Clinical trial results:
A 4-week, open-label, randomized, multi-centre, parallel-group study evaluating the safety and efficacy of 4 actuations Symbicort® (budesonide/formoterol) HFA pMDI 40/2.25 g twice daily, with and without spacer, in children (6-11 years) with asthma

Summary

EudraCT number	2007-002722-29
Trial protocol	HU
Global end of trial date	17 June 2008

Results information

Result version number	v1 (current)
This version publication date	01 February 2017
First version publication date	31 July 2015

Trial information

Trial identification

Sponsor protocol code	D5897C00004

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	AstraZeneca R&D Lund, SE-221 87 Lund, Sweden,
Public contact	Tomas Andersson, MD, AstraZeneca, aztrial_results_posting@astrazeneca.com
Scientific contact	Tomas Andersson, MD, AstraZeneca, aztrial_results_posting@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?	No

Notes:

Results analysis stage

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

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to show that Symbicort pMDI 40/2.25 µg (delivered dose) 4 actuations twice daily (bid) with spacer has a similar systemic steroid potency as Symbicort pMDI 40/2.25 µg, 4 actuations bid in children with asthma.

Protection of trial subjects:

The study was approved in Poland, Hungary and Russia by the Independent Ethics Committees (IECs) in each respective country.

Informed consent was obtained from the patient's parent/legal guardian and assent from the patient before any study-specific procedure was conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 September 2007
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	Poland: 66
Country: Number of subjects enrolled	Hungary: 30
Country: Number of subjects enrolled	Russian Federation: 11
Worldwide total number of subjects	107
EEA total number of subjects	96

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)	107
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:

137 subjects enrolled; 30 non randomised: 26 failed inclusion criteria, 2 voluntary discontinuations, 1 incorrect enrolment, 1 adverse event. 107 subjects were randomised

Pre-assignment

Screening details:

The study consisted of an enrolment visit, a 2 week run-in period, a randomization at Visit 3, and 2 further visits (Visits 4,5) at 2 and 4 weeks. Subjects received 1 of 2 open label treatments allocated in a random order.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	With Spacer

Arm description:

Budesonide/formoterol pMDI 40/2.25ug + spacer

Arm type	Experimental
Investigational medicinal product name	Symbicort pMDI 40/2.25 µg 4 actuations bid with spacer
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

2 actuations bid (every morning and every evening).

Arm title	Without Spacer

Arm description:

Budesonide/formoterol pMDI 40/2.25 ug

Arm type	Experimental
Investigational medicinal product name	Symbicort pMDI 40/2.25 µg 4 actuations bid without spacer
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

2 actuations bid (every morning and every evening).

Number of subjects in period 1	With Spacer	Without Spacer
Started	55	52
Completed	55	52

Baseline characteristics

Reporting groups	
Reporting group title	With Spacer
Reporting group description:	
Budesonide/formoterol pMDI 40/2.25ug + spacer	
Reporting group title	Without Spacer
Reporting group description:	
Budesonide/formoterol pMDI 40/2.25 ug	

Reporting group values	With Spacer	Without Spacer	Total
Number of subjects	55	52	107
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)	55	52	107
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous | Units: years			
arithmetic mean	8.6	8.9	
full range (min-max)	6 to 11	6 to 11	-
Gender, Male/Female Units: Participants			
Female	21	22	43
Male	34	30	64
Race Units: Subjects			
White	55	52	107
Median time since diagnosis Units: years			
median	3	3.55	
full range (min-max)	0.4 to 9	0.6 to 8.7	-

End points

End points reporting groups	
Reporting group title	With Spacer
Reporting group description:	
Budesonide/formoterol pMDI 40/2.25ug + spacer	
Reporting group title	Without Spacer
Reporting group description:	
Budesonide/formoterol pMDI 40/2.25 ug	

Primary: Urinary Free Cortisol (UFC)	
End point title	Urinary Free Cortisol (UFC)
End point description:	
Ratio between the value at the end of treatment and the value at start of treatment, including only patients with values at both baseline and end of treatment	
End point type	Primary
End point timeframe:	
At baseline and 4 weeks	

End point values	With Spacer	Without Spacer		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	51		
Units: Ratio				
geometric mean (full range (min-max))	0.86 (0.2 to 2.4)	1.03 (0.12 to 5.4)		

Statistical analyses

Statistical analysis title	24-hour UFC
Comparison groups	With Spacer v Without Spacer
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1666
Method	ANOVA
Parameter estimate	Ratio
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.713
upper limit	1.061

Secondary: Forced Expiratory Volume in 1 Second (FEV1)	
End point title	Forced Expiratory Volume in 1 Second (FEV1)
End point description:	
Changes in FEV1 from baseline to the mean value at 2 weeks to 4 weeks with the baseline value as a covariate.	
End point type	Secondary
End point timeframe:	
At baseline, at 2 weeks and 4 weeks	

End point values	With Spacer	Without Spacer		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	52		
Units: Liters				
arithmetic mean (full range (min-max))	0.17 (-0.38 to 0.76)	0.14 (-0.34 to 0.82)		

Statistical analyses

Statistical analysis title	Comparison of FEV1
Comparison groups	With Spacer v Without Spacer
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.61
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.0235
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0663
upper limit	0.113

Secondary: Morning Peak Expiratory Flow (mPEF)	
End point title	Morning Peak Expiratory Flow (mPEF)
End point description:	
Change in average value from the run-in to the treatment period, calculated using all available data for the 10 last days of run-in, and all available data after randomisation.Missing data between the first and last entry were estimated using linear interpolation.	
End point type	Secondary

End point timeframe:

Daily during run-in and daily during treatment period of 4 weeks

End point values	With Spacer	Without Spacer		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	52		
Units: Liters/min				
arithmetic mean (full range (min-max))	243 (116 to 413)	256 (153 to 418)		

Statistical analyses

Statistical analysis title	Change in mPEF
Statistical analysis description: change from baseline in mean values during the treatment period	
Comparison groups	With Spacer v Without Spacer
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.087
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	8.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	17.4

Secondary: Evening Peak Expiratory Flow (ePEF)

End point title	Evening Peak Expiratory Flow (ePEF)
End point description: Change in average value from the run-in to the treatment period, calculated using all available data for the 10 last days of run-in, and all available data after randomisation. Missing data between the first and last entry were estimated using linear interpolation.	
End point type	Secondary
End point timeframe: Daily during run-in and daily during treatment period of 4 weeks	

End point values	With Spacer	Without Spacer		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	52		
Units: Liters/min				
arithmetic mean (full range (min-max))	250 (138 to 429)	262 (166 to 420)		

Statistical analyses

Statistical analysis title	Change in ePEF
Statistical analysis description:	
change from baseline in mean values during the treatment period	
Comparison groups	With Spacer v Without Spacer
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.038
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	9.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	18.6

Secondary: Asthma Symptoms at Night

End point title	Asthma Symptoms at Night
End point description:	
Change in average value from the run-in to treatment period, calculated using all available data for the 10 last days of run-in, and all available data after randomisation.Missing data between the first and last entry estimated using linear interpolation. Daily scale:0 = No symptoms; 1 = Mild symptoms; 2 = Moderate symptoms; 3 = Severe symptoms.	
End point type	Secondary
End point timeframe:	
Daily during run-in and daily during treatment period of 4 weeks	

End point values	With Spacer	Without Spacer		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	52		
Units: Units on a scale				
arithmetic mean (full range (min-max))	0.643 (0 to 1.88)	0.705 (0 to 1.93)		

Statistical analyses

Statistical analysis title	Change in Asthma Symptom Scores (night)
Statistical analysis description:	
change from baseline in mean score during the treatment period	
Comparison groups	With Spacer v Without Spacer
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.945
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.005
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.153
upper limit	0.143

Secondary: Asthma Symptoms at Day	
End point title	Asthma Symptoms at Day
End point description:	
Change in average value from the run-in to treatment period, calculated using all available data for the 10 last days of run-in, and all available data after randomisation.Missing data between the first and last entry estimated using linear interpolation. Daily scale:0 = No symptoms; 1 = Mild symptoms; 2 = Moderate symptoms; 3 = Severe symptoms.	
End point type	Secondary
End point timeframe:	
Daily during run-in and daily during treatment period of 4 weeks	

End point values	With Spacer	Without Spacer		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	52		
Units: Units on a scale				
arithmetic mean (full range (min-max))	0.708 (0 to 1.96)	0.806 (0 to 2)		

Statistical analyses

Statistical analysis title	Change in Asthma Symptom Scores (day)
Statistical analysis description:	
change from baseline in mean score during the treatment period	
Comparison groups	With Spacer v Without Spacer
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.987
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.001
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.104
upper limit	0.148

Secondary: Percentage of Nights With Awakenings Due to Asthma	
End point title	Percentage of Nights With Awakenings Due to Asthma
End point description:	
Change in Percentage of nights with awakenings, average value from the run-in to treatment period, calculated using all available data for the 10 last days of run-in, and all available data after randomisation.Missing data between the first and last entry estimated using linear interpolation.	
End point type	Secondary
End point timeframe:	
Daily during run-in and daily during treatment period of 4 weeks	

End point values	With Spacer	Without Spacer		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	52		
Units: Percentage of nights				
arithmetic mean (full range (min-max))	16.1 (0 to 100)	15.5 (0 to 100)		

Statistical analyses

Statistical analysis title	Change in %Nights with Awakenings
Statistical analysis description:	
change from baseline in mean % during the treatment period	
Comparison groups	With Spacer v Without Spacer

Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.724
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.34
upper limit	6.51

Secondary: Use of Rescue Medication at Night

End point title	Use of Rescue Medication at Night

End point description:

Change in average value from the run-in to treatment period, calculated using all available data for the 10 last days of run-in, and all available data after randomisation.Missing data between the first and last entry estimated using linear interpolation.

End point type	Secondary

End point timeframe:

Daily during run-in and daily during treatment period of 4 weeks

End point values	With Spacer	Without Spacer		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	52		
Units: Inhalations				
arithmetic mean (full range (min-max))	0.214 (0 to 2.86)	0.136 (0 to 1.69)		

Statistical analyses

Statistical analysis title	Change in Use of Rescue Medication (night)

Statistical analysis description:

change from baseline in mean use during the treatment period

Comparison groups	With Spacer v Without Spacer
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.692
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.026

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.104
upper limit	0.157

Secondary: Use of Rescue Medication at Day

End point title	Use of Rescue Medication at Day

End point description:

Change in average value from the run-in to treatment period, calculated using all available data for the 10 last days of run-in, and all available data after randomisation.Missing data between the first and last entry estimated using linear interpolation.

End point type	Secondary

End point timeframe:

Daily during run-in and daily during treatment period of 4 weeks

End point values	With Spacer	Without Spacer		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	52		
Units: Inhalations				
arithmetic mean (full range (min-max))	0.277 (0 to 3.14)	0.227 (0 to 1.96)		

Statistical analyses

Statistical analysis title	Change in Use of Rescue Medication (day)

Statistical analysis description:

change from baseline in mean use during the treatment period

Comparison groups	With Spacer v Without Spacer
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.694
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.028
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.166
upper limit	0.111

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were collected from the enrolment visit (visit 1) until visit 5 (4 weeks after randomisation).	
Adverse event reporting additional description:	
Adverse events were recorded by period (run-in, treatment, post-treatment). Only adverse events occuring during the treatment period are included in the summary below.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	10.1

Reporting groups	
Reporting group title	Without Spacer
Reporting group description:	
Budesonide/formoterol pMDI 40/2.25 ug	
Reporting group title	With Spacer
Reporting group description:	
Budesonide/formoterol pMDI 40/2.25ug + spacer	

Serious adverse events	Without Spacer	With Spacer	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 52 (0.00%)	0 / 55 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Without Spacer	With Spacer	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 52 (15.38%)	5 / 55 (9.09%)	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 52 (1.92%)	1 / 55 (1.82%)	
occurrences (all)	1	1	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 52 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	

Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 52 (1.92%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
Abdominal pain upper			
subjects affected / exposed	1 / 52 (1.92%)	0 / 55 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Nasopharyngitis			
subjects affected / exposed	2 / 52 (3.85%)	0 / 55 (0.00%)	
occurrences (all)	2	0	
Cough			
subjects affected / exposed	0 / 52 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
Dysphonia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Nocturia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 52 (3.85%)	0 / 55 (0.00%)	
occurrences (all)	2	0	
Urinary tract infection			
subjects affected / exposed	0 / 52 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	0 / 52 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	1 / 52 (1.92%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
Bronchitis			

subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 55 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported