Clinical trial results:
A comparison of the efficacy of Symbicort® SMART[a] (Symbicort Turbuhaler® 160/4.5 g 1 inhalation bi.d. plus as-needed) and conventional best standard treatment for the treatment of persistent asthma in adolescents and adults. A randomized, open, parallel-group, multicentre, 26 weeks study.

Summary

EudraCT number	2004-000679-32
Trial protocol	FI
Global end of trial date	27 February 2008

Results information

Result version number	v1 (current)
This version publication date	28 April 2016
First version publication date	28 April 2016

Trial information

Trial identification

Sponsor protocol code	D5890L00008

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Roskildevej 22, 2620 Albertslund, Denmark,
Public contact	Stig Waldorff, M, AstraZeneca, clinicaltrialtranparency@astrazeneca.com
Scientific contact	Stig Waldorff, M, AstraZeneca, clinicaltrialtranparency@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	27 February 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 February 2008
Global end of trial reached?	Yes
Global end of trial date	27 February 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 compare the efficacy of treatment with Symbicort® Maintenance and Reliever Therapy (Symbicort® SMART) with treatment according to conventional best practice treatment in patients with persistent asthma.

Protection of trial subjects:

The final study protocol, including the final version of the Written Informed Consent Form, was approved or given a favourable opinion in writing by an IRB or IEC. The coordinating investigator in each country submitted written approval to AstraZeneca before enrolling any patient into the study.

The principal investigator(s) at each centre ensured that the patient/patients legally acceptable representative was given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients were also notified that they were free to discontinue from the study at any time. The patients were given the opportunity to ask questions and allowed time to consider the information provided.

The patient’s signed and dated informed consent were obtained before conducting any procedure specifically for the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 September 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	Finland: 418
Country: Number of subjects enrolled	Denmark: 800
Country: Number of subjects enrolled	Norway: 617
Worldwide total number of subjects	1835
EEA total number of subjects	1835

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)	85
Adults (18-64 years)	1582
From 65 to 84 years	164
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

This was a multicentre trial conducted in 3 countries between September 2004 and October 2006.

Pre-assignment

Screening details:

The study consisted of an enrolment/randomization visit, a randomization at Visit 1, and 3 further visits (Visits 2-4) at 4, 13 and 26 weeks. Subjects received 1 of 2 open label treatments allocated in a random order.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	SMART

Arm description:

Symbicort® Turbuhaler®

Arm type	Experimental
Investigational medicinal product name	Symbicort® Turbuhaler®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

160/4.5 µg/ dose budesonide/formoterol twice daily

Arm title	CBP (Conventional best practice)

Arm description:

Conventional best practice

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	SMART	CBP (Conventional best practice)
Started	921	914
Completed	818	849
Not completed	103	65
Consent withdrawn by subject	22	8
Adverse event, non-fatal	21	9
Other reasons	18	6
Lost to follow-up	12	12
Protocol deviation	30	30

Baseline characteristics

Reporting groups	
Reporting group title	SMART
Reporting group description: Symbicort® Turbuhaler®	
Reporting group title	CBP (Conventional best practice)
Reporting group description: Conventional best practice	

Reporting group values	SMART	CBP (Conventional best practice)	Total
Number of subjects	921	914	1835
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)	0	0	0
Adolescents (12-17 years)	43	42	85
Adults (18-64 years)	790	792	1582
From 65-84 years	86	78	164
85 years and over	2	2	4
Age Continuous Units: years			
arithmetic mean	43	42	
standard deviation	± 15.9	± 15.9	-
Gender Categorical Units: Subjects			
Female	559	536	1095
Male	362	378	740
Race Units: Subjects			
Caucasian	911	901	1812
Black	0	1	1
Oriental	5	8	13
Other	5	4	9

End points

End points reporting groups	
Reporting group title	SMART
Reporting group description: Symbicort® Turbuhaler®	
Reporting group title	CBP (Conventional best practice)
Reporting group description: Conventional best practice	

Primary: Subjects with at least one severe exacerbations	
End point title	Subjects with at least one severe exacerbations
End point description:	
End point type	Primary
End point timeframe: 26 weeks	

End point values	SMART	CBP (Conventional best practice)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	921	914		
Units: Subjects	58	73		

Statistical analyses

Statistical analysis title	Time to first severe exacerbation
Comparison groups	SMART v CBP (Conventional best practice)
Number of subjects included in analysis	1835
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.189
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.12

Secondary: Number of severe exacerbations

End point title	Number of severe exacerbations
End point description:	

End point type	Secondary
End point timeframe:	
26 weeks	

End point values	SMART	CBP (Conventional best practice)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	921	914		
Units: number of severe exacerbations				
No. with 1 event	51	59		
No. with 2 events	3	7		
No. with 3 events	4	6		
No with > 3 events	0	1		

Statistical analyses

Statistical analysis title	Total number of severe exacerbations
Comparison groups	SMART v CBP (Conventional best practice)
Number of subjects included in analysis	1835
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.058
Method	Poisson Regression
Parameter estimate	Risk ratio (RR)
Point estimate	0.741
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.543
upper limit	1.01

Secondary: Average no. of as needed inhalations per day

End point title	Average no. of as needed inhalations per day
End point description:	

End point type	Secondary

End point timeframe:
26 weks

End point values	SMART	CBP (Conventional best practice)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	898	898		
Units: average inhalations per day				
arithmetic mean (full range (min-max))	0.99 (0 to 10)	0.96 (0 to 9)		

Statistical analyses

Statistical analysis title	Average no. of as needed inhalations per day
Comparison groups	SMART v CBP (Conventional best practice)
Number of subjects included in analysis	1796
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9809
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	0.001
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.109
upper limit	0.112

Secondary: Mean daily dose of inhaled steroids

End point title	Mean daily dose of inhaled steroids

End point description:

End point type	Secondary

End point timeframe:
26 weeks

End point values	SMART	CBP (Conventional best practice)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	921	914		
Units: µg				
arithmetic mean (full range (min-max))	482 (320 to 1920)	670 (21 to 3000)		

Statistical analyses

Statistical analysis title	Mean daily dose of inhaled steroids
Comparison groups	SMART v CBP (Conventional best practice)
Number of subjects included in analysis	1835
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	187.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	160
upper limit	215.9

Secondary: Asthma Control Questionnaire

End point title	Asthma Control Questionnaire
End point description:	
End point type	Secondary
End point timeframe:	
26 weeks	

End point values	SMART	CBP (Conventional best practice)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	899	897		
Units: average				
arithmetic mean (full range (min-max))	1.03 (0 to 4.3)	1.08 (0 to 4.6)		

Statistical analyses

Statistical analysis title	Change in Asthma Control Questionnaire
Comparison groups	SMART v CBP (Conventional best practice)
Number of subjects included in analysis	1796
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.003
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	-0.03

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Only serious AEs and AEs leading to discontinuation were collected from visit 1 until visit 4 (26 weeks after randomization). Only events occuring on or after first dose of study medication are included in the summaries.

Adverse event reporting additional description:

A total of 63 patients reported non-serious adverse events; 30 on SMART, 33 on CBP. Numbers for non-serious AEs in the reporting group table are based on the 1% threshold frequency.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	9.1

Reporting groups

Reporting group title	SMART

Reporting group description:

Symbicort® Turbuhaler®

Reporting group title	CBP (Conventional best practice)

Reporting group description:

Conventional best practice

Serious adverse events	SMART	CBP (Conventional best practice)	
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 921 (2.71%)	25 / 914 (2.74%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events		0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 921 (0.00%)	1 / 914 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	0 / 921 (0.00%)	1 / 914 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			

subjects affected / exposed	1 / 921 (0.11%)	0 / 914 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 921 (0.00%)	1 / 914 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Drug abuser			
subjects affected / exposed	0 / 921 (0.00%)	1 / 914 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Postmenopausal haemorrhage			
subjects affected / exposed	1 / 921 (0.11%)	0 / 914 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 921 (0.00%)	1 / 914 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metrorrhagia			
subjects affected / exposed	1 / 921 (0.11%)	0 / 914 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine cyst			
subjects affected / exposed	0 / 921 (0.00%)	1 / 914 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			

subjects affected / exposed	1 / 921 (0.11%)	1 / 914 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	6 / 921 (0.65%)	6 / 914 (0.66%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 921 (0.00%)	1 / 914 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 921 (0.00%)	1 / 914 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 921 (0.00%)	1 / 914 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	1 / 921 (0.11%)	0 / 914 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sleep apnoea syndrome			
subjects affected / exposed	1 / 921 (0.11%)	0 / 914 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Contusion			

subjects affected / exposed	0 / 921 (0.00%)	1 / 914 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 921 (0.00%)	1 / 914 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	0 / 921 (0.00%)	1 / 914 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	0 / 921 (0.00%)	1 / 914 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 921 (0.11%)	0 / 914 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral artery thrombosis			
subjects affected / exposed	1 / 921 (0.11%)	0 / 914 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 921 (0.00%)	1 / 914 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 921 (0.00%)	1 / 914 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	2 / 921 (0.22%)	1 / 914 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 921 (0.11%)	0 / 914 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 921 (0.11%)	0 / 914 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	1 / 921 (0.11%)	0 / 914 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Thyroid haemorrhage			
subjects affected / exposed	1 / 921 (0.11%)	0 / 914 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Chest pain			
subjects affected / exposed	1 / 921 (0.11%)	1 / 914 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess neck			
subjects affected / exposed	0 / 921 (0.00%)	1 / 914 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Diverticulitis			

subjects affected / exposed	2 / 921 (0.22%)	0 / 914 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 921 (0.00%)	2 / 914 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious mononucleosis			
subjects affected / exposed	2 / 921 (0.22%)	0 / 914 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 921 (0.00%)	1 / 914 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 921 (0.11%)	0 / 914 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 921 (0.11%)	0 / 914 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 921 (0.11%)	0 / 914 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 921 (0.00%)	1 / 914 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			

subjects affected / exposed	0 / 921 (0.00%)	1 / 914 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Oedema			
subjects affected / exposed	0 / 921 (0.00%)	1 / 914 (0.11%)	
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: 1 %

Non-serious adverse events	SMART	CBP (Conventional best practice)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 921 (1.52%)	9 / 914 (0.98%)	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	14 / 921 (1.52%)	9 / 914 (0.98%)	
occurrences (all)	14	9	

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