Clinical trial results:
A Comparison of Symbicort SMART (Symbicort Turbuhaler 160/4,5 mcg, 1 inhalation b.i.d. plus as needed) and conventional best practice for the treatment of persistent asthma in adolescents and adults – a 26-week, open-labelled, parallel-group, multicentre study

Summary

EudraCT number	2005-000532-25
Trial protocol	IS LT LV CZ SK
Global end of trial date	06 June 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	D5890L00014

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, Sweden,
Public contact	Tomas LG Andersson, AstraZeneca, clinicaltrialtranparency@astrazeneca.com
Scientific contact	Tomas LG Andersson, 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	03 June 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 June 2008
Global end of trial reached?	Yes
Global end of trial date	06 June 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to compare the efficacy of Symbicort SMART with treatment according to conventional best practice in adolescent and adult patients with persistent asthma.

Protection of trial subjects:

The final study protocol, including the final version of the Informed Consent Form, was approved or given a favourable opinion in writing by an IRB or IEC as appropriate. The investigator submitted written approval to AstraZeneca before he or she enrolled any patient into the study.

The principal investigator(s) at each centre ensured that the patient/patient's 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 patient was given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent was obtained before conducting any procedure specifically for the study,

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 July 2005
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	Chile: 60
Country: Number of subjects enrolled	Croatia: 100
Country: Number of subjects enrolled	Czech Republic: 72
Country: Number of subjects enrolled	Greece: 134
Country: Number of subjects enrolled	Iceland: 100
Country: Number of subjects enrolled	Latvia: 110
Country: Number of subjects enrolled	Lithuania: 110
Country: Number of subjects enrolled	Portugal: 108
Country: Number of subjects enrolled	Slovakia: 121
Country: Number of subjects enrolled	Slovenia: 80
Worldwide total number of subjects	995
EEA total number of subjects	935

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)	52
Adults (18-64 years)	943
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a 26-week, randomised, open-label, parallel group study, recruiting patients from 10 countries.

Pre-assignment

Screening details:

The study consisted of an enrolment/randomization visit, and 3 further visits (Visits 2, 3 and 4) at 4, 13 and 26 weeks, with a telephone contact at weeks 2, 11 and 24. 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	Symbicort 160/4.5µg

Arm description:

Symbicort 160/4.5µg, 1 inhalation b.i.d. + as needed

Arm type	Experimental
Investigational medicinal product name	Symbicort 160/4.5µg, 1 inhalation b.i.d. + as needed
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Symbicort 160/4.5µg, 1 inhalation b.i.d. + as needed

Arm title	Conventional Best Practice (CBP)

Arm description:

Conventional Best Practice

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Symbicort 160/4.5µg	Conventional Best Practice (CBP)
Started	497	498
Completed	470	467
Not completed	27	31
Consent withdrawn by subject	5	2
Adverse event, non-fatal	6	3
Other	5	5
Lost to follow-up	8	18
Protocol deviation	3	3

Baseline characteristics

Reporting groups	
Reporting group title	Symbicort 160/4.5µg
Reporting group description:	
Symbicort 160/4.5µg, 1 inhalation b.i.d. + as needed	
Reporting group title	Conventional Best Practice (CBP)
Reporting group description:	
Conventional Best Practice	

Reporting group values	Symbicort 160/4.5µg	Conventional Best Practice (CBP)	Total
Number of subjects	497	498	995
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)	24	28	52
Adults (18-64 years)	473	470	943
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	44.1	45.2	
standard deviation	± 15.7	± 16.2	-
Gender categorical Units: Subjects			
Female	323	315	638
Male	174	183	357
Time since diagnosis Units: years			
median	10.2	9.2	
full range (min-max)	0.7 to 62.7	0.3 to 70.9	-

End points

End points reporting groups	
Reporting group title	Symbicort 160/4.5µg
Reporting group description: Symbicort 160/4.5µg, 1 inhalation b.i.d. + as needed	
Reporting group title	Conventional Best Practice (CBP)
Reporting group description: Conventional Best Practice	

Primary: Patients with severe exacerbations	
End point title	Patients with severe exacerbations
End point description:	
End point type	Primary
End point timeframe: 26 weeks	

End point values	Symbicort 160/4.5µg	Conventional Best Practice (CBP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	497	498		
Units: Patients	46	61		

Statistical analyses

Statistical analysis title	Time to first severe exacerbation
Comparison groups	Conventional Best Practice (CBP) v Symbicort 160/4.5µg
Number of subjects included in analysis	995
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.107
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.728
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.495
upper limit	1.071

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	Symbicort 160/4.5µg	Conventional Best Practice (CBP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	497	498		
Units: patients				
No. with 1 event	32	47		
No. with 2 events	12	12		
No. with 3 events	1	2		
No. with > 3 events	1	0		

Statistical analyses

Statistical analysis title	Mean number of severe exacerbations
Comparison groups	Symbicort 160/4.5µg v Conventional Best Practice (CBP)
Number of subjects included in analysis	995
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.246
Method	Poisson regression
Parameter estimate	Risk ratio (RR)
Point estimate	0.821
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.589
upper limit	1.146

Secondary: Mean no of inhalations per day

End point title	Mean no of inhalations per day
End point description:	

End point type	Secondary

End point timeframe:
26 weeks

End point values	Symbicort 160/4.5µg	Conventional Best Practice (CBP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	463	462		
Units: average no per day				
arithmetic mean (full range (min-max))	0.95 (0 to 7.357)	1.078 (0 to 8.96)		

Statistical analyses

Statistical analysis title	Mean no of inhalations per day
Comparison groups	Symbicort 160/4.5µg v Conventional Best Practice (CBP)
Number of subjects included in analysis	925
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.14
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.129
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.043

Secondary: As needed free days (%)

End point title	As needed free days (%)

End point description:

End point type	Secondary

End point timeframe:
26 weeks

End point values	Symbicort 160/4.5µg	Conventional Best Practice (CBP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	460	459		
Units: Percentage				
arithmetic mean (full range (min-max))	59.037 (0 to 100)	59.425 (0 to 100)		

Statistical analyses

Statistical analysis title	As needed free days (%)
Statistical analysis description:	
Percentage of as needed rescue medication free days	
Comparison groups	Symbicort 160/4.5µg v Conventional Best Practice (CBP)
Number of subjects included in analysis	919
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.874
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.388
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.184
upper limit	4.408

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	Symbicort 160/4.5µg	Conventional Best Practice (CBP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	463	442		
Units: µg				
arithmetic mean (full range (min-max))	471.9 (320 to 1497.1)	515.5 (125 to 1333.3)		

Statistical analyses

Statistical analysis title	Mean daily dose of inhaled steroids
Comparison groups	Symbicort 160/4.5µg v Conventional Best Practice (CBP)
Number of subjects included in analysis	905
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.002
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	-43.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-71.4
upper limit	-15.6

Secondary: Mean daily dose (µg BDP or equivalent)	
End point title	Mean daily dose (µg BDP or equivalent)
End point description:	
End point type	Secondary
End point timeframe:	
26 weeks	

End point values	Symbicort 160/4.5µg	Conventional Best Practice (CBP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	463	442		
Units: µg BDP or equivalent				
arithmetic mean (full range (min-max))	737.4 (500 to 2339.3)	852 (250 to 2666.7)		

Statistical analyses

Statistical analysis title	Mean daily dose (µg BDP or equivalent)
Comparison groups	Symbicort 160/4.5µg v Conventional Best Practice (CBP)

Number of subjects included in analysis	905
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	-114.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-160.3
upper limit	69

Secondary: Average overall Asthma Control Questionnaire (ACQ) score in the treatment period

End point title	Average overall Asthma Control Questionnaire (ACQ) score in the treatment period

End point description:

End point type	Secondary

End point timeframe:

26 weeks

End point values	Symbicort 160/4.5µg	Conventional Best Practice (CBP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	213	212		
Units: average score				
arithmetic mean (full range (min-max))	1.11 (0 to 4.2)	1.215 (0 to 4.267)		

Statistical analyses

Statistical analysis title	Change in average overall ACQ score

Statistical analysis description:

Change in average overall ACQ score during the treatment period

Comparison groups	Symbicort 160/4.5µg v Conventional Best Practice (CBP)
Number of subjects included in analysis	425
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.092
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.116

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.252
upper limit	0.019

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the enrolment visit until viist 4 (26 weeks after randomisation). Only AEs occuring on or after the first dose of study medication are presented in the summaries below.

Adverse event reporting additional description:

A total of 260 patients reported non-serious adverse events; 125 on Symbicort Symbicort 160/4.5µg, 135 on CBP. Numbers for non-serious AEs in the reporting group table are based on the 5% threshold frequency.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	9.1

Reporting groups

Reporting group title	Conventional Best Practice (CBP)

Reporting group description:

Conventional Best Practice

Reporting group title	Symbicort 160/4.5µg

Reporting group description:

Symbicort 160/4.5µg, 1 inhalation b.i.d. + as needed

Serious adverse events	Conventional Best Practice (CBP)	Symbicort 160/4.5µg	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 493 (2.23%)	6 / 493 (1.22%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events		0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Multiple Myeloma			
subjects affected / exposed	1 / 493 (0.20%)	0 / 493 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 493 (0.00%)	1 / 493 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ischaemic Stroke			

subjects affected / exposed	1 / 493 (0.20%)	0 / 493 (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			
Sudden Cardiac Death			
subjects affected / exposed	1 / 493 (0.20%)	0 / 493 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Immune system disorders			
Angioedema			
subjects affected / exposed	0 / 493 (0.00%)	1 / 493 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diverticulitis			
subjects affected / exposed	0 / 493 (0.00%)	1 / 493 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Adenomyosis			
subjects affected / exposed	1 / 493 (0.20%)	0 / 493 (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			
Bronchitis			
subjects affected / exposed	1 / 493 (0.20%)	0 / 493 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	3 / 493 (0.61%)	0 / 493 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			

subjects affected / exposed	0 / 493 (0.00%)	1 / 493 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis viral			
subjects affected / exposed	0 / 493 (0.00%)	1 / 493 (0.20%)	
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	1 / 493 (0.20%)	0 / 493 (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			
Back Pain			
subjects affected / exposed	1 / 493 (0.20%)	0 / 493 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus lesion			
subjects affected / exposed	0 / 493 (0.00%)	1 / 493 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacterial Infection			
subjects affected / exposed	1 / 493 (0.20%)	0 / 493 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 493 (0.20%)	1 / 493 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Conventional Best Practice (CBP)	Symbicort 160/4.5µg	
Total subjects affected by non-serious adverse events subjects affected / exposed	23 / 493 (4.67%)	20 / 493 (4.06%)	
Respiratory, thoracic and mediastinal disorders Upper respiratory infection subjects affected / exposed occurrences (all)	9 / 493 (1.83%) 13	11 / 493 (2.23%) 11	
Infections and infestations Common cold subjects affected / exposed occurrences (all)	14 / 493 (2.84%) 15	9 / 493 (1.83%) 10	

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