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

Summary

EudraCT number	2020-003216-28
Trial protocol	Outside EU/EEA
Global end of trial date	19 March 2020

Results information

Result version number	v1 (current)
This version publication date	30 September 2020
First version publication date	30 September 2020

Trial information

Trial identification

Sponsor protocol code	A6531002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02651116
WHO universal trial number (UTN)	-
Other trial identifiers	Alias Study Number: CHPA DXM

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 June 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 March 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The objective of this pilot study was to evaluate the endpoints and analyses that might be most appropriate to evaluate the efficacy of dextromethorphan hydrobromide (DXM HBr) 15 milligram (mg) per 10 millilitre (mL) versus placebo in children aged 6 to 11 years in a future study.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 February 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 131
Worldwide total number of subjects	131
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	131
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted in the United States from 25 February 2016 to 19 March 2020.

Pre-assignment

Screening details:

142 subjects were enrolled in a 2 hour run-in period, where they received 10 mL of non-medicinal liquid oral confection for once, and fitted with cough counting device VitaloJAKTM. Subjects who completed run-in period and qualified, were randomised to either dextromethorphan hydrobromide or placebo in a 4-day treatment period.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Dextromethorphan Hydrobromide

Arm description:

Subjects were randomised to receive 9 doses of DXM HBr (15 mg/10 mL) over the course of 4 day study treatment and were fitted with the cough recording device VitaloJAKTM for the first 24 hours of treatment. On Day 1, subjects received a single 10 mL oral dose of DXM HBr syrup each in afternoon and evening. On Day 2 and 3, subjects received a single 10 mL oral dose of DXM HBr syrup each in morning, afternoon and evening. On Day 4, subjects received a single 10 mL oral dose of DXM HBr syrup in morning. Subjects were followed up for 14 days after last dose of study medication.

Arm type	Experimental
Investigational medicinal product name	Dextromethorphan Hydrobromide
Investigational medicinal product code	
Other name	PF-02450388
Pharmaceutical forms	Syrup
Routes of administration	Oral use

Dosage and administration details:

On Day 1, subjects received a single 10 mL oral dose of DXM HBr syrup each in afternoon and evening. On Day 2 and 3, subjects received a single 10 mL oral dose of DXM HBr syrup each in morning, afternoon and evening. On Day 4, subjects received a single 10 mL oral dose of DXM HBr syrup in morning.

Arm title	Placebo

Arm description:

Subjects were randomised to receive 9 doses of placebo matched to 15 mg/10 mL DXM HBr over the course of 4 day study treatment and were fitted with the cough recording device VitaloJAKTM for the first 24 hours of treatment. On Day 1, subjects received a single 10 mL oral dose of placebo syrup each in afternoon and evening. On Day 2 and 3, subjects received a single 10 mL oral dose of placebo syrup each in morning, afternoon and evening. On Day 4, subjects received a single 10 mL oral dose of placebo syrup in morning. Subjects were followed up for 14 days after last dose of study medication.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Syrup
Routes of administration	Oral use

Dosage and administration details:

On Day 1, subjects received a single 10 mL oral dose of placebo syrup matched to DXM HBr each in afternoon and evening. On Day 2 and 3, subjects received a single 10 mL oral dose of placebo syrup each in morning, afternoon and evening. On Day 4, subjects received a single 10 mL oral dose of placebo syrup in morning.

Number of subjects in period 1	Dextromethorphan Hydrobromide	Placebo
Started	68	63
Treated	68	63
Completed	67	62
Not completed	1	1
Adverse Event	-	1
No Longer Willing To Participate In Study	1	-

Baseline characteristics

Reporting groups

Reporting group title	Dextromethorphan Hydrobromide

Reporting group description:

Subjects were randomised to receive 9 doses of DXM HBr (15 mg/10 mL) over the course of 4 day study treatment and were fitted with the cough recording device VitaloJAKTM for the first 24 hours of treatment. On Day 1, subjects received a single 10 mL oral dose of DXM HBr syrup each in afternoon and evening. On Day 2 and 3, subjects received a single 10 mL oral dose of DXM HBr syrup each in morning, afternoon and evening. On Day 4, subjects received a single 10 mL oral dose of DXM HBr syrup in morning. Subjects were followed up for 14 days after last dose of study medication.

Reporting group title	Placebo

Reporting group description:

Subjects were randomised to receive 9 doses of placebo matched to 15 mg/10 mL DXM HBr over the course of 4 day study treatment and were fitted with the cough recording device VitaloJAKTM for the first 24 hours of treatment. On Day 1, subjects received a single 10 mL oral dose of placebo syrup each in afternoon and evening. On Day 2 and 3, subjects received a single 10 mL oral dose of placebo syrup each in morning, afternoon and evening. On Day 4, subjects received a single 10 mL oral dose of placebo syrup in morning. Subjects were followed up for 14 days after last dose of study medication.

Reporting group values	Dextromethorphan Hydrobromide	Placebo	Total
Number of subjects	68	63	131
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	68	63	131
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	8.3	8.0	
standard deviation	± 1.57	± 1.73	-
Gender Categorical Units: Subjects			
Female	35	32	67
Male	33	31	64
Race Units: Subjects			
White	40	39	79
Black	24	22	46
Asian	0	0	0
Other	4	2	6
Ethnicity Units: Subjects			
Hispanic or Latino	4	7	11

Not Hispanic or Latino	64	56	120

End points

End points reporting groups

Reporting group title	Dextromethorphan Hydrobromide

Reporting group description:

Subjects were randomised to receive 9 doses of DXM HBr (15 mg/10 mL) over the course of 4 day study treatment and were fitted with the cough recording device VitaloJAKTM for the first 24 hours of treatment. On Day 1, subjects received a single 10 mL oral dose of DXM HBr syrup each in afternoon and evening. On Day 2 and 3, subjects received a single 10 mL oral dose of DXM HBr syrup each in morning, afternoon and evening. On Day 4, subjects received a single 10 mL oral dose of DXM HBr syrup in morning. Subjects were followed up for 14 days after last dose of study medication.

Reporting group title	Placebo

Reporting group description:

Subjects were randomised to receive 9 doses of placebo matched to 15 mg/10 mL DXM HBr over the course of 4 day study treatment and were fitted with the cough recording device VitaloJAKTM for the first 24 hours of treatment. On Day 1, subjects received a single 10 mL oral dose of placebo syrup each in afternoon and evening. On Day 2 and 3, subjects received a single 10 mL oral dose of placebo syrup each in morning, afternoon and evening. On Day 4, subjects received a single 10 mL oral dose of placebo syrup in morning. Subjects were followed up for 14 days after last dose of study medication.

Primary: Mean of Total Cough Counts: Over 24 Hours Post-First Dose on Day 1

End point title	Mean of Total Cough Counts: Over 24 Hours Post-First Dose on Day 1

End point description:

Total cough count was collected by the cough recording device VitaloJAKTM in an ambulatory setting. The VitaloJAKTM device recorded 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. Data were captured on a data card and the vitalograph analyst evaluated cough counts. Full analysis set included all subjects who were randomised, took Dose 1, had a valid baseline cough count assessment, and provided any post-dosing efficacy data.

End point type	Primary

End point timeframe:

Within 24 hours post-first dose on Day 1

End point values	Dextromethorphan Hydrobromide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	61		
Units: Cough counts				
arithmetic mean (standard deviation)	457.1 (± 367.21)	676.8 (± 814.33)		

Statistical analyses

Statistical analysis title	Dextromethorphan Hydrobromide vs Placebo

Statistical analysis description:

Estimated rate ratio, and corresponding 95% confidence interval (CI) for DXM HBr versus placebo was obtained from negative binomial model with treatment, study site (pooled), age group, and log-

transformed baseline average cough count per hour as factors, with logarithm of the time over which the cough count was evaluated as the offset parameter. Rate ratio refers to, ratio of rate of cough counts per 24 hours for DXM HBr to placebo.

Comparison groups	Dextromethorphan Hydrobromide v Placebo
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.0449 [1]
Method	Negative Binomial Regression
Parameter estimate	Ratio of rates
Point estimate	0.7899
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6273
upper limit	0.9947
Variability estimate	Standard error of the mean
Dispersion value	0.0929

Notes:

[1] - P-Value <=0.05 level was considered significantly better and P-Value lying between 0.05<p<=0.1 level was considered marginally significantly better.

Secondary: Mean of Total Cough Counts: Between Dose 1 to Dose 2 on Day 1

End point title	Mean of Total Cough Counts: Between Dose 1 to Dose 2 on Day 1

End point description:

Total cough count was collected by the cough recording device VitaloJAKTM in an ambulatory setting. The VitaloJAKTM device recorded 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. Data were captured on a data card and the vitalograph analyst evaluated cough counts. Full analysis set included all subjects who were randomised, took Dose 1, had a valid baseline cough count assessment, and provided any post-dosing efficacy data. Here 'Number of Subjects Analysed' signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Between dose 1 to dose 2 on Day 1

End point values	Dextromethorphan Hydrobromide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	61		
Units: Cough counts				
arithmetic mean (standard deviation)	32.73 (± 30.597)	47.03 (± 57.729)		

Statistical analyses

Statistical analysis title	Dextromethorphan Hydrobromide vs Placebo

Statistical analysis description:

Estimated rate ratio, and corresponding 95% CI for DXM HBr versus placebo was obtained from negative binomial model with treatment, study site (pooled), age group, and log-transformed baseline average cough count per hour as factors, with logarithm of the time over which the cough count was evaluated as the offset parameter. Rate ratio refers to, ratio of rate of cough counts per specified duration (used in evaluation of this endpoint) for DXM HBr to placebo.

Comparison groups	Dextromethorphan Hydrobromide v Placebo
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.0552 [2]
Method	Negative Binomial Regression
Parameter estimate	Ratio of rates
Point estimate	0.8048
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6446
upper limit	1.0049
Variability estimate	Standard error of the mean
Dispersion value	0.0912

Notes:

[2] - P-Value <=0.05 level was considered significantly better and P-Value lying between 0.05<p<=0.1 level was considered marginally significantly better.

Secondary: Mean of Total Cough Counts: Between Dose 2 on Day 1 to Dose 3 on Day 2

End point title	Mean of Total Cough Counts: Between Dose 2 on Day 1 to Dose 3 on Day 2

End point description:

Total cough count was collected by the cough recording device VitaloJAKTM in an ambulatory setting. The VitaloJAKTM device recorded 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. Data were captured on a data card and the vitalograph analyst evaluated cough counts. Full analysis set included all subjects who were randomised, took Dose 1, had a valid baseline cough count assessment, and provided any post-dosing efficacy data. Here 'Number of Subjects Analysed' signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Between dose 2 on Day 1 to dose 3 on Day 2 (second dose of Day 1 to first dose of Day 2)

End point values	Dextromethorphan Hydrobromide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	61		
Units: Cough counts				
arithmetic mean (standard deviation)	9.70 (± 8.877)	11.44 (± 13.193)		

Statistical analyses

Statistical analysis title	Dextromethorphan Hydrobromide vs Placebo

Statistical analysis description:

Estimated rate ratio, and corresponding 95% CI for DXM HBr versus placebo was obtained from negative binomial model with treatment, study site (pooled), age group, and log-transformed baseline average cough count per hour as factors, with logarithm of the time over which the cough count was evaluated as the offset parameter. Rate ratio refers to, ratio of rate of cough counts per specified duration (used in evaluation of this endpoint) for DXM HBr to placebo.

Comparison groups	Dextromethorphan Hydrobromide v Placebo
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.7684 [3]
Method	Negative Binomial Regression
Parameter estimate	Ratio of rates
Point estimate	0.9551
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7032
upper limit	1.2971
Variability estimate	Standard error of the mean
Dispersion value	0.1491

Notes:

[3] - P-Value <=0.05 level was considered significantly better and P-Value lying between 0.05<p<=0.1 level was considered marginally significantly better.

Secondary: Mean of Total Cough Counts: Between Dose 3 to Dose 4 on Day 2

End point title	Mean of Total Cough Counts: Between Dose 3 to Dose 4 on Day 2

End point description:

Total cough count was collected by the cough recording device VitaloJAKTM in an ambulatory setting. The VitaloJAKTM device recorded 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. Data were captured on a data card and the vitalograph analyst evaluated cough counts. Full analysis set included all subjects who were randomised, took Dose 1, had a valid baseline cough count assessment, and provided any post-dosing efficacy data. Here 'Number of Subjects Analysed' signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Between dose 3 to dose 4 on Day 2 (between first and second dose of Day 2)

End point values	Dextromethorphan Hydrobromide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	60		
Units: Cough counts				
arithmetic mean (standard deviation)	19.32 (± 16.752)	33.62 (± 47.709)		

Statistical analyses

Statistical analysis title	Dextromethorphan Hydrobromide vs Placebo

Statistical analysis description:

Estimated rate ratio, and corresponding 95% CI for DXM HBr versus placebo was obtained from negative binomial model with treatment, study site (pooled), age group, and log-transformed baseline average cough count per hour as factors, with logarithm of the time over which the cough count was evaluated as the offset parameter. Rate ratio refers to, ratio of rate of cough counts per specified duration (used in evaluation of this endpoint) for DXM HBr to placebo.

Comparison groups	Dextromethorphan Hydrobromide v Placebo
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.022 [4]
Method	Negative Binomial Regression
Parameter estimate	Ratio of rates
Point estimate	0.7014
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5178
upper limit	0.95
Variability estimate	Standard error of the mean
Dispersion value	0.1086

Notes:

[4] - P-Value <=0.05 level was considered significantly better and P-Value lying between 0.05<p<=0.1 level was considered marginally significantly better.

Secondary: Mean of Total Cough Counts: Between Dose 1 to Dose 2 on Day 1, and Between Dose 3 to Dose 4 on Day 2

End point title	Mean of Total Cough Counts: Between Dose 1 to Dose 2 on Day 1, and Between Dose 3 to Dose 4 on Day 2

End point description:

Total cough count was collected by the cough recording device VitaloJAKTM in an ambulatory setting. The VitaloJAKTM device recorded 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. Data were captured on a data card and the vitalograph analyst evaluated cough counts. In this endpoint, as planned combined data is reported for first dosing interval (dose 1 to dose 2) on Day 1 and first dosing interval (dose 3 to dose 4) on Day 2. Full analysis set included all subjects who were randomised, took Dose 1, had a valid baseline cough count assessment, and provided any post-dosing efficacy data. Here 'Number of Subjects Analysed' signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Between dose 1 to dose 2 on Day 1 (between first and second dose of Day 1) and between dose 3 to dose 4 on Day 2 (between first and second dose of Day 2)

End point values	Dextromethorphan Hydrobromide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	61		
Units: Cough counts				
arithmetic mean (standard deviation)	26.13 (± 21.498)	40.39 (± 49.896)		

Statistical analyses

Statistical analysis title	Dextromethorphan Hydrobromide vs Placebo

Statistical analysis description:

Estimated rate ratio, and corresponding 95% CI for DXM HBr versus placebo was obtained from negative binomial model with treatment, study site (pooled), age group, and log-transformed baseline average cough count per hour as factors, with logarithm of the time over which the cough count was evaluated as the offset parameter. Rate ratio refers to, ratio of rate of cough counts per specified duration (used in evaluation of this endpoint) for DXM HBr to placebo.

Comparison groups	Dextromethorphan Hydrobromide v Placebo
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.0098 [5]
Method	Negative Binomial Regression
Parameter estimate	Ratio of rates
Point estimate	0.7454
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5964
upper limit	0.9316
Variability estimate	Standard error of the mean
Dispersion value	0.0848

Notes:

[5] - P-Value <=0.05 level was considered significantly better and P-Value lying between 0.05<p<=0.1 level was considered marginally significantly better.

Secondary: Mean of Total Cough Time Accumulated Over a 24-Hour Period Post-First Dose on Day 1

End point title	Mean of Total Cough Time Accumulated Over a 24-Hour Period Post-First Dose on Day 1

End point description:

Time (in seconds) accumulated over a 24-hour period when cough events occurred was collected by the cough recording device VitaloJAKTM in an ambulatory setting. The VitaloJAKTM device recorded 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. Data were captured on a data card and the vitalograph analyst evaluated total cough time accumulated. Full analysis set included all subjects who were randomised, took Dose 1, had a valid baseline cough count assessment, and provided any post-dosing efficacy data.

End point type	Secondary

End point timeframe:

Within 24 hours post-first dose on Day 1

End point values	Dextromethorphan Hydrobromide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	61		
Units: Seconds				
arithmetic mean (standard deviation)	350.5 (± 268.95)	502.7 (± 566.57)		

Statistical analyses

Statistical analysis title	Dextromethorphan Hydrobromide vs Placebo

Statistical analysis description:

Analysis of covariance (ANCOVA) model contained treatment, study site (pooled), log-transformed baseline cough time and age group terms as factors.

Comparison groups	Dextromethorphan Hydrobromide v Placebo
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.0977 [6]
Method	ANCOVA
Parameter estimate	Difference in least squares mean
Point estimate	-0.221
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4831
upper limit	0.0411
Variability estimate	Standard error of the mean
Dispersion value	0.1324

Notes:

[6] - P-Value <=0.05 level was considered significantly better and P-Value lying between 0.05<p<=0.1 level was considered marginally significantly better.

Other pre-specified: Change From Baseline in Morning Cough Frequency at Day 2, 3, and 4

End point title	Change From Baseline in Morning Cough Frequency at Day 2, 3, and 4

End point description:

Subjects on specified time points were asked to respond to "from when you woke up this morning until now, how much have you been coughing", on a 5-point scale: 0= not at all, 1= a tiny bit, 2= a little, 3= some and 4= a lot. Higher scores indicated higher frequency of cough in morning time. Full analysis set included all subjects who were randomised, took Dose 1, had a valid baseline cough count assessment, and provided any post-dosing efficacy data. Here 'n' signifies number of subjects evaluable for specified time points.

End point type	Other pre-specified

End point timeframe:

Baseline (morning screening visit on Day 1), Within 30 minutes of waking and before morning dose on Days 2, 3, and 4

End point values	Dextromethorphan Hydrobromide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	61		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 67, 61)	3.4 (± 0.65)	3.3 (± 0.63)		
Change at Day 2 (n= 66, 61)	-1.2 (± 1.30)	-0.7 (± 1.15)		
Change at Day 3 (n= 66, 60)	-1.5 (± 1.15)	-1.1 (± 1.38)		
Change at Day 4 (n= 66, 60)	-2.0 (± 1.20)	-1.8 (± 1.40)		

Statistical analyses

Statistical analysis title	Dextromethorphan Hydrobromide vs Placebo

Statistical analysis description:

Analysis of variance (ANOVA) model contained treatment, study site (pooled), the corresponding morning baseline cough frequency by subject, and age group included in the model.

Comparison groups	Dextromethorphan Hydrobromide v Placebo
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.0191 [7]
Method	ANOVA
Parameter estimate	Difference in least squares mean
Point estimate	-0.2881
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5287
upper limit	-0.0475
Variability estimate	Standard error of the mean
Dispersion value	0.1224

Notes:

[7] - P-Value <=0.05 level was considered significantly better and P-Value lying between 0.05<p<=0.1 level was considered marginally significantly better.

Other pre-specified: Change From Baseline in Morning Cough Severity at Day 2, 3, and 4

End point title	Change From Baseline in Morning Cough Severity at Day 2, 3, and 4

End point description:

Subjects on specified time points were asked to respond to "how bad is your cough this morning", on a 5-point scale: 0= no cough, 1= a tiny bit bad, 2= a little bad, 3= bad and 4= very bad. Higher scores indicated more severe cough in morning time. Full analysis set included all subjects who were randomised, took Dose 1, had a valid baseline cough count assessment, and provided any post-dosing efficacy data. Here 'n' signifies number of subjects evaluable for specified time points.

End point type	Other pre-specified

End point timeframe:

Baseline (morning screening visit on Day 1), Within 30 minutes of waking and before morning dose on Days 2, 3, and 4

End point values	Dextromethorphan Hydrobromide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	61		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 67, 61)	3.1 (± 0.54)	3.1 (± 0.60)		
Change at Day 2 (n= 66, 61)	-1.1 (± 0.89)	-0.6 (± 1.19)		
Change at Day 3 (n= 66, 60)	-1.4 (± 0.96)	-1.3 (± 1.22)		
Change at Day 4 (n= 66, 60)	-1.9 (± 1.10)	-1.8 (± 1.15)		

Statistical analyses

Statistical analysis title	Dextromethorphan Hydrobromide vs Placebo

Statistical analysis description:

ANOVA model contained treatment, study site (pooled), the corresponding morning baseline cough severity by subject, and age group included in the model.

Comparison groups	Dextromethorphan Hydrobromide v Placebo
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.0049 [8]
Method	ANOVA
Parameter estimate	Difference in least squares mean
Point estimate	-0.3128
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5299
upper limit	-0.0956
Variability estimate	Standard error of the mean
Dispersion value	0.1104

Notes:

[8] - P-Value <=0.05 level was considered significantly better and P-Value lying between 0.05<p<=0.1 level was considered marginally significantly better.

Other pre-specified: Change From Baseline in Impact of Cough on Sleep at Day 2, 3, and 4

End point title	Change From Baseline in Impact of Cough on Sleep at Day 2, 3, and 4

End point description:

Subjects on specified time points were asked to respond to "last night in bed, how much did your cough keep you awake", on a 5-point scale: 0= not at all, 1= a tiny bit, 2= a little, 3= some and 4= a lot. Higher scores indicated worse impact of cough on sleep. Full analysis set included all subjects who were

randomised, took Dose 1, had a valid baseline cough count assessment, and provided any post-dosing efficacy data. Here 'n' signifies number of subjects evaluable for specified time points.

End point type	Other pre-specified

End point timeframe:

Baseline (morning screening visit on Day 1), Within 30 minutes of waking and before morning dose on Days 2, 3, and 4

End point values	Dextromethorphan Hydrobromide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	61		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 67, 61)	2.8 (± 1.15)	3.0 (± 1.19)		
Change at Day 2 (n= 66, 61)	-0.8 (± 1.56)	-0.7 (± 1.45)		
Change at Day 3 (n= 66, 60)	-1.3 (± 1.59)	-1.4 (± 1.67)		
Change at Day 4 (n= 66, 60)	-1.8 (± 1.57)	-1.9 (± 1.74)		

Statistical analyses

Statistical analysis title	Dextromethorphan Hydrobromide vs Placebo

Statistical analysis description:

ANOVA model contained treatment, study site (pooled), the corresponding morning baseline impact on sleep by subject, and age group included in the model.

Comparison groups	Dextromethorphan Hydrobromide v Placebo
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.2679 [9]
Method	ANOVA
Parameter estimate	Difference in least squares mean
Point estimate	-0.1483
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4112
upper limit	0.1146
Variability estimate	Standard error of the mean
Dispersion value	0.1337

Notes:

[9] - P-Value <=0.05 level was considered significantly better and P-Value lying between 0.05<p<=0.1 level was considered marginally significantly better.

Other pre-specified: Change From Baseline in Afternoon Cough Frequency at Day 2, 3, and 4

End point title	Change From Baseline in Afternoon Cough Frequency at Day 2, 3, and 4

End point description:

Subjects on specified time points were asked to respond to "how much have you been coughing this afternoon" on a 5-point scale: 0= not at all, 1= a tiny bit, 2= a little, 3= some and 4= a lot. Higher scores indicated higher frequency of cough in afternoon time. Full analysis set included all subjects who were randomised, took Dose 1, had a valid baseline cough count assessment, and provided any post-dosing efficacy data. Here 'n' signifies number of subjects evaluable for specified time points.

End point type	Other pre-specified

End point timeframe:

Baseline (afternoon visit on Day 1 before first dose), Before the afternoon dose on Days 2, and 3, Afternoon of Day 4

End point values	Dextromethorphan Hydrobromide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	61		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 67, 61)	3.2 (± 0.80)	3.4 (± 0.73)		
Change at Day 2 (n= 66, 61)	-0.7 (± 1.25)	-0.6 (± 1.06)		
Change at Day 3 (n= 66, 60)	-1.5 (± 1.30)	-1.4 (± 1.27)		
Change at Day 4 (n= 63, 58)	-1.9 (± 1.22)	-1.8 (± 1.41)		

Statistical analyses

Statistical analysis title	Dextromethorphan Hydrobromide vs Placebo

Statistical analysis description:

ANOVA model contained treatment, study site (pooled), the corresponding afternoon baseline cough frequency by subject, and age group included in the model.

Comparison groups	Dextromethorphan Hydrobromide v Placebo
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.0242 [10]
Method	ANOVA
Parameter estimate	Difference in least squares mean
Point estimate	-0.2812
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5255
upper limit	-0.0369
Variability estimate	Standard error of the mean
Dispersion value	0.1242

Notes:

[10] - P-Value <=0.05 level was considered significantly better and P-Value lying between 0.05<p<=0.1 level was considered marginally significantly better.

Other pre-specified: Change From Baseline in Afternoon Cough Severity at Day 2, 3,

and 4

End point title	Change From Baseline in Afternoon Cough Severity at Day 2, 3, and 4

End point description:

Subjects on specified time points were asked to respond to "how bad is your cough this afternoon" on a 5-point scale: 0= no cough, 1= a tiny bit bad, 2= a little bad, 3= bad and 4= very bad. Higher scores indicated more severe cough in afternoon time. Full analysis set included all subjects who were randomised, took Dose 1, had a valid baseline cough count assessment, and provided any post-dosing efficacy data. Here 'n' signifies number of subjects evaluable for specified time points.

End point type	Other pre-specified

End point timeframe:

Baseline (afternoon visit on Day 1 before first dose), Before the afternoon dose on Days 2, and 3, Anytime in afternoon of Day 4

End point values	Dextromethorphan Hydrobromide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	61		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 67, 61)	2.8 (± 0.83)	3.1 (± 0.84)		
Change at Day 2 (n= 66, 61)	-0.7 (± 1.16)	-0.6 (± 0.98)		
Change at Day 3 (n= 66, 60)	-1.4 (± 1.15)	-1.4 (± 1.24)		
Change at Day 4(n= 63, 58)	-1.7 (± 1.08)	-1.6 (± 1.45)		

Statistical analyses

Statistical analysis title	Dextromethorphan Hydrobromide vs Placebo

Statistical analysis description:

ANOVA model contained treatment, study site (pooled), the corresponding afternoon baseline cough severity by subject, and age group included in the model.

Comparison groups	Dextromethorphan Hydrobromide v Placebo
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.0063 [11]
Method	ANOVA
Parameter estimate	Difference in least squares mean
Point estimate	-0.3014
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.517
upper limit	-0.0858
Variability estimate	Standard error of the mean
Dispersion value	0.1096

Notes:

[11] - P-Value <=0.05 level was considered significantly better and P-Value lying between 0.05<p<=0.1 level was considered marginally significantly better.

Other pre-specified: Change From Baseline in Child Global Question at Day 2, 3, and 4

End point title	Change From Baseline in Child Global Question at Day 2, 3, and 4

End point description:

Subjects on specified time points were asked to respond on “how bad is your cold today”, on a 5-point scale; 0= no cold, 1= a tiny bit bad, 2= a little bad, 3= bad, and 4= very bad. Higher scores indicated worse cold. Full analysis set included all subjects who were randomised, took Dose 1, had a valid baseline cough count assessment, and provided any post-dosing efficacy data. Here 'n' signifies number of subjects evaluable for specified time points.

End point type	Other pre-specified

End point timeframe:

Baseline (afternoon visit on Day 1 before first dose), Before the afternoon dose on Day 2, and 3, Anytime in afternoon of Day 4

End point values	Dextromethorphan Hydrobromide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	61		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 67, 61)	3.2 (± 0.42)	3.3 (± 0.46)		
Change at Day 2 (n= 66, 61)	-1.1 (± 1.02)	-0.9 (± 1.01)		
Change at Day 3 (n= 66, 60)	-1.6 (± 0.93)	-1.6 (± 1.13)		
Change at Day 4 (n= 63, 58)	-2.1 (± 0.87)	-1.7 (± 1.26)		

Statistical analyses

Statistical analysis title	Dextromethorphan Hydrobromide vs Placebo

Statistical analysis description:

ANOVA model with treatment, study site (pooled), the baseline assessment in child global question cold assessment by subject and age group included in the model.

Comparison groups	Dextromethorphan Hydrobromide v Placebo
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.0247 [12]
Method	ANOVA
Parameter estimate	Difference in least squares mean
Point estimate	-0.2535
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4745
upper limit	-0.0325

Variability estimate	Standard error of the mean
Dispersion value	0.1124

Notes:

[12] - P-Value <=0.05 level was considered significantly better and P-Value lying between 0.05<p<=0.1 level was considered marginally significantly better.

Other pre-specified: Pediatric Global Assessment of Satisfaction With Study Medication: By Subject, and Caregiver

End point title	Pediatric Global Assessment of Satisfaction With Study Medication: By Subject, and Caregiver

End point description:

Subjects at the end of the study were asked to respond to "How would you rate the study medication for taking away your cough?" on a 7-point scale: 0= excellent, 1= very good, 2= good, 3= fair, 4= poor, 5= very poor, and 6= terrible. Higher scores indicated poorer satisfaction with study medication. Within 20 minutes after subjects completed the assessment parents/legally acceptable representative were asked to respond to "How would you rate the study medication for taking away your child's cough?" on a 7-point scale: 0= excellent, 1= very good, 2= good, 3= fair, 4= poor, 5= very poor, and 6= terrible. Higher scores indicated poorer satisfaction with study medication. Full analysis set included all subjects who were randomised, took Dose 1, had a valid baseline cough count assessment, and provided any post-dosing efficacy data. Here 'Number of Subjects Analysed' signifies subjects evaluable for this endpoint.

End point type	Other pre-specified

End point timeframe:

For subjects: at the end of the study on Day 4; For parents/legally acceptable representatives: within 20 minutes after subject completed assessment at the end of the study on Day 4

End point values	Dextromethorphan Hydrobromide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	61		
Units: Units on a scale				
arithmetic mean (standard deviation)				
By Subject:	1.7 (± 1.20)	1.6 (± 1.26)		
By Caregiver:	1.8 (± 1.07)	1.9 (± 1.16)		

Statistical analyses

Statistical analysis title	Dextromethorphan HBr vs Placebo (Subject)

Statistical analysis description:

ANOVA model with treatment, study site (pooled), and age group included in the model.

Comparison groups	Dextromethorphan Hydrobromide v Placebo
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.5652 [13]
Method	ANOVA
Parameter estimate	Difference in least squares mean
Point estimate	0.1266

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3081
upper limit	0.5614
Variability estimate	Standard error of the mean
Dispersion value	0.2196

Notes:

[13] - P-Value <=0.05 level was considered significantly better and P-Value lying between 0.05<p<=0.1 level was considered marginally significantly better.

Statistical analysis title	Dextromethorphan HBr vs Placebo (Caregiver)

Statistical analysis description:

ANOVA model with treatment, study site (pooled), and age group included in the model.

Comparison groups	Dextromethorphan Hydrobromide v Placebo
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.4914 [14]
Method	ANOVA
Parameter estimate	Difference in least squares mean
Point estimate	-0.1368
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5292
upper limit	0.2556
Variability estimate	Standard error of the mean
Dispersion value	0.1982

Notes:

[14] - P-Value <=0.05 level was considered significantly better and P-Value lying between 0.05<p<=0.1 level was considered marginally significantly better.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to 14 days after last dose of study medication (up to 18 days)

Adverse event reporting additional description:

Same event may appear as Adverse Event (AE) and Serious Adverse Events (SAE), what is presented are distinct events. Event may be categorised as serious in 1 subject and as non-serious in another subject or 1 subject may have experienced both serious and non-serious event during study. Evaluated on all subjects who received the study drug.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects were randomised to receive 9 doses of placebo matched to 15 mg/10 mL DXM HBr over the course of 4 day study treatment and were fitted with the cough recording device VitaloJAKTM for the first 24 hours of treatment. On Day 1, subjects received a single 10 mL oral dose of placebo syrup each in afternoon and evening. On Day 2 and 3, subjects received a single 10 mL oral dose of placebo syrup each in morning, afternoon and evening. On Day 4, subjects received a single 10 mL oral dose of placebo syrup in morning. Subjects were followed up for 14 days after last dose of study medication.

Reporting group title	Dextromethorphan Hydrobromide

Reporting group description:

Subjects were randomised to receive 9 doses of DXM HBr (15 mg/10 mL) over the course of 4 day study treatment and were fitted with the cough recording device VitaloJAKTM for the first 24 hours of treatment. On Day 1, subjects received a single 10 mL oral dose of DXM HBr syrup each in afternoon and evening. On Day 2 and 3, subjects received a single 10 mL oral dose of DXM HBr syrup each in morning, afternoon and evening. On Day 4, subjects received a single 10 mL oral dose of DXM HBr syrup in morning. Subjects were followed up for 14 days after last dose of study medication.

Serious adverse events	Placebo	Dextromethorphan Hydrobromide	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 63 (0.00%)	0 / 68 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Placebo	Dextromethorphan Hydrobromide	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 63 (25.40%)	13 / 68 (19.12%)	
Injury, poisoning and procedural complications			

Joint injury			
subjects affected / exposed	1 / 63 (1.59%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 63 (4.76%)	1 / 68 (1.47%)	
occurrences (all)	3	1	
Psychomotor hyperactivity			
subjects affected / exposed	0 / 63 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	1 / 63 (1.59%)	1 / 68 (1.47%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	1 / 63 (1.59%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Pain			
subjects affected / exposed	0 / 63 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Tympanic membrane hyperaemia			
subjects affected / exposed	0 / 63 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Lip dry			
subjects affected / exposed	1 / 63 (1.59%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 63 (1.59%)	1 / 68 (1.47%)	
occurrences (all)	1	1	
Nasal congestion			
subjects affected / exposed	1 / 63 (1.59%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Nasal dryness			

subjects affected / exposed	1 / 63 (1.59%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Nasal mucosal disorder			
subjects affected / exposed	1 / 63 (1.59%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Nasal oedema			
subjects affected / exposed	1 / 63 (1.59%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Nasal turbinate abnormality			
subjects affected / exposed	1 / 63 (1.59%)	3 / 68 (4.41%)	
occurrences (all)	1	3	
Pharyngeal erythema			
subjects affected / exposed	1 / 63 (1.59%)	1 / 68 (1.47%)	
occurrences (all)	1	1	
Rhinitis allergic			
subjects affected / exposed	0 / 63 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Rhinorrhoea			
subjects affected / exposed	3 / 63 (4.76%)	2 / 68 (2.94%)	
occurrences (all)	3	2	
Rhonchi			
subjects affected / exposed	0 / 63 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Upper-airway cough syndrome			
subjects affected / exposed	2 / 63 (3.17%)	0 / 68 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
Dennie-Morgan fold			
subjects affected / exposed	0 / 63 (0.00%)	2 / 68 (2.94%)	
occurrences (all)	0	2	
Erythema			
subjects affected / exposed	1 / 63 (1.59%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Photosensitivity reaction			
subjects affected / exposed	0 / 63 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	

Infections and infestations			
Bronchiolitis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	1 / 63 (1.59%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Otitis media			
subjects affected / exposed	2 / 63 (3.17%)	0 / 68 (0.00%)	
occurrences (all)	2	0	
Otitis media acute			
subjects affected / exposed	1 / 63 (1.59%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 63 (1.59%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	1 / 63 (1.59%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Viral infection			
subjects affected / exposed	1 / 63 (1.59%)	0 / 68 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported