

**Clinical trial results:****A Phase 3, 12-Week, Double-Blind, Randomized, Parallel-Group, Multicenter Study Investigating the Efficacy and Safety of Symbicort pMDI 80/2.25 g, 2 Actuations Twice Daily, and Symbicort pMDI 80/4.5 g, 2 Actuations Twice Daily, Compared with Budesonide pMDI 80 g, 2 Actuations Twice Daily, in Children Ages 6 to <12 Years with Asthma Summary**

EudraCT number	2013-005293-22
Trial protocol	SK
Global end of trial date	14 April 2016

Results information

Result version number	v1 (current)
This version publication date	27 October 2016
First version publication date	27 October 2016

Trial information**Trial identification**

Sponsor protocol code	D589GC00003
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Pepparedsleden 1, Mölndal, Sweden,
Public contact	Global Clinical Lead Göran Eckerwall, AstraZeneca, information.center@astrazeneca.com
Scientific contact	Global Clinical Lead Göran Eckerwall, Astrazeneca Research and Development, 0046 +46 31 7761000, 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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 May 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 April 2016
Global end of trial reached?	Yes
Global end of trial date	14 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to demonstrate the efficacy of Symbicort pMDI 80/4.5, 2 inhalations bid and Symbicort pMDI 80/2.25, 2 inhalations bid, compared with budesonide pMDI 80 µg, 2 inhalations bid, in children ages 6 to <12 years with asthma.

Protection of trial subjects:

Before subjects can be enrolled into the study or starting the study procedure, an informed consent and child assent forms following the relevant local regulations of subject protection and data privacy must be signed by the subjects and their legal guardian(s).

The study data was stored in a computer database, maintaining confidentiality in accordance with relevant regulations. All data computer-processed by AstraZeneca or representative will be identified by patient enrollment number, randomization number, and study code. The master informed consent and child assent forms will also explain that for data verification purposes, authorized representatives of AstraZeneca, a regulatory authority, an IRB or Independent Ethics Committee (IEC) may require direct access to parts of the hospital or practice records relevant to the study, including the patient's medical history.

The study protocol, Informed Consent/Child Assent Forms and any other written information and/or materials to be provided to the patients were approved by the Institutional Review Board or Ethic committee in accordance with local country regulations.

Patient safety was monitored by the CRO, Quintiles safety group throughout the study conduct. Any reportable adverse events were submitted to the relevant regulatory authorities including IRBs/ECs according to local requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 April 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	United States: 226
Country: Number of subjects enrolled	Panama: 25
Country: Number of subjects enrolled	Mexico: 8
Country: Number of subjects enrolled	Slovakia: 20
Worldwide total number of subjects	279
EEA total number of subjects	20

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)	279
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

881 patients were screened; 237 patients were screen failures and 644 patients received run in medication. Of the patients who received run-in medication, 365 patients were not randomized and 279 patients were randomized.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Carer, Data analyst, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Symbicort pMDI 80/4.5 ug

Arm description:

Symbicort pMDI 80/4.5 ug x 2 BID

Arm type	Experimental
Investigational medicinal product name	Budesonide/formoterol pMDI 80/4.5 ug
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

pMDI HFA for oral inhalation with ACM budesonide/formoterol fumarate dihydrate

Arm title	Symbicort pMDI 80/2.25 ug
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Arm description:

Symbicort pMDI 80/2.25 ug x 2 BID

Arm type	Experimental
Investigational medicinal product name	Budesonide/formoterol pMDI 80/2.25 ug
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

pMDI HFA for oral inhalation with ACM budesonide/formoterol fumarate dihydrate 80/2.25 ug

Arm title	Budesonide pMDI 80 ug
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Arm description:

Budesonide pMDI 80 ug x 2 BID

Arm type	Active comparator
Investigational medicinal product name	Budesonide pMDI 80 ug
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Number of subjects in period 1	Symbicort pMDI 80/4.5 ug	Symbicort pMDI 80/2.25 ug	Budesonide pMDI 80 ug
Started	92	95	92
Completed	85	84	84
Not completed	7	11	8
Consent withdrawn by subject	4	8	3
Adverse event, non-fatal	-	-	2
7 rand in error 1 patient decision	2	3	3
Lost to follow-up	1	-	-

Baseline characteristics

Reporting groups

Reporting group title	Symbicort pMDI 80/4.5 ug
Reporting group description: Symbicort pMDI 80/4.5 ug x 2 BID	
Reporting group title	Symbicort pMDI 80/2.25 ug
Reporting group description: Symbicort pMDI 80/2.25 ug x 2 BID	
Reporting group title	Budesonide pMDI 80 ug
Reporting group description: Budesonide pMDI 80 ug x 2 BID	

Reporting group values	Symbicort pMDI 80/4.5 ug	Symbicort pMDI 80/2.25 ug	Budesonide pMDI 80 ug
Number of subjects	92	95	92
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	92	95	92
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	9	9	9
standard deviation	± 1.6	± 1.6	± 1.4
Gender, Male/Female			
Units: Participants			
Female	42	34	37
Male	50	61	55
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	2	3	3
Asian	0	0	2
Native Hawaiian or Other Pacific Islander	1	0	0
Black or African American	24	26	26
White	61	60	53
More than one race	4	4	7
Unknown or Not Reported	0	2	1
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	38	36	32

Not Hispanic or Latino	54	59	60
Unknown or Not Reported	0	0	0

Body weight Units: kg arithmetic mean standard deviation	38 ± 12.9	38 ± 12.9	40 ± 13.6
Height Units: cm arithmetic mean standard deviation	139 ± 11.1	138 ± 10.9	141 ± 10.5
Duration of asthma Units: years arithmetic mean standard deviation	5.8 ± 3	5.9 ± 3.3	6.2 ± 3.1
FEV1 at randomisation Units: Liters arithmetic mean standard deviation	1.58 ± 0.42	1.57 ± 0.33	1.62 ± 0.36

Reporting group values	Total		
Number of subjects	279		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	279		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age Continuous Units: years arithmetic mean standard deviation	-		
Gender, Male/Female Units: Participants			
Female	113		
Male	166		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	8		
Asian	2		
Native Hawaiian or Other Pacific Islander	1		
Black or African American	76		
White	174		
More than one race	15		

Unknown or Not Reported	3		
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	106		
Not Hispanic or Latino	173		
Unknown or Not Reported	0		
Body weight			
Units: kg			
arithmetic mean			
standard deviation	-		
Height			
Units: cm			
arithmetic mean			
standard deviation	-		
Duration of asthma			
Units: years			
arithmetic mean			
standard deviation	-		
FEV1 at randomisation			
Units: Liters			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Symbicort pMDI 80/4.5 ug
Reporting group description:	
Symbicort pMDI 80/4.5 ug x 2 BID	
Reporting group title	Symbicort pMDI 80/2.25 ug
Reporting group description:	
Symbicort pMDI 80/2.25 ug x 2 BID	
Reporting group title	Budesonide pMDI 80 ug
Reporting group description:	
Budesonide pMDI 80 ug x 2 BID	

Primary: Change from baseline to Week 12 in 1h post-dose FEV1

End point title	Change from baseline to Week 12 in 1h post-dose FEV1
End point description:	
1h post-dose FEV1 is defined as the 1-hour post-dose measurement taken at Week 12 minus the pre dose measurement taken at randomization for patients who remain in the study (irrespective of whether IP has been discontinued).	
End point type	Primary
End point timeframe:	
Week 12	

End point values	Symbicort pMDI 80/4.5 ug	Symbicort pMDI 80/2.25 ug	Budesonide pMDI 80 ug	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	89	93	90	
Units: Liters				
least squares mean (confidence interval 95%)	0.28 (0.22 to 0.34)	0.24 (0.18 to 0.31)	0.17 (0.1 to 0.23)	

Statistical analyses

Statistical analysis title	FEV1 1h post-dose Change from baseline to Week 12
Comparison groups	Symbicort pMDI 80/4.5 ug v Budesonide pMDI 80 ug
Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006 ^[1]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.12

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	0.2

Notes:

[1] - 2-sided p-value

Statistical analysis title	FEV1 1h post-dose Change from baseline to week 12
Comparison groups	Symbicort pMDI 80/4.5 ug v Symbicort pMDI 80/2.25 ug
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.373 ^[2]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.12

Notes:

[2] - 2-sided

Statistical analysis title	FEV1 1h post-dose Change from baseline to week 12
Comparison groups	Budesonide pMDI 80 ug v Symbicort pMDI 80/2.25 ug
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.063 ^[3]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.08
upper limit	0.16

Notes:

[3] - 2-sided

Secondary: Change from baseline to Week 12 in 1h post-dose PEF

End point title	Change from baseline to Week 12 in 1h post-dose PEF
End point description:	
1h post-dose PEF is defined as the 1-hour post-dose measurement taken at Week 12 minus the pre dose measurement taken at randomization for patients who remain in the study (irrespective of whether IP has been discontinued).	
End point type	Secondary

End point timeframe:

Week 12

End point values	Symbicort pMDI 80/4.5 ug	Symbicort pMDI 80/2.25 ug	Budesonide pMDI 80 ug	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	89	93	90	
Units: Liters per minute				
least squares mean (confidence interval 95%)	57.04 (46.12 to 67.97)	41.14 (30.26 to 52.01)	31.57 (20.78 to 42.36)	

Statistical analyses

Statistical analysis title	PEF 1h post dose Change from baseline to Week 12
Comparison groups	Symbicort pMDI 80/4.5 ug v Budesonide pMDI 80 ug
Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 ^[4]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	25.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.94
upper limit	40

Notes:

[4] - 2-sided

Statistical analysis title	PEF 1h post dose Change from baseline to Week 12
Comparison groups	Budesonide pMDI 80 ug v Symbicort pMDI 80/2.25 ug
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.195 ^[5]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	9.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.92
upper limit	24.05

Notes:

[5] - 2-sided

Statistical analysis title	PEF 1h post dose Change from baseline to Week 12
Comparison groups	Symbicort pMDI 80/4.5 ug v Symbicort pMDI 80/2.25 ug
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.032 ^[6]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	15.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.34
upper limit	30.47

Notes:

[6] - 2-sided

Secondary: Change from baseline to Week 12 in 1h post-dose FEF25-75

End point title	Change from baseline to Week 12 in 1h post-dose FEF25-75
End point description:	
1h post-dose FEF25-75 is defined as the 1-hour post-dose measurement taken at Week 12 minus the pre dose measurement taken at randomization for patients who remain in the study (irrespective of whether IP has been discontinued).	
End point type	Secondary
End point timeframe:	
Week 12	

End point values	Symbicort pMDI 80/4.5 ug	Symbicort pMDI 80/2.25 ug	Budesonide pMDI 80 ug	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	89	93	90	
Units: Liters per second				
least squares mean (confidence interval 95%)	0.55 (0.43 to 0.67)	0.47 (0.35 to 0.59)	0.23 (0.11 to 0.35)	

Statistical analyses

Statistical analysis title	FEF25-75 1h post-dose Change from basel to week 12
Comparison groups	Symbicort pMDI 80/4.5 ug v Budesonide pMDI 80 ug

Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 ^[7]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	0.48

Notes:

[7] - 2-sided

Statistical analysis title	FEF25-75 1h post-dose Change from basel to week 12
Comparison groups	Budesonide pMDI 80 ug v Symbicort pMDI 80/2.25 ug
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	0.4

Statistical analysis title	FEF25-75 1h post-dose Change from basel to week 12
Comparison groups	Symbicort pMDI 80/4.5 ug v Symbicort pMDI 80/2.25 ug
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.326 ^[8]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.25

Notes:

[8] - 2-sided

Secondary: Change from baseline to Week 12 in 1h post-dose FVC

End point title	Change from baseline to Week 12 in 1h post-dose FVC
End point description:	
1h post-dose FVC is defined as the 1-hour post-dose measurement taken at Week 12 minus the pre dose measurement taken at randomization for patients who remain in the study (irrespective of whether IP has been discontinued).	
End point type	Secondary
End point timeframe:	
Week 12	

End point values	Symbicort pMDI 80/4.5 ug	Symbicort pMDI 80/2.25 ug	Budesonide pMDI 80 ug	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	89	93	90	
Units: Liters				
least squares mean (confidence interval 95%)	0.22 (0.15 to 0.3)	0.16 (0.09 to 0.23)	0.17 (0.1 to 0.24)	

Statistical analyses

Statistical analysis title	FVC 1h post dose Change from basel to week 12
Comparison groups	Symbicort pMDI 80/4.5 ug v Budesonide pMDI 80 ug
Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.276 ^[9]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.15

Notes:

[9] - 2-sided

Statistical analysis title	FVC 1h post dose Change from basel to week 12
Comparison groups	Symbicort pMDI 80/4.5 ug v Symbicort pMDI 80/2.25 ug
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.165
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.07

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.16

Statistical analysis title	FVC 1h post dose Change from basel to week 12
Comparison groups	Budesonide pMDI 80 ug v Symbicort pMDI 80/2.25 ug
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.759 ^[10]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	0.08

Notes:

[10] - 2-sided

Secondary: Change from baseline to Week 12 in pre-dose FEV1

End point title	Change from baseline to Week 12 in pre-dose FEV1
End point description:	
Pre-dose FEV1 is defined as the pre-dose measurement taken at Week 12 minus the pre dose measurement taken at randomization for patients who remain in the study (irrespective of whether IP has been discontinued).	
End point type	Secondary
End point timeframe:	
Week 12	

End point values	Symbicort pMDI 80/4.5 ug	Symbicort pMDI 80/2.25 ug	Budesonide pMDI 80 ug	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	89	92	89	
Units: Liters				
least squares mean (confidence interval 95%)	0.11 (0.04 to 0.17)	0.1 (0.03 to 0.16)	0.09 (0.03 to 0.15)	

Statistical analyses

Statistical analysis title	FEV1 pre-dose Change from basel to Week 12
Comparison groups	Symbicort pMDI 80/4.5 ug v Budesonide pMDI 80 ug
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.724 ^[11]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.1

Notes:

[11] - 2-sided

Statistical analysis title	FEV1 pre-dose Change from basel to Week 12
Comparison groups	Budesonide pMDI 80 ug v Symbicort pMDI 80/2.25 ug
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.909
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.09

Statistical analysis title	FEV1 pre-dose Change from basel to Week 12
Comparison groups	Symbicort pMDI 80/4.5 ug v Symbicort pMDI 80/2.25 ug
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.811
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.09

Secondary: Change from baseline to Week 12 in pre-dose PEF

End point title	Change from baseline to Week 12 in pre-dose PEF
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End point description:

Pre-dose PEF is defined as the pre-dose measurement taken at Week 12 minus the pre dose measurement taken at randomization for patients who remain in the study (irrespective of whether IP has been discontinued).

End point type	Secondary
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End point timeframe:

Week 12

End point values	Symbicort pMDI 80/4.5 ug	Symbicort pMDI 80/2.25 ug	Budesonide pMDI 80 ug	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	89	92	89	
Units: Liters per minute				
least squares mean (confidence interval 95%)	27.73 (16.37 to 39.08)	15.86 (4.39 to 27.33)	16.01 (4.5 to 27.52)	

Statistical analyses

Statistical analysis title	PEF pre-dose Change from basel to Week 12
Comparison groups	Symbicort pMDI 80/4.5 ug v Budesonide pMDI 80 ug
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.134 ^[12]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	11.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.63
upper limit	27.06

Notes:

[12] - 2-sided

Statistical analysis title	PEF pre-dose Change from basel to Week 12
Comparison groups	Budesonide pMDI 80 ug v Symbicort pMDI 80/2.25 ug

Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.985 ^[13]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.28
upper limit	15.28

Notes:

[13] - 2-sided

Statistical analysis title	FEV1 pre-dose Change from basel to Week 12
Comparison groups	Symbicort pMDI 80/4.5 ug v Budesonide pMDI 80 ug
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.128 ^[14]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	11.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.43
upper limit	27.16

Notes:

[14] - 2-sided

Secondary: Change from baseline to Week 12 in pre-dose FEF25-75

End point title	Change from baseline to Week 12 in pre-dose FEF25-75
End point description:	
Pre-dose FEF25-75 is defined as the pre-dose measurement taken at Week 12 minus the pre dose measurement taken at randomization for patients who remain in the study (irrespective of whether IP has been discontinued).	
End point type	Secondary
End point timeframe:	
Week 12	

End point values	Symbicort pMDI 80/4.5 ug	Symbicort pMDI 80/2.25 ug	Budesonide pMDI 80 ug	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	89	92	89	
Units: Liters per minute				
least squares mean (confidence interval 95%)	0.12 (0.01 to 0.24)	0.13 (0.01 to 0.25)	0.09 (-0.03 to 0.21)	

Statistical analyses

Statistical analysis title	FEF25-75 pre-dose Change from basel to Week 12
Comparison groups	Symbicort pMDI 80/4.5 ug v Budesonide pMDI 80 ug
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.684 ^[15]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	0.19

Notes:

[15] - 2-sided

Statistical analysis title	FEF25-75 pre-dose Change from basel to Week 12
Comparison groups	Budesonide pMDI 80 ug v Symbicort pMDI 80/2.25 ug
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.621 ^[16]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	0.2

Notes:

[16] - 2-sided

Statistical analysis title	FEF25-75 pre-dose Change from basel to Week 12
Comparison groups	Symbicort pMDI 80/4.5 ug v Symbicort pMDI 80/2.25 ug

Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.929 ^[17]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16
upper limit	0.15

Notes:

[17] - 2-sided

Secondary: Change from baseline to Week 12 in pre-dose FVC

End point title	Change from baseline to Week 12 in pre-dose FVC
End point description:	
Pre-dose FVC is defined as the pre-dose measurement taken at Week 12 minus the pre dose measurement taken at randomization for patients who remain in the study (irrespective of whether IP has been discontinued).	
End point type	Secondary
End point timeframe:	
Week 12	

End point values	Symbicort pMDI 80/4.5 ug	Symbicort pMDI 80/2.25 ug	Budesonide pMDI 80 ug	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	89	92	89	
Units: Liters				
least squares mean (confidence interval 95%)	0.11 (0.03 to 0.18)	0.11 (0.04 to 0.19)	0.13 (0.05 to 0.2)	

Statistical analyses

Statistical analysis title	FVC pre-dose Change from basel to Week 12
Comparison groups	Symbicort pMDI 80/4.5 ug v Budesonide pMDI 80 ug
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.664 ^[18]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.02

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	0.08

Notes:

[18] - 2-sided

Statistical analysis title	FVC pre-dose Change from basel to Week 12
Comparison groups	Budesonide pMDI 80 ug v Symbicort pMDI 80/2.25 ug
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.747 ^[19]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	0.08

Notes:

[19] - 2-sided

Statistical analysis title	FVC pre-dose Change from basel to Week 12
Comparison groups	Symbicort pMDI 80/4.5 ug v Symbicort pMDI 80/2.25 ug
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.913 ^[20]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	0.09

Notes:

[20] - 2-sided

Secondary: Change from baseline to Week 12 in 15 min post-dose FEV1

End point title	Change from baseline to Week 12 in 15 min post-dose FEV1
End point description:	
15 min Post-dose FEV1 is defined as the 15 min post-dose measurement taken at Week 12 minus the pre dose measurement taken at randomization for patients who remain in the study (irrespective of whether IP has been discontinued).	
End point type	Secondary

End point timeframe:

Week 12

End point values	Symbicort pMDI 80/4.5 ug	Symbicort pMDI 80/2.25 ug	Budesonide pMDI 80 ug	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	78	80	
Units: Liters				
least squares mean (confidence interval 95%)	0.25 (0.18 to 0.31)	0.19 (0.12 to 0.25)	0.15 (0.08 to 0.21)	

Statistical analyses

Statistical analysis title	FEV1 15m post-dose Change from basel to Week 12
Comparison groups	Symbicort pMDI 80/4.5 ug v Budesonide pMDI 80 ug
Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015 ^[21]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.18

Notes:

[21] - 2-sided

Statistical analysis title	FEV1 15m post-dose Change from basel to Week 12
Comparison groups	Budesonide pMDI 80 ug v Symbicort pMDI 80/2.25 ug
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.342 ^[22]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.12

Notes:

[22] - 2-sided

Statistical analysis title	FEV1 15m post-dose Change from basel to Week 12
Comparison groups	Symbicort pMDI 80/4.5 ug v Symbicort pMDI 80/2.25 ug
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.138 ^[23]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.15

Notes:

[23] - 2-sided

Secondary: Change from baseline to End of Study Average in Total Asthma Symptoms

End point title	Change from baseline to End of Study Average in Total Asthma Symptoms
End point description:	End of study average is defined as the average of available records from 7 days before up to and including the day prior to withdrawal from study or Week 12, minus the baseline measurement at randomization, for patients who remain in the study (irrespective of whether IP has been discontinued).
End point type	Secondary
End point timeframe:	Week 12

End point values	Symbicort pMDI 80/4.5 ug	Symbicort pMDI 80/2.25 ug	Budesonide pMDI 80 ug	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	70	72	73	
Units: Asthma symptom scores				
arithmetic mean (standard deviation)	-0.5 (± 0.73)	-0.6 (± 0.73)	-0.4 (± 0.55)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to End of Study Average in % of night time awakenings due to asthma symptoms

End point title	Change from baseline to End of Study Average in % of night
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End point description:

End of study average is defined as the percentage of nighttime awakenings due to asthma symptoms from 6 days before up to and additionally including the morning of withdrawal from study or Week 12, minus the baseline measurement at randomization, for patients who remain in the study (irrespective of whether IP has been discontinued).

End point type	Secondary
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End point timeframe:

Week 12

End point values	Symbicort pMDI 80/4.5 ug	Symbicort pMDI 80/2.25 ug	Budesonide pMDI 80 ug	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	85	82	
Units: Percent				
arithmetic mean (standard deviation)	-14 (\pm 29.15)	-17.3 (\pm 33.16)	-13 (\pm 21.87)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to End of Study Average in Total daily reliever medication

End point title	Change from baseline to End of Study Average in Total daily reliever medication
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End point description:

End of study average is defined as the average of available records from 7 days before up to and including the day prior to withdrawal from study or Week 12, minus the baseline measurement at randomization, for patients who remain in the study (irrespective of whether IP has been discontinued).

End point type	Secondary
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End point timeframe:

Week 12

End point values	Symbicort pMDI 80/4.5 ug	Symbicort pMDI 80/2.25 ug	Budesonide pMDI 80 ug	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	70	72	73	
Units: Number of reliever medication use				
arithmetic mean (standard deviation)	-0.7 (\pm 1.75)	-1.1 (\pm 2.37)	-0.7 (\pm 1.37)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to Study Period Average in Overall PAQLQ Score

End point title	Change from baseline to Study Period Average in Overall PAQLQ Score
End point description: Study period average is defined as the average of the post-baseline values during the study taken after first dose of investigational product up to and including withdrawal from study or Week 12, minus the baseline assessment at randomization, for patients who remain in the study (irrespective of whether IP has been discontinued).	
End point type	Secondary
End point timeframe: Randomisation up to week 12	

End point values	Symbicort pMDI 80/4.5 ug	Symbicort pMDI 80/2.25 ug	Budesonide pMDI 80 ug	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	80	82	
Units: PAQLQ Scores				
least squares mean (confidence interval 95%)	0.46 (0.3 to 0.62)	0.53 (0.38 to 0.69)	0.62 (0.47 to 0.78)	

Statistical analyses

Statistical analysis title	Overall PAQLQ score, study period average
Comparison groups	Symbicort pMDI 80/4.5 ug v Budesonide pMDI 80 ug
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.098 ^[24]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.36
upper limit	0.03

Notes:

[24] - 2-sided

Statistical analysis title	Overall PAQLQ score, study period average
Comparison groups	Budesonide pMDI 80 ug v Symbicort pMDI 80/2.25 ug

Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.367 ^[25]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	0.11

Notes:

[25] - 2-sided

Statistical analysis title	Overall PAQLQ score, study period average
Comparison groups	Symbicort pMDI 80/4.5 ug v Symbicort pMDI 80/2.25 ug
Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.449 ^[26]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	0.12

Notes:

[26] - 2-sided

Secondary: Number of patients with an asthma exacerbation during study

End point title	Number of patients with an asthma exacerbation during study
End point description: Number of patients that experienced an asthma exacerbation that required either emergency room treatment, hospitalization, systemic steroids, or an increase in, or additional asthma maintenance medication, during the study.	
End point type	Secondary
End point timeframe: Randomisation up to Week 12	

End point values	Symbicort pMDI 80/4.5 ug	Symbicort pMDI 80/2.25 ug	Budesonide pMDI 80 ug	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	90	93	90	
Units: Participants	9	12	12	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

12 weeks

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	Symbicort pMDI 80/4.5 ug
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Reporting group description:

Symbicort pMDI 80/4.5 ug x 2 BID

Reporting group title	Budesonide pMDI 80 ug
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Reporting group description:

Budesonide pMDI 80 ug x 2 BID

Reporting group title	Symbicort pMDI 80/2.25 ug
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Reporting group description:

Symbicort pMDI 80/2.25 ug x 2 BID

Serious adverse events	Symbicort pMDI 80/4.5 ug	Budesonide pMDI 80 ug	Symbicort pMDI 80/2.25 ug
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 90 (0.00%)	2 / 90 (2.22%)	0 / 93 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute lymphocytic leukaemia			
subjects affected / exposed	0 / 90 (0.00%)	1 / 90 (1.11%)	0 / 93 (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
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 90 (0.00%)	1 / 90 (1.11%)	0 / 93 (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

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

Non-serious adverse events	Symbicort pMDI 80/4.5 ug	Budesonide pMDI 80 ug	Symbicort pMDI 80/2.25 ug
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 90 (46.67%)	40 / 90 (44.44%)	41 / 93 (44.09%)
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 90 (4.44%)	0 / 90 (0.00%)	4 / 93 (4.30%)
occurrences (all)	4	0	4
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 90 (4.44%)	4 / 90 (4.44%)	4 / 93 (4.30%)
occurrences (all)	4	4	4
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	2 / 90 (2.22%)	0 / 90 (0.00%)	0 / 93 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	2 / 90 (2.22%)	0 / 90 (0.00%)	3 / 93 (3.23%)
occurrences (all)	2	0	3
Nausea			
subjects affected / exposed	0 / 90 (0.00%)	2 / 90 (2.22%)	0 / 93 (0.00%)
occurrences (all)	0	2	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	7 / 90 (7.78%)	10 / 90 (11.11%)	11 / 93 (11.83%)
occurrences (all)	7	10	11
Rhinitis allergic			
subjects affected / exposed	3 / 90 (3.33%)	4 / 90 (4.44%)	3 / 93 (3.23%)
occurrences (all)	3	5	3
Cough			
subjects affected / exposed	1 / 90 (1.11%)	4 / 90 (4.44%)	4 / 93 (4.30%)
occurrences (all)	1	5	4
Epistaxis			
subjects affected / exposed	1 / 90 (1.11%)	1 / 90 (1.11%)	2 / 93 (2.15%)
occurrences (all)	1	1	2
Nasal congestion			

subjects affected / exposed	2 / 90 (2.22%)	2 / 90 (2.22%)	0 / 93 (0.00%)
occurrences (all)	2	2	0
Oropharyngeal pain			
subjects affected / exposed	2 / 90 (2.22%)	1 / 90 (1.11%)	0 / 93 (0.00%)
occurrences (all)	2	1	0
Wheezing			
subjects affected / exposed	1 / 90 (1.11%)	2 / 90 (2.22%)	0 / 93 (0.00%)
occurrences (all)	1	2	0
Sinus congestion			
subjects affected / exposed	0 / 90 (0.00%)	0 / 90 (0.00%)	2 / 93 (2.15%)
occurrences (all)	0	0	2
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	9 / 90 (10.00%)	4 / 90 (4.44%)	12 / 93 (12.90%)
occurrences (all)	9	4	14
Nasopharyngitis			
subjects affected / exposed	4 / 90 (4.44%)	5 / 90 (5.56%)	2 / 93 (2.15%)
occurrences (all)	4	6	2
Pharyngitis			
subjects affected / exposed	5 / 90 (5.56%)	1 / 90 (1.11%)	3 / 93 (3.23%)
occurrences (all)	5	1	4
Sinusitis			
subjects affected / exposed	2 / 90 (2.22%)	1 / 90 (1.11%)	1 / 93 (1.08%)
occurrences (all)	2	1	1
Influenza			
subjects affected / exposed	1 / 90 (1.11%)	0 / 90 (0.00%)	2 / 93 (2.15%)
occurrences (all)	1	0	2
Pharyngitis streptococcal			
subjects affected / exposed	0 / 90 (0.00%)	1 / 90 (1.11%)	2 / 93 (2.15%)
occurrences (all)	0	1	2
Conjunctivitis			
subjects affected / exposed	1 / 90 (1.11%)	2 / 90 (2.22%)	0 / 93 (0.00%)
occurrences (all)	1	2	0
Rhinitis			
subjects affected / exposed	3 / 90 (3.33%)	2 / 90 (2.22%)	2 / 93 (2.15%)
occurrences (all)	3	2	2

Viral upper respiratory tract subjects affected / exposed occurrences (all)	0 / 90 (0.00%) 0	2 / 90 (2.22%) 2	1 / 93 (1.08%) 1
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More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 December 2014	The primary analysis was revised to include all clinic FEV1 data from all patients, regardless of discontinuation of IP. Text was added to clarify a negative urine pregnancy test result should be obtained (where appropriate) prior to certain procedures at Visit 2 and prior to administration of IP at all other visits. For patients who meet pre-defined asthma worsening criteria, contact by the site within 24 to 48 hours was made mandatory, but the necessity of a clinic visit was changed to be at the discretion of the investigator.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported