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Feasibility testing of clinical assessment tools to evaluate dextromethorphan efficacy in children with acute cough

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Introduction and Research Goals

Dextromethorphan hydrobromide (DXM) is an antitussive agent used in most over-the-counter cough and cold medicines and is *generally recognized as safe and effective* (GRASE) based on a review of adult clinical data [1]. Objective cough count monitoring is recognized as an appropriate tool to demonstrate DXM efficacy in adult studies because of the spontaneous resolution of acute cough and a high placebo response [2-4]. When this pediatric pilot study was fielded, fully validated, age-appropriate clinical assessment tools for acute cough in children were not available. Therefore, this study was conducted to test the feasibility of various objective and subjective assessment tools, including cough count monitoring, to evaluate cough in children. In addition, collected data would be used to determine an appropriate sample size and efficacy endpoints for a future study. The ultimate goal of this research project was to provide evidence of DXM effectiveness for acute cough due to the common cold in a pediatric population.

Methodology

This randomized, parallel-group, double-blind, placebo-controlled pilot study compared a single dose of DXM 15 mg with placebo in children with acute cough due to the common cold. A sample of 240 children, ages 6-11 years, was planned. Eligible subjects had onset of cold symptoms no more than 10 days before screening and had at least five coughs during the last 30 minutes of the baseline cough counting period. Qualifying subjects were randomized to a 10-mL dose of either DXM HBr 7.5 mg/5mL or matching placebo syrup in a 1:1 ratio.

Coughs during the 1-hour baseline and 6-hour postdose evaluation periods were captured by continuous digital audio and video recordings while the subject and parent/caregiver were confined to an exam room. At least one omni-directional external microphone was placed nearby where the subject was seated. Trained assessors quantified individual coughs from the audio recordings using specialized compression software, and video recordings provided supportive documentation. A negative binomial regression model was used to analyze cough count data. Results were presented as the odds ratio and 95% confidence interval (CI) of DXM versus placebo, and p-value. This model included terms for treatment, site, baseline cough count; logarithm of the exposure time was used as the offset parameter.

Each hour during the postdose period, subjects rated: "*How much have you coughed in the last hour?*", using both a 5-point categorical scale (0=not at all, 1=a tiny bit, 2=a little, 3=some and 4=a lot), and an 11-point numerical scale (0=did not cough at all and 10=cough a lot). Study personnel administered the subjective assessment questions by script, and parents could assist with completion. Change from baseline in cough frequency (verbal and numerical scales) at each hour was averaged for the 6-hour postdose period. Treatment differences, 95% CI, and p-value were calculated based on least-square means from an analysis of variance model. This model included terms for treatment, site, and the corresponding baseline cough rating score.

For global assessments at the end of the evaluation period, subjects rated: *"How much have you coughed in the past 6 hours?"*, using the previous categorical scale. They also rated: *"From when you woke up this morning until now, how much better is your cough?"*, using a different categorical scale (0=not at all better, 1=a tiny bit better, 2=a little better, 3=better and 4=a lot better). These data were analyzed by the Cochran-Mantel-Haenszel test, using modified ridit scores stratified by site. The 95% CI for the pair-wise treatment difference were computed using the gamma statistic and its standard error.

Results

The study was approved by Schulman Associates IRB, Inc., (Cincinnati, OH) and conducted at four sites from December 2010 through March 2011 in compliance with good clinical practice guidelines. Written informed consent was provided by the parent/caregiver, and assent was required from each child. Due to methodological and operational issues, the study was terminated with less than half the 240 planned subjects enrolled.

Of 107 subjects enrolled, 52 subjects received 15-mg DXM and 55 received placebo. The study population consisted of 46.7% males and 53.3% females with the mean age of 8.9 years (range: 6-11 years). Most subjects were White (60.7%), followed by Black (30.8%), mixed racial origins (5.6%), Asian (1.9%), and Native American (0.9%). Two subjects were excluded from the efficacy analyses due to protocol compliance issues at one site.

Mean (± standard deviation) total cough counts for DXM and placebo during the 6-hour evaluation period were 190.9 ± 190.6 and

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Table 1. Subjective assessments of cough after a single dose.

Endpoint	PBO (n=53)	DXM (n=52)	Δ LSM	95% CI	P Value*
Hourly Assessments†					
"How much have you coughed in the last hour?" (verbal scale)	1.3 (1.1)	1.1 (1.1)	-0.26	-0.60, 0.08	0.134
"How much have you coughed in the last hour?" (numerical scale)	2.8 (2.5)	2.5 (3.1)	-0.49	-1.43, 0.45	0.304
Global assessments					
"How much have you coughed in the past 6 hours?"	3.1 (0.9)	3.0 (1.3)	0.09	-0.21, 0.39	0.523
"From when you woke up this morning until now, how much better is your coughing?"	2.9 (1.0)	2.7 (1.3)	-0.06	-0.35, 0.24	0.796

* Statistically significant at $p<0.05$
† The average of change-from-baseline measurements of Hours 1 to 6 reported as mean (standard error).
Key: CI – confidence interval, DXM – dextromethorphan, LSM – least squares mean, PBO – placebo

238.7 ± 252.3, respectively. The estimated 17% reduction in cough rate for DXM relative to placebo was not statistically significant (0.83, 95% CI [0.59 to 1.15]; p=0.252). No treatment differences were detected from the subjective assessments of cough (Table 1). However, given that subject enrollment was terminated at 45% of the planned sample size, this pilot study was not sufficiently powered to detect treatment differences.

Thirteen adverse events (AEs) were reported in the DXM (n=9) and placebo (n=4) groups. Blinded investigators rated all AEs as either mild or moderate, and none were considered related to treatment. Four subjects receiving DXM (three with headache and one with dizziness) and none receiving placebo reported AEs in the nervous system disorders classification.

Discussion and Conclusion

This single-dose pilot study was terminated early due to methodological and operational issues associated with the digital audio recordings, resulting in enrollment of only 45% subjects planned. Specifically, background noise was captured in the audio recordings because the exam rooms were not adequately soundproof. This noise interfered with the compression software and was counted as coughs in certain instances; thus, the cough count data were unreliable. In addition, four protocol violations of parental coercion to encourage coughing during the baseline period were discovered by video. Collecting cough counts by this method was therefore deemed not feasible for children because of extraneous noise and having to confine the child in a clinic environment for seven hours.

Other study limitations included subjective cough assessments not fully validated in children and being administered by staff with scoring assistance from parents. None of these subjective assessments had a minimum score specified in the protocol for subject eligibility, so the assay sensitivity needed to detect treatment differences may not have been sufficient.

In conclusion, this pilot study was terminated because of unforeseen methodological issues for which substantial modifications to the existing study design would be required. Therefore, these study results should be interpreted with caution. Nevertheless, key learnings from this study were addressed in designing a second pilot study, which used an ambulatory cough monitoring device over 24 hours and subjective cough assessments validated in children to evaluate the efficacy and safety of multiple doses of DXM [5].

Disclosure

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