Clinical trial results:
Mulitcenter, Randomized, Double-Blind Study Comparing the Clinical Effects of Intravenous Montelukast With Placebo in Pediatric Patients (Ages 6 to 14 Years) With Acute Asthma (MK-0476-301)

Summary

EudraCT number	2005-002650-22
Trial protocol	LT
Global end of trial date	17 March 2008

Results information

Result version number	v1 (current)
This version publication date	08 March 2016
First version publication date	09 May 2015

Trial information

Trial identification

Sponsor protocol code	0476-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00117338
WHO universal trial number (UTN)	-
Other trial identifiers	SINGULAIR®: tradename, MK-0476-301: Protocol number

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.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	17 March 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 March 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study will attempt to find out if the addition of an intravenous form of a drug that is already used for treating asthma in children will help resolve asthma attacks faster than using the current standard care alone. The primary hypothesis of this study is that in pediatric participants with acute asthma, the addition of montelukast to standard therapy will cause a significant improvement in forced expiratory volume in 1 second (FEV1) over the first 60 minutes after administration compared with placebo.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 July 2005
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Chile: 10
Country: Number of subjects enrolled	Colombia: 15
Country: Number of subjects enrolled	Guatemala: 24
Country: Number of subjects enrolled	India: 35
Country: Number of subjects enrolled	Mexico: 43
Country: Number of subjects enrolled	Peru: 58
Country: Number of subjects enrolled	United States: 75
Country: Number of subjects enrolled	Lithuania: 16
Worldwide total number of subjects	276
EEA total number of subjects	16

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)	229
Adolescents (12-17 years)	47
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This international study was conducted in study sites in Guatemala, Lithuania, Chile, Peru, India, Mexico, Colombia, and the United Sates.

Pre-assignment

Screening details:

Of the 395 participants screened for inclusion in this study, 119 participants were excluded during screening and not randomized. One-hundred and ten participants were ineligible for the study, 5 participants withdrew consent, 2 parents withdrew consent, there was one protocol deviation, and 1 participant was excluded for an unknown reason.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo to montelukast sodium for approximately 120 minutes in duration.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Placebo to Montelukast 5.25 mg, 15 mL of the reconstituted study drug will be administered by syringe as a manual bolus over 2 to 5 mintues

Arm title	Montelukast Intravenous (IV) 5.25 mg

Arm description:

Montelukast 5.25 mg, 15 mL of the reconstituted study drug will be administered by syringe as a manual bolus over 2 to 5 mintues.

Arm type	Experimental
Investigational medicinal product name	Montelukast
Investigational medicinal product code	
Other name	MK-0476, SINGULAIR®
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Montelukast 5.25 mg, 15 mL of the reconstituted study drug will be administered by syringe as a manual bolus over 2 to 5 mintues

Number of subjects in period 1	Placebo	Montelukast Intravenous (IV) 5.25 mg
Started	131	145
Completed	127	140
Not completed	4	5
Consent withdrawn by subject	-	1
Adverse event, non-fatal	1	-
Did not meet Inclusion Criteria	-	1
Lack of efficacy	1	-
Protocol deviation	2	3

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo to montelukast sodium for approximately 120 minutes in duration.	
Reporting group title	Montelukast Intravenous (IV) 5.25 mg
Reporting group description:	
Montelukast 5.25 mg, 15 mL of the reconstituted study drug will be administered by syringe as a manual bolus over 2 to 5 mintues.	

Reporting group values	Placebo	Montelukast Intravenous (IV) 5.25 mg	Total
Number of subjects	131	145	276
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)	112	117	229
Adolescents (12-17 years)	19	28	47
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	8.9	9.2	
standard deviation	± 2.32	± 2.36	-
Gender categorical Units: Subjects			
Female	50	55	105
Male	81	90	171
Race/Ethnicity Units: Subjects			
White (Non-Hispanic)	16	16	32
Black	16	18	34
Hispanic	53	59	112
Asian	18	18	36
Multi-Racial	27	34	61
Other	1	0	1
Baseline Forced Expiratory Volume in one second (FEV1)			
FEV1 was measured in Liters (FEV 1 (L). A total of 4/276 (1—montelukast; 3—placebo) randomized participants were excluded from the Full Analysis Set (FAS) of the primary endpoint			
Units: Liters			
arithmetic mean	1	1.06	
standard deviation	± 0.5	± 0.5	-

Baseline FEV1 (Percent predicted)			
Percent of predicted baseline Forced Expiratory Volume in one second (FEV1). A total of 4/276 (1—montelukast; 3—placebo) randomized patients were excluded from the Full Analysis Set (FAS) of the primary endpoint.			
Units: Percent			
arithmetic mean	50.6	51.8	
standard deviation	± 17.4	± 16.8	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo to montelukast sodium for approximately 120 minutes in duration.	
Reporting group title	Montelukast Intravenous (IV) 5.25 mg
Reporting group description:	
Montelukast 5.25 mg, 15 mL of the reconstituted study drug will be administered by syringe as a manual bolus over 2 to 5 mintues.	

Primary: Time Weighted Average Change from Baseline in FEV1 (Forced Expiratory Volume in 1 Second) Over the First 60 Minutes After Study Drug Administration

End point title	Time Weighted Average Change from Baseline in FEV1 (Forced Expiratory Volume in 1 Second) Over the First 60 Minutes After Study Drug Administration
End point description:	
Improvement in FEV1 as the time-weighted average change from baseline over 60 minutes following the end of study drug administration. Time-weighted average of the changes from baseline obtained over the 60 minutes (at 60, 45, 30 and 15) with the time interval between any measurement and the measurement prior to it used as the weighting factor. Full Analysis Set (FAS), the FAS population includes all randomized patients who received double-blind study drug, and with efficacy measurements both at baseline and at least one time point over the time interval considered.	
End point type	Primary
End point timeframe:	
Baseline and (time weighted average over) 60 Minutes	

End point values	Placebo	Montelukast Intravenous (IV) 5.25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128[1]	144[2]		
Units: Liters				
least squares mean (confidence interval 95%)	0.07 (0.01 to 0.12)	0.08 (0.02 to 0.13)		

Notes:

[1] - The FAS Population

[2] - The FAS Population

Statistical analyses

Statistical analysis title	Improvement in FEV1
Statistical analysis description:	
Statistical Analysis 1 for Improvement in FEV1 (Forced Expiratory Volume in 1 Second) Over the First 60 Minutes After Administration	
Comparison groups	Placebo v Montelukast Intravenous (IV) 5.25 mg

Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.775 [3]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.08

Notes:

[3] - Model terms: treatment, region (US, non-US) and baseline FEV1 as covariate

Secondary: Change From Baseline in Modified Pulmonary Index [mPI] Score

End point title	Change From Baseline in Modified Pulmonary Index [mPI] Score

End point description:

Change from baseline in modified pulmonary index [mPI] score assessed 60 minutes following the end of study drug administration. mPI questionnaire scores each component on a scale of 0 to 3 (low to high) with a total possible score of 12. The components are respiratory rate, wheezing, prolongation of expiration (Inspiratory:Expiratory ratio), and accessory muscle use. Full Analysis Set (FAS) population includes all randomized patients who received double-blind study drug, and with efficacy measurements both at baseline and at least one time point over the time interval considered.

End point type	Secondary

End point timeframe:

Baseline and 60 minutes

End point values	Placebo	Montelukast Intravenous (IV) 5.25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128[4]	143[5]		
Units: Score on a scale				
least squares mean (confidence interval 95%)	-2.96 (-3.29 to -2.63)	-2.95 (-3.26 to -2.63)		

Notes:

[4] - The FAS Population

[5] - The FAS Population

Statistical analyses

Statistical analysis title	Change From Baseline in mPI Score

Statistical analysis description:

Statistical Analysis 1 for Change From Baseline in Modified Pulmonary Index [mPI] Score

Comparison groups	Placebo v Montelukast Intravenous (IV) 5.25 mg

Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.931 [6]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.41
upper limit	0.45

Notes:

[6] - Model terms: treatment, region (US, non-US) and baseline FEV1 as covariate

Secondary: Number of Participants With Treatment Failure (Hospitalization or Time to Decision to Discharge > 2 Hours)

End point title	Number of Participants With Treatment Failure (Hospitalization or Time to Decision to Discharge > 2 Hours)

End point description:

Treatment Failure is defined as a.) patients who required hospitalization, or b.) patients for whom a decision to discharge home has not been reached by 2 hours following the end of study drug administration.

Full Analysis Set (FAS). At least one post-randomization measurement obtained subsequent to at least one dose of study treatment was required for inclusion in the analysis of treatment failure endpoint. Baseline FEV1 measurement was also required to assess this endpoint since it was included in the model.

End point type	Secondary

End point timeframe:

120 minutes

End point values	Placebo	Montelukast Intravenous (IV) 5.25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128[7]	144[8]		
Units: Participants				
Hospitalization	33	28		
Decision to Discharge Home not Reached by 2 Hours	26	37		

Notes:

[7] - The FAS Population

[8] - The FAS Population

Statistical analyses

Statistical analysis title	Number of Participants with Treatment Failure

Statistical analysis description:

Statistical Analysis 1 for Number of Participants With Treatment Failure (Hospitalization or Time to Decision to Discharge > 2 Hours)

Comparison groups	Placebo v Montelukast Intravenous (IV) 5.25 mg

Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.975
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.61

Notes:

[9] - Model terms: treatment and baseline FEV1 as covariate

Secondary: Time-Weighted Average Change in FEV1 Over 45 Minutes Following the End of Study Drug Administration

End point title	Time-Weighted Average Change in FEV1 Over 45 Minutes Following the End of Study Drug Administration

End point description:

Improvement in FEV1 as time-weighted average change from baseline over 45 minutes following the end of study drug administration: Time-weighted average of the changes from baseline obtained over the 45 minutes (at 45, 30 and 15) with the time interval between any measurement and the measurement prior to it used as the weighting factor.

Full Analysis Set (FAS). The FAS population includes all randomized patients who received double-blind study drug, and with efficacy measurements both at baseline and at least one time point over the time interval considered.

End point type	Secondary

End point timeframe:

Baseline and (time-weighed average over) 45 Minutes

End point values	Placebo	Montelukast Intravenous (IV) 5.25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127[10]	142[11]		
Units: Liters				
least squares mean (confidence interval 95%)	0.05 (0 to 0.11)	0.07 (0.02 to 0.12)		

Notes:

[10] - The FAS Population

[11] - The FAS Population

Statistical analyses

Statistical analysis title	Time-Weighted Average Change in FEV1

Statistical analysis description:

Statistical Analysis 1 for Time-Weighted Average Change in FEV1 Over 45 Minutes Following the End of Study Drug Administration

Comparison groups	Placebo v Montelukast Intravenous (IV) 5.25 mg

Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.612 [12]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.09

Notes:

[12] - Model terms: treatment, region (US, non-US) and baseline FEV1 as covariate

Secondary: Time-Weighted Average Change in FEV1 Over 30 Minutes Following the End of Study Drug Administration

End point title	Time-Weighted Average Change in FEV1 Over 30 Minutes Following the End of Study Drug Administration

End point description:

Improvement in FEV1 as the time-weighted average change from baseline over 30 minutes following the end of study drug administration. Time-weighted average of the changes from baseline obtained over the 30 minutes (at 30 and 15) with the time interval between any measurement and the measurement prior to it used as the weighting factor.

Full Analysis Set (FAS). The FAS population includes all randomized patients who received double-blind study drug, and with efficacy measurements both at baseline and at least one time point over the time interval considered.

End point type	Secondary

End point timeframe:

Baseline and (time-weighted average over) 30 Minutes

End point values	Placebo	Montelukast Intravenous (IV) 5.25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125[13]	140[14]		
Units: Liters				
least squares mean (confidence interval 95%)	0.05 (0 to 0.11)	0.06 (0.01 to 0.12)		

Notes:

[13] - The FAS Population

[14] - The FAS Population

Statistical analyses

Statistical analysis title	Time-Weighted Average Change in FEV1

Statistical analysis description:

Statistical Analysis 1 for Time-Weighted Average Change in FEV1 Over 30 Minutes Following the End of Study Drug Administration

Comparison groups	Placebo v Montelukast Intravenous (IV) 5.25 mg

Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.774 [15]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.08

Notes:

[15] - Model terms: treatment, region (US, non-US) and baseline FEV1 as covariate

Secondary: Change in FEV1 After 15 Minutes Following the End of Study Drug Administration

End point title	Change in FEV1 After 15 Minutes Following the End of Study Drug Administration

End point description:

Improvement in FEV1 as the time-weighted average change from baseline over the first 15 minutes following the end of study drug administration. Change = 15 minutes value minus Baseline value

Full Analysis Set (FAS). The FAS population includes all randomized patients who received double-blind study drug, and with efficacy measurements both at baseline and at least one time point over the time interval considered.

End point type	Secondary

End point timeframe:

Baseline and 15 Minutes

End point values	Placebo	Montelukast Intravenous (IV) 5.25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115[16]	121[17]		
Units: Liters				
least squares mean (confidence interval 95%)	0.01 (-0.03 to 0.06)	0.06 (0.01 to 0.1)		

Notes:

[16] - The FAS Population

[17] - The FAS Population

Statistical analyses

Statistical analysis title	Change in FEV1

Statistical analysis description:

Statistical Analysis 1 for Change in FEV1 After 15 Minutes Following the End of Study Drug Administration

Comparison groups	Placebo v Montelukast Intravenous (IV) 5.25 mg

Number of subjects included in analysis	236
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.173 [18]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.11

Notes:

[18] - Model terms: treatment, region (US, non-US) and baseline FEV1 as covariate

Secondary: Total Dose of β-agonist Administered Per Patient Over a Period of 2 Hours Following the End of Study Drug Administration

End point title	Total Dose of β-agonist Administered Per Patient Over a Period of 2 Hours Following the End of Study Drug Administration

End point description:

Median total dose of β-agonist administered per patient over a period of 2 hours following the end of study drug administration.

At least one post-randomization measurement obtained subsequent to at least one dose of study treatment was required for inclusion in the analysis of total doses of Beta-Agonist (mg) endpoint.

End point type	Secondary

End point timeframe:

120 minutes

End point values	Placebo	Montelukast Intravenous (IV) 5.25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127[19]	144[20]		
Units: mg				
median (inter-quartile range (Q1-Q3))	0.6 (0 to 3.8)	1 (0 to 4.3)		

Notes:

[19] - The FAS Population

[20] - The FAS Population

Statistical analyses

Statistical analysis title	Total Dose of β-agonist

Statistical analysis description:

Statistical Analysis 1 for Total Dose of β-agonist Administered Per Patient Over a Period of 2 Hours Following the End of Study Drug Administration

Comparison groups	Placebo v Montelukast Intravenous (IV) 5.25 mg

Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.58 [21]
Method	ANCOVA
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Notes:

[21] - ANCOVA model (Nonparametric) based on Tukey's normalized ranks with terms treatment, region (US, non-US) and baseline FEV1 as covariate

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 14 days

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo to montelukast sodium for approximately 120 minutes in duration.

Reporting group title	Montelukast

Reporting group description:

Montelukast 5.25 mg, 15 mL of the reconstituted study drug will be administered by syringe as a manual bolus over 2 to 5 mintues.

Serious adverse events	Placebo	Montelukast	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 131 (1.53%)	2 / 145 (1.38%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	1 / 131 (0.76%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 131 (0.76%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthmatic crisis			
subjects affected / exposed	0 / 131 (0.00%)	2 / 145 (1.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			

Pneumonia			
subjects affected / exposed	0 / 131 (0.00%)	1 / 145 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Montelukast	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 131 (16.03%)	20 / 145 (13.79%)	
Vascular disorders			
Diastolic hypotension			
subjects affected / exposed	1 / 131 (0.76%)	0 / 145 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 131 (0.00%)	1 / 145 (0.69%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 131 (0.76%)	0 / 145 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	1 / 131 (0.76%)	5 / 145 (3.45%)	
occurrences (all)	2	5	
Syncope vasovagal			
subjects affected / exposed	0 / 131 (0.00%)	1 / 145 (0.69%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 131 (0.00%)	1 / 145 (0.69%)	
occurrences (all)	0	1	
Infusion site extravasation			
subjects affected / exposed	1 / 131 (0.76%)	0 / 145 (0.00%)	
occurrences (all)	1	0	
Infusion site pain			

subjects affected / exposed	0 / 131 (0.00%)	1 / 145 (0.69%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 131 (0.76%)	0 / 145 (0.00%)	
occurrences (all)	1	0	
Abdominal pain upper			
subjects affected / exposed	0 / 131 (0.00%)	2 / 145 (1.38%)	
occurrences (all)	0	2	
Constipation			
subjects affected / exposed	1 / 131 (0.76%)	0 / 145 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	1 / 131 (0.76%)	1 / 145 (0.69%)	
occurrences (all)	1	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 131 (0.00%)	1 / 145 (0.69%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	1 / 131 (0.76%)	1 / 145 (0.69%)	
occurrences (all)	1	1	
Vomiting			
subjects affected / exposed	2 / 131 (1.53%)	1 / 145 (0.69%)	
occurrences (all)	3	1	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	7 / 131 (5.34%)	4 / 145 (2.76%)	
occurrences (all)	8	4	
Atelectasis			
subjects affected / exposed	0 / 131 (0.00%)	1 / 145 (0.69%)	
occurrences (all)	0	1	
Rhinitis allergic			
subjects affected / exposed	2 / 131 (1.53%)	0 / 145 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			

Prurigo			
subjects affected / exposed	1 / 131 (0.76%)	0 / 145 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 131 (0.76%)	0 / 145 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 131 (0.76%)	0 / 145 (0.00%)	
occurrences (all)	1	0	
Muscle spasms			
subjects affected / exposed	0 / 131 (0.00%)	1 / 145 (0.69%)	
occurrences (all)	0	1	
Infections and infestations			
Bronchitis bacterial			
subjects affected / exposed	0 / 131 (0.00%)	1 / 145 (0.69%)	
occurrences (all)	0	1	
Gastroenteritis			
subjects affected / exposed	0 / 131 (0.00%)	1 / 145 (0.69%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	1 / 131 (0.76%)	0 / 145 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	2 / 131 (1.53%)	1 / 145 (0.69%)	
occurrences (all)	2	1	
Pharyngitis			
subjects affected / exposed	0 / 131 (0.00%)	1 / 145 (0.69%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	1 / 131 (0.76%)	0 / 145 (0.00%)	
occurrences (all)	1	0	
Sinusitis			
subjects affected / exposed	2 / 131 (1.53%)	0 / 145 (0.00%)	
occurrences (all)	2	0	
Tonsillitis			

subjects affected / exposed occurrences (all)	0 / 131 (0.00%) 0	1 / 145 (0.69%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 February 2005	Updated study procedures for pulse oximetry and intravenous cathether placement and for the use of β-agonist concomitant medications.
12 June 2006	Updated study procedures for the modified pulmonary index score during Period I, diluent for the short-acting β-agonists dose, and the prestudy period (standard care) duration.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported