Clinical trial results:
A multicenter, multi-national, randomized, double-blind, placebo-controlled, study to assess the efficacy and safety of ciclesonide metereddose inhaler at 80 g bid (twice daily) or 40 g bid for 12 weeks in patients aged 4 to <12 years with persistent asthma.

Summary

EudraCT number	2006-004740-22
Trial protocol	HU
Global end of trial date	22 February 2008

Results information

Result version number	v1 (current)
This version publication date	08 June 2017
First version publication date	08 June 2017

Trial information

Trial identification

Sponsor protocol code	EFC6695

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00392288
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	One MedImmune Way, Gaithersburg, United States, 20878
Public contact	AstraZeneca Clinical Study Information Center, AstraZeneca, +1 877-240-9479, information.center@astrazeneca.com
Scientific contact	AstraZeneca Clinical Study Information Center, AstraZeneca, +1 877-240-9479, information.center@astrazeneca.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 March 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 February 2008
Global end of trial reached?	Yes
Global end of trial date	22 February 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary: To demonstrate the efficacy of ciclesonide, compared to placebo, at
80 µg bid or 40 µg bid for 12 weeks in patients aged 4 to <12 years with persistent asthma.
Secondary: To assess the safety of ciclesonide.

Protection of trial subjects:

All study participants or their representative were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 October 2006
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	United States: 180
Country: Number of subjects enrolled	Mexico: 67
Country: Number of subjects enrolled	Poland: 130
Country: Number of subjects enrolled	Russian Federation: 39
Country: Number of subjects enrolled	South Africa: 37
Country: Number of subjects enrolled	Hungary: 75
Worldwide total number of subjects	528
EEA total number of subjects	205

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)	528
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:

Screening period 7-14 days, randomization with subsequent treatment period over 12 weeks

Pre-assignment

Screening details:

The number of subjects in section Participant Flow is related to the number of randomized subjects (= subject who were eligible for treatment period). This number is different to the number of subjects of the Intention to Treat (ITT) population in Outcome Measures. The statistical analyses of the Outcome Measures is related to the ITT population.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo metered dose inhaler (MDI)

Arm description:

Placebo MDI over twelve weeks (ITT population)

Arm type	Placebo
Investigational medicinal product name	Placebo-matching ciclesonide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation vapour, solution
Routes of administration	Inhalation use

Dosage and administration details:

Two puffs once daily, in the evening, via a metered-dose inhaler

Arm title	Ciclesonide MDI 40 µg BID

Arm description:

Ciclesonide MDI 40 µg BID over twelve weeks (ITT population)

Arm type	Experimental
Investigational medicinal product name	Ciclesonide 40 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation vapour, solution
Routes of administration	Inhalation use

Dosage and administration details:

40 µg two puffs once daily, in the evening via a metered-dose inhaler (40 µg ex-actuator corresponds to 50 µg ex-valve)

Arm title	Ciclesonide MDI 80 µg BID

Arm description:

Ciclesonide MDI 80 µg BID over twelve weeks (ITT population)

Arm type	Experimental

Investigational medicinal product name	Ciclesonide 80 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation vapour, solution
Routes of administration	Inhalation use

Dosage and administration details:

80 µg two puffs once daily, in the evening, via a metered-dose inhaler (80 µg ex-actuator corresponds to 100 µg ex-valve)

Number of subjects in period 1	Placebo metered dose inhaler (MDI)	Ciclesonide MDI 40 µg BID	Ciclesonide MDI 80 µg BID
Started	175	177	176
Completed	143	155	159
Not completed	32	22	17
Consent withdrawn by subject	1	-	2
Adverse event, non-fatal	17	7	8
Parent/legal guardian withdrawal	1	2	1
Unknown	3	4	1
Lost to follow-up	1	1	1
Lack of efficacy	8	5	3
Protocol deviation	1	3	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo metered dose inhaler (MDI)
Reporting group description: Placebo MDI over twelve weeks (ITT population)	
Reporting group title	Ciclesonide MDI 40 µg BID
Reporting group description: Ciclesonide MDI 40 µg BID over twelve weeks (ITT population)	
Reporting group title	Ciclesonide MDI 80 µg BID
Reporting group description: Ciclesonide MDI 80 µg BID over twelve weeks (ITT population)	

Reporting group values	Placebo metered dose inhaler (MDI)	Ciclesonide MDI 40 µg BID	Ciclesonide MDI 80 µg BID
Number of subjects	175	177	176
Age Categorical Units: Subjects			
Aged 6 to <12 years	147	148	148
Aged 4 to <6 years	28	29	28
Age continuous			
Age at last birthday			
Units: years median full range (min-max)	 9 4 to 11	 8 4 to 11	 8 4 to 11
Gender, Male/Female Units: Subjects			
Female	63	77	78
Male	112	100	98
Time since first diagnosis of asthma Units: Months median full range (min-max)	 35 3 to 136	 35 3 to 129	 47 3 to 141

Reporting group values	Total		
Number of subjects	528		
Age Categorical Units: Subjects			
Aged 6 to <12 years	443		
Aged 4 to <6 years	85		
Age continuous			
Age at last birthday			
Units: years median full range (min-max)	 -	 	
Gender, Male/Female Units: Subjects			
Female	218		
Male	310		

Time since first diagnosis of asthma Units: Months median full range (min-max)	- 		

End points

End points reporting groups

Reporting group title	Placebo metered dose inhaler (MDI)
Reporting group description:	
Placebo MDI over twelve weeks (ITT population)	
Reporting group title	Ciclesonide MDI 40 µg BID
Reporting group description:	
Ciclesonide MDI 40 µg BID over twelve weeks (ITT population)	
Reporting group title	Ciclesonide MDI 80 µg BID
Reporting group description:	
Ciclesonide MDI 80 µg BID over twelve weeks (ITT population)	

Primary: Change from baseline in forced expiratory volume in one second (FEV1) at week 12.

End point title	Change from baseline in forced expiratory volume in one second (FEV1) at week 12.
End point description:	
Change in FEV1 (Percent of predicted) from baseline to week 12. FEV1 was measured only in children between 6 to <12 years only. Least Squares Mean were adjusted for Baseline FEV1, age [yrs], pooled center, previous corticosteroid therapy and holding chamber.	
End point type	Primary
End point timeframe:	
Baseline and Week 12	

End point values	Placebo metered dose inhaler (MDI)	Ciclesonide MDI 40 µg BID	Ciclesonide MDI 80 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	136	138	146	
Units: Percent of predicted FEV1				
least squares mean (standard error)	5.2 (± 1.06)	5.3 (± 1.06)	7.7 (± 1.06)	

Statistical analyses

Statistical analysis title	Comparison between ciclesonide and placebo
Statistical analysis description:	
This is an analysis of the change from baseline to week 12 or last visit. In this pairwise comparison Ciclesonide was compared with Placebo by testing the average effect of Ciclesonide 40 and Ciclesonide 80 versus Placebo. As statistical test a t-test was used to compare the corresponding least-square means of both treatment groups.	
Comparison groups	Placebo metered dose inhaler (MDI) v Ciclesonide MDI 40 µg BID v Ciclesonide MDI 80 µg BID

Number of subjects included in analysis	420
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2696 [1]
Method	ANCOVA
Confidence interval	
level	95 %

Notes:

[1] - Due to usage of a-priori ordered hypotheses, adjustment of p-values is not necessary. The pre-specified significance level was 0.05. The tests were carried out two-sided.

Statistical analysis title	Comparison between ciclesonide 40 µg and placebo

Statistical analysis description:

This is an analysis of the change from baseline to week 12 or last visit. As statistical test a t-test was used to compare the corresponding least-square means of Ciclesonide 40 versus Placebo.

Comparison groups	Placebo metered dose inhaler (MDI) v Ciclesonide MDI 40 µg BID v Ciclesonide MDI 80 µg BID
Number of subjects included in analysis	420
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9146 [2]
Method	ANCOVA
Confidence interval	
level	95 %

Notes:

[2] - Due to usage of a-priori ordered hypotheses, adjustment of p-values is not necessary. The pre-specified significance level was 0.05. The tests were carried out two-sided.

Statistical analysis title	Comparison between ciclesonide 80 µg and placebo

Statistical analysis description:

This is an analysis of the change from baseline to week 12 or last visit. A t-test was used to compare the least-square means of Ciclesonide 80 versus Placebo.

Comparison groups	Placebo metered dose inhaler (MDI) v Ciclesonide MDI 80 µg BID
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0703 [3]
Method	ANCOVA
Confidence interval	
level	95 %

Notes:

[3] - Due to usage of a-priori ordered hypotheses, adjustment of p-values is not necessary. The pre-specified significance level was 0.05. The tests were carried out two-sided.

Secondary: Change from baseline in total daily asthma symptom score at week 12.

End point title	Change from baseline in total daily asthma symptom score at week 12.

End point description:

Change in total daily asthma symptom score from baseline to week 12. 5-Point, ordinal scale specifying patient's experience of symptoms during day and night from 0 (no symptoms) to 4 (symptoms that prevent the patient from engaging in daily activities or sleep)

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo metered dose inhaler (MDI)	Ciclesonide MDI 40 µg BID	Ciclesonide MDI 80 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	161	165	170	
Units: Scores on a scale				
least squares mean (standard error)	-0.96 (± 0.08)	-1.13 (± 0.08)	-0.99 (± 0.08)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in use of albuterol/salbutamol at week 12.

End point title	Change from baseline in use of albuterol/salbutamol at week 12.
End point description: Change in albuterol/salbutamol use from baseline to week 12	
End point type	Secondary
End point timeframe: Baseline and Week 12	

End point values	Placebo metered dose inhaler (MDI)	Ciclesonide MDI 40 µg BID	Ciclesonide MDI 80 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	162	166	172	
Units: Puffs per day				
least squares mean (standard error)	-0.59 (± 0.08)	-0.87 (± 0.08)	-0.93 (± 0.08)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in morning PEF to Week 12

End point title	Change from baseline in morning PEF to Week 12
End point description: Change in morning PEF from baseline to Week 12	
End point type	Secondary
End point timeframe: Baseline and week 12	

End point values	Placebo metered dose inhaler (MDI)	Ciclesonide MDI 40 µg BID	Ciclesonide MDI 80 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	161	165	172	
Units: L/min				
least squares mean (standard error)	9 (± 2.924)	16.36 (± 2.891)	23.55 (± 2.892)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time the patient gave informed consent at the pre-screening visit (Visit 1) until 14 days after the last administration of study medication.

Adverse event reporting additional description:

The numbers of subjects at risk are based on the Safety Population. It was based on all randomized patients receiving at least one dose of the double-blind study medication after randomization.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups

Reporting group title	Placebo metered dose inhaler (MDI)

Reporting group description:

Placebo MDI over twelve weeks (ITT population)

Reporting group title	Ciclesonide MDI 40 µg BID

Reporting group description:

Ciclesonide MDI 40 µg BID over twelve weeks (ITT population)

Reporting group title	Ciclesonide MDI 80 µg BID

Reporting group description:

Ciclesonide MDI 80 µg BID over twelve weeks (ITT population)

Serious adverse events	Placebo metered dose inhaler (MDI)	Ciclesonide MDI 40 µg BID	Ciclesonide MDI 80 µg BID
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 172 (0.58%)	1 / 174 (0.57%)	4 / 175 (2.29%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
General disorders and administration site conditions			
Electric shock			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 172 (0.00%)	0 / 174 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
alternative dictionary used: MedDRA 11.0			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 172 (0.58%)	0 / 174 (0.00%)	2 / 175 (1.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status asthmaticus			
alternative dictionary used: MedDRA 11.0			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 172 (0.00%)	0 / 174 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Forearm fracture			
alternative dictionary used: MedDRA 11.0			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 172 (0.00%)	1 / 174 (0.57%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo metered dose inhaler (MDI)	Ciclesonide MDI 40 µg BID	Ciclesonide MDI 80 µg BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	53 / 172 (30.81%)	38 / 174 (21.84%)	28 / 175 (16.00%)
Nervous system disorders			
Headache			
alternative dictionary used: MedDRA 11.0			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 172 (2.91%)	12 / 174 (6.90%)	8 / 175 (4.57%)
occurrences (all)	5	18	9
Respiratory, thoracic and mediastinal disorders			
Asthma			
alternative dictionary used: MedDRA 11.0			
alternative assessment type: Non-systematic			

subjects affected / exposed	18 / 172 (10.47%)	10 / 174 (5.75%)	3 / 175 (1.71%)
occurrences (all)	18	10	3
Infections and infestations			
Nasopharyngitis			
alternative dictionary used: MedDRA 11.0			
alternative assessment type: Non-systematic			
subjects affected / exposed	9 / 172 (5.23%)	8 / 174 (4.60%)	7 / 175 (4.00%)
occurrences (all)	11	9	7
Upper respiratory tract infection			
alternative dictionary used: MedDRA 11.0			
alternative assessment type: Non-systematic			
subjects affected / exposed	11 / 172 (6.40%)	4 / 174 (2.30%)	10 / 175 (5.71%)
occurrences (all)	11	5	10
Pharyngitis			
alternative dictionary used: MedDRA 11.0			
alternative assessment type: Non-systematic			
subjects affected / exposed	17 / 172 (9.88%)	7 / 174 (4.02%)	4 / 175 (2.29%)
occurrences (all)	19	7	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 August 2006	Amendment 1: The stratification of the randomization was revised with respect to previous ICS use. Several parts of the instructions were clarified.
12 January 2007	Amendment 2: Criteria for worsening asthma were revised. The inclusion criteria for morning PEF, reversibility and daytime asthma symptom score were revised.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported