



Clinical trial results:

A Dose-ranging, Safety and Pharmacokinetics Study of Candesartan Cilexetil in Hypertensive Pediatric Subjects 1 to Less Than 6 Years of Age:

A 4-week, Multicenter, Randomized, Double-Blind Study with a 1-year Open-label, Follow-up Period

Summary

EudraCT number	2004-004264-75
Trial protocol	BE GB DE DK IT
Global end of trial date	07 August 2008

Results information

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

Trial information

Trial identification

Sponsor protocol code	D2451C0002
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00244621
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Pepparedsleden 1, Molndal, Sweden, 431 83
Public contact	Robin Mukherjee, R&D/GMD/Biometrics & Information Sciences, robin.mukherjee@astrazeneca.com
Scientific contact	Robin Mukherjee, R&D/GMD/Biometrics & Information Sciences, robin.mukherjee@astrazeneca.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	25 March 2009
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 August 2008
Global end of trial reached?	Yes
Global end of trial date	07 August 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to characterize the dose response relationship of candesartan cilexetil (administered once daily) in hypertensive pediatric subjects (1 to <6 years of age) by evaluation of the slope of the linear regression for the change in trough systolic blood pressure (SBP) from baseline (Day 0) to the end of the 4-week, double-blind treatment period (Day 28) as a function of dose.

Protection of trial subjects:

The study ICI and the AstraZeneca Study Physician reviewed and discussed each SAE. In addition, an independent pediatric hypertension expert not otherwise participating in the study reviewed all SAEs, AEs and AEs leading to discontinuation of study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 November 2004
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Åland Islands: 93
Worldwide total number of subjects	93
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)	16
Children (2-11 years)	77
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:

The study population included male and female participants 1 to <6 years of age with mild to moderate hypertension. The participants were recruited during the time period from 04 November 2004 to 07 August 2008 at pediatric clinics in the USA, Puerto Rico and Europe.

Pre-assignment

Screening details:

One to 2 weeks following a screening evaluation, participants underwent a 1-week, single-blind, placebo run-in period to reduce the variability in the baseline blood pressure measurements and to stabilize any concurrent antihypertensive medications.

Period 1

Period 1 title	Double-blind treatment period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Atacand .05 mg

Arm description:

candesartan cilexetil (Atacand) 0.05 mg/kg once daily oral liquid dose

Arm type	Experimental
Investigational medicinal product name	Candesartan cilexetil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

.05mg

Arm title	Atacand .20 mg
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Arm description:

candesartan cilexetil (Atacand) 0.20 mg/kg once daily oral liquid dose

Arm type	Experimental
Investigational medicinal product name	Candesartan cilexetil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

.20mg

Arm title	Atacand .40 mg
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Arm description:

candesartan cilexetil (Atacand) 0.40 mg/kg once daily oral liquid dose

Arm type	Experimental
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Investigational medicinal product name	Candesartan cilexetil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use
Dosage and administration details:	
.40mg	

Number of subjects in period 1	Atacand .05 mg	Atacand .20 mg	Atacand .40 mg
Started	29	32	32
Completed	27	29	30
Not completed	2	3	2
Consent withdrawn by subject	-	1	-
Multiple Reasons	2	1	1
Lost to follow-up	-	-	1
Lack of efficacy	-	1	-

Period 2

Period 2 title	Open-label treatment period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Arm title	Open-Label
Arm description: -	
Arm type	Follow-up
Investigational medicinal product name	Candesartan cilexetil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use
Dosage and administration details:	
0.05mg	

Number of subjects in period 2^[1]	Open-Label
Started	85
Completed	81
Not completed	4
Adverse event, serious fatal	1
Consent withdrawn by subject	1
Lost to follow-up	1
Moved abroad	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: One participant discontinued study due to Adverse Event after completing the double-blind period

Baseline characteristics

Reporting groups

Reporting group title	Atacand .05 mg
Reporting group description: candesartan cilexetil (Atacand) 0.05 mg/kg once daily oral liquid dose	
Reporting group title	Atacand .20 mg
Reporting group description: candesartan cilexetil (Atacand) 0.20 mg/kg once daily oral liquid dose	
Reporting group title	Atacand .40 mg
Reporting group description: candesartan cilexetil (Atacand) 0.40 mg/kg once daily oral liquid dose	

Reporting group values	Atacand .05 mg	Atacand .20 mg	Atacand .40 mg
Number of subjects	29	32	32
Age categorical			
Units: Subjects			
Children (1-5)	29	32	32
Age continuous			
Units: years			
arithmetic mean	3	3.3	3
full range (min-max)	1 to 5	1 to 5	1 to 5
Gender, Male/Female			
Units: Participants			
Female	11	10	12
Male	18	22	20
Age, Customized			
Units: Subjects			
1 to <2 years	6	5	5
2 to <6 years	23	27	27

Reporting group values	Total		
Number of subjects	93		
Age categorical			
Units: Subjects			
Children (1-5)	93		
Age continuous			
Units: years			
arithmetic mean			
full range (min-max)	-		
Gender, Male/Female			
Units: Participants			
Female	33		
Male	60		
Age, Customized			
Units: Subjects			
1 to <2 years	16		
2 to <6 years	77		

End points

End points reporting groups

Reporting group title	Atacand .05 mg
Reporting group description: candesartan cilexetil (Atacand) 0.05 mg/kg once daily oral liquid dose	
Reporting group title	Atacand .20 mg
Reporting group description: candesartan cilexetil (Atacand) 0.20 mg/kg once daily oral liquid dose	
Reporting group title	Atacand .40 mg
Reporting group description: candesartan cilexetil (Atacand) 0.40 mg/kg once daily oral liquid dose	
Reporting group title	Open-Label
Reporting group description: -	

Primary: Mean change from baseline to week 4 in systolic blood pressure (SBP)

End point title	Mean change from baseline to week 4 in systolic blood pressure (SBP)
End point description:	
End point type	Primary
End point timeframe: From randomisation to end of double-blind treatment (4 weeks)	

End point values	Atacand .05 mg	Atacand .20 mg	Atacand .40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	32	32	
Units: mm Hg				
arithmetic mean (standard deviation)	-6 (± 9.4)	-8.9 (± 9.2)	-12 (± 8.3)	

Statistical analyses

Statistical analysis title	Linear Regression
Statistical analysis description: The response variable was the change from baseline to the end of the double-blind treatment period in trough SBP.	
Comparison groups	Atacand .05 mg v Atacand .20 mg v Atacand .40 mg

Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	< 0.0136
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.436
upper limit	-0.1692
Variability estimate	Standard deviation

Notes:

[1] - The independent variables were dose ratio and weight group as a blocking factor.

Secondary: Mean change from baseline to week 4 in diastolic blood pressure (DBP)

End point title	Mean change from baseline to week 4 in diastolic blood pressure (DBP)
End point description:	
End point type	Secondary
End point timeframe:	
From randomisation to end of double-blind treatment (4 weeks)	

End point values	Atacand .05 mg	Atacand .20 mg	Atacand .40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	32	32	
Units: mm Hg				
arithmetic mean (standard deviation)	-5.2 (± 6.7)	-7.9 (± 12.9)	-11.1 (± 9.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in albumin/creatinine (A/C) ratio for each assigned dose level from baseline to Day 28

End point title	Change in albumin/creatinine (A/C) ratio for each assigned dose level from baseline to Day 28
End point description:	
End point type	Secondary
End point timeframe:	
From randomisation to day 28	

End point values	Atacand .05 mg	Atacand .20 mg	Atacand .40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	19	19	19	
Units: Percent change				
median (inter-quartile range (Q1-Q3))	-11.1 (-42.5 to 33.3)	-40.6 (-68.1 to 25)	-50 (-68.9 to 15.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in protein/creatinine (P/C) ratio for each assigned dose level from baseline to Day 28

End point title	Change in protein/creatinine (P/C) ratio for each assigned dose level from baseline to Day 28
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End point description:

End point type	Secondary
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End point timeframe:

From randomisation to day 28

End point values	Atacand .05 mg	Atacand .20 mg	Atacand .40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	26	27	
Units: Percent change				
median (inter-quartile range (Q1-Q3))	0 (-25 to 50)	-29.2 (-50 to 0)	0 (-40.7 to 0)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomisation (study day 0) to end of study (week 56).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	NA
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Reporting groups

Reporting group title	Atacand .05 mg
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Reporting group description:

candesartan cilexetil (Atacand) 0.05 mg/kg once daily oral liquid dose

Reporting group title	Atacand .20 mg
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Reporting group description:

candesartan cilexetil (Atacand) 0.20 mg/kg once daily oral liquid dose

Reporting group title	Atacand .40 mg
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Reporting group description:

candesartan cilexetil (Atacand) 0.40 mg/kg once daily oral liquid dose

Reporting group title	Open-Label
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Reporting group description: -

Serious adverse events	Atacand .05 mg	Atacand .20 mg	Atacand .40 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 29 (3.45%)	0 / 32 (0.00%)	1 / 32 (3.13%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	0 / 29 (0.00%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Vena Cava Thrombosis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Catheter Site Haematoma			
alternative dictionary used: MedDRA 11.0			

subjects affected / exposed	1 / 29 (3.45%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenitis cervical			
subjects affected / exposed	0 / 29 (0.00%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia drug			
subjects affected / exposed	0 / 29 (0.00%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site necrosis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
drug hypersensitivity			
subjects affected / exposed	0 / 29 (0.00%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Glomerulonephritis	Additional description: Chronic		
subjects affected / exposed	0 / 29 (0.00%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrotic Syndrome			
subjects affected / exposed	0 / 29 (0.00%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Urinary Tract Infection			
alternative dictionary used: MedDRA 11.0			

subjects affected / exposed	0 / 29 (0.00%)	0 / 32 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchiolitis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
External ear cellulitis NOS			
subjects affected / exposed	0 / 29 (0.00%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia parainfluenzae viral			
subjects affected / exposed	0 / 29 (0.00%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute NOS			
subjects affected / exposed	0 / 29 (0.00%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 29 (0.00%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Open-Label		
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 85 (16.47%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		

Injury, poisoning and procedural complications Post procedural haemorrhage subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 85 (1.18%) 0 / 1 0 / 0		
Vascular disorders Vena Cava Thrombosis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 85 (1.18%) 0 / 1 0 / 0		
Blood and lymphatic system disorders Catheter Site Haematoma alternative dictionary used: MedDRA 11.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 85 (1.18%) 0 / 1 0 / 1		
Lymphadenitis cervical subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 85 (1.18%) 0 / 1 0 / 0		
General disorders and administration site conditions Pyrexia drug subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 2 / 85 (2.35%) 0 / 2 0 / 0		
Catheter site necrosis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 85 (1.18%) 0 / 1 0 / 0		
Immune system disorders drug hypersensitivity subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 85 (1.18%) 0 / 1 0 / 0		

Renal and urinary disorders			
Glomerulonephritis	Additional description: Chronic		
subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Nephrotic Syndrome			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Urinary Tract Infection			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	3 / 85 (3.53%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Bronchiolitis			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
External ear cellulitis NOS			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia parainfluenzae viral			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis acute NOS			

subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Atacand .05 mg	Atacand .20 mg	Atacand .40 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 29 (62.07%)	20 / 32 (62.50%)	18 / 32 (56.25%)
Injury, poisoning and procedural complications			
Excoriation			
subjects affected / exposed	2 / 29 (6.90%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 29 (3.45%)	3 / 32 (9.38%)	0 / 32 (0.00%)
occurrences (all)	1	3	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 29 (13.79%)	5 / 32 (15.63%)	4 / 32 (12.50%)
occurrences (all)	4	5	4
Fatigue			
subjects affected / exposed	3 / 29 (10.34%)	1 / 32 (3.13%)	1 / 32 (3.13%)
occurrences (all)	3	1	1
Eye disorders			
Conjunctivitis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 32 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2	3 / 32 (9.38%) 3	0 / 32 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2	0 / 32 (0.00%) 0	0 / 32 (0.00%) 0
Abdominal pain subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1	1 / 32 (3.13%) 1	0 / 32 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2	2 / 32 (6.25%) 2	4 / 32 (12.50%) 4
Rhinorrhoea subjects affected / exposed occurrences (all)	3 / 29 (10.34%) 3	2 / 32 (6.25%) 2	2 / 32 (6.25%) 2
Nasal congestion subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	0 / 32 (0.00%) 0	0 / 32 (0.00%) 0
Asthma subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2	0 / 32 (0.00%) 0	0 / 32 (0.00%) 0
Infections and infestations			
Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2	5 / 32 (15.63%) 5	3 / 32 (9.38%) 3
Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1	1 / 32 (3.13%) 1	1 / 32 (3.13%) 1
Otitis media subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	2 / 32 (6.25%) 2	0 / 32 (0.00%) 0
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	0 / 32 (0.00%) 0	2 / 32 (6.25%) 2
Bronchitis			

subjects affected / exposed	1 / 29 (3.45%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Pharyngitis			
subjects affected / exposed	2 / 29 (6.90%)	0 / 32 (0.00%)	1 / 32 (3.13%)
occurrences (all)	2	0	1
Rhinitis			
subjects affected / exposed	2 / 29 (6.90%)	0 / 32 (0.00%)	2 / 32 (6.25%)
occurrences (all)	2	0	2
Gastroenteritis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 29 (6.90%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	2	0	0

Non-serious adverse events	Open-Label		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	64 / 85 (75.29%)		
Injury, poisoning and procedural complications			
Excoriation			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 85 (5.88%)		
occurrences (all)	5		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	32 / 85 (37.65%)		
occurrences (all)	32		
Fatigue			
subjects affected / exposed	3 / 85 (3.53%)		
occurrences (all)	3		
Eye disorders			

Conjunctivitis subjects affected / exposed occurrences (all)	7 / 85 (8.24%) 7		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all)	12 / 85 (14.12%) 12 11 / 85 (12.94%) 11 5 / 85 (5.88%) 5		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Rhinorrhoea subjects affected / exposed occurrences (all) Nasal congestion subjects affected / exposed occurrences (all) Asthma subjects affected / exposed occurrences (all)	32 / 85 (37.65%) 32 12 / 85 (14.12%) 12 5 / 85 (5.88%) 5 2 / 85 (2.35%) 2		
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Otitis media subjects affected / exposed occurrences (all)	15 / 85 (17.65%) 15 15 / 85 (17.65%) 15 13 / 85 (15.29%) 13		

Urinary tract infection			
subjects affected / exposed	10 / 85 (11.76%)		
occurrences (all)	10		
Bronchitis			
subjects affected / exposed	9 / 85 (10.59%)		
occurrences (all)	9		
Pharyngitis			
subjects affected / exposed	6 / 85 (7.06%)		
occurrences (all)	6		
Rhinitis			
subjects affected / exposed	7 / 85 (8.24%)		
occurrences (all)	7		
Gastroenteritis			
subjects affected / exposed	6 / 85 (7.06%)		
occurrences (all)	6		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 85 (2.35%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 February 2006	Centres have been added to reach enrolment goals
20 July 2007	Revision in blood pressure measurement.
12 February 2008	No interim analyses planned but amendment 2 provides the authority to analyse the double-blind dose response phase without waiting until long term open label phase is completed
12 February 2008	Echocardiography is added following recommendation from the Paediatric Committee at EMEA

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/20160654>