Clinical trial results:
A randomized, double blind, parallel-group study with use of budesonide/formoterol “as needed”, or terbutaline “as needed” or regular use of budesonide + terbutaline “as needed”, in patients mild intermittent asthma and exercise induced bronchoconstriction.

Summary

EudraCT number	2009-012805-20
Trial protocol	SE
Global end of trial date	03 May 2011

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	D5890L00032

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, S-221 87 Lund, Sweden,
Public contact	Lars - Göran Carlsson, MD, AstraZeneca, ClinicalTrialTransparency@astrazeneca.com
Scientific contact	Lars - Göran Carlsson, 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	03 May 2011
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 May 2011
Global end of trial reached?	Yes
Global end of trial date	03 May 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the protective effect of the combination of budesonide and formoterol on an as needed basis compared to as needed use of terbutaline on EIB in adults and adolescents with mild intermittent asthma. This was evaluated by measuring maximum post-exercise fall in FEV1 before and after 6 weeks of treatment.

Protection of trial subjects:

The final Study Protocol, including the final version of the Master Informed Consent Form, was approved or given a favourable opinion in writing by an Independent Ethics Committee (IEC). The participating physicians were to submit written approval to AstraZeneca before they enrolled any patient into the Study, as local regulations require.

The participating physician at each centre ensured that the patient and, if applicable, parent/legal guardian was given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the Patient Follow-up Programme. They were notified that it was possible to discontinue from the programme at any time and were given the opportunity to ask questions and allowed time to consider the information provided.

The participating physician obtained and documented the patient's or the legal guardians signed and dated informed consent before conducting any procedure specifically for the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 September 2009
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	Norway: 7
Country: Number of subjects enrolled	Sweden: 59
Worldwide total number of subjects	66
EEA total number of subjects	66

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)	13
Adults (18-64 years)	51
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

On Visit 1, a total of 189 patients, aged 12-67, were enrolled at 10 study sites in 2 countries: Sweden and Norway. Of 189 enrolled patients, 66 patients were randomized and allocated to study treatment on Visit 3 (7 patients in Norway and 59 patients in Sweden).

Pre-assignment

Screening details:

A standardized exercise test (ECT) with duration of 6 minutes, at approximately 90% of maximal aerobic capacity (as defined on Visit 1) was performed on a treadmill while breathing dry air on Visit 2. Patients with exercised induced bronchoconstriction (defined as fall in FEV1 ≥ 10%) could be randomized on Visit 3.

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, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Budesonide/terbutaline

Arm description:

Budesonide once daily and terbutaline before exercise and as needed

Arm type	Experimental
Investigational medicinal product name	Budesonide 400 + terbutaline 0.4 mg as needed
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Budesonide 400 + terbutaline 0.4 mg as needed

Arm title	Terbutaline

Arm description:

Placebo budesonide once daily and terbutaline before exercise and as needed

Arm type	Active comparator
Investigational medicinal product name	Terbutaline 0.4 mg as needed
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Terbutaline 0.4 mg as needed

Arm title	Budesonide/formoterol

Arm description:

Placebo budesonide once daily and budesonide/formoterol before exercise and as needed

Arm type	Experimental

Investigational medicinal product name	Budesonide/formoterol 160/4.5 ug mg as needed
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Budesonide/formoterol 160/4.5 ug mg as needed

Number of subjects in period 1	Budesonide/terbutaline	Terbutaline	Budesonide/formoterol
Started	21	22	23
Completed	19	19	21
Not completed	2	3	2
Consent withdrawn by subject	-	-	1
Incorrectly randomized	1	-	-
Lost to follow-up	-	1	-
Protocol deviation	1	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Budesonide/terbutaline
Reporting group description:	
Budesonide once daily and terbutaline before exercise and as needed	
Reporting group title	Terbutaline
Reporting group description:	
Placebo budesonide once daily and terbutaline before exercise and as needed	
Reporting group title	Budesonide/formoterol
Reporting group description:	
Placebo budesonide once daily and budesonide/formoterol before exercise and as needed	

Reporting group values	Budesonide/terbutaline	Terbutaline	Budesonide/formoterol
Number of subjects	21	22	23
Age Categorical Units: Participants			
<=18 years	6	4	3
Between 18 and 65 years	15	17	19
>=65 years	0	1	1
Age continuous Units: years			
arithmetic mean	25.9	28	30.8
full range (min-max)	12.3 to 47.1	15.7 to 66.6	13.4 to 67.5
Gender, Male/Female Units: Participants			
Female	11	16	9
Male	10	6	14

Reporting group values	Total		
Number of subjects	66		
Age Categorical Units: Participants			
<=18 years	13		
Between 18 and 65 years	51		
>=65 years	2		
Age continuous Units: years			
arithmetic mean			
full range (min-max)	-		
Gender, Male/Female Units: Participants			
Female	36		
Male	30		

End points

End points reporting groups

Reporting group title	Budesonide/terbutaline
Reporting group description: Budesonide once daily and terbutaline before exercise and as needed	
Reporting group title	Terbutaline
Reporting group description: Placebo budesonide once daily and terbutaline before exercise and as needed	
Reporting group title	Budesonide/formoterol
Reporting group description: Placebo budesonide once daily and budesonide/formoterol before exercise and as needed	

Primary: Percent change in maximum post-exercise forced expiratory volume in one second (FEV1) fall after 6 weeks

End point title	Percent change in maximum post-exercise forced expiratory volume in one second (FEV1) fall after 6 weeks
End point description: FEV1	
End point type	Primary
End point timeframe: Baseline and Visit 6	

End point values	Budesonide/terbutaline	Terbutaline	Budesonide/formoterol	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	21	21	
Units: Percent change				
arithmetic mean (standard deviation)	-5.85 (± 6.5)	0.61 (± 10.92)	-5.24 (± 9.64)	

Statistical analyses

Statistical analysis title	Change in FEV1
Comparison groups	Budesonide/terbutaline v Budesonide/formoterol
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Method	ANCOVA
Parameter estimate	LSMean Difference
Point estimate	-1.24

Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	-5.95

Notes:

[1] - The pre-defined non-inferiority limit was specified to be 7.28%

Statistical analysis title	Change in FEV1
Comparison groups	Terbutaline v Budesonide/formoterol
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.017
Method	ANCOVA
Parameter estimate	LSMean difference
Point estimate	6.9278
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.31
upper limit	12.55

Statistical analysis title	Change in FEV1
Comparison groups	Budesonide/terbutaline v Terbutaline
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0026
Method	ANCOVA
Parameter estimate	LSMean difference
Point estimate	8.0994
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.953
upper limit	13.25

Secondary: Percent change in maximum post-exercise FEV1 fall after 3 weeks	
End point title	Percent change in maximum post-exercise FEV1 fall after 3 weeks
End point description: FEV1	
End point type	Secondary
End point timeframe: Baseline and 3 weeks	

End point values	Budesonide/terbutaline	Terbutaline	Budesonide/formoterol	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	21	21	
Units: Percent change				
arithmetic mean (standard deviation)	-4.07 (± 5.56)	-1.19 (± 8.03)	-3.81 (± 8.68)	

Statistical analyses

Statistical analysis title	Percent change in max post-exercise FEV1
Comparison groups	Terbutaline v Budesonide/formoterol
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1131
Method	ANCOVA
Parameter estimate	LSMean Difference
Point estimate	3.5528
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.88
upper limit	7.986

Statistical analysis title	Percent change in max post-exercise FEV1
Comparison groups	Budesonide/terbutaline v Terbutaline
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0509
Method	ANCOVA
Parameter estimate	LSMean Difference
Point estimate	4.0277
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	8.433

Secondary: Bronchial responsiveness to mannitol

End point title	Bronchial responsiveness to mannitol

End point description:

Change in cumulative Mannitol dose in mg in patients with a positive mannitol provocation test at baseline (PD15)

End point type	Secondary

End point timeframe:

Baseline and 6 weeks

End point values	Budesonide/terbutaline	Terbutaline	Budesonide/formoterol	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	6	5	
Units: mg				
arithmetic mean (standard deviation)	67.26 (± 141.98)	-6.15 (± 95.1)	151.87 (± 141.09)	

Statistical analyses

No statistical analyses for this end point

Secondary: Concentration of exhaled nitric oxide

End point title	Concentration of exhaled nitric oxide

End point description:

Fraction of exhaled nitric oxide at 6 weeks. 3 attempts are made by the patient and the mean of these values is recorded.

End point type	Secondary

End point timeframe:

6 weeks

End point values	Budesonide/terbutaline	Terbutaline	Budesonide/formoterol	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	19	18	21	
Units: ppb				
arithmetic mean (standard deviation)	25.9 (± 20.1)	35.5 (± 36.6)	24.4 (± 22.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Use of as-needed medication before exercise and as-needed

End point title	Use of as-needed medication before exercise and as-needed

End point description:	
Mean number of as needed inhalations taken before exercise and as needed.	
End point type	Secondary
End point timeframe:	
6 weeks	

End point values	Budesonide/terbutaline	Terbutaline	Budesonide/formoterol	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	20	21	
Units: number of inhalations per day				
arithmetic mean (standard deviation)	0.8 (± 0.7)	0.9 (± 0.5)	0.8 (± 0.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Asthma control measured by a 5-item asthma control questionnaire (ACQ5)

End point title	Asthma control measured by a 5-item asthma control questionnaire (ACQ5)
End point description:	
Change in overall ACQ5. ACQ5 measures asthma control and a lower values shows a better asthma control, a higher value is worse. A decrease in the ACQ5 shows an improvement during the treatment period. Range of ACQ5 is 0-5, with 0 as the best value and 5 as the worst value. Further information at www.qoltech.co.uk.	
End point type	Secondary
End point timeframe:	
Baseline and 6 weeks	

End point values	Budesonide/terbutaline	Terbutaline	Budesonide/formoterol	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	21	22	
Units: units on a scale				
arithmetic mean (standard deviation)	-0.3 (± 0.7)	-0.2 (± 0.8)	-0.4 (± 0.7)	

Statistical analyses

Statistical analysis title	Change in ACQ5
Comparison groups	Terbutaline v Budesonide/formoterol

Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3724
Method	ANCOVA
Parameter estimate	LSMean differnce
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.55

Statistical analysis title	change in ACQ5
Comparison groups	Budesonide/terbutaline v Terbutaline
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3623
Method	ANCOVA
Parameter estimate	LSMean difference
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.56

Secondary: Diary recording of asthma symptoms	
End point title	Diary recording of asthma symptoms
End point description:	
Asthma symptoms during days with exercise	
End point type	Secondary
End point timeframe:	
6 weeks	

End point values	Budesonide/terbutaline	Terbutaline	Budesonide/formoterol	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	20	21	
Units: Percent of exercise days				
arithmetic mean (standard deviation)	51.1 (± 30.5)	50.9 (± 36.6)	49.8 (± 26.1)	

Statistical analyses

Statistical analysis title	Diary recording of asthma symptoms
Statistical analysis description: Asthma symptoms during days with exercise	
Comparison groups	Terbutaline v Budesonide/formoterol
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9078
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	1.112
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18
upper limit	20.3

Statistical analysis title	Diary recordings of asthma symptoms
Statistical analysis description: Asthma symptoms during days with exercise	
Comparison groups	Budesonide/terbutaline v Terbutaline
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9844
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	-0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20
upper limit	19.2

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from the enrolment visit (visit 1) until visit 6 (42 days after randomisation). Only AEs occuring on or after first dose of study medication are inluded in the summaries below.

Adverse event reporting additional description:

A total of 27 patients reported non-serious adverse events; 8 on Budesonide/terbutaline, 9 on Terbutaline, 10 on Budesonide/formoterol. 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	13.1

Reporting groups

Reporting group title	Budesonide/terbutaline
Reporting group description:	
Budesonide once daily and terbutaline before exercise and as needed	
Reporting group title	Terbutaline
Reporting group description:	
Placebo budesonide once daily and terbutaline before exercise and as needed	
Reporting group title	Budesonide/formoterol
Reporting group description:	
Placebo budesonide once daily and budesonide/formoterol before exercise and as needed	

Serious adverse events	Budesonide/terbutaline	Terbutaline	Budesonide/formoterol
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Budesonide/terbutaline	Terbutaline	Budesonide/formoterol
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 21 (28.57%)	10 / 22 (45.45%)	10 / 23 (43.48%)
Injury, poisoning and procedural complications			

Fall			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	2
General disorders and administration site conditions			
Headache			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	1 / 21 (4.76%)	2 / 22 (9.09%)	0 / 23 (0.00%)
occurrences (all)	1	2	0
Slight Fever			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 21 (0.00%)	1 / 22 (4.55%)	0 / 23 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal disorders			
Gastroenteritis			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	1 / 21 (4.76%)	0 / 22 (0.00%)	2 / 23 (8.70%)
occurrences (all)	1	0	3
Respiratory, thoracic and mediastinal disorders			
Cough			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 21 (0.00%)	3 / 22 (13.64%)	1 / 23 (4.35%)
occurrences (all)	0	3	1
Sore throat			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	4 / 23 (17.39%)
occurrences (all)	0	0	4
Infections and infestations			
Common cold			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	5 / 21 (23.81%)	7 / 22 (31.82%)	4 / 23 (17.39%)
occurrences (all)	5	7	5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 July 2009	Further explanations/ changes regarding the Maximal exercise test, ECT and Mannitol challenge. The leaning would not be more then up to 10% during the aximal exercise test. The standardized exercise test would be at 90% of maximal aerobic capacity instead of 80%, since this were active patients and well trained. The measurement of FEV1 at baseline (pre test) would always be 3, but during a test this was too much for the patient, and therefore we made these changes. ATS had new guidelines regarding FENO - measurement. It was enough with 2 measurements instead of 3. Clarification regarding leukotriene antagonists taken before randomisation was needed
11 December 2009	Clarification regarding coffee and other drinks with caffeine before visits. A clarification regarding which reference value should be used for children since European Community for Steel and Coal is limited to adults. A reversibility test will be allowed at visit 1 for those patients with FEV1 ≥75.0% but <80.0% of predicted normal value. Since most of the sites are using NIOX MINO, the text regarding the service is not applicable.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported