



Clinical trial results:

A 52-week, double-blind, randomised, multi-centre, parallel-group, Phase III 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 terbutaline Turbuhaler® 0.4 mg 'as needed' and with Pulmicort® (budesonide) Turbuhaler® 200 g twice daily plus terbutaline Turbuhaler® 0.4 mg 'as needed'

Summary

EudraCT number	2013-004474-96
Trial protocol	HU GB PL RO BG
Global end of trial date	20 July 2017

Results information

Result version number	v1 (current)
This version publication date	20 May 2018
First version publication date	20 May 2018

Trial information

Trial identification

Sponsor protocol code	D589SC00001
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1153-1803

Notes:

Sponsors

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	Prepparedsleden 1, Mölndal, Sweden,
Public contact	Information Center, AstraZeneca, 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	20 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 July 2017
Global end of trial reached?	Yes
Global end of trial date	20 July 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 superior to 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 4, 16, 28, 40 and 52 wks of treatment. Electronic diary alerted patients to signs that their asthma was worsening and prompted them to contact investigator for further assessment. Patients were instructed to contact their investigator if they needed to take more than 12 inhalations of as needed study medication/day and any time they needed medical assistance.

Investigators could prescribe additional glucocorticosteroid treatment to patients having asthma exacerbations or long-term poor asthma control. Study specific discontinuation criteria were applied for patients in case of severe asthma exacerbation with duration > 3 weeks or 2 severe asthma exacerbations within 3 mths or 3 severe exacerbations in total during the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 July 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: 490
Country: Number of subjects enrolled	Bulgaria: 337
Country: Number of subjects enrolled	Hungary: 223
Country: Number of subjects enrolled	Romania: 140
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	China: 334
Country: Number of subjects enrolled	Philippines: 257
Country: Number of subjects enrolled	Vietnam: 216
Country: Number of subjects enrolled	Korea, Republic of: 159

Country: Number of subjects enrolled	Russian Federation: 378
Country: Number of subjects enrolled	Ukraine: 283
Country: Number of subjects enrolled	Canada: 136
Country: Number of subjects enrolled	South Africa: 100
Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	Mexico: 279
Country: Number of subjects enrolled	Peru: 252
Country: Number of subjects enrolled	Chile: 139
Country: Number of subjects enrolled	Brazil: 103
Worldwide total number of subjects	3836
EEA total number of subjects	1193

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)	478
Adults (18-64 years)	3094
From 65 to 84 years	262
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

5721 patients enrolled; 5003 run-in, 718 not run-in; 3849 randomised, 1154 not randomised: 1022 did not meet incl/excl criteria, 4 adverse event, 5 severe non-compliance to protocol, 104 subject decision, 7 subject lost to follow-up, 12 other reason.

Pre-assignment

Screening details:

Eligibility was assessed at Visits 1, 2 and 3. IC was obtained at V1. At V2, eligible patients stopped prescribed asthma medication and entered a 2-4 week run-in period, treated only with SABA Bricanyl Turbuhaler 0.5 mg, 'as needed'. Lung function was performed by spirometry to confirm eligibility. Eligible patients were randomised at Visit 3.

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

Dosage and administration details:

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

Arm title	Placebo bid + terbutaline 'as needed'
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Arm description:

Placebo for budesonide (Placebo Turbuhaler) + Terbutaline Turbuhaler 0.4 mg 'as needed'

Arm type	Active comparator
Investigational medicinal product name	Terbutaline Turbuhaler 0.4 mg (terbutaline sulphate 0.4 mg) + Placebo for budesonide (Placebo Turbuhaler)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

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

Arm title	Pulmicort bid + terbutaline 'as needed'
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Arm description:

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

Arm type	Active comparator
Investigational medicinal product name	Pulmicort Turbuhaler 200 µg (budesonide 200 µg) + Terbutaline Turbuhaler 0.4 mg (terbutaline sulphate 0.4 mg)
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'	Placebo bid + terbutaline 'as needed'	Pulmicort bid + terbutaline 'as needed'
Started	1277	1277	1282
Patients who completed treatment	1144	1084	1135
Completed	1144	1084	1135
Not completed	133	193	147
Adverse event, serious fatal	-	-	1
Eligibility criteria not fulfilled	9	14	8
Consent withdrawn by subject	75	93	77
Adverse event, non-fatal	6	15	9
NotSpecified	20	25	20
Study specific withdrawal criteria	4	21	6
Lost to follow-up	3	12	11
Protocol deviation	16	13	15

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

Reporting group values	Placebo bid + Symbicort 'as needed'	Placebo bid + terbutaline 'as needed'	Pulmicort bid + terbutaline 'as needed'
Number of subjects	1277	1277	1282
Age, Customized Units: Subjects			
>=12 - <18	161	144	173
>=18 - <50	711	739	736
>=50 - <65	308	315	285
>=65 - <85	97	78	87
>=85	0	1	1
Age continuous Units: years			
arithmetic mean	39.8	40.0	39.0
standard deviation	± 16.9	± 16.3	± 16.7
Sex: Female, Male Units: Subjects			
Female	777	771	797
Male	500	506	485

Reporting group values	Total		
Number of subjects	3836		
Age, Customized Units: Subjects			
>=12 - <18	478		
>=18 - <50	2186		
>=50 - <65	908		
>=65 - <85	262		
>=85	2		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Subjects			
Female	2345		

Male	1491		
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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	Placebo bid + terbutaline 'as needed'
Reporting group description: Placebo for budesonide (Placebo Turbuhaler) + Terbutaline Turbuhaler 0.4 mg 'as needed'	
Reporting group title	Pulmicort bid + terbutaline 'as needed'
Reporting group description: Pulmicort Turbuhaler (budesonide 200 µg) + Terbutaline Turbuhaler 0.4 mg 'as needed'	

Primary: 'Well-controlled asthma week' - a derived binary variable (Yes/No)

End point title	'Well-controlled asthma week' - a derived binary variable (Yes/No) ^[1]
End point description: A well-controlled asthma week is defined as the fulfilment of both conditions A) and B) below: A) Two or more of the following criteria are fulfilled: – No more than 2 days with a daily asthma symptom score >1 – No more than 2 days of 'as needed' medication use, up to a maximum of 4 occasions per week (multiple occasions per day should be regarded as separate occasions) – Morning PEF ≥80% of Predicted Normal every day B) Both of the following criteria are fulfilled: – No nighttime awakenings due to asthma – No additional inhaled and/or systemic glucocorticosteroid treatment due to asthma. The binary variable well-controlled asthma week was derived for each patient and study week. In addition, for each week, the percent of patients with well-controlled asthma week was derived. It is required that the eDiary had to be completed on at least 5 days in a week to be evaluable for a well-controlled asthma week.	
End point type	Primary
End point timeframe: Weekly, 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'	Placebo bid + terbutaline 'as needed'	Pulmicort bid + terbutaline 'as needed'	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1269	1272	1279	
Units: Percentage				
arithmetic mean (standard deviation)	34.4 (± 36.02)	31.1 (± 34.90)	44.4 (± 39.10)	

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
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End point description:

End point type	Secondary
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End point timeframe:
up to 52 weeks

End point values	Placebo bid + Symbicort 'as needed'	Placebo bid + terbutaline 'as needed'	Pulmicort bid + terbutaline 'as needed'	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1277	1277	1282	
Units: N patients with sev asthma exacerbation				
Number of patients with events	71	152	78	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first moderate or severe asthma exacerbation

End point title	Time to first moderate or severe asthma exacerbation
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End point description:

End point type	Secondary
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End point timeframe:
up to 52 weeks

End point values	Placebo bid + Symbicort 'as needed'	Placebo bid + terbutaline 'as needed'	Pulmicort bid + terbutaline 'as needed'	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1277	1277	1282	
Units: No. patients with asthma exacerbation				
Number of patients with events	131	274	143	

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
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End point description:

End point type	Secondary
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End point timeframe:

Study weeks 0,4,16,28,40,52

End point values	Placebo bid + Symbicort 'as needed'	Placebo bid + terbutaline 'as needed'	Pulmicort bid + terbutaline 'as needed'	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1261	1243	1261	
Units: mL				
least squares mean (confidence interval 95%)	65 (47.6 to 82.4)	11.2 (-6.4 to 28.9)	119.3 (101.9 to 136.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Average change from baseline in Morning PEF

End point title	Average change from baseline in Morning PEF
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End point description:

End point type	Secondary
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End point timeframe:

up to 52 weeks

End point values	Placebo bid + Symbicort 'as needed'	Placebo bid + terbutaline 'as needed'	Pulmicort bid + terbutaline 'as needed'	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1273	1272	1280	
Units: L/min				
arithmetic mean (standard deviation)	-4.55 (± 52.07)	-16.74 (± 54.15)	5.48 (± 56.54)	

Statistical analyses

No statistical analyses for this end point

Secondary: Average change from baseline in Evening PEF

End point title	Average change from baseline in Evening PEF
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End point description:

End point type	Secondary
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End point timeframe:
up to 52 weeks

End point values	Placebo bid + Symbicort 'as needed'	Placebo bid + terbutaline 'as needed'	Pulmicort bid + terbutaline 'as needed'	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1271	1274	1280	
Units: L/min				
arithmetic mean (standard deviation)	-11.67 (± 51.45)	-22.59 (± 54.14)	-5.28 (± 54.00)	

Statistical analyses

No statistical analyses for this end point

Secondary: Average change from baseline in number of inhalations of 'as needed' medication.

End point title	Average change from baseline in number of inhalations of 'as needed' medication.
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End point description:

End point type	Secondary
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End point timeframe:
up to 52 weeks

End point values	Placebo bid + Symbicort 'as needed'	Placebo bid + terbutaline 'as needed'	Pulmicort bid + terbutaline 'as needed'	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1276	1273	1281	
Units: Number of inhalations per day				
least squares mean (confidence interval 95%)	-0.96 (-0.99 to -0.93)	-0.80 (-0.83 to -0.77)	-1.04 (-1.07 to -1.00)	

Statistical analyses

No statistical analyses for this end point

Secondary: Average change from baseline in symptom score

End point title	Average change from baseline in symptom score
End point description:	
End point type	Secondary
End point timeframe: up to 52 weeks	

End point values	Placebo bid + Symbicort 'as needed'	Placebo bid + terbutaline 'as needed'	Pulmicort bid + terbutaline 'as needed'	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1271	1272	1280	
Units: Score (0-6)				
arithmetic mean (standard deviation)	-0.22 (± 0.85)	-0.11 (± 0.80)	-0.30 (± 0.82)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Nighttime Awakenings due to asthma: Change from baseline

End point title	Percentage of Nighttime Awakenings due to asthma: Change from baseline
End point description:	
End point type	Secondary
End point timeframe: up to 52 weeks	

End point values	Placebo bid + Symbicort 'as needed'	Placebo bid + terbutaline 'as needed'	Pulmicort bid + terbutaline 'as needed'	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1273	1272	1280	
Units: % of nights				
arithmetic mean (standard deviation)	-7.5 (± 24.0)	-4.6 (± 23.4)	-9.8 (± 22.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Symptom-free days: Change from baseline

End point title	Percentage of Symptom-free days: Change from baseline
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End point description:

End point type	Secondary
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End point timeframe:
up to 52 weeks

End point values	Placebo bid + Symbicort 'as needed'	Placebo bid + terbutaline 'as needed'	Pulmicort bid + terbutaline 'as needed'	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1273	1274	1280	
Units: % of days				
arithmetic mean (standard deviation)	4.2 (± 25.9)	1.3 (± 24.8)	6.8 (± 27.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of 'As needed' free days: Change from baseline

End point title	Percentage of 'As needed' free days: Change from baseline
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End point description:

End point type	Secondary
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End point timeframe:
up to 52 weeks

End point values	Placebo bid + Symbicort 'as needed'	Placebo bid + terbutaline 'as needed'	Pulmicort bid + terbutaline 'as needed'	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1276	1273	1281	
Units: % of days				
arithmetic mean (standard deviation)	44.2 (± 31.0)	45.0 (± 30.7)	51.7 (± 30.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Asthma control days: Change from baseline

End point title	Percentage of Asthma control days: Change from baseline
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End point description:

Asthma control days (%) change from baseline. An asthma control day is defined as the fulfilment of all

of the following criteria; a day and night with no asthma symptoms, a night with no awakenings due to asthma symptoms and a day and night with no use of 'as needed' medication.

End point type	Secondary
End point timeframe:	
up to 52 weeks	

End point values	Placebo bid + Symbicort 'as needed'	Placebo bid + terbutaline 'as needed'	Pulmicort bid + terbutaline 'as needed'	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1273	1272	1280	
Units: % of days				
arithmetic mean (standard deviation)	13.2 (± 23.9)	12.8 (± 23.3)	18.5 (± 28.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to asthma related discontinuation

End point title	Time to asthma related discontinuation
End point description:	
End point type	Secondary
End point timeframe:	
up to 52 weeks	

End point values	Placebo bid + Symbicort 'as needed'	Placebo bid + terbutaline 'as needed'	Pulmicort bid + terbutaline 'as needed'	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1277	1277	1282	
Units: Number of patients				
Severe asthma exacerbation with duration > 3 weeks	0	2	0	
Two severe asthma exacerbations during 3 months	3	18	6	
Three severe asthma exacerbations during the study	1	1	0	
No study-specific asthma related discontinuation	1273	1256	1276	

Statistical analyses

No statistical analyses for this end point

Secondary: Poorly controlled asthma weeks

End point title	Poorly controlled asthma weeks
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End point description:

A poorly-controlled asthma week is defined as a week meeting any one of the following conditions: Two or more consecutive days with awakenings due to asthma on both nights; A recorded use of 'as needed' medication for symptom relief of at least 3 occasions per day, for at least 2 consecutive days; Additional systemic GCS treatment required for severe exacerbation. If there were sufficient data within a week available to confirm the week was not poorly-controlled, the week is labelled as 'does not meet criteria for poorly-controlled'.

End point type	Secondary
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End point timeframe:

Weekly for up to 52 weeks

End point values	Placebo bid + Symbicort 'as needed'	Placebo bid + terbutaline 'as needed'	Pulmicort bid + terbutaline 'as needed'	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1277	1277	1282	
Units: % of weeks				
arithmetic mean (standard deviation)				
% of poorly-controlled asthma weeks, per patient	15.83 (± 26.29)	21.79 (± 28.77)	13.75 (± 25.20)	
No. of poorly-controlled asthma weeks, per patient	7.7 (± 13.3)	9.7 (± 13.8)	6.7 (± 12.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to additional steroids for asthma

End point title	Time to additional steroids for asthma
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End point description:

End point type	Secondary
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End point timeframe:

up to 52 weeks

End point values	Placebo bid + Symbicort 'as needed'	Placebo bid + terbutaline 'as needed'	Pulmicort bid + terbutaline 'as needed'	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1277	1277	1282	
Units: Number of patients				
Number of patients with events	164	345	187	

Statistical analyses

No statistical analyses for this end point

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

End point title	Average change from baseline in Asthma Control Questionnaire (ACQ-5)
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End point description:

Asthma Control Questionnaire 5-item version score change from baseline. 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
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End point timeframe:

Study weeks 0,4,16,28,40,52

End point values	Placebo bid + Symbicort 'as needed'	Placebo bid + terbutaline 'as needed'	Pulmicort bid + terbutaline 'as needed'	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1241	1225	1237	
Units: ACQ-5 Score				
least squares mean (confidence interval 95%)	-0.33 (-0.36 to -0.29)	-0.17 (-0.21 to -0.14)	-0.48 (-0.51 to -0.44)	

Statistical analyses

No statistical analyses for this end point

Secondary: Average change from baseline in Asthma Quality of Life Questionnaire; standard version (AQLQ(S))

End point title	Average change from baseline in Asthma Quality of Life Questionnaire; standard version (AQLQ(S))
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End point description:

Asthma Quality of Life Questionnaire Standardised Version (AQLQ (S)) overall score change from baseline. 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
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End point timeframe:

Study weeks 0,16,28,40,52

End point values	Placebo bid + Symbicort 'as needed'	Placebo bid + terbutaline 'as needed'	Pulmicort bid + terbutaline 'as needed'	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1184	1137	1187	
Units: AQLQ(S) Score				
least squares mean (confidence interval 95%)	0.313 (0.276 to 0.351)	0.186 (0.148 to 0.225)	0.415 (0.377 to 0.453)	

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: up to 52 weeks	

End point values	Placebo bid + Symbicort 'as needed'	Placebo bid + terbutaline 'as needed'	Pulmicort bid + terbutaline 'as needed'	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1276	1273	1281	
Units: % of days				
arithmetic mean (standard deviation)	30.8 (± 28.7)	5.6 (± 16.8)	85.6 (± 19.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Annual severe asthma exacerbation rate

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

End point values	Placebo bid + Symbicort 'as needed'	Placebo bid + terbutaline 'as needed'	Pulmicort bid + terbutaline 'as needed'	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1277	1277	1282	
Units: Annual rate of exacerbations				
least squares mean (confidence interval 95%)	0.07 (0.06 to 0.09)	0.20 (0.16 to 0.24)	0.09 (0.07 to 0.11)	

Statistical analyses

No statistical analyses for this end point

Secondary: Annual moderate or severe asthma exacerbation rate

End point title	Annual moderate or severe asthma exacerbation rate
End point description:	
End point type	Secondary
End point timeframe: up to 52 weeks	

End point values	Placebo bid + Symbicort 'as needed'	Placebo bid + terbutaline 'as needed'	Pulmicort bid + terbutaline 'as needed'	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1277	1277	1282	
Units: Annual rate of exacerbations				
least squares mean (confidence interval 95%)	0.14 (0.12 to 0.17)	0.36 (0.31 to 0.42)	0.15 (0.13 to 0.18)	

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 randomised treatment period and including the follow-up period until the last telephone follow-up or the last contact. Serious adverse events were recorded from the time of informed consent.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Placebo bid + Symbicort 'as needed'
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Reporting group description:

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

Reporting group title	Placebo bid + terbutaline 'as needed'
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Reporting group description:

Placebo for budesonide (Placebo Turbuhaler) + Terbutaline Turbuhaler 0.4 mg 'as needed'

Reporting group title	Pulmicort bid + terbutaline 'as needed'
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Reporting group description:

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

Serious adverse events	Placebo bid + Symbicort 'as needed'	Placebo bid + terbutaline 'as needed'	Pulmicort bid + terbutaline 'as needed'
Total subjects affected by serious adverse events			
subjects affected / exposed	38 / 1277 (2.98%)	50 / 1277 (3.92%)	37 / 1282 (2.89%)
number of deaths (all causes)	0	0	2
number of deaths resulting from adverse events	0	0	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Brain neoplasm			
subjects affected / exposed	0 / 1277 (0.00%)	0 / 1277 (0.00%)	1 / 1282 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Breast cancer female			
subjects affected / exposed	2 / 1277 (0.16%)	0 / 1277 (0.00%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive ductal breast carcinoma			

subjects affected / exposed	1 / 1277 (0.08%)	0 / 1277 (0.00%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatic adenoma			
subjects affected / exposed	0 / 1277 (0.00%)	1 / 1277 (0.08%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	1 / 1277 (0.08%)	0 / 1277 (0.00%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 1277 (0.00%)	0 / 1277 (0.00%)	1 / 1282 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	1 / 1277 (0.08%)	0 / 1277 (0.00%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Adenomyosis			
subjects affected / exposed	0 / 1277 (0.00%)	1 / 1277 (0.08%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometriosis			
subjects affected / exposed	0 / 1277 (0.00%)	1 / 1277 (0.08%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine polyp			
subjects affected / exposed	1 / 1277 (0.08%)	0 / 1277 (0.00%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Uterine prolapse			
subjects affected / exposed	1 / 1277 (0.08%)	0 / 1277 (0.00%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal prolapse			
subjects affected / exposed	1 / 1277 (0.08%)	0 / 1277 (0.00%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	6 / 1277 (0.47%)	16 / 1277 (1.25%)	8 / 1282 (0.62%)
occurrences causally related to treatment / all	0 / 6	1 / 22	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal polyps			
subjects affected / exposed	1 / 1277 (0.08%)	0 / 1277 (0.00%)	2 / 1282 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Adjustment disorder			
subjects affected / exposed	0 / 1277 (0.00%)	1 / 1277 (0.08%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Patient-device incompatibility			
subjects affected / exposed	0 / 1277 (0.00%)	0 / 1277 (0.00%)	1 / 1282 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood pressure increased			
subjects affected / exposed	1 / 1277 (0.08%)	0 / 1277 (0.00%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Animal bite			

subjects affected / exposed	0 / 1277 (0.00%)	0 / 1277 (0.00%)	1 / 1282 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	1 / 1277 (0.08%)	0 / 1277 (0.00%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	1 / 1277 (0.08%)	0 / 1277 (0.00%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand fracture			
subjects affected / exposed	0 / 1277 (0.00%)	1 / 1277 (0.08%)	1 / 1282 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 1277 (0.00%)	1 / 1277 (0.08%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc injury			
subjects affected / exposed	0 / 1277 (0.00%)	1 / 1277 (0.08%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	1 / 1277 (0.08%)	0 / 1277 (0.00%)	1 / 1282 (0.08%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar limb fracture			
subjects affected / exposed	1 / 1277 (0.08%)	0 / 1277 (0.00%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			

subjects affected / exposed	0 / 1277 (0.00%)	1 / 1277 (0.08%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple injuries			
subjects affected / exposed	0 / 1277 (0.00%)	1 / 1277 (0.08%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 1277 (0.00%)	1 / 1277 (0.08%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 1277 (0.00%)	1 / 1277 (0.08%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 1277 (0.00%)	1 / 1277 (0.08%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 1277 (0.00%)	0 / 1277 (0.00%)	1 / 1282 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	0 / 1277 (0.00%)	1 / 1277 (0.08%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 1277 (0.00%)	0 / 1277 (0.00%)	2 / 1282 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			

subjects affected / exposed	1 / 1277 (0.08%)	0 / 1277 (0.00%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block			
subjects affected / exposed	0 / 1277 (0.00%)	1 / 1277 (0.08%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 1277 (0.08%)	0 / 1277 (0.00%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 1277 (0.00%)	1 / 1277 (0.08%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	0 / 1277 (0.00%)	0 / 1277 (0.00%)	1 / 1282 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular insufficiency			
subjects affected / exposed	1 / 1277 (0.08%)	0 / 1277 (0.00%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 1277 (0.00%)	1 / 1277 (0.08%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple sclerosis			
subjects affected / exposed	0 / 1277 (0.00%)	0 / 1277 (0.00%)	1 / 1282 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			

subjects affected / exposed	1 / 1277 (0.08%)	0 / 1277 (0.00%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 1277 (0.08%)	0 / 1277 (0.00%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 1277 (0.00%)	1 / 1277 (0.08%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Amaurosis			
subjects affected / exposed	0 / 1277 (0.00%)	0 / 1277 (0.00%)	1 / 1282 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract			
subjects affected / exposed	1 / 1277 (0.08%)	0 / 1277 (0.00%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	1 / 1277 (0.08%)	0 / 1277 (0.00%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fissure			
subjects affected / exposed	1 / 1277 (0.08%)	0 / 1277 (0.00%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic gastritis			
subjects affected / exposed	0 / 1277 (0.00%)	1 / 1277 (0.08%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Crohn's disease			
subjects affected / exposed	1 / 1277 (0.08%)	0 / 1277 (0.00%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 1277 (0.00%)	0 / 1277 (0.00%)	1 / 1282 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	1 / 1277 (0.08%)	0 / 1277 (0.00%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Food poisoning			
subjects affected / exposed	0 / 1277 (0.00%)	1 / 1277 (0.08%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis erosive			
subjects affected / exposed	1 / 1277 (0.08%)	0 / 1277 (0.00%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hernial eventration			
subjects affected / exposed	1 / 1277 (0.08%)	0 / 1277 (0.00%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	1 / 1277 (0.08%)	2 / 1277 (0.16%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis chronic			
subjects affected / exposed	0 / 1277 (0.00%)	1 / 1277 (0.08%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			

subjects affected / exposed	0 / 1277 (0.00%)	1 / 1277 (0.08%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 1277 (0.00%)	1 / 1277 (0.08%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 1277 (0.08%)	0 / 1277 (0.00%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder polyp			
subjects affected / exposed	0 / 1277 (0.00%)	0 / 1277 (0.00%)	1 / 1282 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 1277 (0.00%)	1 / 1277 (0.08%)	1 / 1282 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Hidradenitis			
subjects affected / exposed	1 / 1277 (0.08%)	0 / 1277 (0.00%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prurigo			
subjects affected / exposed	0 / 1277 (0.00%)	1 / 1277 (0.08%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	0 / 1277 (0.00%)	0 / 1277 (0.00%)	1 / 1282 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Calculus urinary			
subjects affected / exposed	0 / 1277 (0.00%)	1 / 1277 (0.08%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	1 / 1277 (0.08%)	0 / 1277 (0.00%)	1 / 1282 (0.08%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive uropathy			
subjects affected / exposed	0 / 1277 (0.00%)	1 / 1277 (0.08%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 1277 (0.00%)	0 / 1277 (0.00%)	1 / 1282 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Goitre			
subjects affected / exposed	0 / 1277 (0.00%)	0 / 1277 (0.00%)	1 / 1282 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Chondropathy			
subjects affected / exposed	1 / 1277 (0.08%)	0 / 1277 (0.00%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 1277 (0.00%)	0 / 1277 (0.00%)	1 / 1282 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 1277 (0.00%)	1 / 1277 (0.08%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations Abscess intestinal subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 1277 (0.08%) 0 / 1 0 / 0	 0 / 1277 (0.00%) 0 / 0 0 / 0	 0 / 1282 (0.00%) 0 / 0 0 / 0
Anal abscess subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 1277 (0.00%) 0 / 0 0 / 0	 0 / 1277 (0.00%) 0 / 0 0 / 0	 1 / 1282 (0.08%) 0 / 1 0 / 0
Atypical mycobacterial pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 1277 (0.00%) 0 / 0 0 / 0	 1 / 1277 (0.08%) 0 / 1 0 / 0	 0 / 1282 (0.00%) 0 / 0 0 / 0
Atypical pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 1277 (0.00%) 0 / 0 0 / 0	 1 / 1277 (0.08%) 0 / 1 0 / 0	 0 / 1282 (0.00%) 0 / 0 0 / 0
Cholecystitis infective subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 1277 (0.00%) 0 / 0 0 / 0	 1 / 1277 (0.08%) 0 / 1 0 / 0	 0 / 1282 (0.00%) 0 / 0 0 / 0
Chronic sinusitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 1277 (0.00%) 0 / 0 0 / 0	 0 / 1277 (0.00%) 0 / 0 0 / 0	 3 / 1282 (0.23%) 0 / 3 0 / 0
Clostridium difficile infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 1277 (0.00%) 0 / 0 0 / 0	 1 / 1277 (0.08%) 0 / 2 0 / 0	 0 / 1282 (0.00%) 0 / 0 0 / 0
Cystitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 1277 (0.00%) 0 / 0 0 / 0	 0 / 1277 (0.00%) 0 / 0 0 / 0	 1 / 1282 (0.08%) 0 / 1 0 / 0
Dengue fever			

subjects affected / exposed	0 / 1277 (0.00%)	0 / 1277 (0.00%)	1 / 1282 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	0 / 1277 (0.00%)	1 / 1277 (0.08%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 1277 (0.00%)	0 / 1277 (0.00%)	1 / 1282 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Keratitis viral			
subjects affected / exposed	0 / 1277 (0.00%)	1 / 1277 (0.08%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngitis			
subjects affected / exposed	0 / 1277 (0.00%)	0 / 1277 (0.00%)	1 / 1282 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	1 / 1277 (0.08%)	0 / 1277 (0.00%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritoneal abscess			
subjects affected / exposed	1 / 1277 (0.08%)	0 / 1277 (0.00%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	1 / 1277 (0.08%)	0 / 1277 (0.00%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	2 / 1277 (0.16%)	2 / 1277 (0.16%)	2 / 1282 (0.16%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 1277 (0.00%)	1 / 1277 (0.08%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 1277 (0.00%)	1 / 1277 (0.08%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	1 / 1277 (0.08%)	0 / 1277 (0.00%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	0 / 1277 (0.00%)	1 / 1277 (0.08%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	1 / 1277 (0.08%)	0 / 1277 (0.00%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis bacterial			
subjects affected / exposed	1 / 1277 (0.08%)	0 / 1277 (0.00%)	0 / 1282 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo bid + Symbicort 'as needed'	Placebo bid + terbutaline 'as needed'	Pulmicort bid + terbutaline 'as needed'
Total subjects affected by non-serious adverse events subjects affected / exposed	471 / 1277 (36.88%)	527 / 1277 (41.27%)	497 / 1282 (38.77%)
Nervous system disorders Headache subjects affected / exposed occurrences (all)	23 / 1277 (1.80%) 44	25 / 1277 (1.96%) 54	29 / 1282 (2.26%) 32
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all) Rhinitis allergic subjects affected / exposed occurrences (all)	32 / 1277 (2.51%) 40 28 / 1277 (2.19%) 33	95 / 1277 (7.44%) 125 28 / 1277 (2.19%) 32	50 / 1282 (3.90%) 61 19 / 1282 (1.48%) 19
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all) Viral upper respiratory tract infection subjects affected / exposed occurrences (all) Pharyngitis subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed occurrences (all)	71 / 1277 (5.56%) 86 75 / 1277 (5.87%) 90 33 / 1277 (2.58%) 39 33 / 1277 (2.58%) 39	76 / 1277 (5.95%) 95 79 / 1277 (6.19%) 95 34 / 1277 (2.66%) 41 41 / 1277 (3.21%) 44	93 / 1282 (7.25%) 125 84 / 1282 (6.55%) 98 48 / 1282 (3.74%) 54 37 / 1282 (2.89%) 48

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 November 2014	Percentage of controller use days added as a secondary variable: To further evaluate controller medication use in the study. Description of target patient population amended: To clarify pre-study treatment according to GINA Step 2 (GINA 2012); Rationale for study design, doses and control groups amended: To clarify pre-study treatment according to GINA Step 2 (GINA 2012); Inclusion Criteria 4, 5, and Exclusion Criteria 5 and 17 amended: To clarify pre-study treatment according to GINA Step 2 (GINA 2012); Exclusion Criterion 9 amended: To clarify that smoking history of ≥ 10 pack years applies to both current and previous smokers.; Methods for assigning treatment groups amended: To clarify pre-study treatment according to GINA Step 2 (GINA 2012); Visit 1 to 2 window amended: To allow performing of Visits 1 and 2 on the same day, and to clarify and to emphasize the importance of the fact that concomitant medications might have effect on lung function measurements.; Run-in procedures at Visit 2 amended: To clarify that all asthma-related treatments (including maintenance treatment with ICS or LTRA) will be stopped at Visit 2.; Definitions of moderate and severe asthma exacerbations amended: To provide clarification on depot steroid injection use, emergency room visit and steroid use end date, and to further clarify how moderate and severe asthma exacerbations will be counted.; To clarify how to distinguish long term poor asthma control and asthma exacerbations for the purpose of reporting in this study.; Reversibility test amended: To clarify pre-study treatment according to GINA Step 2 (GINA 2012)
17 August 2015	<p>Inclusion Criterion 6 amended Within the patient population targeted for recruitment, FEV1 and/or FEV1 reversibility vary over time. Allowing use of documented historical reversibility within 12 months for all patients who failed reversibility test at Visit 2 and Visit 3 was expected to enhance recruitment without changing the characterization of the study patient population or jeopardizing patient safety.</p> <p>Discontinuation of IP amended To clarify that discontinuation of IP is obligatory in cases of pregnancy or study specific discontinuation criteria met.</p> <p>Details related to enrolment failures amended Within the patient population targeted for recruitment, FEV1 and/or FEV1 reversibility vary over time. Allowing two 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, was expected to enhance recruitment without changing the characterization of the study patient population or jeopardizing patient safety.</p> <p>Recording of asthma history amended To clarify that only severe asthma exacerbations (and not mild or moderate asthma exacerbations) have to be reported as part of asthma history in the medical records and the eCRF.</p> <p>Added training for patients on correct use of Turbuhaler To emphasize the importance of correct Turbuhaler user technique, check of inhalation technique at study visits and re-training of patient if needed.</p> <p>Timing of visits in relation to spirometry assessments amended To give flexibility around timing of visits and to clarify the importance of timing of assessment to ± 1 hour in relation to time of spirometry at Visit 2.</p>
24 February 2016	Addition of qualitative sub-study as exploratory objective A sub-study with qualitative interviews in a subset of patients is being added to the protocol (to be reported separately from main CSR)

22 December 2016	<p>Implementation of external, independent evaluation of all deaths The Steering Committee (see Section 2.3) recommended that independent review and adjudication of fatal events be introduced following the first death (triggered by asthma exacerbation).</p> <p>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.</p> <p>Amendment of WCAW (primary endpoint) algorithm and analysis Study week was included in the model to estimate WCAW, as a continuous variable. It was changed to a categorical measure to allow the model to reflect the nature of the variable.</p> <p>It was specified that up to 2 days of missed diary entries in a week were allowed in the evaluation of the WCAW. This was in line with the practice of requiring a minimum number of days with information to derive a weekly summary based on data collected on a daily basis (Bateman et al 2004, Thomas et al 2016, Jones et al 2016). At least five days in a week will provide sufficient information to evaluate the status of a patient in a week.</p>
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported