Clinical trial results:
A Multicenter, Randomised, Double Blind Study Comparing the Clinical Effects of Intravenous Montelukast With Placebo in Patients With Acute Asthma

Summary

EudraCT number	2004-000614-39
Trial protocol	IT DK
Global end of trial date	12 March 2007

Results information

Result version number	v2 (current)
This version publication date	20 May 2016
First version publication date	10 April 2015
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	0476-288

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00092989
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharpe & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharpe & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharpe & 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	12 March 2007
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 March 2007
Global end of trial reached?	Yes
Global end of trial date	12 March 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to evaluate the safety and efficacy of montelukast (Singulair™) 7 mg, a leukotriene receptor antagonist, in the treatment of acute exacerbations of asthma when given as an intravenous (IV) bolus dose in addition to a standard care regimen consistent with the Global Initiative for Asthma (GINA) guideline recommendations. During a 60 minute screening period, change from baseline (BL) in lung function was quantified as forced expiratory volume in 1 second (FEV1) before and after the administration of standard care for acute asthma in an emergency department. The primary hypothesis was that in adult patients with acute asthma, the addition of montelukast IV 7 mg to standard therapy will cause a significant improvement in FEV1 within the first 60 minutes after administration (i.e., average change in FEV1 from preallocation baseline over the first 60 minutes after study drug 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. The following additional measures for this study were in place for the protection of trial participants: Rescue medication was available for participants that required rescue therapy within 3 hours following the end of study drug administration. Rescue therapy was defined as the administration of any of the following treatments within 30 minutes prior to end of study drug administration, or at least 10 minutes after end of study drug administration and within 3 hours following the end of study drug administration: systemic corticosteroids (prednisone/prednisolone), short-acting β-agonists (albuterol/salbutamol), short-acting anti-cholinergic drugs (ipratropium), magnesium.

Background therapy:

Upon entering the Screening Period (Period 1), standardized treatment for an acute severe asthma episode was initiated and continued throughout the Treatment Period (Period 2) for all participants. Standardized treatment could consist of: (1) β-agonist, (2) oxygen therapy, (3) inhaled ipratropium (optional), and 4) systemic corticosteroids (only administered following completion of study drug in Period 2).

Evidence for comparator: -

Actual start date of recruitment	06 July 2004
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	Peru: 59
Country: Number of subjects enrolled	Guatemala: 10
Country: Number of subjects enrolled	South Africa: 22
Country: Number of subjects enrolled	New Zealand: 5
Country: Number of subjects enrolled	Mexico: 40

Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	Colombia: 24
Country: Number of subjects enrolled	United States: 318
Country: Number of subjects enrolled	Brazil: 4
Country: Number of subjects enrolled	Chile: 6
Country: Number of subjects enrolled	India: 19
Country: Number of subjects enrolled	Israel: 14
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	France: 28
Country: Number of subjects enrolled	Italy: 28
Worldwide total number of subjects	583
EEA total number of subjects	57

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)	0
Adolescents (12-17 years)	9
Adults (18-64 years)	529
From 65 to 84 years	45
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from 34 sites in the United States and 28 sites in 15 countries.

Pre-assignment

Screening details:

Screening began at participant arrival at the study site and consisted of the time between the start of urgent treatment (oxygen, short-acting β-agonist) and IV montelukast or placebo, not to exceed 60 minutes

Pre-assignment period milestones

Number of subjects started	1147[1]
Number of subjects completed	583

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Participant ineligible: 545
Reason: Number of subjects	Consent withdrawn by subject: 14
Reason: Number of subjects	Protocol deviation: 5

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The worldwide number represents the number of eligible enrolled participants that were treated on study. 1147 participants were screened for inclusion.

Period 1

Period 1 title	Pre-allocation Evaluation and Treatment
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Pre-allocation Evaluation and Treatment

Arm description:

Participants admitted to the study site because of an acute exacerbation of asthma entered the screening period (Period 1) and received standard therapy regimen recommended by international guidelines for an acute severe asthma episode (e.g. oxygen, short-acting β-agonist, corticosteroid, ipratropium).

Arm type	Pre-study Evaluation and Treatment

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Pre-allocation Evaluation and Treatment
Started	583
Completed	583

Period 2

Period 2 title	Active Treatment
Is this the baseline period?	Yes[2]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Montelukast 7 mg + Standard Treatment

Arm description:

During Period 2, randomised participants received IV montelukast 7 mg in addition to a standard therapy regimen recommended by international guidelines for an acute severe asthma episode (e.g. oxygen, short-acting β-agonist, corticosteroid, ipratropium). Time-weighted change in FEV1 as a measure of lung function was determined for up to 120 minutes post-infusion of montelukast.

Arm type	Experimental
Investigational medicinal product name	Montelukast sodium
Investigational medicinal product code	
Other name	Singulair™
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

Participants received IV montelukast administered in one 7 mg dose after reconstitution of a vial containing montelukast sodium in a lypophilised powder form dissolved in 20 mL of a solution of 3.3% dextrose/0.3% sodium chloride and given as a manual bolus over a period of 2 to 5 minutes.

Arm title	Placebo + Standard Treatment

Arm description:

During Period 2, randomised participants received IV placebo for montelukast in addition to a standard therapy regimen recommended by international guidelines for an acute severe asthma episode (e.g. oxygen, short-acting β-agonist, corticosteroid, ipratropium). Time-weighted change in FEV1 as a measure of lung function was determined for up to 120 minutes post-infusion of IV placebo.

Arm type	Placebo
Investigational medicinal product name	Placebo for montelukast
Investigational medicinal product code	
Other name	Singulair™
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

Participants received matching placebo for montelukast supplied as a lyophilised powder in light-protected vials. Placebo powder was reconstituted in 20 mL of a solution of 3.3% dextrose/0.3% sodium chloride and given as a manual bolus infusion over 2 to 5 minutes.

Notes:

[2] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 was a screening period to determine eligible participants and to randomize participants. For the purpose of reporting baseline characteristics by reporting arm, Period 2 has been designated the baseline period.

Number of subjects in period 2	Montelukast 7 mg + Standard Treatment	Placebo + Standard Treatment
Started	291	292
Completed	288	285
Not completed	3	7
Randomization error	1	-
Unable to do spirometry due to AEs	-	1
Consent withdrawn by subject	-	1
Unable to complete spirometry	1	-
Adverse event, non-fatal	-	1
Discontinued due to chest xray findings	1	-
Protocol deviation	-	1
Lack of efficacy	-	3

Period 3

Period 3 title	Post-study (14 Days)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Montelukast 7 mg + Standard Treatment: Post-Study

Arm description:

During the follow-up period, montelukast-treated participants received a telephone call approximately 14 days after the participant had completed Period 2 to review information on subsequent asthma-related healthcare contacts (doctor visits, emergency visits, and/or hospitalizations), asthma-related medication usage, impact on work, concomitant therapies, adverse experiences, and procedures that may have been performed within the 14 ± 3 days.

Arm type	Follow-up

No investigational medicinal product assigned in this arm

Arm title	Placebo + Standard Treatment: Post-Study

Arm description:

During the follow-up period, placebo-treated participants received a telephone call approximately 14 days after the participant had completed Period 2 to review information on subsequent asthma-related healthcare contacts (doctor visits, emergency visits, and/or hospitalizations), asthma-related medication usage, impact on work, concomitant therapies, adverse experiences, and procedures that may have been performed within the 14 ± 3 days.

Arm type	Follow-up

No investigational medicinal product assigned in this arm

Number of subjects in period 3	Montelukast 7 mg + Standard Treatment: Post-Study	Placebo + Standard Treatment: Post-Study
Started	288	285
Completed	291	292

Joined	3	7
Follow-up call, though did not complete Period 2	3	7

Baseline characteristics

Reporting groups	
Reporting group title	Montelukast 7 mg + Standard Treatment
Reporting group description:	
During Period 2, randomised participants received IV montelukast 7 mg in addition to a standard therapy regimen recommended by international guidelines for an acute severe asthma episode (e.g. oxygen, short-acting β-agonist, corticosteroid, ipratropium). Time-weighted change in FEV1 as a measure of lung function was determined for up to 120 minutes post-infusion of montelukast.	
Reporting group title	Placebo + Standard Treatment
Reporting group description:	
During Period 2, randomised participants received IV placebo for montelukast in addition to a standard therapy regimen recommended by international guidelines for an acute severe asthma episode (e.g. oxygen, short-acting β-agonist, corticosteroid, ipratropium). Time-weighted change in FEV1 as a measure of lung function was determined for up to 120 minutes post-infusion of IV placebo.	

Reporting group values	Montelukast 7 mg + Standard Treatment	Placebo + Standard Treatment	Total
Number of subjects	291	292	583
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	41.1	41	
standard deviation	± 15	± 15.3	-
Gender categorical			
Units: Subjects			
Female	153	175	328
Male	138	117	255
Baseline FEV1			
Baseline FEV1 was defined as last measurement obtained prior to the administration of study drug. Data were available for 287 in the Montelukast 7 mg group and 284 in the Placebo group.			
Units: Liters			
arithmetic mean	1.3	1.2	
standard deviation	± 0.4	± 0.4	-

End points

End points reporting groups

Reporting group title	Pre-allocation Evaluation and Treatment

Reporting group description:

Participants admitted to the study site because of an acute exacerbation of asthma entered the screening period (Period 1) and received standard therapy regimen recommended by international guidelines for an acute severe asthma episode (e.g. oxygen, short-acting β-agonist, corticosteroid, ipratropium).

Reporting group title	Montelukast 7 mg + Standard Treatment

Reporting group description:

During Period 2, randomised participants received IV montelukast 7 mg in addition to a standard therapy regimen recommended by international guidelines for an acute severe asthma episode (e.g. oxygen, short-acting β-agonist, corticosteroid, ipratropium). Time-weighted change in FEV1 as a measure of lung function was determined for up to 120 minutes post-infusion of montelukast.

Reporting group title	Placebo + Standard Treatment

Reporting group description:

During Period 2, randomised participants received IV placebo for montelukast in addition to a standard therapy regimen recommended by international guidelines for an acute severe asthma episode (e.g. oxygen, short-acting β-agonist, corticosteroid, ipratropium). Time-weighted change in FEV1 as a measure of lung function was determined for up to 120 minutes post-infusion of IV placebo.

Reporting group title	Montelukast 7 mg + Standard Treatment: Post-Study

Reporting group description:

During the follow-up period, montelukast-treated participants received a telephone call approximately 14 days after the participant had completed Period 2 to review information on subsequent asthma-related healthcare contacts (doctor visits, emergency visits, and/or hospitalizations), asthma-related medication usage, impact on work, concomitant therapies, adverse experiences, and procedures that may have been performed within the 14 ± 3 days.

Reporting group title	Placebo + Standard Treatment: Post-Study

Reporting group description:

During the follow-up period, placebo-treated participants received a telephone call approximately 14 days after the participant had completed Period 2 to review information on subsequent asthma-related healthcare contacts (doctor visits, emergency visits, and/or hospitalizations), asthma-related medication usage, impact on work, concomitant therapies, adverse experiences, and procedures that may have been performed within the 14 ± 3 days.

Primary: Time-weighted Average Change from Baseline in FEV1 (0 to 60 minutes)

End point title	Time-weighted Average Change from Baseline in FEV1 (0 to 60 minutes)

End point description:

Time-weighted average change from baseline in FEV1 over the first 60 minutes after IV montelukast or placebo administration. Changes from baseline in FEV1 were computed at 10, 20, 40 and 60 minutes post study drug administration and then used to calculate a time-weighted average for 0-60 minutes, with the time interval between any measurement and the measurement prior to it being used as the weighting factor. The Full Analysis Set (FAS), comprised of all participants who started study drug and had efficacy measurements (FEV1) both at BL and at least one time point over the time interval considered, was used for this analysis.

End point type	Primary

End point timeframe:

0 minutes (baseline), 10, 20, 40, and 60 minutes after IV bolus infusion of montelukast 7 mg or placebo.

End point values	Montelukast 7 mg + Standard Treatment	Placebo + Standard Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	287[1]	284[2]		
Units: Liters				
least squares mean (confidence interval 95%)	0.32 (0.27 to 0.37)	0.22 (0.17 to 0.27)		

Notes:

[1] - Participants starting study drug with FEV1 both at BL and at least 1 time point over interval (FAS).

[2] - Participants starting study drug with FEV1 both at BL and at least 1 time point over interval (FAS).

Statistical analyses

Statistical analysis title	Time-weighted Average ΔFEV1 (0-60 min)

Statistical analysis description:

Time-weighted average change from baseline (BL) in FEV1, computed in the interval 0-60 minutes, was analysed using an analysis of covariance (ANCOVA) model with the baseline FEV1 as a covariate and including treatment, prior therapy with systemic corticosteroids and/or anti-leukotriene (yes or no), and region (US or non-US) as factors. The ANCOVA model was used to estimate the least squares mean (LS mean) for treatment, between-treatment difference, and 95% CI.

Comparison groups	Montelukast 7 mg + Standard Treatment v Placebo + Standard Treatment
Number of subjects included in analysis	571
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.001 [3]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.16

Notes:

[3] - P-value for LS mean difference between treatments, montelukast 7 mg versus placebo.

Secondary: Percentage of Participants with Treatment Failure

End point title	Percentage of Participants with Treatment Failure

End point description:

The percentage of participants with treatment failure was summarized. Treatment failure was defined as: (1) participants that required hospitalization; or (2) participants for whom a decision to discharge home had not been reached by 3 hours following the end of study drug administration. The FAS was used for this analysis.

End point type	Secondary

End point timeframe:

Up to ≥ 3 hours after IV manual bolus infusion of montelukast 7 mg or placebo.

End point values	Montelukast 7 mg + Standard Treatment	Placebo + Standard Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	287[4]	284[5]		
Units: Percentage of Participants				
number (not applicable)	26.8	29.9		

Notes:

[4] - Participants starting study drug with FEV1 both at BL and at least 1 time point over interval (FAS).

[5] - Participants starting study drug with FEV1 both at BL and at least 1 time point over interval (FAS).

Statistical analyses

Statistical analysis title	Percentage of Participants With Treatment Failure

Statistical analysis description:

A logistic regression model was used for analysis of the FAS population to compare the percentage of treatment failures between treatment groups. Factors in the model included treatment, prior therapy with systemic corticosteroids and/or anti-leukotriene, and baseline FEV1 was used as a covariate. Descriptive statistics by treatment group provided by definition of treatment failure: participants requiring hospitalization or participants for whom decision to discharge home not reached by 3 hours.

Comparison groups	Montelukast 7 mg + Standard Treatment v Placebo + Standard Treatment
Number of subjects included in analysis	571
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.654 [7]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	1.34

Notes:

[6] - Treatment differences were summarized by the odds ratio (OR) derived from the logistic regression model and the 95% CI.

[7] - Percentage of treatment failures in the IV montelukast 7 mg group compared to the placebo treatment group.

Secondary: Time-weighted Average Change from Baseline in FEV1 (0 to 40 minutes)

End point title	Time-weighted Average Change from Baseline in FEV1 (0 to 40 minutes)

End point description:

Time-weighted average change from baseline in FEV1 over the first 40 minutes after IV montelukast or placebo administration. Changes from baseline in FEV1 were computed at 10, 20, and 40 minutes post study drug administration and then used to calculate a time-weighted average for 0-40 minutes, with the time interval between any measurement and the measurement prior to it being used as the weighting factor. The FAS was used for this analysis.

End point type	Secondary

End point timeframe:

0 minutes (BL), 10, 20, and 40 minutes after IV bolus infusion of montelukast 7 mg or placebo.

End point values	Montelukast 7 mg + Standard Treatment	Placebo + Standard Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	287[8]	283[9]		
Units: Liters				
least squares mean (confidence interval 95%)	0.28 (0.23 to 0.33)	0.18 (0.13 to 0.23)		

Notes:

[8] - Participants starting study drug with FEV1 both at BL and at least 1 time point over interval (FAS).

[9] - Participants starting study drug with FEV1 both at BL and at least 1 time point over interval (FAS).

Statistical analyses

Statistical analysis title	Time-weighted Average ΔFEV1 (0-40 min)

Statistical analysis description:

The time weighted average change from baseline in FEV1, computed in the interval 0-40 minutes, was analysed with an ANCOVA model using the baseline FEV1 as a covariate and including treatment, prior therapy with systemic corticosteroids and/or anti-leukotriene (yes/no), and region (US/Non-US) as factors. This ANCOVA model was used to estimate the least squares mean (LS-mean) for each treatment, between-treatment difference, and 95% CI.

Comparison groups	Montelukast 7 mg + Standard Treatment v Placebo + Standard Treatment
Number of subjects included in analysis	570
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.001 [10]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.15

Notes:

[10] - P-value for LS mean difference between treatments, montelukast 7 mg versus placebo.

Secondary: Time-weighted Average Change From Baseline in FEV1 (0 to 20 minutes)

End point title	Time-weighted Average Change From Baseline in FEV1 (0 to 20 minutes)

End point description:

Time-weighted average change from baseline in FEV1 over the first 20 minutes after IV montelukast or placebo administration. Changes from baseline in FEV1 were computed at 10 and 20 minutes post study drug administration and then used to calculate a time-weighted average for 0-20 minutes, with the time interval between any measurement and the measurement prior to it being used as the weighting factor. The FAS was used for this analysis.

End point type	Secondary

End point timeframe:

0 minutes (BL), 10, and 20 minutes after IV bolus infusion of montelukast 7 mg or placebo.

End point values	Montelukast 7 mg + Standard Treatment	Placebo + Standard Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	287[11]	282[12]		
Units: Liters				
least squares mean (confidence interval 95%)	0.23 (0.19 to 0.28)	0.15 (0.1 to 0.2)		

Notes:

[11] - Participants starting study drug with FEV1 both at BL and at least 1 time point over interval (FAS).
[12] - Participants starting study drug with FEV1 both at BL and at least 1 time point over interval (FAS).

Statistical analyses

Statistical analysis title	Time-weighted Average ΔFEV1 (0-20 min)

Statistical analysis description:

The time weighted average change from baseline in FEV1, computed in the interval 0-20 minutes, was analysed with an ANCOVA model using the baseline FEV1 as a covariate and including treatment, prior therapy with systemic corticosteroids and/or anti-leukotriene (yes/no), and region (US/Non-US) as factors. This ANCOVA model was used to estimate the least squares mean (LS-mean) for each treatment, between-treatment difference, and 95% CI.

Comparison groups	Montelukast 7 mg + Standard Treatment v Placebo + Standard Treatment
Number of subjects included in analysis	569
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 [13]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	0.14

Notes:

[13] - P-value for LS mean difference between treatments, i.e., montelukast 7 mg versus placebo.

Secondary: Average Change from Baseline in FEV1 at 10 minutes

End point title	Average Change from Baseline in FEV1 at 10 minutes

End point description:

Average change from baseline in FEV1 at 10 minutes after IV montelukast or placebo. The FAS was used for this analysis.

End point type	Secondary

End point timeframe:

0 minutes (baseline), 10 minutes after IV manual bolus infusion of montelukast 7 mg or placebo.

End point values	Montelukast 7 mg + Standard Treatment	Placebo + Standard Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	269[14]	260[15]		
Units: Liters				
least squares mean (confidence interval 95%)	0.2 (0.15 to 0.26)	0.12 (0.06 to 0.17)		

Notes:

[14] - Participants starting study drug with FEV1 both at BL and at least 1 time point over interval (FAS).
[15] - Participants starting study drug with FEV1 both at BL and at least 1 time point over interval (FAS).

Statistical analyses

Statistical analysis title	Average ΔFEV1 at 10 min

Statistical analysis description:

The average change from baseline in FEV1, computed at 10 minutes, was analysed with an ANCOVA model using the baseline FEV1 as a covariate and including treatment, prior therapy with systemic corticosteroids and/or anti-leukotriene (yes/no), and region (US/Non-US) as factors. This ANCOVA model was used to estimate the least squares mean (LS-mean) for each treatment, between treatment difference, and 95% CI.

Comparison groups	Montelukast 7 mg + Standard Treatment v Placebo + Standard Treatment
Number of subjects included in analysis	529
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008 [16]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.15

Notes:

[16] - P-value for LS mean difference between treatments, i.e., montelukast 7 mg versus placebo.

Secondary: Total Dose of β-agonist Administered Within 3 Hours

End point title	Total Dose of β-agonist Administered Within 3 Hours

End point description:

Total dose of β-agonist in mg administered per participant within 3 hours following end of study drug administration or placebo. Participants hospitalised prior to 3 hours post IV montelukast or placebo administration were assigned the largest total dose of β-agonist observed over all randomised participants plus 1 mg, or 5 mg plus 1 mg, whichever is larger.

End point type	Secondary

End point timeframe:

Up to 3 hours following end of IV manual bolus infusion of montelukast 7 mg or placebo.

End point values	Montelukast 7 mg + Standard Treatment	Placebo + Standard Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	287[17]	284[18]		
Units: mg				
median (inter-quartile range (Q1-Q3))	5 (1 to 10)	5 (0.9 to 10)		

Notes:

[17] - Participants starting study drug with FEV1 both at BL and at least 1 time point over interval (FAS).
[18] - Participants starting study drug with FEV1 both at BL and at least 1 time point over interval (FAS).

Statistical analyses

Statistical analysis title	Total Dose of β-Agonist

Statistical analysis description:

A non-parametric ANCOVA model based on Tukey's normalised ranks was used with factors for treatment, prior therapy with systemic corticosteroids and/or anti-leukotriene, region, and rank of BL FEV1 as covariate. Total dose of β-agonist administered per participant over a period of 3 hours following end of study drug administration was compared between treatment groups. Within-treatment effect was described using medians. Difference between medians were computed by the Hodges-Lehmann estimation.

Comparison groups	Montelukast 7 mg + Standard Treatment v Placebo + Standard Treatment
Number of subjects included in analysis	571
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	= 0.952 [20]
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:

[19] - Distribution-free confidence interval was based on the rank-sum test.

[20] - P-value for comparison between treatment groups, IV montelukast 7 mg versus placebo treatment.

Secondary: Number of Doses of β-agonist Administered Within 3 Hours

End point title	Number of Doses of β-agonist Administered Within 3 Hours

End point description:

Number of times a dose of a β-agonist was administered per participant within 3 hours following end of study drug or placebo administration. Participants hospitalised prior to 3 hours post study drug or placebo administration were assigned the largest number of β-agonist doses administered as observed over all randomised patients.

End point type	Secondary

End point timeframe:

Up to 3 hours after IV manual bolus infusion of montelukast 7 mg or placebo.

End point values	Montelukast 7 mg + Standard Treatment	Placebo + Standard Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	287	284		
Units: Doses				
median (inter-quartile range (Q1-Q3))	2 (1 to 3)	2 (1 to 4)		

Statistical analyses

Statistical analysis title	Number of Doses of β-agonist

Statistical analysis description:

A non-parametric ANCOVA model based on Tukey's normalised ranks was used with factors for treatment, prior therapy with systemic corticosteroids and/or anti-leukotriene, region, and rank of BL FEV1 as covariate. Number of doses of β-agonist administered per participant over a period of 3 hours following end of study drug administration was compared between treatment groups. Within-treatment effect was described using medians. Difference of medians was computed by the Hodges-Lehmann estimation.

Comparison groups	Montelukast 7 mg + Standard Treatment v Placebo + Standard Treatment
Number of subjects included in analysis	571
Analysis specification	Pre-specified
Analysis type	other[21]
P-value	= 0.265 [22]
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] - Distribution-free confidence interval was based on the rank-sum test.

[22] - P-value for comparison between treatment groups, IV montelukast 7 mg versus placebo treatment.

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

During the treatment period after IV montelukast or placebo administration until permanent discontinuation (end of Period 2) plus 14 days (Post-study, Period 3).

Adverse event reporting additional description:

All randomised patients who started study drug were included in the All-Participants-as-Treated (APaT) set for the safety analyses. The participant's treatment group was determined by the actual treatment received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	Placebo + Standard Treatment

Reporting group description:

During Period 2, randomised participants received IV placebo for montelukast in addition to a standard therapy regimen recommended by international guidelines for an acute severe asthma episode (e.g. oxygen, short-acting β-agonist, corticosteroid, ipratropium). Time-weighted change in FEV1 as a measure of lung function was determined for up to 120 minutes post-infusion of IV placebo.

Reporting group title	Montelukast 7 mg + Standard Treatment

Reporting group description:

During Period 2, randomised participants received IV montelukast 7 mg in addition to a standard therapy regimen recommended by international guidelines for an acute severe asthma episode (e.g. oxygen, short-acting β-agonist, corticosteroid, ipratropium). Time-weighted change in FEV1 as a measure of lung function was determined for up to 120 minutes post-infusion of montelukast.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No nonserious adverse events reaching the cut-off of >5% on at least one treatment arm were reported.

Serious adverse events	Placebo + Standard Treatment	Montelukast 7 mg + Standard Treatment	
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 292 (8.90%)	28 / 291 (9.62%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Drug Toxicity			
subjects affected / exposed	1 / 292 (0.34%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Transient ischaemic attack			

subjects affected / exposed	0 / 292 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 292 (0.34%)	0 / 291 (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	23 / 292 (7.88%)	23 / 291 (7.90%)	
occurrences causally related to treatment / all	1 / 24	0 / 24	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 292 (0.00%)	2 / 291 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 292 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status asthmaticus			
subjects affected / exposed	1 / 292 (0.34%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Varicella			
subjects affected / exposed	1 / 292 (0.34%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			

subjects affected / exposed	0 / 292 (0.00%)	1 / 291 (0.34%)	
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 + Standard Treatment	Montelukast 7 mg + Standard Treatment	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 292 (0.00%)	0 / 291 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 March 2005	Amendment 01: Primary reasons for the amendment were to incorporate revisions to the inclusion and exclusion criteria, add language that removes the requirement to report hospitalisation due to worsening asthma (which is also a study endpoint) as a serious adverse experience, and include an updated montelukast sodium product circular that includes new in vitro data regarding CYP2C8.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported