Protocol A6531002

A Placebo Controlled, Double Blind, Randomized, Parallel Group Pilot Study to Evaluate the Efficacy of Dextromethorphan Hydrobromide on Acute Cough in a Pediatric Population

Statistical Analysis Plan
(SAP)

Version: 2

Date: 23-Aug-2018

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1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study A6531002 is based on the protocol dated 18JUL2018.

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1	Not Applicable	Not Applicable
2	The baseline covariate average cough count per hour based on the Baseline Run-in Period will be included in the negative binomial model after a log-transformation.	In the negative binomial regression using SAS GENMOD procedure, log link function is used for modeling event rates, thus the predictor baseline average cough count per hour will be log-transformed to be included in the model.

Note: In this document any text taken directly from the protocol is *italicized*.

2. INTRODUCTION

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

DXM is the most commonly used oral antitussive ingredient in both adult and pediatric non-prescription medications (Dicpinigaitis, 2004), 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). Efficacy in children is less well established and results have been equivocal (Shadkam et al, 2010; Paul, 2004a; Paul, 2004b; Yoder, 2006). 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.

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) and has recently been validated in children (Elghamoudi, 2015). 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.

The cough recording device VitaloJAK™ provides the means to sense voice and cough activity from a subject, record this information and store it to a Compact Flash™ memory card for later analysis. The data is uncompressed so that no information is lost due to data compression methods. The VitaloJAK is capable of recording 24hrs worth of information continuously, uninterrupted without the need to replace batteries. The VitaloJAK also contains a Real Time Clock in order to provide time information for the data recorded. All the cough count endpoints will be derived using the VitaloJAK™.

2.1. Study 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. Study Design

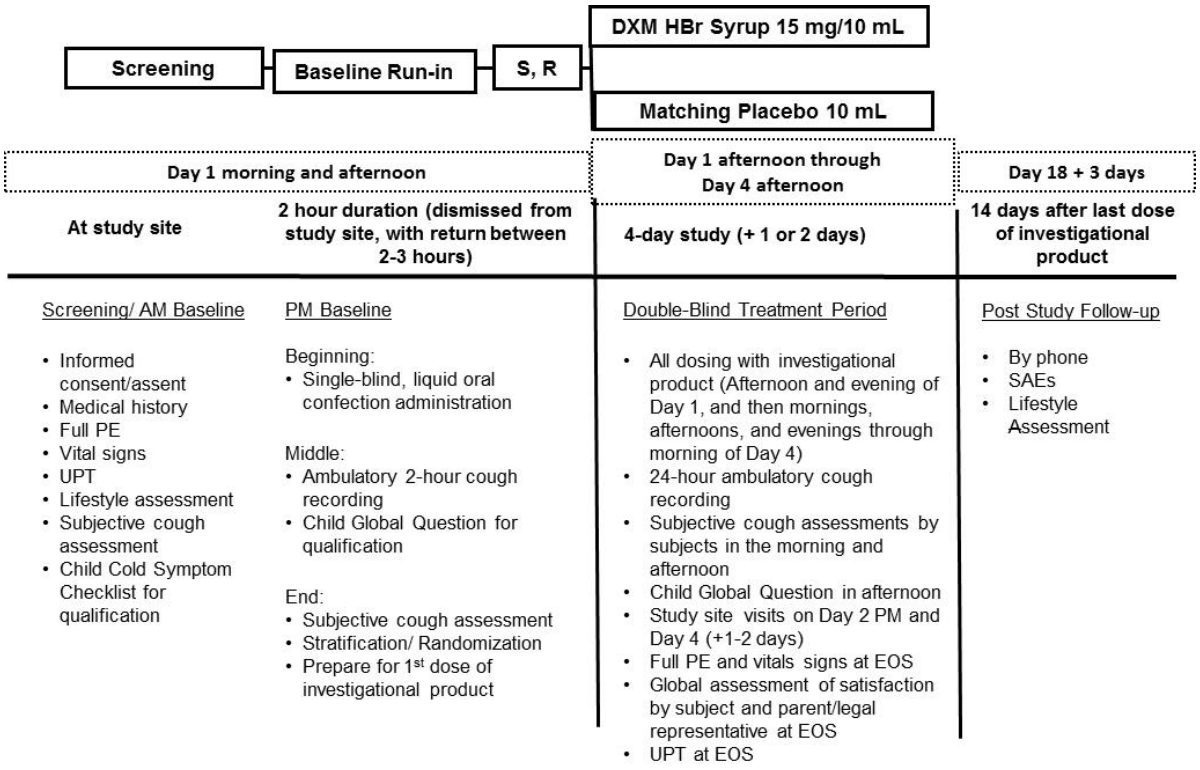
This is a randomized, stratified by age group (6-8 years and 9-11 years), parallel, double-blind, placebo-controlled, multicenter pilot study in approximately 150 males and

[redacted]

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 Figure 1 and the dosing schedule in shown in Table 2. The schedule of activities (Table 3) provided an overview of the protocol visits and procedures.

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 2. 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)

[redacted]

Table 2. Dosing Schedule

DAY	TIME OF ADMINISTRATION		
	MORNING	AFTERNOON	EVENING
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.

Table 3. 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										

[redacted]

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**
Diary/investigational product/APAP dispensed/retrieved		X			X						X	
Study Medication administration[j]		X	X	X	X	X	X	X	X	X		
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 no more than 3 days prior to Visit 1.

[redacted]

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 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.

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.

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.

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.*

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- *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.*

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

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.

Cough events were recorded using the device VitaloJak. When a cough event occurred, date and time were recorded, with the date recorded in the format of YYYYMMDD, and time in the format of HHMMSS.

As described in the Vitalograph Cough Analysis Plan, cough events could be flagged as "poor quality" or "early removal", and multiple cough events could occur within one second. As this is a pilot study to evaluate the endpoints, the primary endpoint will be derived including all cough events regardless of the flags during the entire recording period.

The entire recording period, or the exposure time, will be derived as: exposure = end time – first dosing time + 1. Specifically, the end time will be chosen from the following, whichever occurred first:

- Session stop date and time recoded by the VitaloJAK internal time clock, analyzed by Vitalograph staff (available in the transferred data);
- Time subjects discontinued.

3.2. Secondary Endpoint(s)

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

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 (i.e., night time cough count);*

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

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;*

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

Secondary endpoints 1st - 4th listed above will be derived similarly to the primary endpoint. All the cough events collected during the recording period will be included in the cough count endpoints.

In the event that either the start time or the end time is missing (i.e., Dose 2, and/or Dose 3, and/or Dose 4 time), the corresponding endpoint will be considered as missing. No imputation will be applied.

3.3. Other Endpoints

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;*

The morning subjective cough assessments will be completed at Screening/Morning Baseline (Visit 1, Day 1), and before the morning dose on Days 2-4 (Appendix 3). For each assessment with respect to cough frequency/cough severity/impact on sleep, change from screening evaluation is calculated as the assessment collected in the morning of each day (Days 2-4) minus the assessment collected at Screening Visit on Day 1, respectively.

- *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;*

The afternoon subjective cough assessments will be completed at the Afternoon Baseline visit (Visit 2, Day 1), and in the afternoon of Days 2-4 of the Treatment Period (Appendix 4). For each assessment with respect to cough frequency/cough severity, change from baseline evaluation is calculated as the assessment collected in the afternoon of each day (Days 2-4) minus the assessment collected at Baseline Visit on Day 1, respectively.

- *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;*

The Child Global Question will be completed at the Baseline (Visit 2, Day 1), and in the afternoon of Days 2-4 (Appendix 2). The change from baseline evaluation is calculated as the assessment collected in the afternoon of each day (Days 2-4) minus the assessment collected at Baseline, respectively.

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

Global satisfaction with the study medication will be assessed by the subjects and 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 Day 5 or 6 (Appendix 5).

3.4. Baseline Variables

Baseline variables are those collected prior to dosing and can occur at pre-screening, screening, or run-in period prior to Dose 1 during the study period (see Figure 1).

Demographic Data: Sex, race, ethnicity, age, height and weight will be collected at screening. These variables will be summarized and listed.

Background Information: Past and current medical history (non-drug allergies) will be collected at screening and will be summarized by treatment and total in a similar manner as adverse events (AEs) using the MedDRA system organ class (SOC) and preferred term. The corresponding listing will be also produced. Drug allergies will be also collected at this time but will only be listed.

Baseline Run-in Cough Counts: Subjects who met the inclusion and exclusion criteria will be eligible to enter the Baseline Run-in Period. During this period, subjects will be assigned a VitaloJAK™ device; after the device is checked for correct operation, the subjects will be given a single-blind, inactive, liquid oral confection. 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.

Subjects and their parent/legally acceptable representative will be instructed to return to the study site after at least 2 hours (+1 hour) after the VitaloJAK™ cough count recording begins, and the cough counts recorded during the 2-3 hour period will be considered as baseline run-in cough counts (or baseline cough counts).

The baseline average cough count per hour will be derived as the total cough counts collected during the Baseline Run-in Period divided by the duration of this period (in hours).

Child Cold Symptom Checklist: This checklist will be collected at screening and used for checking subject eligiblily for enrollment, which includes 9 questions intended to assess the severity of the subject's cold symptoms on a 5 point categorical scale. See Appendix 1 for details.

Child Global Question: At Visit 2 on Day 1, 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.

Subjective Cough Assessments: The subjective cough assessments collected at Screening visit and Baseline visit (Visit 1 and 2 on Day 1) will be considered as morning baseline and afternoon baseline assessments, respectively. See Appendix 3 and Appendix 4 for details.

3.4.1. Stratification Variables

Subjects were stratified by age group (6-8 years and 9-11 years), and randomized to receive investigational product. The term age group will be used as a stratification variable in the statistical analysis.

3.4.2. Covariates

For the analysis of the primary endpoint, the corresponding log-transformed baseline average cough count per hour will be used as a covariate, and the logarithm of the time over which the cough count is evaluated will be used as the offset variable in fitting the negative binomial model. The statistical specifications for these variables or related analysis are described in Section 5.2.1.

Due to difficulty in recruitment, the number of subjects to be enrolled is not limited at each study site. In a model-based analysis using Site as a term, investigator sites may be pooled to alleviate issues such as model convergence due to data sparseness. The pooling rules will be determined prior to final database lock and release.

3.5. Safety Endpoints

Adverse event analyses will include all events which initially occurred, or worsened following treatment.

3.5.1. Adverse Events

An adverse event is considered treatment emergent relative to a given treatment (called treatment emergent adverse events [TEAE]) if:

- the event occurs for the first time during the treatment and was not seen prior to the start of treatment (i.e., receiving investigational product), or
- the event was seen prior to the start of treatment but increased in severity during treatment.

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.

No tier-1 events (pre-specified events of clinical importance) have been identified in the Safety Review Plan (SRP) for the product. However, for this study, AEs included in the Targeted Medical Event (TME) list of the SRP (See Appendix 7) will be summarized in a similar manner as Tier-1 events if any are identified . Therefore, a 3-tier approach will be used to summarize these type of AEs. Under this approach, AEs are classified into 1 of 3 tiers.

Tier-1 events: These are pre-specified events of clinical importance and are maintained in a list in the product's TME of the SRP. For this study TME in the SRP are considered as Tier-1 events.

Tier-2 events: These are events that are not tier-1 but are "common". A MedDRA preferred (PT) is defined as a tier-2 event if its frequency is at least 2% in any treatment group.

Tier-3 events: These are events that are neither tier-1 nor tier-2 events.

3.5.2. Vital Signs

Each subject's vital signs (including sitting blood pressure, pulse rate, respiratory rate, and temperature) will be measured and recorded at Screening and Visit 4 (or end of study). They will be summarized/listed as described in Section 6.6.2.

3.5.3. Physical Examination

Physical examinations will be performed at Screening and Visit 4 (or end of study). 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. They will be summarized/listed as described in Section 6.6.3.

3.5.4. Other Safety Endpoints

The medication use data such as prior medication, and concomitant medication will be inquired and collected at each visit (See Table 3). They will be summarized/listed as described in Section 6.5.3.

4. ANALYSIS SETS

Data for all subjects will be assessed to determine if subjects meet the criteria for inclusion in each analysis population prior to releasing the database and unblinding. The classifications will be documented per standard operating procedures.

4.1. Full Analysis Set

The Full Analysis Set (FAS) is the intent-to-treat (ITT) subject 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 assigned to the randomized treatment group regardless of the treatment received. This analysis set will be used for all efficacy analyses.

4.2. Per Protocol Analysis Set

The per-protocol (PP) analysis set will be a subset of the FAS 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.

4.3. Safety Analysis Set

The safety analysis set will include all subjects who received the study product. Subjects will be analyzed according to the treatment they actually receive regardless of which treatment group they are randomized. A randomized but not treated subject will be excluded from the safety analyses. A treated but not randomized subject will be reported under the treatment actually received.

4.4. Other Analysis Sets

Not applicable.

5. GENERAL METHODOLOGY AND CONVENTIONS

The final analysis of data will be performed after unblinding of the treatment codes.

5.1. Hypotheses and Decision Rules

The statistical alternative hypothesis tested will be that DXM HBr will be better than placebo with respect to a parameter evaluated.

Statistically significant treatment differences will be declared if the probability of random occurrence between the two treatment groups (p) is ≤ 0.05. Treatment differences will be declared marginally significant if $0.05 < p \leq 0.10$. All tests will be 2-sided.

[redacted]

5.2. General Methods

For all the efficacy endpoints, descriptive statistics including sample size, mean, standard deviation, median, minimum, and maximum will be provided by treatment group.

5.2.1. Analyses for Count Data

Negative Binomial Regression

Analyses of count data endpoints (primary endpoint and 1st -4th secondary endpoints) will use the negative binomial regression model (SAS Proc GENMOD). The model will contain treatment, study site (pooled), log-transformed baseline average cough count per hour (based on the Baseline Run-in Period), and age group as factors, with logarithm of the time over which the cough count is evaluated as the offset parameter. The rate ratio and corresponding 95% confidence limit for DXM HBr vs placebo will be obtained and presented. See Appendix 6 for an example.

Additional assessment will be conducted on the primary endpoint by adding the interaction term for 1) treatment by log-transformed baseline average cough count, and 2) treatment by age group, separately, into the negative binomial regression model.

5.2.2. Analyses for Continuous Data

The primary endpoint, total cough count collected over a 24-hour period, will be log-transformed and analyzed using ANCOVA model with treatment, study site (pooled), log-transformed baseline average cough count per hour (based on the Baseline Run-in Period), and age group terms in the model.

The hourly cough count collected during the first dosing interval, will be log-transformed and analyzed using a similar ANCOVA model with treatment, study site (pooled), log-transformed baseline average cough count per hour, and age group terms in the model.

The 5th secondary endpoint, cough time accumulated over a 24-hour period, will be log transformed and analyzed using a similar ANCOVA model with treatment, study site (pooled), the log-transformed baseline cough time, and age group included in the model.

For the analyses of subjective cough assessments (including change from baseline in cough frequency, cough severity, impact on sleep), and the analysis of Child Global Question cold assessment, an analysis of variance (ANOVA) model will be applied. The model will contain treatment, study site (pooled), the corresponding screening/baseline assessment by subject, and age group as factors.

For the global assessments of satisfaction, an ANOVA model with treatment, study site (pooled), and age group will be included in the model.

Additionally, the interaction of treatment by age group may be assessed by adding the interaction term to the initial model for each of the PRO assessments, respectively.

For each pairwise comparison of interest, the treatment difference based on the least-squares means (LSM), its standard error (SE), the p-value and the associated 95% confidence interval (CI) will be presented.

5.2.3. Analyses for Patient-Reported Outcome Data

For each of the Other endpoints as assessed by PRO in Section 3.3, the answers at each visit will be descriptively summarized with count and proportion by treatment.

Additional psychometric evaluation of PRO measures will be performed by external vendor (Adelphi Values) for validation purpose only; those results will be independently presented and reported.

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5.3. Methods to Manage Missing Data

No imputation will be applied for missing data in the cough count endpoints or the dosing time.

For subjects who had missing data in the PRO assessments, no imputation will be used.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint

6.1.1. Primary Analysis

- Endpoint: The total cough count collected during 24 hour post first dose;
- Analysis population: Full Analysis Set;
- Analysis methodology: The negative binomial regression model will contain treatment, study site (pooled), log-transformed baseline average cough count per hour (based on the Baseline Run-in Period), and age group as factors, with logarithm of the time over which the cough count is evaluated as the offset parameter (specified in Section 5.2.1).
- Supporting objective: Primary Objective.

Reporting results:

- Raw data: the total cough count will be summarized with sample size, mean, standard deviation, median, minimum and maximum for each treatment arm.
- The rate ratio, p-value, and corresponding 95% confidence limit for DXM HBr vs placebo will be obtained and presented.

Figures

- Line chart showing the mean cough counts on the y-axis over the time (by hour) on the x-axis by treatment showing the change over the 24-hour based on the raw mean cough count.

6.1.1.1. Additional Analyses

To support the primary analysis, the primary endpoint will be log-transformed and analyzed using an ANCOVA model.

- Analysis population: Full Analysis Set;
- Analysis methodology: The ANCOVA model will contain treatment, study site (pooled), log-transformed baseline average cough count per hour (based on the Baseline Run-in Period), and age group terms in the model.

Reporting results:

- The treatment difference based on the LSM, its SE, the p-value and the associated 95% confidence interval (CI) will be presented.

[redacted]

In the event that more than 10% of the ITT subjects are excluded from the full analysis set, the following analyses will be performed:

- Analysis population: Per Protocol Analysis Set;
- Analysis methodology: The total cough count during 24 hour interval will be analyzed using the same negative binomial regression model as the primary analysis.

Reporting results:

- Raw data: the total cough count will be summarized with sample size, mean, standard deviation, median, minimum and maximum for each treatment arm.
- The rate ratio, p-value, and corresponding 95% confidence limit for DXM HBr vs placebo will be obtained and presented.

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6.2. Secondary Endpoint(s)

6.2.1. Secondary Cough Count Endpoints

- 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 (i.e., night time cough count);

[redacted]

- 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). (i.e., daytime cough count).

These secondary endpoints are derived similarly to the primary endpoint, by counting all cough events within each dosing interval.

- Analysis population: Full Analysis Set;

- Analysis methodology: The negative binomial regression model will be used, which contains treatment, study site (pooled), log-transformed baseline average cough count per hour (based on the Baseline Run-in Period), and age group as factors, with logarithm of the time over which the cough count is evaluated as the offset parameter (specified in Section 5.2.1).

Reporting results:

- Raw data: the hourly cough count will be summarized with sample size, mean, standard deviation, median, minimum and maximum for each treatment arm.

- The rate ratio, p-value, and corresponding 95% confidence limit for DXM HBr vs placebo will be obtained and presented.

Additional analysis will be conducted on the first secondary endpoint, i.e., the total cough count collected during the first dosing interval on Day 1:

- Analysis population: Full Analysis Set;

- Analysis methodology: The hourly cough count collected during the first dosing interval, will be log-transformed and analyzed using an ANCOVA model with treatment, study site (pooled), log-transformed baseline average cough count per hour, and age group terms in the model.

Reporting results:

- The treatment difference based on the LSM, its SE, the p-value and the associated 95% confidence interval (CI) will be presented.

6.2.2. Secondary Cough Time Endpoint

This secondary endpoint, derived by adding up all the time when cough events actually occurred over a 24-hour period, will be log-transformed and analyzed with ANCOVA model.

- Endpoint: Cough time accumulated over a 24-hour period when cough events occurred.
- Analysis population: Full Analysis Set;
- Analysis methodology: The ANCOVA model will contain treatment, study site (pooled), log-transformed baseline cough time (based on the Baseline Run-in Period), and age group terms in the model.

Reporting results:

- The treatment difference based on the LSM, its SE, the p-value and the associated 95% CI will be presented.

6.3. Other Endpoint(s)

6.3.1. Subjective Cough Assessments

The defintions of the other[CCI] endpoints were specified in Section 3.3.

- Endpoints:
  - Cough frequency: change in evaluations in the morning of each day (Days 2-4) from morning baseline on Day 1, and change in evaluations in afternoon of each day (Days 2-4) from afternoon baseline on Day 1.
  - Cough severity: change in evaluations in the morning of each day (Days 2-4) from morning baseline on Day 1, and change in evaluations in afternoon of each day (Days 2-4) from afternoon baseline on Day 1.
  - Impact on sleep: change in evaluations in the morning of each day (Days 2-4) from morning baseline on Day 1.
- Analysis population: Full Analysis Set;
- Analysis methodology: ANOVA model will be used, with treatment, study site (pooled), the corresponding morning baseline (or afternoon baseline) assessment by subject, and age group included in the model.

Reporting results:

- Raw data: The categorical answers at each visit will be descriptively summarized with count and proportion by treatment. The numerical answers (change from baseline) will be summarized with sample size, mean, standard deviation, median, minimum and maximum by visit and by treatment.
- The treatment difference based on the LSM, its SE, the p-value and the associated 95% CI will be presented.

[redacted]

6.3.2. Child Global Question

- Endpoint:
  - Daily assessment of cold: Change in evaluations in the afternoon of each day (Days 2-4) from the afternoon baseline on Day 1.
- Analysis population: Full Analysis Set;
- Analysis methodology: ANOVA model will be used, with treatment, study site (pooled), the baseline assessment by subject, and age group included in the model.

Reporting results:

- Raw data: The categorical answers at each visit will be descriptively summarized with count and proportion by treatment. The numerical answers (change from baseline) will be summarized with sample size, mean, standard deviation, median, minimum and maximum by visit and by treatment.
- The treatment difference based on the LSM, its SE, the p-value and the associated 95% CI will be presented.

6.3.3. Global Assessments of Satisfaction

- Endpoint: Subject and parent/legally acceptable representative global assessments of satisfaction with investigational product at the end of the study.
- Analysis population: Full Analysis Set;
- Analysis methodology: ANOVA model will be used, with treatment, study site (pooled), and age group included in the model.

Reporting results:

- Raw data: The categorical answers will be descriptively summarized with count and proportion by treatment. The numerical answers will be summarized with sample size, mean, standard deviation, median, minimum and maximum for each treatment arm.
- The treatment difference based on the LSM, its SE, the p-value and the associated 95% CI will be presented.

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6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

6.5.1.1. Demographic Data

- Analysis population: Safety population;
- Analysis methodology: Descripive statistics.

Reporting results:

- The number and percentage of subjects within each category in gender, race, ethnicity, and age group will be presented; while for age, height, weight and BMI, the overall mean, standard deviation, median, minimum, and maximum values will be provided. The sample size overall and by treatment will be also listed.

6.5.1.2. Background Information

- Endpoints: Medical history, drug allergies;
- Analysis population: Safety population;
- Analysis methodology: Descripive statistics.

Reporting results:

- Medical history: The sample size, number and percentage of subjects within each SOC and preferred term will be presented by treatment and overall in a similar manner as adverse events (AEs). The corresponding listing will be also produced.
- Drug allergies: listing will be provided.

6.5.1.3. Baseline Run-in Cough Counts

- Endpoint: Baseline average cough count per hour;
- Analysis population: Full Analysis Set;
- Analysis methodology: Descripive statistics.

Reporting results:

- The baseline average cough count per hour will be summarized with sample size, mean, standard deviation, Q1, median, Q3, minimum and maximum for each treatment arm and overall.

6.5.1.4. Child Cold Symptom Checklist

- Endpoint: Child Cold Symptom Checklist at Screening visit;
- Analysis population: Full Anlaysis Set;
- Analysis methodology: Descriptive statistics.

Reporting results:

- For each question, the number and percentage of subjects in each category will be provided overall and by treatment.

6.5.1.5. Child Global Question

- Endpoint: Child Global Question at the Baseline visit (Visit 2, Day 1);
- Analysis population: Full Anlaysis Set;
- Analysis methodology: Descriptive statistics.

Reporting results:

- The categorical answers will be descriptively summarized with count and proportion overall and by treatment. The numerical answers will be summarized with sample size, mean, standard deviation, median, minimum and maximum overall and by treatment.

6.5.1.6. Subjective Cough Assessment

- Endpoints: The subjective cough assessments at Screening visit (Morning Baseline) and Baseline visit (Afternoon Baseline) assessed at Visit 1 and 2 on Day 1, respectively;
- Analysis population: Full Anlaysis Set;
- Analysis methodology: Descriptive statistics.

Reporting results:

- For each baseline assessment, the categorical answers will be descriptively summarized with count and proportion overall and by treatment. The numerical answers will be summarized with sample size, mean, standard deviation, median, minimum and maximum overall and by treatment.

6.5.2. Study Conduct and Subject Disposition

Subject disposition and populations groups will be summarized using frequencies and percentages. No treatment comparabilities will be assessed.

6.5.3. Concomitant Medications and Non-Drug Treatments

Prior and concomitant medications will be summarized using the preferred drug name from WHODrug. No treatment comparabilities will be assessed.

Concomitant non-drug treatment or procedures will be listed.

6.6. Safety Summaries and Analyses

6.6.1. Adverse Events

Adverse event analyses will include all events collected during the active collection period of the study. Adverse events will be summarized by the MedDRA 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 worst relationship.

All non-TEAE will be summarized according to the MedDRA preferred term.

No tier-1 events (pre-specified events of clinical importance) are identified in the SRP for the study product. However, for this study, AEs included in the TME list of the SRP (See Appendix 7) will be summarized in a similar manner as Tier-1 events if any are identified. Therefore, AEs will additionally be summarized using a 3-tier approach. AEs will be

classified into 3 tiers as defined in Section 3.5.1. All tier-1, 2, or 3 AEs will be tabulated and listed separately in a similar manner as all other AEs. The AEs will be sorted alphabetically within a system organ class.

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6.6.2. 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).

The values at screening, end of study (or Visit 4), as well as the change from screening for the vital signs data will be summarized by descripive statistics, overall and by treatment group for the safety population. The number and percentage of subjects with vital sign data out-of-normal ranges will be summarized both at screening and end of study.

Corresponding listing will be created and subjects with out-of-normal ranges values will be flagged.

6.6.3. Physical Examination

Physical examination data will be summarized both at screening and at end of study for the safety population.

6.6.4. Laboratory Data

Laboratory data will not be entered in the database and thus will not be summarized.

7. INTERIM ANALYSES

7.1. Introduction

Protocol Amendment #4 introduced an interim analysis to assess whether or not the study would be continued. The rationale is based upon the challenging enrollment in the vulnerable subject population (pediatrics) for the trial. The main focus of this interim analysis is the primary endpoint (total cough count collected during 24 hour post first dose) and the first secondary endpoint (total cough count collected 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

interim statistical analysis plan. Only one interim analysis is planned for this study, and it will be conducted after at least 50% subjects complete the study or discontinue early.

7.2. Interim Analyses and Summaries

The methodology used in the interim analysis is based on the calculation of conditional power using the weighted z-score test method[1,2,3] for the primary endpoint and the first secondary endpoint. The interim analysis will not consider the control of type-1 error, and sample size will not be re-estimated in this interim analysis.

In the interim analysis, the primary endpoint will be analyzed using the primary model (negative binomial regression model) as discussed in Section 6.1.1 and the ANCOVA model as discussion in Section 6.1.1.1, respectively, based on the FAS. Similar analyses will be performed for the first secondary endpoint as discussed in Section 6.2.1. From the two analyses for each endpoint, the estimate of treatment effect between DXM HBr and placebo will be obtained and presented. These treatment differences and corresponding standard errors will be used to obtain conditional powers based on the weighted z-score test.

If a conditional power is at least 25% for either analysis of the primary endpoint, or for either analysis of the first secondary endpoint, the expected recommendation would be to continue the study with the planned sample size (n=150). Otherwise, if all conditional powers lie below 25%, the recommendation would be to terminate it early.

8. REFERENCES

1. Lan, K. K. G. and Zucker, M., Sequential monitoring of clinical trials: the role of information and Brownian motion. Statistics in Medicine 1993; 12: 753–765.

2. Fisher, LD. Self-designing clinical trials. Statistics in Medicine 1998; 17:1551-1562.

3. Cui, L, Huang, HMJ, Wang, SJ. Modification of sample size in group sequential clinical trials. Biometrics 1999; 55:853-857.

9. APPENDICES

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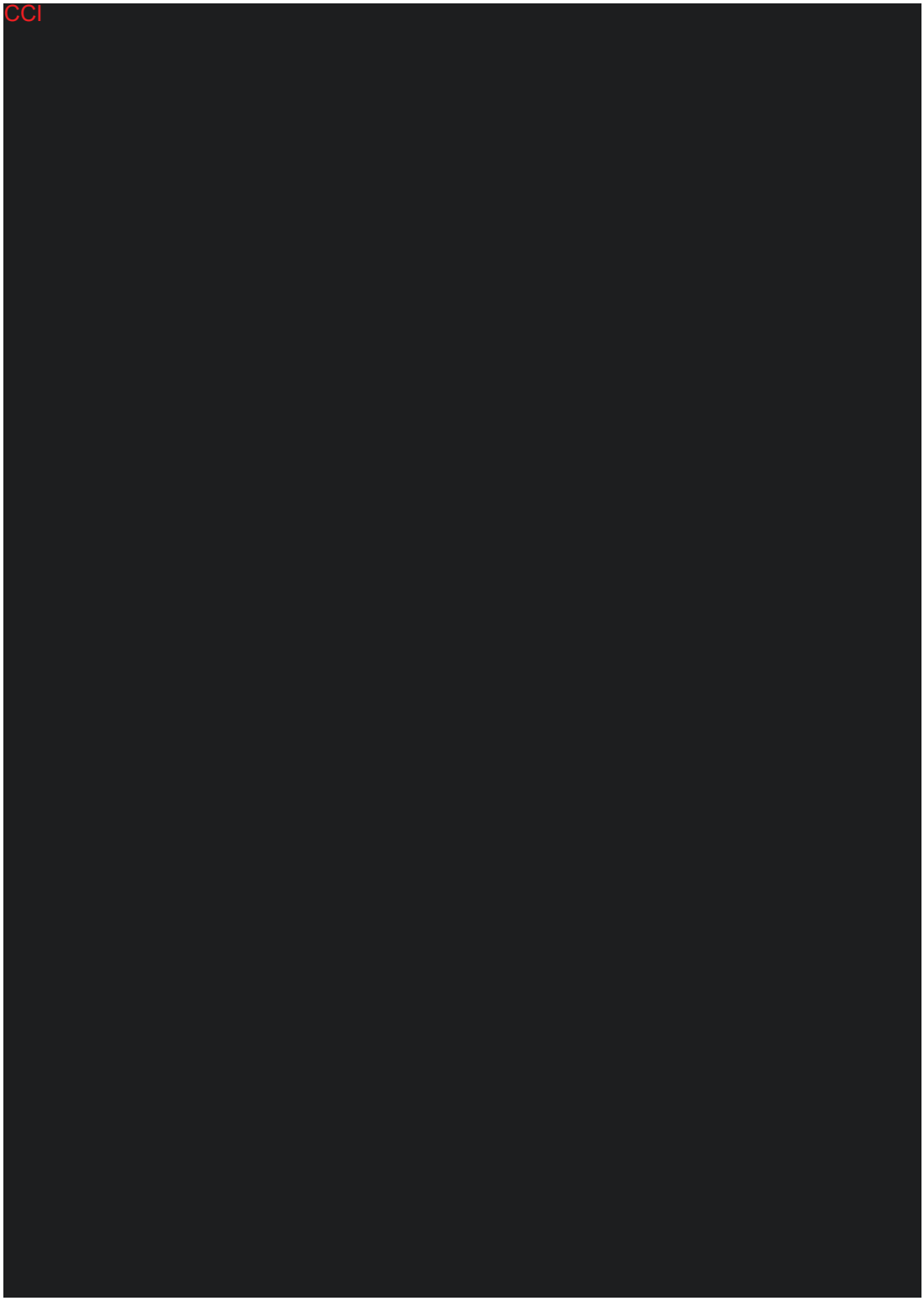

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Appendix 5. Global Satisfaction

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 6. Statistical Methodology Details

The following SAS code will be used to calculate the rate ratio in negative binomial model for count data.

```
proc genmod data=cough_data;
  class trt agegrp site /param=glm;
  model count= trt  site  agegrp  log(basecough)/dist=nb link=log  offset=logdur type3;
  estimate "log rate ratio Dex vs Pbo" trt 1 -1 / exp;
```

[redacted]

```
  lsmeans trt / exp diff cl;

run;
```

Where

trt= Treatment (1 and 2 = Treatments being compared)

Appendix 7. Target Medical Event (TME) List

BRAND or TRADE Name	TARGET MEDICAL EVENT TERM	TME Safety Area of Interest and RATIONALE FOR INCLUDING TME	LEVEL (PT, LLT, HLT, HLGT & SOC?)
Dextromethorphan Hydrobromide	Hypersensitivity	Event of PV interest	PT
	Nausea	Event of PV interest	PT
	Vomiting	Event of PV interest	PT
	Dizziness	Event of PV interest	PT
	Dysarthria	Event of PV interest	PT
	Myoclonus	Event of PV interest	PT
	Tremor	Event of PV interest	PT
	Somnolence	Event of PV interest	PT
	Dysarthria	Event of PV interest	PT
	Nystagmus	Event of PV interest	PT
	Excitability	Event of PV interest	PT
	confusional state	Event of PV interest	PT
	psychotic disorders	Event of PV interest	PT
	Respiratory depression	Event of PV interest	PT