ≤0.05. Treatment differences will be declared marginally significant if $0.05<p\leq0.10$. All tests will be 2-sided.

No formal sample size determination was performed, as information on cough count using the VitaloJAK™ device in children in an ambulatory setting is limited. The sample size of approximately 150 subjects to be enrolled in the study was based on clinical judgment. The primary efficacy parameter (total cough count collected in an ambulatory setting over the 24-hour period post-first dose on Day 1) will be analyzed with a negative binomial regression model (SAS Proc GENMOD) with effects for treatment, study site, baseline cough count (average per hour, based on the Baseline Run-in Period), and age group terms in the model, with logarithm of the time over which the cough count is evaluated as the offset parameter.

AEs will be summarized by severity, and relationship to study treatment.

## SCHEDULE OF ACTIVITIES

The schedule of activities (Table 2) provides an overview of the protocol visits and procedures. Refer to the Study Procedures and Assessments sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the subject.

## Table 2. Schedule of Activities

| Visit Identifier | Screening /Run-In Period | Randomization/ First Dose | Active Treatment Period | | | | | | | | End Study | Post Study Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day 1 Visit 1 | Day 1 Visit 2 | Day 1 | Day 2 Visit 3 | | | Day 3 | | | Day 4 | Days 4-6 | Day 18 +3 days |
| **Protocol Activity** | **AM** | **Afternoon** | **PM** | **AM** | **Afternoon[h]** | **PM** | **AM** | **Afternoon** | **PM** | **AM** | **Visit 4 (afternoon) or Early Termination** | **Phone call** |
| Informed consent/assent[a] | X | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | |
| Inclusion/Exclusion Criteria | X | | | | | | | | | | | |
| Medical history[b] | X | | | | | | | | | | | |
| Physical examination | X | | | | | | | | | | X | |
| Vital signs (height, weight, respirations, temperature, sitting BP, pulse rate)[c] | X | | | | | | | | | | X[c] | |
| Urine pregnancy test[d] | X | | | | | | | | | | X | |
| Lifestyle Assessment[e] | X | | | | | | | | | | | |
| Morning subjective cough assessments | X | | | X | | | X | | | X | | |
| Afternoon subjective cough assessments[f] | | X | | | X | | | X | | | X[f] | |
| Child Cold Symptom Checklist | X | | | | | | | | | | | |
| Child Global Question[f] | | X | | | X | | | X | | | X[f] | |
| Single-blind, liquid oral confection administration[g] | X | | | | | | | | | | | |
| Ambulatory 2-hour cough recording[i] | X | | | | | | | | | | | |
| Stratification and randomization | | X | | | | | | | | | | |
| Diary/investigational product/APAP dispensed/retrieved | | X | | | X | | | | | | X | |
| Study Medication administration[j] | | X | X | X | X | X | X | X | X | X | | |

| **Visit Identifier** | **Screening /Run-In Period** | **Randomization/ First Dose** | **Active Treatment Period** | | | | | | | | **End Study** | **Post Study Follow-up** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Day 1 Visit 1** | **Day 1 Visit 2** | **Day 1** | **Day 2 Visit 3** | | | **Day 3** | | | **Day 4** | **Days 4-6** | **Day 18 +3 days** |
| **Protocol Activity** | **AM** | **Afternoon** | **PM** | **AM** | **Afternoon[h]** | **PM** | **AM** | **Afternoon** | **PM** | **AM** | **Visit 4 (afternoon) or Early Termination** | **Phone call** |
| Ambulatory 24-hour cough recording[k] | | X | → | | X | | | | | | | |
| Ambulatory cough recorder removal/retrieval | | X | | | X | | | | | | | |
| Assessment of compliance with study medication | | | | | X | | | | | | X | |
| Prior/concomitant treatments | X → | | | | | | | | | | | |
| Global Satisfaction by subject and parent/legally acceptable representative | | | | | | | | | | | X | |
| Adverse events[l,m] | SAE → | | | | | | | | | | X[l] | |
| | | Non-SAE → | | | | | | | | | | |

Visit 1 and Visit 2 (Screening/Morning Baseline, Afternoon Baseline Run-In Period, and Randomization/First Dose) occur on Day 1 of the study. Visit 4 (End of Study) may occur on the afternoon of Day 4, or on Days 5 or 6. Early termination visit is not restricted to an afternoon timeframe.

Abbreviations: APAP = acetaminophen; BP = blood pressure; SAE = serious adverse event.

a. Parent/legally acceptable representative will provide informed consent, and child will provide assent.

b. Subject must be symptomatic with a common cold or acute URTI, with onset of symptoms within 3 days of Visit 1, as determined by the subject or parent/legally acceptable representative (ie, Visit 1 should not occur later than on Day 3 of symptoms).

c. Height and weight will only be collected at screening, but not at Visit 4 or Early Termination Visit.

d. Pregnancy test for post-menarchal females.

e. The Lifestyle Assessment (Section 4.4) is the opportunity to assess reproductive/childbearing status, communicate the protocol requirement for complete sexual abstinence and document the discussion.

f. Afternoon subjective cough assessments and Child Global Question should be completed before afternoon dosing on Days 1, 2 and 3 and in the afternoon on Day 4 (even if the End of Study visit occurs on Day 5 or 6). In the event of early termination, the subject-assessed afternoon cough assessment and the Child Global Question will not be performed.

g. The baseline, single-blind (to the parent/legally acceptable representative and subject), liquid oral confection will be administered at Visit 1 (Day 1), recommended to be before 11:30 am.

h. Visit 3 (Day 2 afternoon) will occur at the study site at least 24 hours after the start cough recording that began on Day 1.

i. Ambulatory 2-hour cough recording should be set up before the baseline, single-blind confection is administered, with cough recording beginning immediately (+5 minutes) after dosing. The parent/legally acceptable representative will be advised regarding VitaloJAK™ use as specified in Section 6 Study Procedures.

j. Dose 1 of double-blind investigational product will be administered at Visit 2 (Day 1) at the study site after at least 2 hours of baseline cough recording. At Visit 3 (Day 2), the afternoon dose (Dose 4) will also be administered at the study site. All other doses (Doses 5-9) of investigational product will be administered to the subject by the parent/legally acceptable representative. Subjects vomiting after the administration of Dose 1 at the clinic will not be re-dosed, and all the subsequent clinical procedures and dosings should be continued and performed as described in the protocol.

k. Ambulatory 24-hour cough recording should be set up before the first investigational product dose (Dose 1) is administered at Visit 2 (Day 1), with cough recording beginning immediately (+5 minutes) after dosing. The parent/legally acceptable representative will be advised regarding VitaloJAK™ use as specified in Section 6 Study Procedures.

l. Serious adverse event (SAE) collection begins from the time of informed consent and non-serious AE collection begins from the time that the subject receives the first dose of investigational product.

m. Post study follow-up visit will occur by phone 14 (+ up to 3 days for scheduling flexibility) days after the last dose of investigational product. The study site staff should inquire about any SAEs that may have occurred.

# 1. INTRODUCTION

## 1.1. Mechanism of Action/Indication

Dextromethorphan (DXM) is a cough suppressant used to temporarily relieve cough due to minor throat and bronchial irritation as may occur with a cold.

## 1.2. Background and Rationale

DXM is the most commonly used oral antitussive ingredient in both adult and pediatric non-prescription medications (Dicpinigaitis, 2004)[3], and is "*Generally Recognized as Safe and Effective*" (GRASE) under the over-the-counter (OTC) Monograph system (21 CFR 341.14). The product is intended for use in adults and children 2 years of age and over, with the indication:

- Temporarily relieves cough due to minor throat and bronchial irritation as may occur with a cold (21 CFR 341.74(b)(1)). Under 21 CFR 341.74(d)(iii), DXM can be formulated as syrups and as solid oral dosage forms, with age-dependent dosing as follows:
    - Adults and children 12 years of age and older: 10 to 20 mg every 4 hours up to 6 doses/day or 30 mg every 6-8 hours up to 4 doses/day, not to exceed 120 mg/day;
    - Children 6 to under 12 years of age: 5 to 10 mg every 4 hours up to 6 doses/day or 15 mg every 6-8 hours up to 4 doses/day, not to exceed 60 mg/day;
    - Children 2 to under 6 years of age: 2.5 to 5 mg every 4 hours or 7.5 mg every 6 to 8 hours; not to exceed 30 mg/day.

The safety and efficacy of DXM in adults at the United States monograph-approved dose of 30 mg has been established in a variety of studies (Pavesi et al., 2001).[13] Efficacy in children is less well established and results have been equivocal (Shadkam et al, 2010; Paul, 2004a; Paul, 2004b; Yoder, 2006).[14,11,12,19] The difficulty in establishing efficacy in children is at least partially due to the lack of a standardized methodology and a validated device to evaluate objective antitussive effects, ie, a reduction in cough count, in the natural environment.

The leading pharmaceutical manufacturers of over-the-counter (OTC) pediatric cough and cold products, via the Consumer Healthcare Products Association (CHPA), and in consultation with the Food and Drug Administration (FDA), announced in 2008 that they are transitioning product labeling as it relates to children aged less than 4 years of age. The product labeling now states *"Do not use in children under four years of age."* The safety of the ingredients in these products was not in question; it was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children (CHPA, 2008).[2]

This pilot study is being conducted to identify the appropriate endpoints and sample size for a subsequent definitive pediatric cough study that will evaluate the efficacy of dextromethorphan hydrobromide (DXM HBr) at the approved monograph dose in children aged 6 to 11 years. This current pilot study will utilize the 510(k) status- cough recording device (VitaloJAK™, Vitalograph Ltd, Ennis, Ireland), which has been validated for use in adults (McGuiness, 2012)[7] and has recently been validated in children (Elghamoudi, 2015).[5] A subject completed patient-reported outcome (PRO) self-assessment of cough symptoms will also be included as a secondary endpoint, to provide another endpoint for evaluation.

Complete information for this compound may be found in the Single Reference Safety Document (SRSD), which for this study is the Investigator's Brochure (IB). The product labeling (monograph) for APAP is also considered a SRSD.

## 2. STUDY OBJECTIVES AND ENDPOINTS

### 2.1. Objectives

The objective of this pilot study is to evaluate the endpoints and analyses that may be most appropriate to evaluate the efficacy of DXM HBr 15 mg/10 mL versus placebo in children ages 6 to 11 years in a future study.

### 2.2. Endpoints

The primary endpoint of this study is the total cough count collected by the cough recording device in an ambulatory setting over a 24-hour period post-first dose on Day 1 after randomization to DXM HBr or placebo.

Secondary endpoints are the total cough count collected in the dosing intervals of interest during the 24-hour interval:

- Total cough count collected by the cough recording device during the first dosing interval (Dose 1 to Dose 2) on Day 1;
- Total cough count collected by the cough recording device over the dosing interval from evening dose (Dose 2) on Day 1 to morning dose (Dose 3) on Day 2 (ie, night time cough count);
- Total cough count collected by the cough recording device over the first dosing interval on Day 2 (interval between morning dose and afternoon dose on Day 2, ie, Dose 3 to Dose 4);
- Total cough count collected by the cough recording device over the first dosing interval on Day 1 (Dose 1 to Dose 2) and the first dosing interval on Day 2 (Dose 3 to Dose 4). These 2 dose intervals approximately represent the daytime cough count;
- Time accumulated over a 24-hour period when cough events occurred.

Other endpoints as assessed by PRO include:

- Change from screening evaluation (assessed in the morning) in morning cough frequency ("from when you woke up this morning until now, how much have you been coughing"), cough severity ("how bad is your cough this morning") and impact on sleep ("last night in bed, how much did your cough keep you awake"), assessed by subject;

- Change from baseline evaluation (assessed at afternoon) in afternoon cough frequency ("how much have you been coughing this afternoon") and severity ("how bad is your cough this afternoon") in the afternoon of Days 2-4, assessed by subject;

- Change from baseline evaluation (assessed at afternoon) in daily assessment of the cold in the Child Global Question ("how bad is your cold today"), assessed by subject;

- Subject and parent/legally acceptable representative global assessment of satisfaction with study medication at the end of the study.

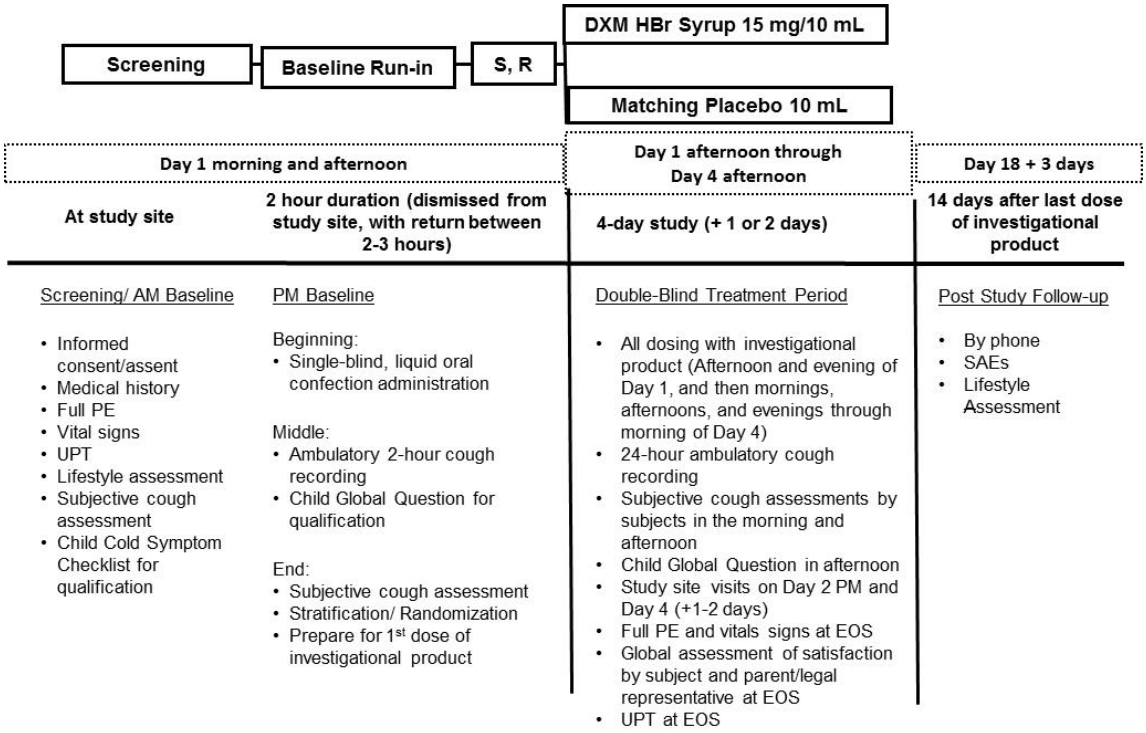
CCI [redacted]

Protocol Amendment #4 introduced an interim analysis to assess whether or not the study would be continued. The rationale is based upon the vulnerable subject population (pediatrics) being studied and in association with the extended recruitment period and challenging enrollment for the trial. The main focus of this interim analysis is the primary endpoint and the first secondary endpoint (cough count during the first dosing interval), but other secondary CCI [redacted] endpoints may also be considered by the independent committee established to review the information as detailed in the committee charter and described in Section 9.4. The interim analysis will be conducted after at least 50% subjects complete the study or discontinue early. AEs will be collected to assess the safety of DXM HBr and placebo during the study period.

## 3. STUDY DESIGN

This is a randomized, stratified by age group (6-8 years and 9-11 years), parallel, double-blind, placebo-controlled, multicenter pilot study in approximately 150 males and females aged 6 to 11 years, inclusive, who exhibit cough associated with common cold or acute upper respiratory tract infection (URTI) but are otherwise healthy. Prior to performing any study-related activities and after having been informed of the study by the investigator or authorized designee, the parent/legally acceptable representative will provide informed consent, and the subject will provide assent to participate. The study design is shown in below. The dosing schedule is shown in Figure 1 below.

## Figure 1. Study Design Schematic




DXM = dextromethorphan; HBr = hydrobromide; PE = physical examination; R = randomization; S = stratification; UPT = urine pregnancy test for post-menarchal females; EOS = end of study

## Table 1. Dosing Schedule

| DAY | TIME OF ADMINISTRATION | | |
|---|---|---|---|
| | MORNING | AFTERNOON | EVENING |
| 1 | Single-Blind, Liquid Oral Confection (In the morning, recommended to be before 11:30 am, at the study site) | Dose 1[a,b] (Recommended to before 3:30 pm, at the study site) | Dose 2[a,c] (Prior to bedtime [within 30 minutes], 6-8 hours after Dose 1) |
| 2 | Dose 3[a] (In the morning, within 30 minutes of waking up) | Dose 4[a] (6-8 hours after morning dose and at least 24 hours after Dose 1; administered at the study site) | Dose 5[a] (Prior to bedtime [within 30 minutes], 6-8 hours after afternoon dose) |
| 3 | Dose 6[a] (In the morning, within 30 minutes of waking up) | Dose 7[a] (6-8 hours after morning dose) | Dose 8[a] (Prior to bedtime [within 30 minutes], 6-8 hours after afternoon dose) |
| 4 | Dose 9[a] (In the morning, within 30 minutes of waking up) | | |

[a] Double blind randomized investigational product.
[b] Subjects vomiting after the administration of Dose 1 at the clinic will not be re-dosed. In addition, all the subsequent clinical procedures and dosings should be continued and performed as described in the protocol.
[c] Although not encouraged, to allow the parent/legally acceptable representative some flexibility regarding the timing of the second dose, the second dose may be taken as early as 4 hours post-Dose 1, but not earlier.

Subjects who meet screening criteria, including sufficient cough and acute URTI or common cold symptoms, will be enrolled in a 2-hour Baseline Run-in Period and follow the procedures below:

- The subject will be fitted with the VitaloJAK™ device at the study site for at least 2 hours of ambulatory cough count monitoring.

- The parent/legal representative will be advised that the VitaloJAK™ is a sound recording device, and therefore may inadvertently capture confidential information from casual speech within its range; and that Vitalograph has standard operation procedures and measures in place to ensure that any such information is kept confidential, including removing such speech to a certain extent. While wearing the device, the subject should also avoid overly noisy locations.

- The subject will be given a single-blind (to the parent/legally acceptable representative and subject), inactive (non-medicinal), liquid oral confection at the study site, recommended to be before 11:30 am. The 2-hour recording will begin immediately (+5 minutes) after the confection is administered. The time and date of administration and recording start date and time will be recorded in the CRF by the study site staff.

- The subject and parent/legally acceptable representative will be released from the study site during the 2-hour ambulatory cough count monitoring and instructed to engage in normal activities. Alternatively, they may stay at the study site, if convenient. The study site staff will capture in the CRF whether or not the subject leaves the study site.

- The subject and parent/legally acceptable representative will return to the study site after at least 2 hours and preferably before 2:30 pm, the device will be removed, and the time and date when the recording stops will be recorded in the CRF by the study site staff. The subject will complete subjective cough assessments and the Child Global Question, and then be enrolled in the 24-hour Treatment Period if all eligibility requirements are met.

Activities for the Treatment Period are as follows:

- The study site staff will set up the VitaloJAK™ device for 24 hours of ambulatory cough count recording and re-fit the subject with the device.

- The subject will be stratified based on the subject's age (6-8 years or 9-11 years) and randomized to receive investigational product. The time and date of the first administration will be recorded in CRF by the study site staff.

- The subject will receive the first dose of double blind investigational product at the study site, recommended to be before 3:30 pm. Subjects vomiting after the administration of Dose 1 at the clinic will not be re-dosed, and all the subsequent clinical procedures and dosings should be continued and performed as described in the protocol. The 24-hour recording will begin immediately (+5 minutes) after the dose is administered. The date and time of the first dose and the recording start date and time will be recorded in the CRF by the study site staff.

- The subject and parent/legally acceptable representative will receive investigational product, permitted APAP as concomitant medication, and subject diary. In addition, the subject will be wearing the VitaloJAK™ device and will receive instructions regarding its use.

- After receiving instructions for diary completion and investigational product administration for the remaining days, the subject and parent/legally acceptable representative will be allowed to leave the study site to engage in normal activities.

- The subject will receive investigational product in the evenings of Days 1-3 prior to bedtime, the mornings of Days 2-4, and the afternoons of Days 2-3.

- The subject will complete subjective cough assessments in the mornings and afternoons of Days 2-4, immediately prior to morning and afternoon dosing with the investigational product (as applicable).

- The subject will complete the Child Global Question in the afternoons of Days 2-4.

- A subject diary will be used to record the time and date of investigational product dosing; the time and date of APAP dosing if applicable; and the time, date, and entries for the subjective cough assessments/Child Global Question. The subject diary will be used from the afternoon of Day 1 through the afternoon of Day 4. The parent/legally acceptable representative may assist or complete diary entries for dates and times, but the subject should choose the responses for the subjective cough assessments and the Child Global Question without assistance.

- The subject and parent/legally acceptable representative will return to the study site on Day 2 in the afternoon, at least 24 hours after the cough recording began on Day 1, for removal of the VitaloJAK™ device, for assessment of compliance with the investigational product and diary completion, and evaluation of concomitant treatments and adverse events. The date and stop time of the 24-hour ambulatory cough count recording will be recorded in the CRF by the study site staff. If the device was taken off before 24 hours, the parent/legally acceptable representative will be asked to report the time and date when the device was taken off at Visit 3 (when they return the device).

- The subject and parent/legally acceptable representative will return to the study site for the End of Study visit on Day 4 (+1 to 2 days for scheduling flexibility). A global assessment of product satisfaction will be completed by the subject and parent/legally acceptable representative at this visit. The afternoon subjective cough assessments and Child Global Question should be completed on the afternoon of Day 4, even if the End of Study visit occurs on Day 5 or 6. Compliance with the investigational product and diary completion, and evaluation of concomitant treatments and adverse events, will be assessed at this visit. All study materials should be returned at this visit.

- A post-study follow-up phone visit will occur 14 (+ up to 3 days for scheduling flexibility) days after the last dose of investigational product (ie, Day 18). The study site staff will call the subject and parent/legally acceptable representative to inquire about any SAEs that may have occurred

## 4. SUBJECT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol.

### 4.1. Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Evidence of a personally signed and dated informed consent document indicating the parent/legally acceptable representative has been informed of all pertinent aspects of the study.

2. Evidence of a personally signed or printed and dated assent document or verbal assent, indicating the subject is willing to participate in the study.

3. Generally healthy male or female children/adolescents ages 6 to 11 years, inclusive.

4. Subject has:

    a. An acute cough and other symptoms consistent with a common cold/acute URTI diagnosis as deemed by the investigator or qualified designee based on findings from medical history review, full physical examination, and vital signs.

    b. An onset of symptoms within 3 days of Visit 1, as determined by the subject or parent/legally acceptable representative (ie, Visit 1 should not occur later than on Day 3 of symptoms).

5. The subject self-reports on the Child Cold Symptom Checklist (Appendix 2):

   - At least "Some" on the 5-point scale for the cough and sore throat questions and;
   - At least 'Some' for at least 1 other symptom of sneezing, runny nose, stuffy nose, or difficulty breathing deeply.

     The remaining symptoms (hurting head, hurting face, and aching arms and legs) are additional non-qualifying symptoms assessed as part of the checklist.

6. Parent/legally acceptable representative, and subject agrees the subject will not use any other cough or cold treatments during the study, such as:

   - Systemic antibiotics;
   - Ear or eye drop antibiotics (local cream/ointment antibiotics are allowed);
   - Bronchodilators (inhaled and oral);
   - Inhaled or oral glucocorticosteroids;
   - Intranasal sprays containing antihistamines, decongestants, glucocorticosteroids, or chromones;
   - Antitussives;
   - Expectorants;
   - Mucolytics;
   - Decongestants (oral or nasal);
   - Antihistamine-containing products (solid forms and syrups);
   - Cough/throat lozenges;
   - Any cough/cold medications;
   - Hard candies;
   - Honey, chocolate or cocoa-containing products;
   - Any herbal/dietary supplemental cold/flu preparation (eg, *Echinacea*, zinc, vitamin C in doses above the recommended daily allowance, etc.);
   - Aspirin;

- Vaporizers and steam inhalation treatments;
- Menthol containing products (including topical ointments and patches).

7. Subject and parent/legally acceptable representative are considered reliable, cooperative and of adequate intelligence to comprehend the study procedures in the opinion of the investigator.

8. Subject and parent/legally acceptable representative are willing and able to comply with scheduled visits, treatment plan, study procedures and laboratory tests (if required).

### 4.2. Exclusion Criteria

Subjects with any of the following clinical characteristics/conditions will not be included in the study:

1. A subchronic, or chronic cough due to any condition other than an URTI or common cold as established by the investigator, nurse practitioner, or physician's assistant, in accordance with the American College of Chest Physicians' (ACCP) Guidelines for Diagnosis and Management of Cough (Irwin, 2006).[6] Special attention should be paid to highly prevalent conditions commonly presenting with cough such as asthma, rhinitis, or gastroesophageal reflux disease (GERD).
2. Symptoms of runny nose, stuffy nose, sore throat, or sneezing due to any condition other than URTI or common cold (eg, seasonal or perennial allergic rhinitis, sinusitis, strep throat, vasomotor rhinitis, etc.) as established by the investigator.
3. An acute cough that occurs with excessive phlegm (mucus) or is chronic such as occurs with smoking, asthma, bronchitis, allergies, or a gastroesophageal condition (eg, acid reflux and GERD) or history of such a cough.
4. Clinical features of a complication of the common cold during the physical examination at screening (eg, otitis media, sinusitis, or pneumonia) with or without the need for systematic antibiotics.
5. Pneumonia (active or with a symptom-free period of <30 days), asthma (active or with a symptom-free period of <1 year), or other significant pulmonary diseases.
6. Fever greater than 39ºC (102ºF oral temperature) at the time of screening if, in the judgment of the investigator, the individual is too ill to participate in the study or the fever is due to reasons other than URTI.
7. Signs of dehydration (as may be due to vomiting, diarrhea, or lack of fluid intake) during the physical examination at screening.
8. Diabetes or hypoglycemic disorders.

9. Known contraindications to the investigational product or APAP.

10. Sitting blood pressure reading at or above the limits as documented in Appendix 7. If the initial blood pressure reading is at or above the limits as documented in Appendix 7, the subject will be allowed to rest for 15 minutes and the blood pressure measurement repeated 2 additional times consecutively approximately 5 minutes apart. These three readings will be averaged. Subjects who have an average systolic and/or diastolic blood pressure reading at or above the established limit will be excluded from the study.

11. Other severe acute or chronic medical or psychiatric condition that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

12. Obstructive sleep apnea caused by enlarged tonsils and adenoids, low muscle tone, or allergies (Mukherjee, 2015).[9]

13. History of known or suspected allergy or hypersensitivity to DXM or APAP, or any of the non-medicinal ingredients contained in the single-blind confection, double-blind investigational products, or APAP:

    a. Investigational products (DXM HBr; Placebo): benzoic acid; citric acid; dibasic sodium phosphate; edetate disodium; artificial and natural flavors; propylene glycol, red dye #40, purified water, sorbitol or sucrose.

    b. Grenadine: high fructose sugar; citric acid; natural and artificial flavors; sodium citrate; sodium benzoate; Red 40; Blue 1.

    c. APAP: anhydrous citric acid, butylparaben, calcium sulfate, carrageenan, FD&C red #40, flavor, glycerin, high fructose corn syrup, hydroxyethyl cellulose, microcrystalline cellulose and carboxymethylcellulose sodium, propylene glycol, purified water, sodium benzoate, sorbitol solution, tribasic sodium phosphate.

14. Pregnant female subjects; breastfeeding female subjects; male subjects able to father children and female subjects of childbearing potential who are unwilling or unable to agree to sexual abstinence as outlined in this protocol for the duration of the study and for 28 days after the last dose of investigational product (Section 4.4.1).

15. History of taking any of the following prohibited medications or products within the corresponding washout periods, if applicable, prior to taking the first dose of investigational product:

    - Systemic antibiotics: 5 times the elimination half-life;
    - Ear or eye drop antibiotics: 5 days;
    - Bronchodilators (inhaled and oral): subject should not have used within the 6 months prior to screening;

- Inhaled or oral glucocorticosteroids: subject should not have used inhaled or oral glucocorticosteroids within the 6 months prior to screening;
- Intranasal sprays containing antihistamines, decongestants, glucocorticosteroids, or chromones: 5 times the elimination half-life;
- Monoamine oxidase inhibitors: 2 weeks;
- First or second generation antihistamines (certirizine, fexofenadine, loratadine, brompheniramine, diphenhydramine, hydroxyzine, chlorpheniramine): 5 times the elimination half-life;
- Oral decongestants: phenylephrine and short-acting pseudoephedrine, 12 hours; long-acting pseudoephedrine, 24 hours;
- Expectorants/mucolytics (guaifenesin, N-acetylcysteine): 12 hours;
- DXM: 20 hours;
- Opioids (eg, codeine): 5 times the elimination half-life;
- Other cough suppressants: 24 hours;
- Long-acting analgesics and cyclooxygenase -2 (COX-2) inhibitors: 5 times the elimination half-life;
- Honey: 12 hours;
- Cough lozenges: 12 hours;
- Cough/cold herbal medications, dietary supplements, beta-agonists: 24 hours;
- Mentholated topical ointments or patches: 12 hours;
- Any other cough/cold medication, saline rinses or washes, herbal remedy, homeopathic remedy, steam inhalation (humidifier): 12 hours;
- Potent CYP3A inhibitors: (eg, ritonavir, ketoconazole, clarithromycin): 5 times the elimination half-life;
- Selective serotonin uptake inhibitors: 5 times the elimination half-life;
- Angiotensin-converting enzyme inhibitors such as captopril (Capoten®) or enalapril (Vasotec®): 5 times the elimination half-life;
- Products with grapefruit, grapefruit juice, papaya or pomegranate: 72 hours (DiMarco, 2002).[4]

16. History of taking a medication that is sedating within the past 24 hours prior to screening (eg, sedatives, hypnotics, tranquilizers, anticonvulsants, benzodiazepines, and clonidine).

17. Current smoker or has smoked tobacco/nicotine-containing products, or been exposed to secondhand smoke (eg, living in the same household with a family member who smokes routinely in the home) within 6 months of entry into the study (Note: smoking or exposure to secondhand smoke is defined as 3 or more cigarettes per week).

18. History of substance abuse within 1 year prior to screening.

19. Subject has a sibling contemporaneously participating in this study.

20. Participation in other studies involving investigational drug(s) within 30 days prior to study entry and/or during study participation.

21. Previous participation in this study.

22. Investigational site staff members directly involved in the conduct of the study and their family members, study site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees directly involved in the conduct of the study. However, children related to hospital/clinical unit staff members not directly involved with the study may be enrolled.

### 4.3. Randomization Criteria

Subjects must meet all of the following criteria to be eligible for randomization:

1. Subjects must complete the 2-hour ambulatory cough counting baseline run-in recording period and must return to the study site for randomization at least 2 hours (+1 hour) after the recording started.

2. Subjects whose equipment failed, preventing collection of cough count data for at least 2 hours during the Baseline Run-in Period, or those who took off the device during this period will be excluded from further study participation.

3. Subjects who do not return to the study site (before 3:30 pm) in time for the afternoon dose will not be randomized.

4. The Child Global Question will be completed (Appendix 3). Subjects will rate the severity of their cold on a 5-point categorical scale in response to the question, “How bad is your cold today?” Subjects must have a response of at least ‘bad’ to be randomized into the study. The study site staff or parent/legally acceptable representative may assist the child with reading the words of the questions or responses, but may not assist in choosing the responses.

5. In addition, to qualify for the study, subjects must agree to follow the study requirements outlined in this protocol.

### 4.4. Lifestyle Guidelines

#### 4.4.1. Contraception

All male subjects who are able to father children and female subjects who, are of childbearing potential and in the opinion of the investigator, are sexually active and at risk for pregnancy, must agree that it is their preferred and usual lifestyle to abstain from sexual activity and must agree to continue to do so for the duration of the active treatment period and for 28 days after the last dose of investigational product. Abstinence is defined as refraining from all heterosexual intercourse; periodic abstinence (eg, calendar, ovulation, symptothermal or postovulation methods) and withdrawal are not acceptable for this study. The investigator or his/her designee will discuss with the subject and his/her parent/legally acceptable representative the need to remain abstinent according to the schedule of activities and document such conversation in the subject's chart. In addition, the investigator or his or her designee will instruct the subject to call immediately if he/she is unable/unwilling to comply or if pregnancy is known or suspected in the subject or the subject's partner.

### 4.5. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation and team SharePoint site.

To facilitate access to appropriately qualified medical personnel on study related medical questions or problems, subjects or parents/legally acceptable representatives are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, subject study number, contact information for the investigational site and contact details for a contact center in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should only be used in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace the established communication pathways between the investigational site and study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject or parent/legally acceptable representative directly and if a subject calls that number they will be directed back to the investigational site.

## 5. STUDY TREATMENTS

At the beginning of the Baseline Run-in Period, and in order to preserve the blinding due to potential taste differences between the double-blind active and placebo investigational products in this study, all subjects will be given a single-blind (to the parent/legally acceptable representative and subject), inactive (non-medicinal), liquid oral confection (Table 3) by a qualified member of the study site staff. The sponsor will supply bottles of Rose's Grenadine syrup for this purpose along with dosing cups.

**Table 3. Investigational Product for Baseline Run-In Period**

| Treatment Group | Per Unit | Per Dose/Route |
|---|---|---|
| Inactive (non-medicinal) Liquid Oral Confection - Rose's Grenadine Syrup<br>WH-0001-0569-(XXX) where XXX identifies the Investigational Product manufacturing supply lot | ---- | 10 mL, orally |

The sponsor will supply the following investigational product in double-blind fashion for administration during the Treatment Period (Table 4).

Subjects will be stratified by age group (6-8 years and 9-11 years) and randomized in a 1:1 ratio to receive investigational product during the 4 days of study participation. Subject enrollment will be actively monitored with the goal of attaining at least 40% population in the younger group (6-8 years).

Dosing is 10 mL orally administered 3 times daily except on Day 1 (when the subjects will receive 2 doses), and Day 4 (when the subjects will receive 1 dose in the morning).

**Table 4. Investigational Product for Treatment Period**

| Treatment Group | Per Unit | Per Dose/Route |
|---|---|---|
| DXM HBr Cough Syrup (118 mL/bottle) – Children's Robitussin Cough Long-Acting<br>WH-0508-0006-(XXX) where XXX identifies the Investigational Product manufacturing supply lot | Dextromethorphan HBr 15 mg/10 mL | 15 mg (10 mL, orally) |
| Placebo Oral Syrup (118 mL/bottle)<br>WH-1285-0009-(XXX) where XXX identifies the Investigational Product manufacturing supply lot | ---- | 10 mL orally |

During the Treatment Period, APAP will be provided by the sponsor as a permitted concomitant medication if required for headache, fever and/or body aches and pains associated with the common cold. The product will be provided as described in Table 5, and dosing will be as directed per the product label, based on weight or age.

**Table 5. Concomitant Medication**

| Concomitant Medication | Per Unit | Per Dose/Route |
|---|---|---|
| Acetaminophen 160 mg/5 mL oral suspension – Good Neighbor Pharmacy Children's Pain and Fever Suspension (Cherry) (118 mL bottle) WH-0001-0568-(XXX) where XXX identifies the concomitant medication supply lot | 160 mg/5 mL | Based on weight or age per product label directions, administered orally |

For the purposes of this study, and per International Conference on Harmonization (ICH) guidelines investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

### 5.1. Allocation to Treatment

Treatment assignments will be determined by a computer-generated randomization schedule created and maintained by Pfizer.

Subjects completing the Baseline Run-in Period as required will be randomized to 1 of 2 treatments, DXM HBr or placebo, in a 1:1 ratio, and stratified according to their age group, 6-8 and 9-11 years. Subjects 6-8 years will be assigned numbers in sequential order from PPD; subjects 9-11 years will be assigned numbers in sequential order from PPD.

The randomization list will be provided to Pfizer Consumer Health (PCH) Consumer Study Supplies for packaging and labeling.

### 5.2. Breaking the Blind (If Applicable)

In the event of a medical emergency that necessitates breaking the code, the sealed disclosure on the label containing emergency identification of the package contents may be opened. The blind will only be broken by the investigator in the event of an emergency for which knowledge of the subject's double-blind investigational product will have a direct impact on treatment decisions. Every effort will be made to discuss the decision to break the blind with the PCH monitor in advance.

When the blind is broken, the investigator will notify the sponsor's Clinical/Medical Monitor within 24 hours after determining that it is necessary to unblind the treatment assignment and document the reason and date of the unblinding. The event will also be recorded on the case report form (CRF) and in the source document. Any AE or serious adverse event (SAE) associated with breaking the blind must be recorded and reported as specified in this protocol.

## 5.3. Subject Compliance

- At Visit 2 (Day 2) and Visit 4 (Day 4, 5, or 6), study staff will assess compliance by visually evaluating remaining product quantities and subject diary information. Study staff will query the parent/legally acceptable representative if product quantity and subject diary information appears discrepant.

At the end of study completion, the subject and parent/legally acceptable representative will return all used and unused bottles of investigational product (ie, blinded investigational product), the outer study kit package, and the APAP concomitant medication.

Subject accountability will be assessed by verifying the number of doses recorded in the CRF (9±1 doses required, per protocol), as described in Section 5.7.

## 5.4. Investigational Product Supplies

### 5.4.1. Dosage Form(s) and Packaging

All study products will be code-labeled by the sponsor (PCH) or an appropriate designee.

Double-blinded investigational product will be packaged in identical 118 mL bottles, with a three-part tear-off label. Each bottle of investigational product will include a dose cup for product dispensing. The double-blind investigational products will be similar in flavor, scent, color and viscosity.

The inactive liquid oral confection for administration during the Baseline Run-In Period will be supplied in bulk bottles and will be labeled for investigational use. Dosing cups to dispense the oral confection will be provided.

Each subject will receive 1 bottle of APAP (liquid suspension 160 mg/5 mL, provided as a 118 mL commercially-labeled bottle) as unblinded permitted concomitant medication. The bottles of commercially marketed APAP will receive study labels.

Investigational product will be packaged in a numbered study kit containing the bottle of blinded investigational product, such that subjects randomized to DXM HBr will receive 1 bottle of DXM HBr oral syrup, and subjects randomized to placebo will receive 1 bottle of placebo oral syrup.

APAP oral suspension will also be provided to subjects for this study, allowed as a permitted concomitant medication if required for headache, fever and/or body aches and pains associated with the common cold. Prior to July, 2018, the APAP was provided as part of the investigational study kit. After Amendment #4, July 2018 (inclusive), APAP will be provided separate from the study kit.

### 5.4.2. Preparation and Dispensing

After completing the screening activities and confirming eligibility, all qualifying subjects will be given a single-blind (to the parent/legally acceptable representative and subject), inactive (non-medicinal) liquid oral confection at the beginning of the Baseline Run-in

Period. The liquid oral confection will be prepared at the study site in a room separate from other subject screening and baseline activities, by measuring the liquid oral confection into a dose cup (provided by the sponsor) prior to dispensing to the subject.

Upon return of the study subject after the 2-hour Baseline Run-in Period is completed, the investigator or qualified member of the study site staff will determine the appropriate stratification for the subject based on the subject's age, and randomize the subject by assigning the next available randomization number within the appropriate randomization block. The investigator or qualified member of the study site staff will remove the tear-off portion of the 3-part study label from the blinded investigational product bottle included in the study kit, prior to dispensing. The tear-off portion will be placed on a dispensing record, and the assigned subject number and kit number will be recorded on the dispensing log.

The investigator or qualified member of the study site staff will dispense the 10 mL dose of the appropriate investigational product, using the dose cup provided with the bottle.

The dispensing of the:

- single-blind liquid oral confection at the Baseline Run-in Period,
- first dose of double-blind investigational product at the clinical study site,
- the study kit with remaining investigational product, and
- the bottle of APAP.

will be documented on dispensing logs.

### 5.5. Administration

A dose cup will be provided to measure and dispense all double-blind investigational product doses. The dates and times for all doses administered by the parent/legally acceptable representative while away from the study site will be recorded in the subject's diary.

The dosing schedule is shown in Table 1. Recommended to be before 11:30 am, the investigator or qualified member of the study site staff will administer the single-blind (to the parent/legally acceptable representative and subject), inactive, liquid oral confection to subjects who qualify for the Baseline Run-in Period. If desired, the subject may have a drink of water. The time of administration will be recorded in the CRF.

Subsequent to the subject's return to the study site after the 2-hour Baseline Run-in Period is completed, each qualifying subject will be randomized to double-blind investigational product. The investigator or qualified member of the study site staff will administer the first dose of double-blind investigational product of DXM HBr 15mg/10mL or 10 mL of placebo to the subject, recommended to be before 3:30 pm, and record the time of dosing in the CRF. If desired, the subject may have a drink of water.

Subjects vomiting after the administration of Dose 1 at the clinic will not be re-dosed, and all the subsequent clinical procedures and dosings should be continued and performed as described in the protocol.

After the first dose of investigational product is administered, the subject will begin the 24-hour recording period using the VitaloJAK™ ambulatory cough count recording device. The investigator or qualified member of the study site staff will explain the dosing instructions for the subsequent doses to the parent/legally acceptable representative and then dispense the study kit (including the opened bottle of investigational product and dose cup) to the parent/legally acceptable representative. Prior to July 2018, the bottle of APAP was provided with the study kit; after Amendment #4, July 2018 (inclusive), APAP will be provided separate from the study kit.

On Day 1, the parent/legally acceptable representative will administer the second dose of double-blind investigational product to the subject within 30 minutes before bedtime, 6-8 hours from the previous dose (Dose 1). Although not encouraged, to allow the parent/legally acceptable representative some flexibility regarding the timing of the second dose, the second dose may be taken as early as 4 hours post-Dose 1, but not earlier.

The justification for the safety of a one-time 4-hour dosing window between Doses 1 and 2 for DXM 15 mg in children ages 6 to 11 years is based on summary safety data and overdose information in this age range. At exposures similar to the monograph dose or slightly above, the adverse event reporting rate for DXM is very low. Most reports of toxicity occur at high dosages because of misuse, ingestion with suicidal intent, or drug abuse. DXM is considered to have a wide margin of safety; in addition, pharmacokinetic polymorphism known to be a factor with DXM does not pose a clinically significant safety risk when therapeutic doses of DXM are used for short-term cough suppression, such as its use in this study (Bem, 1992).[1] In addition, on Day 1 of this study, 2 doses will be administered, for a total daily dose of 30 mg (half of the allowed maximum dose per monograph of 60 mg/day).

On Day 2 after completion of the morning subjective cough assessments, the parent/legally acceptable representative will administer the third dose of double-blind investigational product to the subject within 30 minutes of waking. In the afternoon, at least 24 hours after the first dose of the double-blind treatment and start of the cough recording, a study site visit will occur, during which time the VitaloJAK™ device will be removed, and the subject will complete the afternoon subjective cough assessment and the Child Global Question. If subjects and parent/legally acceptable representative return to the clinic in less than 24 hours, they will be asked to wait until the 24-hour recording period is complete for the device removal. The Day 2 afternoon dose will be administered by the parent/legally acceptable representative at the study site under supervision of study site staff.

The Day 2 evening dose, the Day 3 morning, afternoon, and evening doses, and the Day 4 morning dose will be administered by the parent/legally acceptable representative. The Day 4 morning dose is the final dose of study product to be administered during the study even if the End of Study visit (Visit 4) occurs on Day 5 or Day 6.

## 5.6. Investigational Product Storage

The investigator, or an approved representative, eg, pharmacist, will ensure that all investigational products including the inactive (non-medicinal) liquid oral confection and APAP are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational product should be stored in its original container and in accordance with the label. Storage conditions stated in the single reference safety document (SRSD) (eg, IB for DXM HBr and product labeling [monograph] for APAP) will be superseded by the storage conditions stated in the labeling.

The liquid oral confection (Rose's Grenadine Syrup) should be stored in accordance with the bottle label.

Study site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all study site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This information should be captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or study site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Controlled room temperature is defined as the temperature maintained thermostatically that encompasses at the usual and customary working environment of 20°-25°C (68°-77 °F). Excursions between 15° and 30°C (59° and 86 °F) that are experienced in pharmacies, hospitals, and warehouses, and during shipping, are allowed. Transient spikes up to 40° are permitted as long as these increases do not exceed 24 h in duration. Any excursions from the product label storage conditions should be reported upon discovery. The study site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor. Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to sponsor approval will be considered a protocol deviation.

Specific details regarding information the study site should report for each excursion will be provided to the study site.

Study site staff will instruct the subject's parent or legally acceptable representative on the proper storage requirements for take-home investigational products, and the need to return all unused products to the study site at Visit 3 and the End of Study visit.

### 5.7. Investigational Product Accountability

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies.

At the end of study completion, the subject and parent/legally acceptable representative will return all used and unused bottles of investigational product and the outer study kit package, as well as the APAP concomitant medication. Investigational product accountability will be assessed by the study monitor, who will measure the volume of the investigational product remaining in the returned bottle (ie, approximately 28±10 mL should remain in each bottle).

In addition, the monitor will inspect the storage facility at appropriate time intervals throughout the clinical investigation, depending on the length of the study. The principal investigator must account for any significant discrepancy and/or deficiency.

#### 5.7.1. Destruction of Investigational Product Supplies

At the end of the study, all used investigational study product (empty containers), as well as all unused study product will then be returned to:

Pfizer Consumer Healthcare Consumer Study Supplies
PPD
Attention: Consumer Study Supplies
Protocol No. A6531002
Phone: PPD

### 5.8. Concomitant Treatment(s)

Subjects who require medication on a continuing basis may be entered into the study provided none of the medications or the conditions which the medications are treating are excluded by the inclusion/exclusion criteria. All concomitant medication used during the study will be reported to the investigator or his/her staff and recorded on the subject's CRF.

During the Treatment Period, APAP will be permitted as a concomitant relief medication if required for headache, fever and/or body aches and pains associated with the common cold. If requested by parent/legally acceptable representative, use of ibuprofen (IBU) will be permitted after consultation with the investigator or designee. However, IBU will not be supplied by the sponsor. Dosing will be as directed per the product label, based on weight or age and must not exceed recommended dosage. The dates and times for all APAP doses will be recorded in the subject diary and IBU use will be recorded as a concomitant medication on the CRF.

No other medications expected to confound the evaluation of the investigational product will be allowed during the course of the study.

### 5.9. Rescue Medication

No rescue medication will be permitted during the study, in accordance with the prohibited treatments as outlined in Inclusion Criterion 6 and Exclusion Criterion 15.

## 6. STUDY PROCEDURES

### 6.1. Screening and Baseline

#### 6.1.1. Pre-Screening

Study personnel will pre-screen potential subjects by parental/legally acceptable representative interview. Those who meet all inclusion/exclusion criteria that can be assessed during pre-screening will be scheduled for Visit 1. In addition, a parent /legally acceptable representative must verbally confirm the availability to report to the study site at the scheduled time.

On the day of the observation period (Day 1), subjects will be asked to wear a comfortable T-shirt from home that can be worn through the completion of the 24-hour ambulatory cough recording period on Day 2.

#### 6.1.2. Screening/Morning Baseline (Day 1)

After the parent/legally acceptable representative has provided informed consent (See Section 12.2.1) and the subject has provided assent, subjects will then undergo eligibility screening, including:

- Review of demographics;
- Medical history;
- Medication history (including a discussion of all current medications and all medications, including vitamins and herbal supplements, taken up to 14 days prior to Visit 1);
- Vital signs assessment (sitting blood pressure, pulse rate, respiratory rate and temperature) as specified in Section 7.2.3;
- Height and weight measurements as detailed in Section 7.2.4;
- Lifestyle Assessments for boys and girls of child bearing potential will be reviewed as detailed in Section 4.4. A subject is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children (ie, post-menarchal);
- Urine pregnancy test for females of childbearing potential will be collected. A subject is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children (ie, post-menarchal);

- Inclusion/exclusion criteria review. Subjects who do not initially meet screening inclusion and exclusion criteria, may be re-screened for study participation if re-screening occurs at least 30 days after the initial screening period. Any subject re-screened will undergo all screening and baseline assessments. A subject may be re-screened only once;

- A full physical examination (including oropharyngeal examination) performed by a physician, physician's assistant or nurse practitioner as specified in Section 7.2.2. Examination findings must be consistent with signs of a cold or acute URTI;

- Subjects will provide responses to the subjective cough assessments at screening (Appendix 4). The study site staff or parent/ legally acceptable representative may assist the child with reading the words of the questions or responses, but may not assist in choosing the responses;

- Subjects will complete the Child Cold Symptom Checklist (Appendix 2). The study site staff or parent/ legally acceptable representative may assist the subject with reading the words of the questions or responses, but may not assist in choosing the responses.

### 6.1.3. Afternoon Baseline/Run-in Period: Visit 1 (Day 1)

Subjects who qualify for study participation, based on the inclusion and exclusion criteria described in Section 4.1 and Section 4.2, will be eligible for the Baseline Run-in Period. Scheduling of the Baseline Run-in Period must allow for administration of the baseline confection, recommended to be before 11:30 am.

Subjects will be assigned a VitaloJAK™ device. The study site staff will program the VitaloJAK™ and insert a new data card and batteries into the device, per Vitalograph instructions. The VitaloJAK™ lapel microphone will be clipped to the subject's clothing at the neck or upper chest level, and the chest wall sensor will be attached to the subject's chest at the top of the sternum for audio recording.

The parent/legally acceptable representative will be advised that the VitaloJAK™ is a sound recording device, and therefore may inadvertently capture confidential information from casual speech within its range; and that Vitalograph has standard operation procedures and measures in place to ensure that any such information is kept confidential, including removing such speech to a certain extent. While wearing the device the subject should also avoid overly noisy locations.

After the VitaloJAK™ device is checked for correct operation, the subject will be given a single-blind (to the parent/legally acceptable representative and subject), inactive (non-medicinal), liquid oral confection in a dose cup by a qualified member of the study site staff. -If desired by the subject, water will be provided. The recording will begin immediately (+5 minutes) after administration of the single-blind oral confection and the date and start time of the 2-hour run-in recording will be recorded in the CRF.

During the Baseline Run-in Period, continuous digital audio recordings will be obtained through the VitaloJAK™ device, clipped to the subject using a belt or fanny pack.

The subject and parent/legally acceptable representative will be released from the study site and instructed to engage in normal activities during the 2-hour ambulatory cough count monitoring. Alternatively, they may stay at the study site, if convenient. The study site staff will capture in the CRF whether or not the subject leaves the study site.

Subjects and their parent/legally acceptable representative will be instructed to return to the study site after at least 2 hours (+1 hour) after beginning the VitaloJAK™ cough count recording begins, and in time for a first dose recommended to be before 3:30 pm.

### 6.1.4. Randomization/First Dose: Visit 2 (Day 1)

Upon return to the study site after the 2-hour Baseline Run-in Period is completed, the VitaloJAK™ device will be removed and re-set with a new data card and batteries in accordance with the device instructions, in preparation for monitoring during the 24-hour Treatment Period. The date and stop time for the run-in recording will be recorded in the CRF.

Subjects must meet all of the following criteria to be eligible for randomization:

- Subjects must complete the 2-hour ambulatory cough counting period and return to the study site for randomization at least 2 hours (+1 hour) after the baseline cough count recording start.
    - Subjects whose equipment failed, preventing collection of cough count data for at least 2 hours during the Baseline Run-in Period, or those who took off the device during this period, will be excluded from further study participation.
- Subjects who do not return to the study site in time for the afternoon dose (recommended to be before 3:30 pm) will not be randomized.
- The Child Global Question will be completed (Appendix 3). Subjects will rate the severity of their cold on a 5-point categorical scale in response to the question, “How bad is your cold today?” Subjects must have a response of at least ‘bad’ to qualify for the study. The study site staff or parent/ legally acceptable representative may assist the subject with reading the words of the questions or responses, but may not assist in choosing the responses.
- In addition, subjects must agree to follow the study requirements outlined in this protocol.

Subjects who continue to qualify for the study and meet the randomization criteria will be:

- Stratified according to the subject's age, and randomized to receive DXM HBr (15 mg/10 mL) or placebo (10 mL) treatment;
- Instructed to complete the afternoon subjective cough assessments (Appendix 5) prior to dosing. The study site staff or parent/ legally acceptable representative may assist the subject with reading the words of the questions or responses, but may not assist in choosing the responses;
- Administered the first dose of double-blind investigational product, using the provided dose cup to measure the correct dose. The date and time of the first dose will be recorded in the CRF. Subjects vomiting after the administration of Dose 1 at the clinic will not be re-dosed, and all the subsequent clinical procedures and dosings should be continued and performed as described in the protocol;
- Set up with the VitaloJAKTM device, programmed for monitoring during the 24-hour Treatment Period. It will be placed on the subject as described for the Baseline Run-in Period (Section 6.1.3). At the time of administration of the assigned double-blind investigational product, the 24-hour ambulatory cough count recording period will begin (+5 minutes for scheduling purposes). The date and the start time of the 24-hour recording will be recorded in the CRF.

Prior to being dismissed from the study site the study site staff will provide the subject and the parent/legally acceptable representative:

- A diary for collection of assessments and doses administered while not at the study site. The study site staff will instruct the subject and parent/representative on how the diary should be completed, the times when each assessment should be completed each day, and what to do if an assessment is missed (ie, to leave it blank);
- Instructions for the ambulatory cough count recorder;
- Study medication (1 bottle of blinded investigational product with dose cup; and 1 bottle of open-label APAP with dose cup), along with dosing instructions for the remainder of Day 1 and Day 2 (ie, within 30 minutes of bedtime on Day 1, and the morning of Day 2 within 30 minutes of waking);
- Instructions to return for the next study visit on the afternoon of Day 2 with the cough recorder and accessories, the diary, and the investigational product and APAP bottles. The parent/legally acceptable representative will be instructed to not administer the afternoon dose of investigational product on Day 2 until returning to the study site;
- Instructions to not administer any of the prohibited treatments as outlined in inclusion criterion 6 and exclusion criterion 15.

Study site staff will assess any SAEs that may have occurred since signing consent/assent.

## 6.2. Treatment Period (Day 1 Evening – Day 4 Morning)

- Day 1 evening;

  Within 30 minutes of the subject's bedtime and ideally, approximately 6-8 hours after the afternoon dose, the parent/legally acceptable representative will administer the evening dose of double-blind investigational product to the subject, following the instructions provided by the study site staff. Although not encouraged, to allow the parent/legally acceptable representative some flexibility regarding the timing of the second dose, the second dose may be taken as early as 4 hours post-Dose 1, but not earlier.

- Day 2 morning;

  Within 30 minutes of waking, the subject will complete the Day 2 morning subjective cough assessments and receive the morning dose of double-blind investigational product. Any doses of APAP taken should be recorded in the diary.

- Day 2 afternoon (at study site);

  After the 24-hour ambulatory cough count recording is completed, the subject and parent/legally acceptable representative will return to the study site for removal and retrieval of the ambulatory cough count recorder and auxiliary equipment (device, microphone, sensor, instructions, etc.). The date and stop time for cough recording will be recorded by the study site staff on the CRF. Study site personnel will also assess compliance with the diary and dosing instructions to-date, and inquire about concomitant medication use and adverse events or SAEs.

- Prior to double-blind investigational product dosing, the subject will complete the Day 2 afternoon subjective cough assessments (Appendix 5), and then complete the Child Global Question found in Appendix 3;

- The parent/legally acceptable representative will administer the fourth dose of double-blind investigational product, following the instructions provided in Section 5.5. The date and time of dosing will be recorded in the CRF;

- The subject and parent/legally acceptable representative will be dismissed from the study site, with instructions for completing the study through Day 4, and an appointment to return on either the afternoon of Day 4 (or on Day 5 or 6 for scheduling flexibility) for the end of study visit. The subject and parent/legally acceptable representative will be instructed to return all study-related medications and the subject diary at the end of study visit.

Data collection required by subject and parent/legally acceptable representative from Day 1 evening through the afternoon of Day 4 of the study is indicated below:

- Times and dates of evening, morning, and afternoon dosing through morning of Day 4 for doses not taken at the study site (collected via diary);

- Subjective cough assessments by the subject in the morning and afternoon on Days 2 through 4 (collected via diary);
- The Child Global Question on the afternoons of Days 2-4 (collected via diary);
- The use of APAP (collected via diary).

### 6.3. Visit 4 (End of Study Visit; Day 4 Afternoon or Day 5 or 6)

An end of study visit will be scheduled in the afternoon of Day 4 (or Day 5 or 6 for scheduling flexibility), and will include the following activities:

- Collect bottles of double-blind investigational product and APAP, and assess compliance by visually evaluating remaining product quantities and subject diary information;
- Conduct full physical exam as outlined in Section 7.2.2;
- Conduct vital signs assessment (sitting blood pressure, pulse rate, respiratory rate and temperature);
- Collect and review subject diary;
- Review AE/SAE and concomitant treatment information during the study period (collected via CRF);
- Collect urine pregnancy test for females of childbearing potential. A subject is of childbearing potential if, in the opinion of the investigator, she is biologically capable of having children (ie, post-menarchal);
- Collect separate evaluations of subject and parent/legally acceptable representative global assessment of product satisfaction (collected via CRF).

### 6.4. Early Termination Visit

If an early termination occurs on Day 1, 2 or 3, the Early Termination Visit could be on those days. If not, an early termination visit should be scheduled to occur as soon as possible. (The early termination visit is not restricted to an afternoon timeframe. In the event of early termination, the subject-assessed afternoon cough assessment and the Child Global Question will not be performed). The Early Termination Visit will include the following activities:

- Collect bottles of double-blind investigational product and APAP, and assess compliance by visually evaluating remaining product quantities and subject diary information;
- Conduct full physical exam as outlined in Section 7.2.2;

- Conduct vital signs assessment (sitting blood pressure, pulse rate, respiratory rate and temperature;
- Collect and review subject diary;
- Review AE/SAE and concomitant treatment information during the study period (collected via CRF);
- Collect urine pregnancy test for females of childbearing potential. A subject is of childbearing potential if, in the opinion of the investigator, she is biologically capable of having children (ie, post- menarchal);
- Collect separate evaluations of subject and parent/legally acceptable representative global assessment of product satisfaction (collected via CRF).

### 6.5. Post-Study Follow-up

Fourteen days after the last dose of investigational product (ie, Day 18 + up to 3 days for scheduling flexibility), the study site staff will call the subject and parent/legally acceptable representative to inquire about any SAEs that may have occurred. This call should be documented in the source documentation and any SAE should be reported as specified in Section 8.1.4.

### 6.6. Subject Discontinuation

Changes in the subject's medical condition or diagnosis may require discontinuation from the study. Subjects who develop a complication of the common cold (eg, otitis media, sinusitis, or pneumonia) with or without the need for systemic antibiotics, become too ill to continue participation in the judgment of the investigator, show signs of dehydration (as may be due to vomiting, diarrhea, or lack of fluid intake), or develop a cough that occurs with excessive phlegm (mucus) should be discontinued. In addition, if the subject develops any condition that requires the use of any prohibited treatment as outlined in Inclusion Criterion 6 or Exclusion Criterion 15, the subject should be discontinued. If a parent/legally acceptable representative inadvertently administers any of these treatments the subject does not need to be discontinued, but the treatment must be recorded in the CRF. Attempts should be made to complete the study procedures outlined for the Early Termination Visit.

### 6.7. Subject Withdrawal

Withdrawal of consent: Subjects or their parent/legally acceptable representative who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject or their parent/legally acceptable representative specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject or their parent/legally acceptable representative to provide this information. Subjects or their parent/legally acceptable representative should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is

only from further receipt of investigational product or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Lost to follow-up: All reasonable efforts must be made to locate subjects or their parent/legally acceptable representative to determine and report their ongoing status. This includes follow-up with persons authorized by the subject or their parent/legally acceptable representative as noted above. Lost to follow-up is defined by the inability to reach the subject or parent/legally acceptable representative after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the subject or their parent/legally acceptable representative to one (1) registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed assent or their parent/legally acceptable representative informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject or their parent/legally acceptable representative remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

Subjects or their parent/legally acceptable representative may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject or their parent/legally acceptable representative. All attempts to contact the subject or their parent/legally acceptable representative and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return all unused investigational product(s) and study-related equipment, request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved adverse events (AEs).

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

# 7. ASSESSMENTS

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol required test cannot be performed the investigator will document the reason for this and any corrective and preventive actions which he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

## 7.1. Efficacy

### 7.1.1. Cough Counts

The primary efficacy assessment is based on objective cough counts, obtained from an ambulatory cough recording device (VitaloJAK™) that records cough sounds for a 24-hour period. The 24-hour cough recording period will begin after the 2-hour Baseline Run-in Period cough recording period is completed, at the time (+5 minutes) of the first dose of double-blind investigational product administration. The VitaloJAK™ device records continuous digital audio obtained through both a lapel microphone clipped to the subject's clothing at the neck or upper chest level, and a chest wall sensor attached to the subject's chest at the top of the sternum. Additional information regarding set-up and use of the VitaloJAK™ device and data retrieval/storage requirements are provided in the study-specific site manual prepared by Vitalograph, and supporting materials (eg, VitaloJAK™ Model 7100 User Manual) on file for this study.

The parent/legally acceptable representative will be advised that the VitaloJAK™ is a sound recording device, and therefore may inadvertently capture confidential information from casual speech within its range; and that Vitalograph has standard operation procedures and measures in place to ensure that any such information is kept confidential, including removing such speech to a certain extent. While wearing the device the subject should also avoid overly noisy locations.

Cough data will be retrieved from the VitaloJAK™ device, as available from the data cards (1 card from the Baseline Run-in Period and 1 card from the double-blind Treatment Period). Cough data will be downloaded by study site staff via a secure Vitalograph web portal, to a secure server with daily data back-up and firewall protection.

Vitalograph Cough Analysts, trained at the University of Manchester Respiratory Research Group, Manchester, United Kingdom, will follow standard operating procedures in obtaining objective counts of individual coughs from the audio recordings. These analysts will follow the standard cough counting procedures of the University of Manchester Respiratory Research Group. The counting process is described in Appendix 8.

The number of individual coughs will be quantified by counting the number of explosive sounds. An explosive sound is always present in a cough and is the characteristic sound recognized as cough (Smith, 2006a; Smith, 2008).[15,17] In a series of individual coughs, each expiration will be counted as 1 cough. Cough counts will be reported out in consecutive 1-hour segments over the entire 2-hour Baseline Run-in and 24-hour Treatment Periods.

### 7.1.2. Subjective Assessments

Subjective subject assessments of cough frequency, severity and impact on sleep will be obtained during this study, as described below. The self-assessment of cough symptoms will be completed using a validated PRO.

#### 7.1.2.1. Subjective Cough Assessments (Screening/Mornings)

Subjects will complete the following 3 questions at the Screening Visit on Day 1 morning as part of the screening evaluations (Appendix 4). Study site staff or parent/legally acceptable representative may assist the subject with reading the words of the questions or responses, but may not assist in choosing the responses.

Randomized subjects will complete the same questions on the mornings of Days 2-4 of the Treatment Period (within 30 minutes of waking and before their morning dose).

- Last night in bed, how much did your cough keep you awake?
- How bad is your cough this morning?
- From when you woke this morning until now, how much have you been coughing?

#### 7.1.2.2. Subjective Cough Assessments (Baseline/Afternoons)

Subjects will complete the following 2 questions at the Baseline Visit on Day 1 afternoon as part of the baseline evaluations before the first dose of double-blind investigational product (Appendix 5). Study site staff or parent/legally acceptable representative may assist the subject with reading the words of the questions or responses, but may not assist in choosing the responses.

Randomized subjects will complete the same questions on the afternoons of Days 2-4 of the Treatment Period (before the afternoon dose on Days 2 and 3). The assessment should be completed in the afternoon of Day 4 even if the End of Study visit occurs on Day 5 or 6.

- How bad is your cough this afternoon?
- How much have you been coughing this afternoon?

#### 7.1.2.3. Child Global Question

The Child Global Question below will be completed on Day 1 afternoon at Baseline (Visit 2) and on the afternoons of Days 2 through 4 (Appendix 3). The Child Global Question should be completed after afternoon subjective cough assessments, but before dosing. On Day 4, the

question should be completed in the afternoon even if the End of Study visit occurs on Day 5 or 6. The study site staff or parent/ legally acceptable representative may assist the child with reading the words of the question or responses, but may not assist the child in choosing the response

To be randomized into the treatment phase of the study on Day 1 (Visit 2), subjects must have a response of at least 'bad' to the Child Global Question.

- How bad is your cold today?

#### 7.1.2.4. Global Satisfaction by Subject

- Global satisfaction with the study medication will be self-assessed by the subject at the end of study site visit, scheduled on the afternoon of Day 4, or on Days 5 or 6 (Appendix 6). The study site staff or parent/legally acceptable representative may assist the subject with reading the words of the questions or responses, but may not assist in choosing the responses.

  - How would you rate the study medication for taking away your cough?

#### 7.1.2.5. Global Satisfaction by Parent/Legally Acceptable Representative

Global satisfaction with the study medication will be assessed by the parent/legally acceptable representative (after the subject assessment is completed) at the end of study office visit, scheduled on the afternoon of Day 4, or on Days 5 or 6 (Appendix 6). The parent/legally acceptable representative should complete this assessment (within + 20 minutes) after the subject has completed the global satisfaction assessment.

- How would you rate the study medication for taking away your child's cough?

### 7.2. Screening Assessments

#### 7.2.1. Pregnancy Testing

For female subjects of childbearing potential, a urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed before investigational product administration at the screening visit and at the end of treatment visit. A negative pregnancy result is required before the subject may receive the investigational product. A subject is of childbearing potential if, in the opinion of the investigator, she is biologically capable of having children (ie, post-menarchal). Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected), and/or at the end of the study to confirm the subject has not become pregnant during the study. In the case of a positive confirmed pregnancy test, the subject will be withdrawn from administration of investigational product but may remain in the study. Pregnancy tests may also be repeated as per request of Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) or if required by local regulations.

### 7.2.2. Physical Examination

Physical examinations (including oropharyngeal examination) may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation. A full physical examination will include head, ears, eyes, nose, mouth, skin, neck, throat, heart and lung examinations, lymph nodes, gastrointestinal, musculoskeletal, and neurological systems. Examinations will be performed at screening and Visit 4 (or end of study) and findings should be consistent with signs of a cold or acute URTI.

### 7.2.3. Vital Signs

Vital signs (sitting blood pressure, pulse rate, respiratory rate, and temperature) will be assessed at screening and Visit 4 (or end of study).

If a subject with no history of hypertension has a blood pressure reading at or above the limits specified in Appendix 7, the subject will be allowed to rest for 15 minutes and the blood pressure measurement repeated 2 additional times consecutively approximately 5 minutes apart. These three readings will be averaged. Subjects who have an average systolic and/or diastolic blood pressure reading at or above the established limit will be excluded from the study. The same arm (preferably the dominant arm) should be used throughout the study whenever possible.

Supine/sitting pulse rate will be between the ranges of 40 - 120 beats per minute (bpm), and respiration rates will be between 14 – 22 respirations/minute. If values are not within these set guidelines, a medically qualified study site staff member will determine if the subject is appropriate to continue in the study and will document in the CRF.

Temperature should be obtained orally.

### 7.2.4. Height and Weight Measurements

Height and weight measurements will only be collected at screening. Subject height should be obtained after removal of shoes, on a flat surface, with the heels touching the wall. If available, a stadiometer should be used. Height will be measured in inches, and weight will be measured in pounds.

## 7.3. Assessment of Suicidal Ideation and Behavior

A suicidality assessment evaluation is not a required assessment for DXM HBr for this study, given that this product is being dosed within product labeling, and given the product's use profile over at least 50 years with no documented signal for suicidality relative to the general population (Bem, 1992).[1]

## 7.4. Child Cold Symptom Checklist

The Child Cold Symptom Checklist (Appendix 2), a validated questionnaire that includes 9 questions intended to assess the severity of the subject's cold symptoms on a 5-point categorical scale, will be completed by the subject. For study qualification, subjects must have a self-reported: 1) rating of at least "Some" for cough and sore throat [questions 2 and

7, respectively], and 2) a rating of at least 'Some' for at least 1 other symptom of sneezing, runny nose, stuffy nose, and difficulty breathing deeply (hurting head, hurting face and aching arms and legs are additional non-qualifying symptoms assessed as part of the checklist). The study site staff or parent/ legal representative may assist the subject with reading the words of the questions or responses, but may not assist in choosing the responses.

## 8. ADVERSE EVENT REPORTING

### 8.1. Adverse Events

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

| **Safety Event** | **Recorded on the CRF** | **Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness** |
|---|---|---|
| SAE | All | All |
| Non-serious AE | All | None |
| Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure | All (regardless of whether associated with an AE), **except occupational exposure** | Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE) |

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain information adequate both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

As noted in the Protocol-Specified Serious Adverse Events section, should an investigator judge one of the identified protocol-specified SAEs to have a causal relationship with the investigational product, the investigator must report the SAE to Pfizer Safety within 24 hours of investigator awareness.

### 8.1.1. Additional Details on Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

### 8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study subject/parent(s)/legal guardian/legally acceptable representative. In addition, each study subject/parent(s)/legal guardian/legally acceptable representative will be questioned about the occurrence of AEs in a non-leading manner.

### 8.1.3. Withdrawal From the Study Due to Adverse Events (see Also the Subject Withdrawal Section)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

### 8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each subject begins from the time the subject provides informed consent, which is obtained before the subject's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 14 calendar days after the last administration of the investigational product.

For subjects who are screen failures, the active collection period ends when screen failure status is determined.

#### 8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a subject after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

#### 8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

### 8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

### 8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

## 8.2. Definitions

### 8.2.1. Adverse Events

An AE is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

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

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;

- Occupational exposure.

### 8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms and/or
- Test result requires additional diagnostic testing or medical/surgical intervention and/or
- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy and/or
- Test result is considered to be an AE by the investigator or sponsor.

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

### 8.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are 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.

### 8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same day surgeries (as outpatient/same day/ambulatory procedures).
- Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:
    - Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment laboratory abnormality);
    - Social admission (eg, subject has no place to sleep);
    - Administrative admission (eg, for yearly physical examination);
    - Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
    - Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
    - Hospitalization for observation without a medical AE;

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

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

### 8.3. Severity

If required on the AE case report forms, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:

| | |
|---|---|
| MILD | Does not interfere with subject's usual function |
| MODERATE | Interferes to some extent with subject's usual function |
| SEVERE | Interferes significantly with subject's usual function |

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

### 8.4. Special Situations

#### 8.4.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported to Pfizer Safety by the investigator as described in previous sections, and will be handled as SAEs in the safety database.

#### 8.4.2. Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

Liver function tests (LFTs) are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to assess LFTs because a subject presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For subjects with baseline AST OR ALT OR TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

- Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN or if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The subject should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous

analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

### 8.4.3. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

#### 8.4.3.1. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, due to treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product.

2. An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

3. A male has been exposed (eg, due to treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study subject or study subject's partner becomes or is found to be pregnant during the subject's treatment with the investigational product, the investigator must submit this information to the Pfizer Drug Safety Unit on the CT SAE report form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant

woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product;

- Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

#### 8.4.3.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

#### 8.4.3.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to the drug safety unit within 24 hours of the investigator's awareness, using the CT SAE report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a CRF; however, a copy of the completed SAE report form is maintained in the investigator site file.

### 8.4.4. Medication Errors

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

| Safety Event | Recorded on the CRF | Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness |
|---|---|---|
| Medication errors | All (regardless of whether associated with an AE) | Only if associated with an SAE |

#### 8.4.4.1. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong subject, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and non-serious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

### 8.5. Medical Device Complaint Reporting Requirements

All medical device complaints, regardless of whether the medical device complaint is associated with an AE, will be recorded on the applicable pages within the CRF. This includes potential incidents or malfunctions associated with the use of a medical device product. An incident or malfunction is an event that might have led to death or serious deterioration in health, or if it occurred again might lead to death or serious deterioration in health.

Pfizer is to be notified of all medical device complaints within 24 hours of the investigator's awareness of the event.

## 9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan, which will be maintained by the sponsor. This document may modify the plans outlined in this protocol; however, any major modifications to the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

### 9.1. Sample Size Determination

As there is limited information on cough count data for acute cough in pediatric population using this device in an ambulatory setting, a formal sample size determination cannot be performed. The sample size of approximately 150 subjects to be enrolled in the study was based on clinical judgment.

### 9.2. Efficacy Analysis

All computations will be performed using the SAS version 9.3 or later. Statistically significant treatment differences will be declared if the probability of random occurrence among or between the treatment groups (p) is $\leq 0.05$. Treatment differences will be declared marginally significant if $0.05 < p \leq 0.10$. All tests will be 2-sided.

Primary efficacy population (Full Analysis Set) will be the intent-to-treat population, defined as all subjects who are randomized, take Dose 1, have a valid baseline cough count assessment, and provide any post-dosing efficacy data. Subjects will be classified according to randomized treatment. This analysis set will be used for all efficacy analyses.

The per-protocol (PP) analysis set will be a subset of the FAS (Full Analysis Set) excluding data from subjects with important protocol deviations. The following deviations are considered to be important deviations leading to the exclusion from PP analysis set:

- Subjects who missed Dose 2 or Dose 3, or both
- Time of Dose 2 is missing.

- Subjects have less than one hour of cough count recording (ie, the post randomization recording period is shorter than one hour) in the first dosing interval.

Per Protocol analysis will only be performed for the primary and secondary endpoints.

### 9.2.1. Analysis of Primary Endpoint

The primary efficacy variable will be the total cough count collected by the cough recording device during the 24-hour interval post-first dose on Day 1.

The cough count during the 24-hour interval will be analyzed via a negative binomial regression model (SAS Proc GENMOD) with treatment, study site, baseline average cough count per hour (based on the Baseline Run-in Period), and age group terms in the model, with logarithm of the time over which the cough count is evaluated as the offset parameter. The ratio of rates and corresponding 95% confidence limit for DXM HBr vs placebo will be obtained from the primary model.

Further assessment will be conducted on the primary endpoint by adding the interaction term for 1) treatment by baseline average cough count, and 2) treatment by age group, separately, into the initial model.

If the treatment by age group interaction is significant ($p \leq 0.10$), the primary and the secondary end points may be analyzed by the levels of this stratifying factor.

In addition, the total 24-hour cough count will be log-transformed and analyzed using a linear model with treatment, study site, log-transformed baseline average cough count per hour (based on the Baseline Run-in Period), and age group terms in the model.

### 9.2.2. Analysis of Secondary Endpoints

- Total cough count collected by the cough recording device during the first dosing interval on Day 1 (interval between Dose 1 and Dose 2);

- Total cough count collected by the cough recording device over the dosing interval from Dose 2 on Day 1 to Dose 3 on Day 2 (ie, night time cough count);

- Total cough count collected by the cough recording device over the first dosing interval on Day 2 (interval between Dose 3 and Dose 4);

- Total cough count collected by the cough recording device over the first dosing interval on Day 1 (Dose 1 to Dose 2) and the first dosing interval on Day 2 (Dose 3 to Dose 4). These 2 dose intervals approximately represent the daytime cough count;

- Time accumulated over a 24-hour period when cough events occurred.

These first four endpoints (cough counts) will be analyzed via a similar negative binomial regression model as used for the primary parameter.

The cough time accumulated over a 24-hour period will be log transformed and analyzed with analysis of covariance (ANCOVA) model with treatment, study site, the log-transformed baseline cough time, and age group included in the model.

### 9.2.3. Analysis of Other Endpoints

- Change from screening evaluation (assessed in the morning) in morning cough frequency ("from when you woke up this morning until now, how much have you been coughing"), cough severity ("how bad is your cough this morning") and impact on sleep ("last night in bed, how much did your cough keep you awake"), assessed by subject.

These parameters collected from the PRO assessment will be analyzed using an ANOVA model with treatment, study site, the corresponding screening assessment by subject, and age group included in the model. The 95% confidence limit for the treatment difference will be based on the least squares means and their standard errors obtained from the final model.

- Change from baseline evaluation (assessed at afternoon) in afternoon cough frequency ("how much have you been coughing this afternoon") and severity ("how bad is your cough this afternoon") in the afternoon of Days 2-4, assessed by subject.

These parameters collected from the PRO assessment will be analyzed using an ANOVA model with treatment, study site, the corresponding baseline assessment by subject, and age group included in the model. The 95% confidence limit for the treatment difference will be based on the least squares means and their standard errors obtained from the final model.

- Change from baseline evaluation (assessed at afternoon) in daily assessment of the cold in the Child Global Question ("how bad is your cold today"), assessed by subject.

This parameter collected from the PRO assessment will be analyzed using an ANOVA model with treatment, study site, the baseline assessment in Child Global Question cold assessment by subject and age group included in the model. The 95% confidence limit for the treatment difference will be based on the least squares means and their standard errors obtained from the final model.

- Subject and parent/legally acceptable representative global assessments of satisfaction with investigational product at the end of the study.

The global satisfaction assessments collected from the PRO assessment (completed by subjects and parents) will also be analyzed by an ANOVA model with treatment, study site, and age group included in the model. The 95% confidence limit for the treatment difference will be based on the least squares means and their standard errors obtained from the final model.

Additionally, the interaction of treatment by stratification factor may be assessed by adding the interaction term to the initial model.

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### 9.3. Safety Analysis

The safety population will consist of all subjects who take at least one dose of investigational product (DXM HBr or placebo).

AEs will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term and classified according to their severity (mild, moderate, or severe) and relationship (related, or not related) to study product. For the summary by severity, subjects who have multiple occurrences of the same AE will be classified according to the worst reported severity of the AE. Similarly, for the summary by relationship to the study product, the AE will be classified according to the closest relationship.

Specifically, AEs occurred on Day 1 following the first dose will be summarized by treatment and by various intervals: 0- ≤4 hours, 4- ≤6 hours, 6- ≤8 hours, and >8 hours till midnight after first dose, separately for subjects who take their 2$^{nd}$ dose in (1) Hour 4 - ≤6; (2) Hour 6 - ≤8; and (3) later than Hour 8 on Day 1.

In addition, screening vital signs (blood pressure, pulse rate, rate of respiration, and temperature) will be summarized.

### 9.4. Interim Analysis

Due to the slow recruitment in children aged 6 to 11 years, an interim analysis is planned to assess the futility of the study at interim after at least 50% subjects have either completed or discontinued from the study. The interim analysis will be performed by an Internal Review Committee (IRC). The interim analysis details including decision criteria will be pre-specified and documented in the IRC charter and the interim statistical analysis plan. The results of the interim analysis will not be distributed to anyone directly involved in the management of all or part of the study or data collection including investigators and subjects. After reviewing the tabular data, the IRC members will make one of the following recommendations:

1. Continue the study unaltered; or

2. Terminate the study early.

Only one interim analysis will be performed in this study. This interim analysis does not consider the control of type-1 error, and sample size will not be re-estimated in this interim analysis.

The methodology used in the interim analysis is based on the calculation of conditional power using the weighted z-score test method[20-22] for the primary endpoint and one secondary endpoint. No efficacy claim will be made at the interim analysis.

### 9.5. Data Monitoring Committee

This study will use an IRC.

The IRC will evaluate the study data for the planned interim analysis according to and as pre-specified and documented in an IRC charter and an interim statistical analysis plan. The recommendations made by the IRC to continue or stop the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

## 10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practice (GCP) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the study site may be subject to review by the institutional review board (IRB)/ethics committee (EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the study site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

## 11. DATA HANDLING AND RECORD KEEPING

### 11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital or the physician's subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigative site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

### 11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent and assent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to ICH guidelines, according to local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

# 12. ETHICS

## 12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent/assent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/IEC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/IEC and Pfizer in writing immediately after the implementation.

## 12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

### 12.2.1. Subject Information and Consent/Assent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or in any other disclosures, except where required by laws.

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, address and other identifiable data will be replaced by a numerical code based on a numbering system provided by Pfizer in order to de-identify the study subjects. The study site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

The informed consent and assent document must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent and assent document(s) used during the informed consent process must be reviewed by the sponsor, approved by the IRB/IEC before use, and available for inspection.

The investigator must ensure that each study subject or his or her parent/legally acceptable representative is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a subject's parent/legally acceptable representative, the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject's decisional capacity is so limited he/she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his or her own consent, the source documents must record why the subject did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, parent, spouse), and that the subject's assent was obtained, or waived. If assent is obtained verbally it must be documented in the source documents.

The investigator, or a person designated by the investigator, will obtain written informed consent from each parent/legally acceptable representative before any study-specific activity is performed. In addition, assent will be obtained from the subject, except in instances where they cannot provide assent. The investigator will retain the original of each subject's signed consent and assent documents.

### 12.3. Subject Recruitment

Advertisements approved by IRBs/EC and investigator databases may be used as recruitment procedures. Advertisements may mention that compensation may be offered, but will not indicate the amount of compensation to which the subject or parent/legally acceptable representative may be entitled subsequent to study participation.

Pfizer will have an opportunity to review and approve the content of any study recruitment materials directed to potential study subjects before such materials are used.

### 12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH Good Clinical Practice

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP of that the investigator becomes aware of.

## 13. DEFINITION OF END OF TRIAL

### 13.1. End of Trial in Participating Countries

End of Trial is defined as last subject last visit (LSLV).

## 14. SPONSOR DISCONTINUATION CRITERIA

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

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 3 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

## 15. PUBLICATION OF STUDY RESULTS

### 15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies conducted in patients that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary completion date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

### 15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by principal investigator of the results of the study based on information collected or generated by principal investigator, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "Publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all study sites, and that any subsequent publications by the principal investigator will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating study sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any Attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

## 16. REFERENCES

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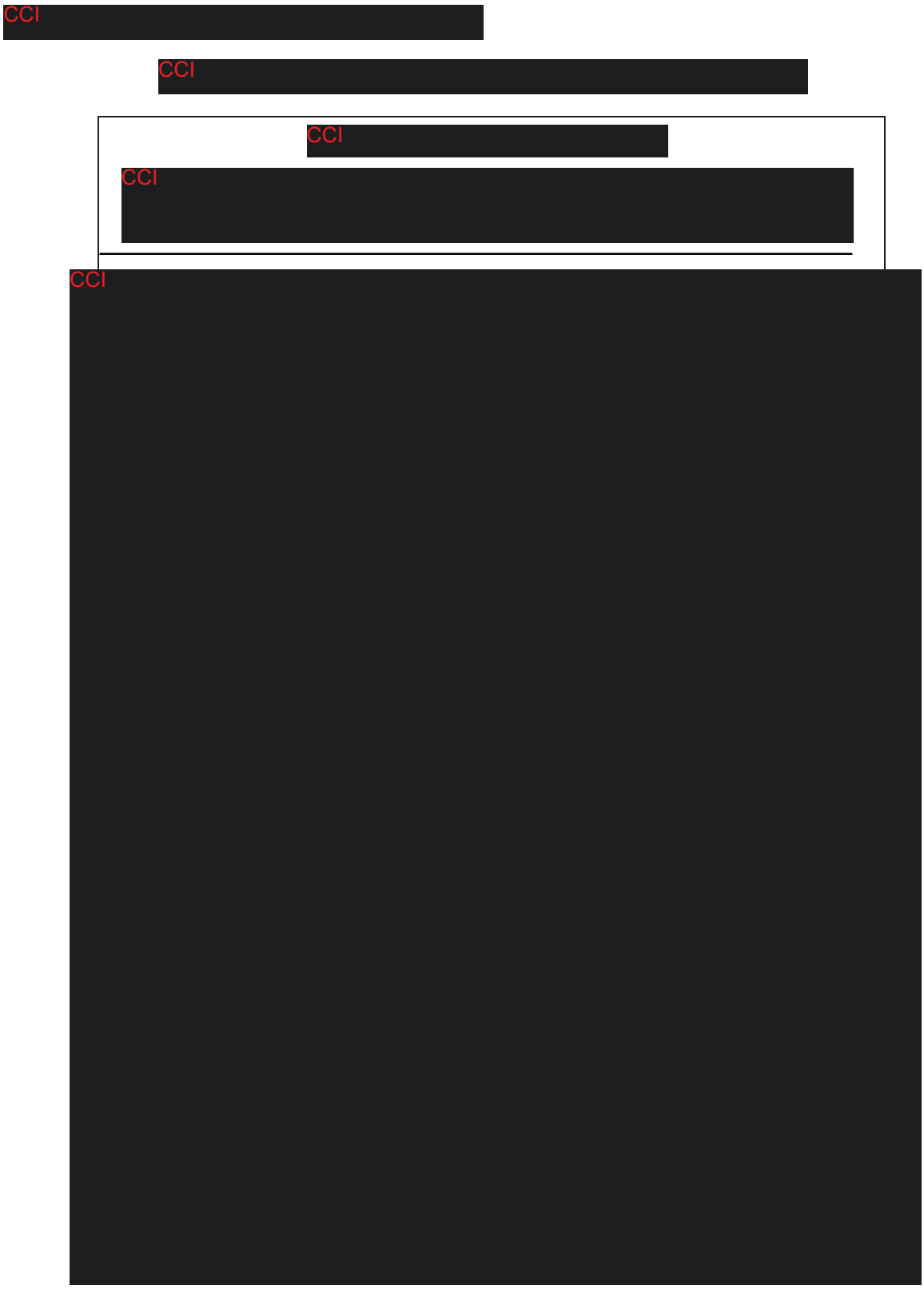
## Appendix 1. Abbreviations

This is a list of abbreviations that may be used in the protocol.

| Abbreviation | Term |
|---|---|
| ACCP | American College of Chest Physicians |
| AE | adverse event |
| ALT | alanine aminotransferase |
| ANCOVA | analysis of covariance |
| APAP | Acetaminophen |
| AST | aspartate aminotransferase |
| BP | blood pressure |
| bpm | beats per minute |
| CFR | Code of Federal Regulations |
| CHPA | Consumer Healthcare Products Association |
| COX-2 | cyclooxygenase-2 |
| CRF | case report form |
| CSA | clinical study agreement |
| CT | clinical trial |
| CYP3A | cytochrome P450, family 3, subfamily A |
| DXM | Dextromethorphan |
| DXM HBr | dextromethorphan hydrobromide |
| EC | ethics committee |
| EDP | exposure during pregnancy |
| EMEA | European Medicines Agency |
| EU | European Union |
| FAS | full analysis set |
| FDA | Food and Drug Administration (United States) |
| FSH | follicle stimulating hormone |
| GCP | Good Clinical Practice |
| GERD | gastroesophageal reflux disease |
| GRASE | Generally Considered as Safe and Effective |
| IB | investigator's brochure |
| IBU | Ibuprofen |
| ICH | International Conference on Harmonisation |
| IEC | independent ethics committee |
| IRB | institutional review board |
| IRC | internal review committee |
| IND | Investigational New Drug |
| INR | international normalized ratio |
| IUD | intrauterine device |
| LFT | liver function test |
| LSLV | last subject last visit |
| MedDRA | Medical Dictionary for Regulatory Activities |

| Abbreviation | Term |
|---|---|
| N/A | not applicable |
| OTC | over-the-counter |
| PCH | Pfizer Consumer Healthcare |
| PE | physical examination |
| PRO | patient-reported outcome |
| PT | prothrombin time |
| SAE | serious adverse event |
| SOC | System Organ Class |
| SRSD | single reference safety document |
| TEAEs | treatment-emergent adverse events |
| ULN | upper limit of normal |
| UPT | urine pregnancy test |
| URTI | upper respiratory tract infection |
| UK | United Kingdom |
| US | United States |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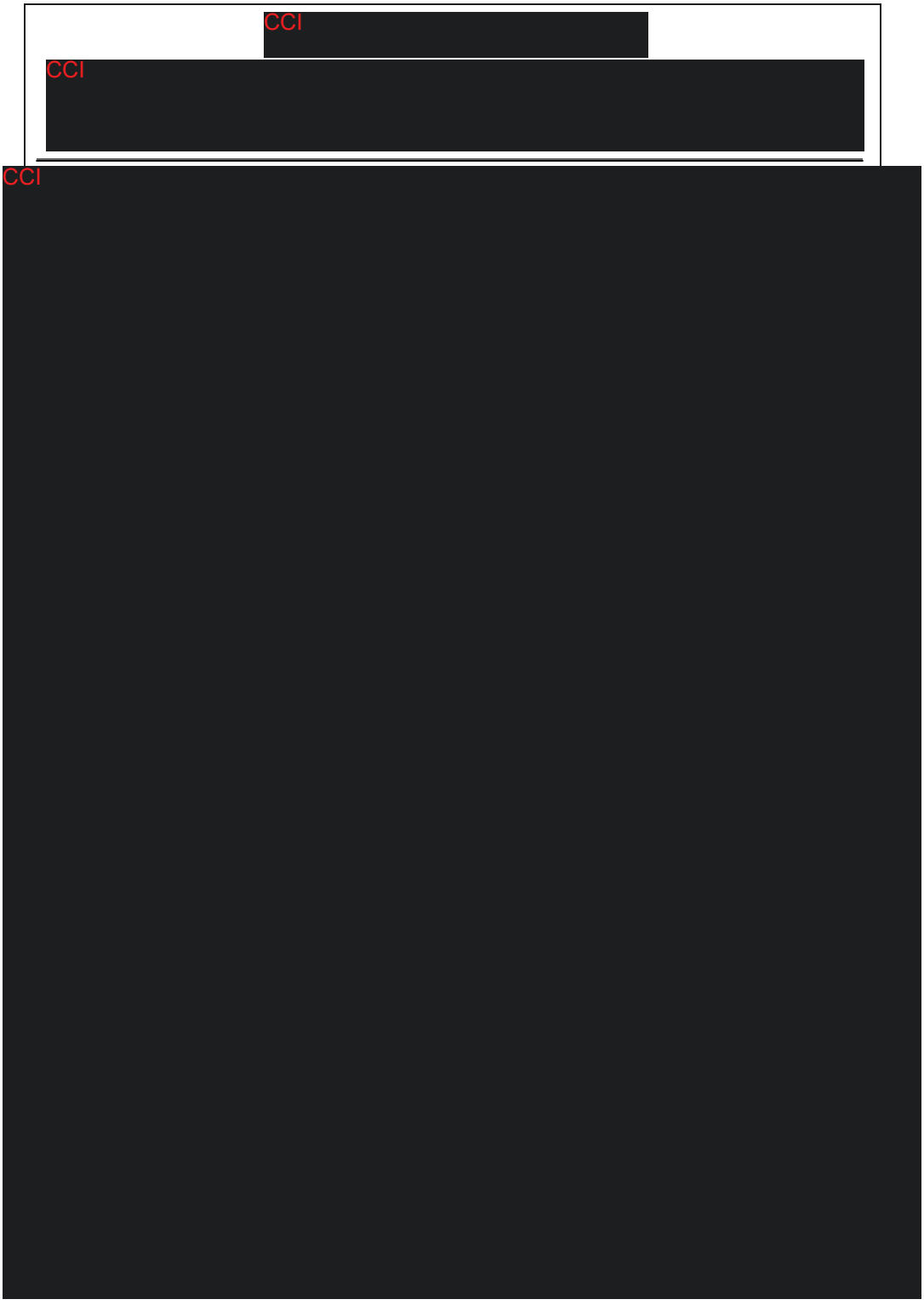
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## Appendix 6. Global Satisfaction

The global satisfaction question will be self-assessed by the subject at the end of study visit after all other activities have been completed. The corresponding question for the parent/legally acceptable representative should be completed after the subject's assessment (within +20 minutes).

**GLOBAL SATISFACTION BY SUBJECT**

**Circle one answer**

"How would you rate the study medication for taking away your cough?"

| 0 | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| Excellent | Very good | Good | Fair | Poor | Very poor | Terrible |

**GLOBAL SATISFACTION BY PARENT/LEGALLY ACCEPTABLE REPRESENTATIVE**

**Circle one answer**

"How would you rate the study medication for taking away your child's cough?"

| 0 | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| Excellent | Very good | Good | Fair | Poor | Very poor | Terrible |

## Appendix 7. Blood Pressure Levels for Boys and Girls

A simplified blood pressure table is provided below, which indicates when the provider should consult reference standards for identifying pediatric hypertension (extracted from Mitchell, 2011).[8]

| Look up blood pressure value if… | | |
|---|---|---|
| **Age in years** | **Systolic BP (mmHg)** | **Diastolic BP (mmHg)** |
| 6 to <9 | ≥105 | >70 |
| 9 to <12 | ≥110 | >75 |

If BP must be assessed further to determine study eligibility, systolic or diastolic blood pressure level at or above the 95$^{th}$ percentile by gender, age, and height (NHBPEPWG, 2004)[10] should be excluded. Reference tables are provided below.

## Blood Pressure Levels for Boys by Age and Height Percentile

| Age (Year) | BP Percentile ↓ | Systolic BP (mmHg) ← Percentile of Height → | | | | | | | Diastolic BP (mmHg) ← Percentile of Height → | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 5th | 10th | 25th | 50th | 75th | 90th | 95th | 5th | 10th | 25th | 50th | 75th | 90th | 95th |
| 1 | 50th | 80 | 81 | 83 | 85 | 87 | 88 | 89 | 34 | 35 | 36 | 37 | 38 | 39 | 39 |
| | 90th | 94 | 95 | 97 | 99 | 100 | 102 | 103 | 49 | 50 | 51 | 52 | 53 | 53 | 54 |
| | 95th | 98 | 99 | 101 | 103 | 104 | 106 | 106 | 54 | 54 | 55 | 56 | 57 | 58 | 58 |
| | 99th | 105 | 106 | 108 | 110 | 112 | 113 | 114 | 61 | 62 | 63 | 64 | 65 | 66 | 66 |
| 2 | 50th | 84 | 85 | 87 | 88 | 90 | 92 | 92 | 39 | 40 | 41 | 42 | 43 | 44 | 44 |
| | 90th | 97 | 99 | 100 | 102 | 104 | 105 | 106 | 54 | 55 | 56 | 57 | 58 | 58 | 59 |
| | 95th | 101 | 102 | 104 | 106 | 108 | 109 | 110 | 59 | 59 | 60 | 61 | 62 | 63 | 63 |
| | 99th | 109 | 110 | 111 | 113 | 115 | 117 | 117 | 66 | 67 | 68 | 69 | 70 | 71 | 71 |
| 3 | 50th | 86 | 87 | 89 | 91 | 93 | 94 | 95 | 44 | 44 | 45 | 46 | 47 | 48 | 48 |
| | 90th | 100 | 101 | 103 | 105 | 107 | 108 | 109 | 59 | 59 | 60 | 61 | 62 | 63 | 63 |
| | 95th | 104 | 105 | 107 | 109 | 110 | 112 | 113 | 63 | 63 | 64 | 65 | 66 | 67 | 67 |
| | 99th | 111 | 112 | 114 | 116 | 118 | 119 | 120 | 71 | 71 | 72 | 73 | 74 | 75 | 75 |
| 4 | 50th | 88 | 89 | 91 | 93 | 95 | 96 | 97 | 47 | 48 | 49 | 50 | 51 | 51 | 52 |
| | 90th | 102 | 103 | 105 | 107 | 109 | 110 | 111 | 62 | 63 | 64 | 65 | 66 | 66 | 67 |
| | 95th | 106 | 107 | 109 | 111 | 112 | 114 | 115 | 66 | 67 | 68 | 69 | 70 | 71 | 71 |
| | 99th | 113 | 114 | 116 | 118 | 120 | 121 | 122 | 74 | 75 | 76 | 77 | 78 | 78 | 79 |
| 5 | 50th | 90 | 91 | 93 | 95 | 96 | 98 | 98 | 50 | 51 | 52 | 53 | 54 | 55 | 55 |
| | 90th | 104 | 105 | 106 | 108 | 110 | 111 | 112 | 65 | 66 | 67 | 68 | 69 | 69 | 70 |
| | 95th | 108 | 109 | 110 | 112 | 114 | 115 | 116 | 69 | 70 | 71 | 72 | 73 | 74 | 74 |
| | 99th | 115 | 116 | 118 | 120 | 121 | 123 | 123 | 77 | 78 | 79 | 80 | 81 | 81 | 82 |
| 6 | 50th | 91 | 92 | 94 | 96 | 98 | 99 | 100 | 53 | 53 | 54 | 55 | 56 | 57 | 57 |
| | 90th | 105 | 106 | 108 | 110 | 111 | 113 | 113 | 68 | 68 | 69 | 70 | 71 | 72 | 72 |
| | 95th | 109 | 110 | 112 | 114 | 115 | 117 | 117 | 72 | 72 | 73 | 74 | 75 | 76 | 76 |
| | 99th | 116 | 117 | 119 | 121 | 123 | 124 | 125 | 80 | 80 | 81 | 82 | 83 | 84 | 84 |
| 7 | 50th | 92 | 94 | 95 | 97 | 99 | 100 | 101 | 55 | 55 | 56 | 57 | 58 | 59 | 59 |
| | 90th | 106 | 107 | 109 | 111 | 113 | 114 | 115 | 70 | 70 | 71 | 72 | 73 | 74 | 74 |
| | 95th | 110 | 111 | 113 | 115 | 117 | 118 | 119 | 74 | 74 | 75 | 76 | 77 | 78 | 78 |
| | 99th | 117 | 118 | 120 | 122 | 124 | 125 | 126 | 82 | 82 | 83 | 84 | 85 | 86 | 86 |
| 8 | 50th | 94 | 95 | 97 | 99 | 100 | 102 | 102 | 56 | 57 | 58 | 59 | 60 | 60 | 61 |
| | 90th | 107 | 109 | 110 | 112 | 114 | 115 | 116 | 71 | 72 | 72 | 73 | 74 | 75 | 76 |
| | 95th | 111 | 112 | 114 | 116 | 118 | 119 | 120 | 75 | 76 | 77 | 78 | 79 | 79 | 80 |
| | 99th | 119 | 120 | 122 | 123 | 125 | 127 | 127 | 83 | 84 | 85 | 86 | 87 | 87 | 88 |
| 9 | 50th | 95 | 96 | 98 | 100 | 102 | 103 | 104 | 57 | 58 | 59 | 60 | 61 | 61 | 62 |
| | 90th | 109 | 110 | 112 | 114 | 115 | 117 | 118 | 72 | 73 | 74 | 75 | 76 | 76 | 77 |
| | 95th | 113 | 114 | 116 | 118 | 119 | 121 | 121 | 76 | 77 | 78 | 79 | 80 | 81 | 81 |
| | 99th | 120 | 121 | 123 | 125 | 127 | 128 | 129 | 84 | 85 | 86 | 87 | 88 | 88 | 89 |
| 10 | 50th | 97 | 98 | 100 | 102 | 103 | 105 | 106 | 58 | 59 | 60 | 61 | 61 | 62 | 63 |
| | 90th | 111 | 112 | 114 | 115 | 117 | 119 | 119 | 73 | 73 | 74 | 75 | 76 | 77 | 78 |
| | 95th | 115 | 116 | 117 | 119 | 121 | 122 | 123 | 77 | 78 | 79 | 80 | 81 | 81 | 82 |
| | 99th | 122 | 123 | 125 | 127 | 128 | 130 | 130 | 85 | 86 | 86 | 88 | 88 | 89 | 90 |

## Blood Pressure Levels for Boys by Age and Height Percentile (Continued)

| Age (Year) | BP Percentile ↓ | Systolic BP (mmHg) ← Percentile of Height → | | | | | | | Diastolic BP (mmHg) ← Percentile of Height → | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 5th | 10th | 25th | 50th | 75th | 90th | 95th | 5th | 10th | 25th | 50th | 75th | 90th | 95th |
| 11 | 50th | 99 | 100 | 102 | 104 | 105 | 107 | 107 | 59 | 59 | 60 | 61 | 62 | 63 | 63 |
| | 90th | 113 | 114 | 115 | 117 | 119 | 120 | 121 | 74 | 74 | 75 | 76 | 77 | 78 | 78 |
| | 95th | 117 | 118 | 119 | 121 | 123 | 124 | 125 | 78 | 78 | 79 | 80 | 81 | 82 | 82 |
| | 99th | 124 | 125 | 127 | 129 | 130 | 132 | 132 | 86 | 86 | 87 | 88 | 89 | 90 | 90 |
| 12 | 50th | 101 | 102 | 104 | 106 | 108 | 109 | 110 | 59 | 60 | 61 | 62 | 63 | 63 | 64 |
| | 90th | 115 | 116 | 118 | 120 | 121 | 123 | 123 | 74 | 75 | 75 | 76 | 77 | 78 | 79 |
| | 95th | 119 | 120 | 122 | 123 | 125 | 127 | 127 | 78 | 79 | 80 | 81 | 82 | 82 | 83 |
| | 99th | 126 | 127 | 129 | 131 | 133 | 134 | 135 | 86 | 87 | 88 | 89 | 90 | 90 | 91 |
| 13 | 50th | 104 | 105 | 106 | 108 | 110 | 111 | 112 | 60 | 60 | 61 | 62 | 63 | 64 | 64 |
| | 90th | 117 | 118 | 120 | 122 | 124 | 125 | 126 | 75 | 75 | 76 | 77 | 78 | 79 | 79 |
| | 95th | 121 | 122 | 124 | 126 | 128 | 129 | 130 | 79 | 79 | 80 | 81 | 82 | 83 | 83 |
| | 99th | 128 | 130 | 131 | 133 | 135 | 136 | 137 | 87 | 87 | 88 | 89 | 90 | 91 | 91 |
| 14 | 50th | 106 | 107 | 109 | 111 | 113 | 114 | 115 | 60 | 61 | 62 | 63 | 64 | 65 | 65 |
| | 90th | 120 | 121 | 123 | 125 | 126 | 128 | 128 | 75 | 76 | 77 | 78 | 79 | 79 | 80 |
| | 95th | 124 | 125 | 127 | 128 | 130 | 132 | 132 | 80 | 80 | 81 | 82 | 83 | 84 | 84 |
| | 99th | 131 | 132 | 134 | 136 | 138 | 139 | 140 | 87 | 88 | 89 | 90 | 91 | 92 | 92 |
| 15 | 50th | 109 | 110 | 112 | 113 | 115 | 117 | 117 | 61 | 62 | 63 | 64 | 65 | 66 | 66 |
| | 90th | 122 | 124 | 125 | 127 | 129 | 130 | 131 | 76 | 77 | 78 | 79 | 80 | 80 | 81 |
| | 95th | 126 | 127 | 129 | 131 | 133 | 134 | 135 | 81 | 81 | 82 | 83 | 84 | 85 | 85 |
| | 99th | 134 | 135 | 136 | 138 | 140 | 142 | 142 | 88 | 89 | 90 | 91 | 92 | 93 | 93 |
| 16 | 50th | 111 | 112 | 114 | 116 | 118 | 119 | 120 | 63 | 63 | 64 | 65 | 66 | 67 | 67 |
| | 90th | 125 | 126 | 128 | 130 | 131 | 133 | 134 | 78 | 78 | 79 | 80 | 81 | 82 | 82 |
| | 95th | 129 | 130 | 132 | 134 | 135 | 137 | 137 | 82 | 83 | 83 | 84 | 85 | 86 | 87 |
| | 99th | 136 | 137 | 139 | 141 | 143 | 144 | 145 | 90 | 90 | 91 | 92 | 93 | 94 | 94 |
| 17 | 50th | 114 | 115 | 116 | 118 | 120 | 121 | 122 | 65 | 66 | 66 | 67 | 68 | 69 | 70 |
| | 90th | 127 | 128 | 130 | 132 | 134 | 135 | 136 | 80 | 80 | 81 | 82 | 83 | 84 | 84 |
| | 95th | 131 | 132 | 134 | 136 | 138 | 139 | 140 | 84 | 85 | 86 | 87 | 87 | 88 | 89 |
| | 99th | 139 | 140 | 141 | 143 | 145 | 146 | 147 | 92 | 93 | 93 | 94 | 95 | 96 | 97 |

BP, blood pressure

* The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.

For research purposes, the standard deviations in Appendix Table B–1 allow one to compute BP Z-scores and percentiles for boys with height percentiles given in Table 3 (i.e., the 5th,10th, 25th, 50th, 75th, 90th, and 95th percentiles). These height percentiles must be converted to height Z-scores given by (5% = -1.645; 10% = -1.28; 25% = -0.68; 50% = 0; 75% = 0.68; 90% = 1.28%; 95% = 1.645) and then computed according to the methodology in steps 2–4 described in Appendix B. For children with height percentiles other than these, follow steps 1–4 as described in Appendix B.

## Blood Pressure Levels for Girls by Age and Height Percentile

| Age (Year) | BP Percentile ↓ | Systolic BP (mmHg) ← Percentile of Height → | | | | | | | Diastolic BP (mmHg) ← Percentile of Height → | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 5th | 10th | 25th | 50th | 75th | 90th | 95th | 5th | 10th | 25th | 50th | 75th | 90th | 95th |
| 1 | 50th | 83 | 84 | 85 | 86 | 88 | 89 | 90 | 38 | 39 | 39 | 40 | 41 | 41 | 42 |
| | 90th | 97 | 97 | 98 | 100 | 101 | 102 | 103 | 52 | 53 | 53 | 54 | 55 | 55 | 56 |
| | 95th | 100 | 101 | 102 | 104 | 105 | 106 | 107 | 56 | 57 | 57 | 58 | 59 | 59 | 60 |
| | 99th | 108 | 108 | 109 | 111 | 112 | 113 | 114 | 64 | 64 | 65 | 65 | 66 | 67 | 67 |
| 2 | 50th | 85 | 85 | 87 | 88 | 89 | 91 | 91 | 43 | 44 | 44 | 45 | 46 | 46 | 47 |
| | 90th | 98 | 99 | 100 | 101 | 103 | 104 | 105 | 57 | 58 | 58 | 59 | 60 | 61 | 61 |
| | 95th | 102 | 103 | 104 | 105 | 107 | 108 | 109 | 61 | 62 | 62 | 63 | 64 | 65 | 65 |
| | 99th | 109 | 110 | 111 | 112 | 114 | 115 | 116 | 69 | 69 | 70 | 70 | 71 | 72 | 72 |
| 3 | 50th | 86 | 87 | 88 | 89 | 91 | 92 | 93 | 47 | 48 | 48 | 49 | 50 | 50 | 51 |
| | 90th | 100 | 100 | 102 | 103 | 104 | 106 | 106 | 61 | 62 | 62 | 63 | 64 | 64 | 65 |
| | 95th | 104 | 104 | 105 | 107 | 108 | 109 | 110 | 65 | 66 | 66 | 67 | 68 | 68 | 69 |
| | 99th | 111 | 111 | 113 | 114 | 115 | 116 | 117 | 73 | 73 | 74 | 74 | 75 | 76 | 76 |
| 4 | 50th | 88 | 88 | 90 | 91 | 92 | 94 | 94 | 50 | 50 | 51 | 52 | 52 | 53 | 54 |
| | 90th | 101 | 102 | 103 | 104 | 106 | 107 | 108 | 64 | 64 | 65 | 66 | 67 | 67 | 68 |
| | 95th | 105 | 106 | 107 | 108 | 110 | 111 | 112 | 68 | 68 | 69 | 70 | 71 | 71 | 72 |
| | 99th | 112 | 113 | 114 | 115 | 117 | 118 | 119 | 76 | 76 | 76 | 77 | 78 | 79 | 79 |
| 5 | 50th | 89 | 90 | 91 | 93 | 94 | 95 | 96 | 52 | 53 | 53 | 54 | 55 | 55 | 56 |
| | 90th | 103 | 103 | 105 | 106 | 107 | 109 | 109 | 66 | 67 | 67 | 68 | 69 | 69 | 70 |
| | 95th | 107 | 107 | 108 | 110 | 111 | 112 | 113 | 70 | 71 | 71 | 72 | 73 | 73 | 74 |
| | 99th | 114 | 114 | 116 | 117 | 118 | 120 | 120 | 78 | 78 | 79 | 79 | 80 | 81 | 81 |
| 6 | 50th | 91 | 92 | 93 | 94 | 96 | 97 | 98 | 54 | 54 | 55 | 56 | 56 | 57 | 58 |
| | 90th | 104 | 105 | 106 | 108 | 109 | 110 | 111 | 68 | 68 | 69 | 70 | 70 | 71 | 72 |
| | 95th | 108 | 109 | 110 | 111 | 113 | 114 | 115 | 72 | 72 | 73 | 74 | 74 | 75 | 76 |
| | 99th | 115 | 116 | 117 | 119 | 120 | 121 | 122 | 80 | 80 | 80 | 81 | 82 | 83 | 83 |
| 7 | 50th | 93 | 93 | 95 | 96 | 97 | 99 | 99 | 55 | 56 | 56 | 57 | 58 | 58 | 59 |
| | 90th | 106 | 107 | 108 | 109 | 111 | 112 | 113 | 69 | 70 | 70 | 71 | 72 | 72 | 73 |
| | 95th | 110 | 111 | 112 | 113 | 115 | 116 | 116 | 73 | 74 | 74 | 75 | 76 | 76 | 77 |
| | 99th | 117 | 118 | 119 | 120 | 122 | 123 | 124 | 81 | 81 | 82 | 82 | 83 | 84 | 84 |
| 8 | 50th | 95 | 95 | 96 | 98 | 99 | 100 | 101 | 57 | 57 | 57 | 58 | 59 | 60 | 60 |
| | 90th | 108 | 109 | 110 | 111 | 113 | 114 | 114 | 71 | 71 | 71 | 72 | 73 | 74 | 74 |
| | 95th | 112 | 112 | 114 | 115 | 116 | 118 | 118 | 75 | 75 | 75 | 76 | 77 | 78 | 78 |
| | 99th | 119 | 120 | 121 | 122 | 123 | 125 | 125 | 82 | 82 | 83 | 83 | 84 | 85 | 86 |
| 9 | 50th | 96 | 97 | 98 | 100 | 101 | 102 | 103 | 58 | 58 | 58 | 59 | 60 | 61 | 61 |
| | 90th | 110 | 110 | 112 | 113 | 114 | 116 | 116 | 72 | 72 | 72 | 73 | 74 | 75 | 75 |
| | 95th | 114 | 114 | 115 | 117 | 118 | 119 | 120 | 76 | 76 | 76 | 77 | 78 | 79 | 79 |
| | 99th | 121 | 121 | 123 | 124 | 125 | 127 | 127 | 83 | 83 | 84 | 84 | 85 | 86 | 87 |
| 10 | 50th | 98 | 99 | 100 | 102 | 103 | 104 | 105 | 59 | 59 | 59 | 60 | 61 | 62 | 62 |
| | 90th | 112 | 112 | 114 | 115 | 116 | 118 | 118 | 73 | 73 | 73 | 74 | 75 | 76 | 76 |
| | 95th | 116 | 116 | 117 | 119 | 120 | 121 | 122 | 77 | 77 | 77 | 78 | 79 | 80 | 80 |
| | 99th | 123 | 123 | 125 | 126 | 127 | 129 | 129 | 84 | 84 | 85 | 86 | 86 | 87 | 88 |

## Blood Pressure Levels for Girls by Age and Height Percentile (Continued)

| Age (Year) | BP Percentile ↓ | Systolic BP (mmHg) ← Percentile of Height → | | | | | | | Diastolic BP (mmHg) ← Percentile of Height → | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 5th | 10th | 25th | 50th | 75th | 90th | 95th | 5th | 10th | 25th | 50th | 75th | 90th | 95th |
| 11 | 50th | 100 | 101 | 102 | 103 | 105 | 106 | 107 | 60 | 60 | 60 | 61 | 62 | 63 | 63 |
| | 90th | 114 | 114 | 116 | 117 | 118 | 119 | 120 | 74 | 74 | 74 | 75 | 76 | 77 | 77 |
| | 95th | 118 | 118 | 119 | 121 | 122 | 123 | 124 | 78 | 78 | 78 | 79 | 80 | 81 | 81 |
| | 99th | 125 | 125 | 126 | 128 | 129 | 130 | 131 | 85 | 85 | 86 | 87 | 87 | 88 | 89 |
| 12 | 50th | 102 | 103 | 104 | 105 | 107 | 108 | 109 | 61 | 61 | 61 | 62 | 63 | 64 | 64 |
| | 90th | 116 | 116 | 117 | 119 | 120 | 121 | 122 | 75 | 75 | 75 | 76 | 77 | 78 | 78 |
| | 95th | 119 | 120 | 121 | 123 | 124 | 125 | 126 | 79 | 79 | 79 | 80 | 81 | 82 | 82 |
| | 99th | 127 | 127 | 128 | 130 | 131 | 132 | 133 | 86 | 86 | 87 | 88 | 88 | 89 | 90 |
| 13 | 50th | 104 | 105 | 106 | 107 | 109 | 110 | 110 | 62 | 62 | 62 | 63 | 64 | 65 | 65 |
| | 90th | 117 | 118 | 119 | 121 | 122 | 123 | 124 | 76 | 76 | 76 | 77 | 78 | 79 | 79 |
| | 95th | 121 | 122 | 123 | 124 | 126 | 127 | 128 | 80 | 80 | 80 | 81 | 82 | 83 | 83 |
| | 99th | 128 | 129 | 130 | 132 | 133 | 134 | 135 | 87 | 87 | 88 | 89 | 89 | 90 | 91 |
| 14 | 50th | 106 | 106 | 107 | 109 | 110 | 111 | 112 | 63 | 63 | 63 | 64 | 65 | 66 | 66 |
| | 90th | 119 | 120 | 121 | 122 | 124 | 125 | 125 | 77 | 77 | 77 | 78 | 79 | 80 | 80 |
| | 95th | 123 | 123 | 125 | 126 | 127 | 129 | 129 | 81 | 81 | 81 | 82 | 83 | 84 | 84 |
| | 99th | 130 | 131 | 132 | 133 | 135 | 136 | 136 | 88 | 88 | 89 | 90 | 90 | 91 | 92 |
| 15 | 50th | 107 | 108 | 109 | 110 | 111 | 113 | 113 | 64 | 64 | 64 | 65 | 66 | 67 | 67 |
| | 90th | 120 | 121 | 122 | 123 | 125 | 126 | 127 | 78 | 78 | 78 | 79 | 80 | 81 | 81 |
| | 95th | 124 | 125 | 126 | 127 | 129 | 130 | 131 | 82 | 82 | 82 | 83 | 84 | 85 | 85 |
| | 99th | 131 | 132 | 133 | 134 | 136 | 137 | 138 | 89 | 89 | 90 | 91 | 91 | 92 | 93 |
| 16 | 50th | 108 | 108 | 110 | 111 | 112 | 114 | 114 | 64 | 64 | 65 | 66 | 66 | 67 | 68 |
| | 90th | 121 | 122 | 123 | 124 | 126 | 127 | 128 | 78 | 78 | 79 | 80 | 81 | 81 | 82 |
| | 95th | 125 | 126 | 127 | 128 | 130 | 131 | 132 | 82 | 82 | 83 | 84 | 85 | 85 | 86 |
| | 99th | 132 | 133 | 134 | 135 | 137 | 138 | 139 | 90 | 90 | 90 | 91 | 92 | 93 | 93 |
| 17 | 50th | 108 | 109 | 110 | 111 | 113 | 114 | 115 | 64 | 65 | 65 | 66 | 67 | 67 | 68 |
| | 90th | 122 | 122 | 123 | 125 | 126 | 127 | 128 | 78 | 79 | 79 | 80 | 81 | 81 | 82 |
| | 95th | 125 | 126 | 127 | 129 | 130 | 131 | 132 | 82 | 83 | 83 | 84 | 85 | 85 | 86 |
| | 99th | 133 | 133 | 134 | 136 | 137 | 138 | 139 | 90 | 90 | 91 | 91 | 92 | 93 | 93 |

BP, blood pressure

* The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.

For research purposes, the standard deviations in Appendix Table B–1 allow one to compute BP Z-scores and percentiles for girls with height percentiles given in Table 4 (i.e., the 5th,10th, 25th, 50th, 75th, 90th, and 95th percentiles). These height percentiles must be converted to height Z-scores given by (5% = -1.645; 10% = -1.28; 25% = -0.68; 50% = 0; 75% = 0.68; 90% = 1.28%; 95% = 1.645) and then computed according to the methodology in steps 2–4 described in Appendix B. For children with height percentiles other than these, follow steps 1–4 as described in Appendix B.

## Appendix 8. Cough Counting Process and Timing

### Cough Recordings during Baseline Run-in and Treatment Periods

Subjects will receive a single-blind (to the parent/legally acceptable representative and subject), inactive (non-medicinal), liquid oral confection at the onset of the Baseline Run-in Period, and will wear an ambulatory cough recording device during the 2-hour period. During the initial Treatment Period, subjects will receive the first dose of double-blind study medicine (DXM HBr or placebo) and then wear the ambulatory cough recording device for approximately 24 hours. The second and third doses (Day 1 evening and Day 2 morning) of medication will be given while the subject is undergoing monitoring. Of importance, subjects will be instructed to not take their fourth dose (Day 2 afternoon) of double-blind investigational product (DXM HBr or placebo) until they are at the study site and the VitaloJAK™ device has been removed.

### VitaloJAK™ and Cough Counting Process

The VitaloJAK™ system uses a contact microphone placed on the chest wall and a custom-made digital recording device to detect cough from sound. A lapel microphone is also attached to make simultaneous free-field recordings for validation purposes (manual cough counting). Data are captured on a data card, and downloaded to a secure server. The Vitalograph analysts' count the data files by accessing the secure server, and runs a compression algorithm on each file.

As subjects cough, acoustic parameters from these voluntary coughs can be used to develop a 24-hour sound recording and identify spontaneous cough sounds. Initial evaluation in 10 subjects (5 with chronic cough, 5 with asthma) suggested that the equipment and process have a sensitivity and specificity of approximately 98% (Smith, 2008).[17]

For the purpose of this study, coughs will be counted by explosive first phases (Smith, 2008).[17] The following definitions are provided below:

> Cough: Inspiration, followed by glottis closure, contraction of the expiratory muscles against the closed glottis, and followed by the sudden glottis opening with rapid expulsion of air accompanied by a characteristic cough sound. Cough sounds can occur as individual events or as a long series of explosive cough sounds often known as cough bouts, epochs, peals, or attacks.
>
> Individual cough: A typical cough is characterized by an early, loud, explosive phase, followed by an intermediate phase, and in about half of coughs, a subsequent voiced phase.
>
> Cough bouts: These cough sounds may vary enormously in length and have voiced phases interspersed. It is possible for a cough bout to include more than 1 explosive first phase.

Digital cough counting has been shown to have excellent agreement with simultaneous video recordings in a research environment (Smith, 2006b).[16] In addition, cough counts obtained from cut-down files are comparable to those obtained from full recordings, with agreement comparable to that seen between 2 trained observers (Sumner, 2010).[18]

**Data Transfer**

PCH will receive completed cough count data for individual subjects by hourly segments for analysis. The cough count specifications will minimally include the date/time of each cough, number of coughs per segment, and total coughs for the full recording periods (2 or 24 hour). The data will be provided in a secure fashion.