Clinical trial results:
A comparison of Symbicort Single inhaler Therapy (Symbicort Turbohaler 160/4.5 g, 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, randomised, open-label, parallel-group, multi-centre study (SALTO)

Summary

EudraCT number	2004-001107-36
Trial protocol	BE
Global end of trial date	20 June 2008

Results information

Result version number	v1
This version publication date	28 April 2016
First version publication date	28 April 2016

Trial information

Trial identification

Sponsor protocol code	D5890L00009

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 NV/SA, B-1180 Brussels, Belgium,
Public contact	Guy Vandenhoven MD, AstraZeneca, ClinicalTrialTransparency@astrazeneca.com
Scientific contact	Guy Vandenhoven MD, AstraZeneca, ClinicalTrialTransparency@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	20 June 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 June 2008
Global end of trial reached?	Yes
Global end of trial date	20 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 compare the efficacy of SMART (Symbicort Turbohaler160/4.5µg, 1 inhalation b.i.d. + as needed in response to symptoms) with treatment according to conventional best practice in adolescent and adult patients with persistent asthma.

The primary efficacy variable was the time to first severe asthma exacerbation.

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 Institutional Review Board (IRB) or Independent Ethics Committee (IEC) as appropriate. The investigator submitted written approval to AstraZeneca NV/SA before enrolling any patient into the study.

The principal investigator(s) at each centre ensured that the patient 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.

In patients below the age of consent, informed consent was obtained from both the patient and the patient’s parent/legal guardian. The patient’s signed and dated informed consent was obtained before conducting any study-specific procedure

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 December 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	Belgium: 912
Worldwide total number of subjects	912
EEA total number of subjects	912

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)	64
Adults (18-64 years)	724
From 65 to 84 years	122
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The study consisted of 912 randomised patients from Belgium between December 2004 and January 2006.

Pre-assignment

Screening details:

The study consisted of five scheduled visits to the clinic: at the start of the run-in period, at randomisation to the treatment groups and after 4, 13 and 26 weeks of study. Patients were allocated to one of 2 treatment groups in a random manner.

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 SMART

Arm description:

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

Arm type	Experimental
Investigational medicinal product name	Symbicort Turbohaler: budesonide 160 µg/inhalation (delivered dose) and formoterol fumarate dehydrate 4.5 µg/inhalation (delivered dose)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

160/4.5 µg, 1 inhalation b.i.d. plus 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 SMART	Conventional Best Practice (CBP)
Started	452	460
Completed	423	444
Not completed	29	16
Consent withdrawn by subject	4	1
Adverse event, non-fatal	4	2
Other	4	1
Lost to follow-up	5	3

Protocol deviation	12	9

Baseline characteristics

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

Reporting group values	Symbicort SMART	Conventional Best Practice (CBP)	Total
Number of subjects	452	460	912
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)	32	32	64
Adults (18-64 years)	358	366	724
From 65-84 years	61	61	122
85 years and over	1	1	2
Age continuous Units: years			
arithmetic mean	43.4	42.9	
full range (min-max)	12 to 87	13 to 85	-
Gender categorical Units: Subjects			
Female	253	271	524
Male	199	189	388
Median time since diagnosis Units: years			
median	21	20.3	
full range (min-max)	0 to 86	0 to 78	-

End points

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

Primary: No of patients with severe exacerbations	
End point title	No of patients with severe exacerbations
End point description:	
End point type	Primary
End point timeframe:	
26 weeks	

End point values	Symbicort SMART	Conventional Best Practice (CBP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	452	460		
Units: patients	12	19		

Statistical analyses

Statistical analysis title	Time to first severe Exacerbation
Comparison groups	Symbicort SMART v Conventional Best Practice (CBP)
Number of subjects included in analysis	912
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7599
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
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	Symbicort SMART	Conventional Best Practice (CBP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	452	460		
Units: exacerbations				
No, of patients with 1 event	10	15		
No, of patients with 2 events2	2	3		
No, of patients with 3 events	0	0		
No, of patients with >3 events	0	1		

Statistical analyses

Statistical analysis title	Mean number of severe asthma exacerbations
Comparison groups	Symbicort SMART v Conventional Best Practice (CBP)
Number of subjects included in analysis	912
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0896
Method	Poisson Regression
Parameter estimate	Risk ratio (RR)
Point estimate	0.5554
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	1.21

Secondary: Average number of inhalations per day

End point title	Average number of inhalations per day
End point description:	

End point type	Secondary

End point timeframe:
26 weeks

End point values	Symbicort SMART	Conventional Best Practice (CBP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	445	457		
Units: average inhalations per day				
arithmetic mean (full range (min-max))	0.93 (0 to 6.95)	0.99 (0 to 10.4)		

Statistical analyses

Statistical analysis title	Average no of inhalations per day
Comparison groups	Symbicort SMART v Conventional Best Practice (CBP)
Number of subjects included in analysis	902
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1471
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	0.04

Secondary: As needed free-days

End point title	As needed free-days
End point description:	
Percentage of days without medication use during the treatment period.	
End point type	Secondary
End point timeframe:	
26 weeks	

End point values	Symbicort SMART	Conventional Best Practice (CBP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	445	457		
Units: Percentage use				
arithmetic mean (full range (min-max))	60.5 (0 to 102.4)	62.4 (0 to 114.3)		

Statistical analyses

Statistical analysis title	As needed free-days
Statistical analysis description:	
Percentage of as needed medication free days in the treatment period	
Comparison groups	Symbicort SMART v Conventional Best Practice (CBP)
Number of subjects included in analysis	902
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5108
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.77
upper limit	2.38

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 SMART	Conventional Best Practice (CBP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	452	460		
Units: µg				
arithmetic mean (full range (min-max))	482 (329 to 1473)	589 (247 to 2000)		

Statistical analyses

Statistical analysis title	Mean daily dose of inhaled steroids
Comparison groups	Symbicort SMART v Conventional Best Practice (CBP)
Number of subjects included in analysis	912
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	-107.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-141.2
upper limit	-73.76

Secondary: PEF pre-BD at end of treatment	
End point title	PEF pre-BD at end of treatment
End point description:	
End point type	Secondary
End point timeframe:	
26 weeks	

End point values	Symbicort SMART	Conventional Best Practice (CBP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	452	460		
Units: L/min				
arithmetic mean (full range (min-max))	423.72 (85 to 748)	417.84 (60 to 763)		

Statistical analyses

Statistical analysis title	PEF pre-BD at end of treatment
Comparison groups	Symbicort SMART v Conventional Best Practice (CBP)

Number of subjects included in analysis	912
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5991
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	2.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.81
upper limit	10.07

Secondary: PEF post-BD at end of treatment

End point title	PEF post-BD at end of treatment
End point description:	

End point type	Secondary
End point timeframe:	
26 weeks	

End point values	Symbicort SMART	Conventional Best Practice (CBP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	452	460		
Units: L/min				
arithmetic mean (full range (min-max))	446.36 (100 to 770)	442.83 (100 to 804)		

Statistical analyses

Statistical analysis title	PEF post-BD at end of treatment
Comparison groups	Symbicort SMART v Conventional Best Practice (CBP)
Number of subjects included in analysis	912
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6537
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	1.68

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.65
upper limit	9

Secondary: FEV1 pre-BD at end of treatment

End point title	FEV1 pre-BD at end of treatment
End point description:	
End point type	Secondary
End point timeframe:	
26 weeks	

End point values	Symbicort SMART	Conventional Best Practice (CBP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	137	136		
Units: L/min				
arithmetic mean (full range (min-max))	2.76 (0.9 to 6.2)	2.87 (0.7 to 6)		

Statistical analyses

Statistical analysis title	FEV1 pre-BD at end of treatment
Comparison groups	Symbicort SMART v Conventional Best Practice (CBP)
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4135
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.004
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	0.05

Secondary: FEV1 post-BD at end of treatment

End point title	FEV1 post-BD at end of treatment

End point description:

End point type	Secondary
End point timeframe:	
26 weeks	

End point values	Symbicort SMART	Conventional Best Practice (CBP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	137	136		
Units: L/min				
arithmetic mean (full range (min-max))	2.91 (0.9 to 6.3)	3 (0.8 to 6)		

Statistical analyses

Statistical analysis title	FEV1 post-BD at end of treatment
Comparison groups	Symbicort SMART v Conventional Best Practice (CBP)
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3285
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.004
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	0.03

Secondary: Mean overall ACQ score	
End point title	Mean overall ACQ score
End point description:	
Mean ACQ score (overall) during the treatment period	
End point type	Secondary
End point timeframe:	
26 weeks	

End point values	Symbicort SMART	Conventional Best Practice (CBP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	446	451		
Units: mean score				
arithmetic mean (full range (min-max))	1.1 (0 to 4.2)	1.16 (0 to 5.2)		

Statistical analyses

Statistical analysis title	Change in ACQ score
Statistical analysis description:	
Change in mean ACQ score (overall) during the treatment period	
Comparison groups	Symbicort SMART v Conventional Best Practice (CBP)
Number of subjects included in analysis	897
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0026
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	-0.04

Secondary: Mean overall SATQ score

End point title	Mean overall SATQ score
End point description:	
Satisfaction with Asthma Treatment Questionnaire (SATQ) : to measure patients satisfaction with their inhaled asthma medication. It consists of 26 questions on a 7 point scale within 4 domains (effectiveness, ease of use, burden of asthma medication, side effects and worries). Higher scores indicates satisfaction with inhaled asthma medication.	
End point type	Secondary
End point timeframe:	
26 weeks	

End point values	Symbicort SMART	Conventional Best Practice (CBP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	421	421		
Units: mean score				
arithmetic mean (full range (min-max))	4.81 (3.1 to 6.3)	4.82 (3.4 to 6.6)		

Statistical analyses

Statistical analysis title	Change in SATQ score
Comparison groups	Symbicort SMART v Conventional Best Practice (CBP)
Number of subjects included in analysis	842
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5039
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.04

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Only information regarding SAEs, and discontinuations due to AE was collected, from the run-in period until visit 5 (26 weeks after randomisation).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	7.0

Reporting groups

Reporting group title	Conventional Best Practice (CBP)

Reporting group description:

Conventional Best Practice

Reporting group title	Symbicort SMART

Reporting group description:

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

Serious adverse events	Conventional Best Practice (CBP)	Symbicort SMART	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 460 (2.61%)	10 / 452 (2.21%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast Cancer			
subjects affected / exposed	1 / 460 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic Syndrome			
subjects affected / exposed	0 / 460 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine Leiomyoma			
subjects affected / exposed	1 / 460 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Transient Ischaemic Attack			

subjects affected / exposed	1 / 460 (0.22%)	0 / 452 (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			
Completed suicide			
subjects affected / exposed	0 / 460 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Asthma			
subjects affected / exposed	1 / 460 (0.22%)	2 / 452 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Salpingitis			
subjects affected / exposed	1 / 460 (0.22%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign Prostatic Hyperplasia			
subjects affected / exposed	1 / 460 (0.22%)	0 / 452 (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			
Tonsillitis			
subjects affected / exposed	0 / 460 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial Infarction			
subjects affected / exposed	1 / 460 (0.22%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			

Cerebrovascular Accident			
subjects affected / exposed	1 / 460 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial Palsy			
subjects affected / exposed	0 / 460 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Labyrinthine Fistula			
subjects affected / exposed	1 / 460 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastric Ulcer			
subjects affected / exposed	0 / 460 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	2 / 460 (0.43%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urethral Meatus Stenosis			
subjects affected / exposed	1 / 460 (0.22%)	0 / 452 (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			
Intervertebral Disc Protusion			
subjects affected / exposed	0 / 460 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			

subjects affected / exposed	0 / 460 (0.00%)	1 / 452 (0.22%)	
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: 0 %

Non-serious adverse events	Conventional Best Practice (CBP)	Symbicort SMART	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 460 (0.22%)	1 / 452 (0.22%)	
Cardiac disorders			
Dyspnoea			
subjects affected / exposed	0 / 460 (0.00%)	1 / 452 (0.22%)	
occurrences (all)	0	1	
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	0 / 460 (0.00%)	1 / 452 (0.22%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Pharyngolaryngeal Pain			
subjects affected / exposed	1 / 460 (0.22%)	0 / 452 (0.00%)	
occurrences (all)	1	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