Clinical trial results:
A 52-week, double-blind, randomised, multi-centre, phase III, parallel-group study in patients 12 years and older with asthma, evaluating the efficacy and safety of Symbicort (budesonide/formoterol) Turbuhaler 160/4.5 g ‘as needed’ compared with Pulmicort (budesonide) Turbuhaler 200 g twice daily plus terbutaline Turbuhaler 0.4 mg ‘as needed’

Summary

EudraCT number	2013-004473-28
Trial protocol	SE DE HU CZ SK BG ES PL
Global end of trial date	16 August 2017

Results information

Result version number	v2 (current)
This version publication date	20 May 2018
First version publication date	28 February 2018
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	D589SC00003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1157-4476

Notes:

Sponsors

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	Prepparedsleden 1, Molndal, Sweden,
Public contact	AstraZeneca, Information Center, information.center@astrazeneca.com
Scientific contact	Millie Wang (Senior Medical Lead), AstraZeneca, information.center@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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 August 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 August 2017
Global end of trial reached?	Yes
Global end of trial date	16 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that Symbicort Turbuhaler 160/4.5 µg 'as needed' is non-inferior to Pulmicort Turbuhaler 200 µg twice daily plus terbutaline Turbuhaler 0.4 mg 'as needed'

Protection of trial subjects:

The final protocol, informed consent form (ICF) and other written materials provided to patients were submitted to and approved by an Independent Ethics Committee (IEC). The investigator at each study centre ensured that patients were given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Patients were told they were free to discontinue the study at any time. Each patient was given the chance to ask questions and allowed time to consider the information. The PI ensured that each patient provided a signed ICF before any study procedures and ensured that any incentives or provisions for patients harmed as a result of study participation were described in the ICF.
Patients with a history of life-threatening asthma, including intubation and intensive care unit admission, or other significant disease or disorder were ineligible for the study. Patients attended clinic visits at 17, 34 and 52 wks of treatment and phone calls were made by site staff at wks 8, 25 and 42. Study specific treatment discontinuation criteria were applied for patients in case of severe asthma exacerbation with length greater than 3 wks or 3 severe exacerbations within 6 mths. Patients were instructed to contact their investigator for reassessment if they needed to take more than 12 inhalations of as needed study medication and any time they needed medical assistance.
An Adjudication Committee (AC) provided an independent, external and unbiased assessment of fatal events reported during the study in order to determine whether any death might be asthma-related. The AC was blinded to patients' allocation to randomised study treatment. Unblinding of the asthma-related events could be triggered and a data safety monitoring board set up if there was a total of ≥3 deaths adjudicated to be asthma related across the SYGMA 1 and SYGMA 2 trials. The number of deaths adjudicated to be asthma related was not high enough to trigger unblinding.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 November 2014
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: 378
Country: Number of subjects enrolled	Bulgaria: 274
Country: Number of subjects enrolled	Hungary: 265
Country: Number of subjects enrolled	Germany: 201
Country: Number of subjects enrolled	Romania: 174
Country: Number of subjects enrolled	Slovakia: 135
Country: Number of subjects enrolled	Czech Republic: 88

Country: Number of subjects enrolled	Spain: 30
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	Russian Federation: 579
Country: Number of subjects enrolled	Ukraine: 370
Country: Number of subjects enrolled	South Africa: 160
Country: Number of subjects enrolled	New Zealand: 91
Country: Number of subjects enrolled	Saudi Arabia: 48
Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	Vietnam: 288
Country: Number of subjects enrolled	Philippines: 172
Country: Number of subjects enrolled	Thailand: 139
Country: Number of subjects enrolled	Korea, Republic of: 133
Country: Number of subjects enrolled	Peru: 213
Country: Number of subjects enrolled	Mexico: 187
Country: Number of subjects enrolled	Brazil: 107
Country: Number of subjects enrolled	Chile: 97
Country: Number of subjects enrolled	Colombia: 29
Worldwide total number of subjects	4176
EEA total number of subjects	1556

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)	411
Adults (18-64 years)	3396
From 65 to 84 years	369
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

6634 patients enrolled; 5740 entered run-in period. Of these, 4215 were randomised,1525 not randomised due to the following reasons: 1407 did not meet inclusion/exclusion criteria, 21 adverse events, 3 severe non-compliance to protocol, 68 subject decision, 14 subject lost to follow-up, 12 other.

Pre-assignment

Screening details:

Eligibility was assessed at Visits 1, 2 and 3. IC was obtained at V1. At V2, patients stopped pre-study asthma medications and entered a 2 to 4 week run-in period on SABA as needed only (Bricanyl Turbuhaler 0.5 mg). Lung function was assessed by spirometry to confirm eligibility. Eligible patients were randomised at V3.

Period 1

Period 1 title	Overall Trial (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	Placebo bid + Symbicort 'as needed'

Arm description:

Placebo for budesonide (Placebo Turbuhaler) + Symbicort Turbuhaler (budesonide/formoterol 160/4.5 µg)

Arm type	Experimental
Investigational medicinal product name	Placebo for budesonide (Placebo Turbuhaler)+Symbicort Turbuhaler 160/4.5 µg (Budesonide / formoterol fumarate dihydrate 160/4.5 µg)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Placebo powder for inhalation, 200 doses + Budesonide / formoterol fumarate dehydrate powder for inhalation, 160 µg budesonide and 4.5 µg formoterol per inhalation, 120 doses

Arm title	Pulmicort bid + terbutaline 'as needed'

Arm description:

Pulmicort Turbuhaler (budesonide 200 µg) + Terbutaline Turbuhaler 0.4mg 'as needed'

Arm type	Active comparator
Investigational medicinal product name	Pulmicort Turbuhaler 200 µg (budesonide 200 µg) + Terbutaline Turbuhaler 0.4 mg/dose
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Budesonide powder for inhalation, 200 µg per inhalation, 200 doses + Terbutaline sulphate powder for inhalation, 0.4 mg terbutaline per inhalation, 120 doses

Number of subjects in period 1	Placebo bid + Symbicort 'as needed'	Pulmicort bid + terbutaline 'as needed'
Started	2089	2087
Completed	1983	1979
Not completed	106	108
Severe non-compliance to protocol	2	2
Adverse event, serious fatal	1	1
Eligibility criteria not fulfilled	4	7
Subject decision	58	50
Adverse event, non-fatal	1	3
Investigator decision	4	3
Subject moved	-	1
Sponsor decision (prematurely closed site)	7	6
Lost to follow-up	27	35
Pregnancy	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo bid + Symbicort 'as needed'
Reporting group description:	
Placebo for budesonide (Placebo Turbuhaler) + Symbicort Turbuhaler (budesonide/formoterol 160/4.5 µg)	
Reporting group title	Pulmicort bid + terbutaline 'as needed'
Reporting group description:	
Pulmicort Turbuhaler (budesonide 200 µg) + Terbutaline Turbuhaler 0.4mg 'as needed'	

Reporting group values	Placebo bid + Symbicort 'as needed'	Pulmicort bid + terbutaline 'as needed'	Total
Number of subjects	2089	2087	4176
Age categorical Units: Subjects			
Adolescents (12-17 years)	205	206	411
Adults (18-64 years)	1705	1691	3396
From 65-84 years	179	190	369
Age Continuous Units: years			
arithmetic mean	41.3	40.7	
standard deviation	± 16.8	± 17.1	-
Sex/Gender, Customized Units: Subjects			
Female	1308	1289	2597
Male	781	798	1579

End points

End points reporting groups

Reporting group title	Placebo bid + Symbicort 'as needed'
Reporting group description:	
Placebo for budesonide (Placebo Turbuhaler) + Symbicort Turbuhaler (budesonide/formoterol 160/4.5 µg)	
Reporting group title	Pulmicort bid + terbutaline 'as needed'
Reporting group description:	
Pulmicort Turbuhaler (budesonide 200 µg) + Terbutaline Turbuhaler 0.4mg 'as needed'	

Primary: Annual severe asthma exacerbation rate - Non-inferiority analysis

End point title	Annual severe asthma exacerbation rate - Non-inferiority analysis[1]
End point description:	
End point type	Primary
End point timeframe:	
up to 52 weeks	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Manuscript in press

End point values	Placebo bid + Symbicort 'as needed'	Pulmicort bid + terbutaline 'as needed'		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2084	2083		
Units: Annual rate of exacerbations				
least squares mean (confidence interval 95%)	0.11 (0.10 to 0.13)	0.12 (0.10 to 0.14)		

Statistical analyses

No statistical analyses for this end point

Primary: Annual severe asthma exacerbation rate - Superiority analysis

End point title	Annual severe asthma exacerbation rate - Superiority
End point description:	
End point type	Primary
End point timeframe:	
up to 52 weeks	

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Manuscript in press

End point values	Placebo bid + Symbicort 'as needed'	Pulmicort bid + terbutaline 'as needed'		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2089	2087		
Units: Annual rate of exacerbations				
least squares mean (confidence interval 95%)	0.11 (0.10 to 0.13)	0.12 (0.10 to 0.14)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first severe asthma exacerbation

End point title	Time to first severe asthma exacerbation

End point description:

End point type	Secondary

End point timeframe:

up to 52 weeks

End point values	Placebo bid + Symbicort 'as needed'	Pulmicort bid + terbutaline 'as needed'		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2089	2087		
Units: N patients with sev. asthma exacerbation	177	184		

Statistical analyses

No statistical analyses for this end point

Secondary: Average change from baseline in pre-dose FEV1

End point title	Average change from baseline in pre-dose FEV1

End point description:

End point type	Secondary

End point timeframe:

Study weeks 0,17, 34, 52

End point values	Placebo bid + Symbicort 'as needed'	Pulmicort bid + terbutaline 'as needed'		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1996	1981		
Units: mL				
least squares mean (confidence interval 95%)	104.0 (88.5 to 119.6)	136.6 (121.1 to 152.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to study specific asthma related discontinuation

End point title	Time to study specific asthma related discontinuation

End point description:

Study specific discontinuation of IP criteria: - A severe asthma exacerbation with a duration for more than 3 weeks - Three severe asthma exacerbations during 6 months

End point type	Secondary

End point timeframe:

up to 52 weeks

End point values	Placebo bid + Symbicort 'as needed'	Pulmicort bid + terbutaline 'as needed'		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2089	2087		
Units: Participants	0	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Average change from baseline in ‘as needed’ use

End point title	Average change from baseline in ‘as needed’ use

End point description:

End point type	Secondary

End point timeframe:

Week 0 up to 52 weeks

End point values	Placebo bid + Symbicort 'as needed'	Pulmicort bid + terbutaline 'as needed'		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2089	2084		
Units: Number of inhalations per day				
least squares mean (confidence interval 95%)	-0.84 (-0.86 to -0.81)	-0.87 (-0.89 to -0.84)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in percent of 'as needed' free days

End point title	Change from baseline in percent of 'as needed' free days

End point description:

End point type	Secondary

End point timeframe:

Week 0 up to 52 weeks

End point values	Placebo bid + Symbicort 'as needed'	Pulmicort bid + terbutaline 'as needed'		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2089	2084		
Units: Percentage of 'as needed' free days				
arithmetic mean (standard deviation)	41.4 (± 29.6)	48.3 (± 29.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of controller use days

End point title	Percentage of controller use days

End point description:

End point type	Secondary

End point timeframe:

Week 0 up to 52 weeks

End point values	Placebo bid + Symbicort 'as needed'	Pulmicort bid + terbutaline 'as needed'		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2089	2084		
Units: Percentage of controller use days				
arithmetic mean (standard deviation)	30.8 (± 28.2)	68.3 (± 28.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Average change from baseline in Asthma Control Questionnaire (5-item version) - ACQ-5 score

End point title	Average change from baseline in Asthma Control Questionnaire (5-item version) - ACQ-5 score

End point description:

ACQ questionnaire contains five questions on patients' symptoms, which are assessed on a 7-point scale from 0 (representing good control) to 6 (representing poor control). The score is the mean score of all questions for which responses are provided.

End point type	Secondary

End point timeframe:

Study weeks 0, 17, 34, 52

End point values	Placebo bid + Symbicort 'as needed'	Pulmicort bid + terbutaline 'as needed'		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1963	1947		
Units: ACQ-5 Score				
least squares mean (confidence interval 95%)	-0.35 (-0.38 to -0.32)	-0.46 (-0.49 to -0.43)		

Statistical analyses

No statistical analyses for this end point

Secondary: Average change from baseline in Asthma Quality of Life Questionnaire Standardised Version - AQLQ(S) score

End point title	Average change from baseline in Asthma Quality of Life Questionnaire Standardised Version - AQLQ(S) score

End point description:

AQLQ(S) consists of 32 questions in 4 domains. Each question is assessed on a 7-point scale from 1 to

7, with higher values indicating better health-related quality of life. The overall score is calculated as the mean score of all 32 items.

End point type	Secondary

End point timeframe:

Study weeks 0,17, 34, 52

End point values	Placebo bid + Symbicort 'as needed'	Pulmicort bid + terbutaline 'as needed'		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1907	1897		
Units: AQLQ(S) overall score				
least squares mean (confidence interval 95%)	0.335 (0.305 to 0.366)	0.431 (0.400 to 0.461)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from Visit 2 throughout the entire treatment period and during the follow-up period until the last telephone follow-up, or the last contact. SAEs were recorded from the time of informed consent.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Pulmicort bid + terbutaline 'as needed'

Reporting group description:

Pulmicort Turbuhaler (budesonide 200ug) + Terbutaline Turbuhaler 0.4 mg 'as needed'

Reporting group title	Placebo bid + Symbicort 'as needed'

Reporting group description:

Placebo for budesonide (Placebo Turbuhaler) + Symbicort Turbuhaler (budesonide/formoterol 160/4.5 ug)

Serious adverse events	Pulmicort bid + terbutaline 'as needed'	Placebo bid + Symbicort 'as needed'	
Total subjects affected by serious adverse events			
subjects affected / exposed	73 / 2087 (3.50%)	66 / 2089 (3.16%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign neoplasm of skin			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer female			
subjects affected / exposed	0 / 2087 (0.00%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervix carcinoma			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibroadenoma of breast			

subjects affected / exposed	0 / 2087 (0.00%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sebaceous adenoma			
subjects affected / exposed	0 / 2087 (0.00%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seborrhoeic keratosis			
subjects affected / exposed	0 / 2087 (0.00%)	1 / 2089 (0.05%)	
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	2 / 2087 (0.10%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 2087 (0.00%)	2 / 2089 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 2087 (0.05%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 2087 (0.00%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			

Anaphylactic reaction			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Adenomyosis			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast mass			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial hyperplasia			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometriosis			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Menorrhagia			
subjects affected / exposed	0 / 2087 (0.00%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Rectocele			
subjects affected / exposed	0 / 2087 (0.00%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine polyp			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (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			
Asthma			
subjects affected / exposed	17 / 2087 (0.81%)	17 / 2089 (0.81%)	
occurrences causally related to treatment / all	0 / 17	0 / 20	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nasal polyps			
subjects affected / exposed	1 / 2087 (0.05%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal turbinate hypertrophy			
subjects affected / exposed	0 / 2087 (0.00%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 2087 (0.00%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord polyp			
subjects affected / exposed	0 / 2087 (0.00%)	1 / 2089 (0.05%)	
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 / 2087 (0.00%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Abdominal injury			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	1 / 2087 (0.05%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthropod bite			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 2087 (0.00%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 2087 (0.00%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	2 / 2087 (0.10%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 2087 (0.05%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Humerus fracture			
subjects affected / exposed	0 / 2087 (0.00%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament injury			
subjects affected / exposed	0 / 2087 (0.00%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	0 / 2087 (0.00%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbosacral plexus injury			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural complication			
subjects affected / exposed	0 / 2087 (0.00%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural swelling			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	1 / 2087 (0.05%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			

subjects affected / exposed	0 / 2087 (0.00%)	1 / 2089 (0.05%)	
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	1 / 2087 (0.05%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 2087 (0.00%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	0 / 2087 (0.00%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	0 / 2087 (0.00%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Adams-Stokes syndrome			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			

subjects affected / exposed	1 / 2087 (0.05%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrilation			
subjects affected / exposed	2 / 2087 (0.10%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 2087 (0.00%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiomyopathy			
subjects affected / exposed	0 / 2087 (0.00%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Degenerative aortic valve disease			
subjects affected / exposed	0 / 2087 (0.00%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			

subjects affected / exposed	1 / 2087 (0.05%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar radiculopathy			
subjects affected / exposed	0 / 2087 (0.00%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculopathy			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness neurosensory			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 2087 (0.00%)	2 / 2089 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual impairment			
subjects affected / exposed	1 / 2087 (0.05%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 2087 (0.00%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated umbilical hernia			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 2087 (0.00%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocholecystitis			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sphincter of Oddi dysfunction			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			

subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 2087 (0.00%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hirsutism			
subjects affected / exposed	0 / 2087 (0.00%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Cystistis interstitial			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric stenosis			
subjects affected / exposed	0 / 2087 (0.00%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 2087 (0.00%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protusion			
subjects affected / exposed	2 / 2087 (0.10%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	2 / 2087 (0.10%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Rotator cuff syndrome			
subjects affected / exposed	0 / 2087 (0.00%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	0 / 2087 (0.00%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 2087 (0.00%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 2087 (0.05%)	2 / 2089 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic sinusitis			
subjects affected / exposed	0 / 2087 (0.00%)	2 / 2089 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 2087 (0.00%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (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 / 2087 (0.05%)	2 / 2089 (0.10%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	2 / 2087 (0.10%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 2087 (0.00%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			

subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (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 / 2087 (0.05%)	0 / 2089 (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 bacterial			
subjects affected / exposed	0 / 2087 (0.00%)	1 / 2089 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular neuronitis			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 2087 (0.05%)	0 / 2089 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Pulmicort bid + terbutaline 'as needed'	Placebo bid + Symbicort 'as needed'	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	883 / 2087 (42.31%)	863 / 2089 (41.31%)	
Nervous system disorders			
Headache			
subjects affected / exposed	50 / 2087 (2.40%)	51 / 2089 (2.44%)	
occurrences (all)	68	69	
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	84 / 2087 (4.02%)	81 / 2089 (3.88%)	
occurrences (all)	96	95	
Rhinitis allergic			
subjects affected / exposed	44 / 2087 (2.11%)	51 / 2089 (2.44%)	
occurrences (all)	46	56	
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	168 / 2087 (8.05%)	155 / 2089 (7.42%)	
occurrences (all)	206	188	
Bronchitis			
subjects affected / exposed	78 / 2087 (3.74%)	64 / 2089 (3.06%)	
occurrences (all)	83	70	
Upper respiratory tract infection			
subjects affected / exposed	89 / 2087 (4.26%)	81 / 2089 (3.88%)	
occurrences (all)	112	90	
Pharyngitis			
subjects affected / exposed	62 / 2087 (2.97%)	51 / 2089 (2.44%)	
occurrences (all)	74	55	
Influenza			
subjects affected / exposed	42 / 2087 (2.01%)	33 / 2089 (1.58%)	
occurrences (all)	46	34	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 October 2014	Rationale for study design, doses and control groups amended:To clarify pre-study treatment according to GINA step 2 (GINA 2012). Inclusion criterion 4, 5 and Exclusion criterion 5 and 17 amended:To clarify pre-study treatment according to GINA step 2 (GINA 2012). Discontinuation of IP amended:To clarify that asthma deterioration event fulfilling study specific discontinuation criteria will meet AE criteria in all cases. Details related to enrolment failures amended:Wording added to clarify that re-enrolment of patients who were reported as enrolment failures due to technical reasons is allowed. Run-in procedures at Visit 2 amended: 1) To clarify the importance that concomitant medication may have effect on lung function measurements. 2) To clarify that all asthma-related treatments (including maintenance treatment with ICS or LTRA) will be stopped at Visit 2 Definition of severe asthma exacerbations amended: To provide clarification on depot steroid injection use, emergency room visit and steroid use end date. Details related to maternal exposure amended:To clarify that if a patient becomes pregnant during the course of the study IP should be discontinued immediately, but the patient will remain in the study and will be followed up for severe asthma exacerbation, AEs and concomitant medications.
17 August 2015	Study period amended: Date of last visit was postponed. Inclusion Criterion 6 amended: Allowing use of documented historical reversibility within 12 months for all patients who failed reversibility test at Visit 2 and Visit 3. Discontinuation of IP amended: To clarify that discontinuation of IP is obligatory in cases of pregnancy or study specific discontinuation criteria met. Details related to enrolment failures amended: Allowing 2 opportunities for patients to demonstrate a pre- and post-bronchodilator morning clinic FEV1 within the specified range as well as allowing re-enrolment of patients on short-acting bronchodilators as-needed who have been screen-failed prior to the current amendment but who have documented historical reversibility. Recording of asthma history amended: To clarify that only severe asthma exacerbations (and not mild/moderate asthma exacerbations) have to be reported as part of asthma history in the medical records and the eCRF. Timing of visits in relation to Patient training in how to use Turbuhaler and TUM amended and checking inhalation technique and re-training if needed added: Run-in procedures at Visit 2 amended: To give flexibility around timing of visit and spirometry at Visit 2. Treatment period amended: To clarify that assessment of inclusion criterion 7 (Bricanyl as-needed use) can be done more than once during the run-in period within the allowed visit windows. Timing of visits in relation to spirometry assessments amended: To clarify that requirement of performing spirometry ±1 hour in relation to the time of spirometry at Visit 2 should be taken into account for timing of visits. Administration of patient reported outcome questionnaires amended: To clarify that at Visit 2 patient can complete questionnaires after it has been verified that patient is eligible to enter run-in period based on lung function criterion (inclusion criterion number 5).
15 February 2016	Exclusion Criterion 2 amended To exclude patients previously randomised in another study of the same clinical program.

12 October 2016	• Hypothesis testing for primary objective changed from a superiority to a non-inferiority hypothesis, while keeping the superiority as a secondary comparison. • Implementation of external, independent evaluation of all deaths. The Steering Committee recommended that independent review and adjudication of fatal events be introduced following the first death (triggered by asthma exacerbation), which occurred on 19 July 2016. The rationale for this decision is that asthma related deaths are rare events and a group of specialists acting independently of all individuals associated with the conduct of the study can facilitate the collection of appropriate data and perform unbiased evaluation of each case.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported