Clinical trial results:
A Phase 2, randomized, blinded, 5-period cross-over, placebo and active-controlled, multicenter, dose-finding study of single doses of formoterol 2.25 g, 4.5 g, and 9 g delivered via Symbicort pMDI and Foradil® Aerolizer® 12 g evaluating the bronchodilating effects and safety
in children, ages 6 to <12 years, with asthma who are receiving background treatment with budesonide pMDI 160 g bid

Summary

EudraCT number	2010-018316-32
Trial protocol	HU
Global end of trial date	16 October 2012

Results information

Result version number	v1 (current)
This version publication date	01 February 2017
First version publication date	07 August 2015

Trial information

Trial identification

Sponsor protocol code	D589GC00002

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	AstraZeneca R&D, 431 83 Mölndal, Sweden,
Public contact	Göran Eckerwall, MSD, AstraZeneca, ClinicalTrialTransparency@astrazeneca.com
Scientific contact	Göran Eckerwall, MSD, AstraZeneca, ClinicalTrialTransparency@astrazeneca.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 October 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 October 2012
Global end of trial reached?	Yes
Global end of trial date	16 October 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the bronchodilating effects of 3 doses of formoterol given in combination with budesonide as Symbicort pMDI in a population of asthmatic children demonstrated to be stable on a medium dose range of ICS therapy.

Protection of trial subjects:

An Ethics Committee (EC)/Institutional Review Board (IRB) approved the final clinical study protocol (CSP), including the final version of the Informed Consent Form (ICF) and any other written information, to be provided to the patients.

The principal investigator at each center ensured that both the patient (assent) and the parent or legal guardian (consent) were given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients were notified that they were free to withdraw from the study at any time. The patient was given the opportunity to ask questions and allowed time to consider the information provided.

The patient’s signed and dated informed assent and the parent or legal guardian’s consent were obtained and documented before conducting any study procedures.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 October 2010
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: 54
Worldwide total number of subjects	54
EEA total number of subjects	0

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	0

months)	
Children (2-11 years)	54
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:

This multicenter study was conducted in the United States between 7 October 2010 and 3 January 2012.

This was a 5-way cross-over study comparing single doses of 2.25 µg, 4.5 µg, and 9 µg of inhaled formoterol given as Symbicort pMDI and Foradil Aerolizer 12 µg dry powder inhaler with placebo, given in combination with budesonide pMDI 160 µg.

Pre-assignment

Screening details:

The study consisted of a screening visit, an enrolment visit, a 1- to 2-week run-in period, randomization at Visit 3, and 4 further visits (Visits 4-7)separated by approximately 7-day wash-out periods. Subjects received 1 of 5 single-dose treatments at Visits 3-7, in random order.

Period 1

Period 1 title	BUD 160/FM 2.25
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Data analyst, Carer, Assessor, Subject

Arms

Arm title	BUD 160/FM 2.25
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	BUD 160/FM 2.25
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

2.25 µg formoterol (as 80/2.25 µg Symbicort pMDI

Number of subjects in period 1	BUD 160/FM 2.25
Started	54
Completed	54

Period 2	
Period 2 title	BUD 160/FM 2.25 Washout
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms	
Arm title	BUD 160/FM 2.25 Washout
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	BUD 160/FM 2.25 Washout
Started	54
Completed	53
Not completed	1
Consent withdrawn by subject	1

Period 3	
Period 3 title	BUD 160/FM 4.5
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms	
Arm title	BUD 160/FM 4.5
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	BUD 160/FM 4.5
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

placebo HFA pMDI x 1 inhalation + 4.5 µg formoterol

Number of subjects in period 3	BUD 160/FM 4.5
Started	53
Completed	53

Period 4	
Period 4 title	BUD 160/FM 4.5 Washout
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	BUD 160/FM 4.5 Washout
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 4	BUD 160/FM 4.5 Washout
Started	53
Completed	53

Period 5	
Period 5 title	BUD 160/FM 9.0
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Arm title	BUD 160/FM 9.0
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	BUD 160/FM 9.0
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

placebo HFA pMDI x 1 inhalation + 9 µg formoterol

Number of subjects in period 5	BUD 160/FM 9.0
Started	53
Completed	53

Period 6	
Period 6 title	BUD 160/FM 9.0 Washout
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	BUD 160/FM 9.0 Washout
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 6	BUD 160/FM 9.0 Washout
Started	53
Completed	51
Not completed	2
Consent withdrawn by subject	1
Adverse event, non-fatal	1

Period 7	
Period 7 title	BUD 160
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Arm title	BUD 160
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	BUD 160
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

placebo HFA pMDI x 1 inhalation + 80 µg budesonide HFA pMDI

Number of subjects in period 7	BUD 160
Started	51
Completed	51

Period 8	
Period 8 title	BUD 160 Washout
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	BUD 160 Washout
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 8	BUD 160 Washout
Started	51
Completed	51

Period 9	
Period 9 title	BUD 160/Foradil 12.0
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Arm title	BUD 160/Foradil 12.0
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	BUD 160/Foradil 12.0
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Foradil Aerolizer 12 µg x 1 inhalation + 80 µg

Number of subjects in period 9	BUD 160/Foradil 12.0
Started	51
Completed	51

Period 10	
Period 10 title	BUD 160/Foradil 12.0 Washout
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms	
Arm title	BUD 160/Foradil 12.0 Washout
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 10	BUD 160/Foradil 12.0 Washout
Started	51
Completed	50
Not completed	1
Adverse event, non-fatal	1

Baseline characteristics

Reporting groups	
Reporting group title	BUD 160/FM 2.25

Reporting group description: -

Reporting group values	BUD 160/FM 2.25	Total	
Number of subjects	54	54	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	54	54	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous | Units: years			
arithmetic mean	9.2		
full range (min-max)	6 to 11	-	
Gender, Male/Female Units: participants			
Female	23	23	
Male	31	31	
Age group Units: Subjects			
>=6 to <8	11	11	
>=8 to <12	43	43	
Months since Diagnosis Units: months			
arithmetic mean	73.2		
standard deviation	± 39.16	-	

End points

End points reporting groups	
Reporting group title	BUD 160/FM 2.25
Reporting group description: -	
Reporting group title	BUD 160/FM 2.25 Washout
Reporting group description: -	
Reporting group title	BUD 160/FM 4.5
Reporting group description: -	
Reporting group title	BUD 160/FM 4.5 Washout
Reporting group description: -	
Reporting group title	BUD 160/FM 9.0
Reporting group description: -	
Reporting group title	BUD 160/FM 9.0 Washout
Reporting group description: -	
Reporting group title	BUD 160
Reporting group description: -	
Reporting group title	BUD 160 Washout
Reporting group description: -	
Reporting group title	BUD 160/Foradil 12.0
Reporting group description: -	
Reporting group title	BUD 160/Foradil 12.0 Washout
Reporting group description: -	

Primary: Average 12 hour forced expiratory volume in 1 second (FEV1)	
End point title	Average 12 hour forced expiratory volume in 1 second (FEV1)

End point description:

Pulmonary function tests consisted of 3 forced expiratory maneuvers in which the patient expired forcefully from total lung capacity to residual volume, recorded using a spirometer. FEV1 was obtained from the full expiratory flow-volume-time curve. FEV1 was measured at 3, 9, 15, 60, 120, 180, 240, 360, 480, 600 and 720 minutes post administration of randomized study medication. Twelve-hour serial FEV1 was calculated through an AUC determination and then divided by time, so that the final value is expressed in liters. One subject was incorrectly administered BUD 160/ formoterol (FM) 9.0 rather than BUD 160/ Foradil 12.0 at Period 4. Hence this subject is included in the Efficacy Analysis Set, but not the Safety Analysis Set for BUD 160/ Foradil 12.0. LOCF imputation method used.

End point type	Primary

End point timeframe:

at 3, 9, 15, 60, 120, 180, 240, 360, 480, 600 and 720 minutes postdose

End point values	BUD 160/FM 2.25	BUD 160/FM 4.5	BUD 160/FM 9.0	BUD 160
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	54	53	53	51
Units: liters				
least squares mean (standard error)	1.546 (± 0.0097)	1.594 (± 0.0099)	1.603 (± 0.0099)	1.489 (± 0.0101)

End point values	BUD 160/Foradil 12.0			
Subject group type	Reporting group			
Number of subjects analysed	51			
Units: liters				
least squares mean (standard error)	1.603 (± 0.0101)			

Statistical analyses

Statistical analysis title	Average 12-hour FEV1
Statistical analysis description:	
Factors in the ANCOVA model included: patient, visit, treatment, and the covariate pre-dose FEV1 from each visit. LOCF imputation method used.	
Comparison groups	BUD 160/FM 9.0 v BUD 160
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.114
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.087
upper limit	0.142
Variability estimate	Standard error of the mean
Dispersion value	0.014

Statistical analysis title	Average 12-hour FEV1
Statistical analysis description:	
Factors in the ANCOVA model included: patient, visit, treatment, and the covariate pre-dose FEV1 from each visit. LOCF imputation method used.	
Comparison groups	BUD 160/FM 4.5 v BUD 160
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.105

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.078
upper limit	0.133
Variability estimate	Standard error of the mean
Dispersion value	0.014

Statistical analysis title	Average 12-hour FEV1
Statistical analysis description:	
Factors in the ANCOVA model included: patient, visit, treatment, and the covariate pre-dose FEV1 from each visit. LOCF imputation method used.	
Comparison groups	BUD 160/FM 2.25 v BUD 160
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0001
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.058
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	0.085
Variability estimate	Standard error of the mean
Dispersion value	0.0141

Statistical analysis title	Average 12-hour FEV1
Statistical analysis description:	
Factors in the ANCOVA model included: patient, visit, treatment, and the covariate pre-dose FEV1 from each visit. LOCF imputation method used.	
Comparison groups	BUD 160/FM 4.5 v BUD 160/FM 9.0
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5223
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.009
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.036
upper limit	0.018
Variability estimate	Standard error of the mean
Dispersion value	0.0139

Statistical analysis title	Average 12-hour FEV1
Statistical analysis description:	
Factors in the ANCOVA model included: patient, visit, treatment, and the covariate pre-dose FEV1 from each visit. LOCF imputation method used.	
Comparison groups	BUD 160/FM 2.25 v BUD 160/FM 9.0
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0001
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.057
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.084
upper limit	-0.029
Variability estimate	Standard error of the mean
Dispersion value	0.0139

Statistical analysis title	Average 12-hour FEV1
Statistical analysis description:	
Factors in the ANCOVA model included: patient, visit, treatment, and the covariate pre-dose FEV1 from each visit. LOCF imputation method used.	
Comparison groups	BUD 160/FM 2.25 v BUD 160/FM 4.5
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0007
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.048
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.075
upper limit	-0.02
Variability estimate	Standard error of the mean
Dispersion value	0.0138

Statistical analysis title	Average 12-hour FEV1
Statistical analysis description:	
Factors in the ANCOVA model included: patient, visit, treatment, and the covariate pre-dose FEV1 from each visit. LOCF imputation method used.	

Comparison groups	BUD 160 v BUD 160/Foradil 12.0
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.114
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.142
upper limit	-0.086
Variability estimate	Standard error of the mean
Dispersion value	0.0141

Statistical analysis title	Average 12-hour FEV1
Statistical analysis description:	
Factors in the ANCOVA model included: patient, visit, treatment, and the covariate pre-dose FEV1 from each visit. LOCF imputation method used.	
Comparison groups	BUD 160/FM 2.25 v BUD 160/Foradil 12.0
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0001
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.056
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.084
upper limit	-0.028
Variability estimate	Standard error of the mean
Dispersion value	0.0141

Statistical analysis title	Average 12-hour FEV1
Statistical analysis description:	
Factors in the ANCOVA model included: patient, visit, treatment, and the covariate pre-dose FEV1 from each visit. LOCF imputation method used.	
Comparison groups	BUD 160/FM 4.5 v BUD 160/Foradil 12.0

Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5394
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.009
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.036
upper limit	0.019
Variability estimate	Standard error of the mean
Dispersion value	0.0141

Statistical analysis title	Average 12-hour FEV1
Statistical analysis description:	
Factors in the ANCOVA model included: patient, visit, treatment, and the covariate pre-dose FEV1 from each visit. LOCF imputation method used.	
Comparison groups	BUD 160/FM 9.0 v BUD 160/Foradil 12.0
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9863
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.027
upper limit	0.028
Variability estimate	Standard error of the mean
Dispersion value	0.014

Secondary: FEV1 at 12 hours after study medication inhalation

End point title	FEV1 at 12 hours after study medication inhalation
End point description:	
Pulmonary function tests consisted of 3 forced expiratory maneuvers in which the patient expired forcefully from total lung capacity to residual volume, recorded using a spirometer. The FEV1 value at 12 hours after dosing was taken as the 12-hour measurement (720 minutes) from the serial spirometry. One subject was incorrectly administered BUD 160/ formoterol (FM) 9.0 rather than BUD 160/ Foradil 12.0 at Period 4. Hence this subject is included in the Efficacy Analysis Set, but not the Safety Analysis Set for BUD 160/ Foradil 12.0. LOCF imputation method used.	
End point type	Secondary
End point timeframe:	
12 hours after dosing	

End point values	BUD 160/FM 2.25	BUD 160/FM 4.5	BUD 160/FM 9.0	BUD 160
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	54	53	53	51
Units: liters				
least squares mean (standard error)	1.641 (± 0.0175)	1.692 (± 0.0177)	1.731 (± 0.0177)	1.626 (± 0.0181)

End point values	BUD 160/Foradil 12.0			
Subject group type	Reporting group			
Number of subjects analysed	51			
Units: liters				
least squares mean (standard error)	1.709 (± 0.0182)			

Statistical analyses

Statistical analysis title	FEV1 at 12 hours after study medication
Statistical analysis description:	
Factors in the ANCOVA model included: patient, visit, treatment, and the covariate pre-dose FEV1 from each visit. LOCF imputation method used.	
Comparison groups	BUD 160/FM 9.0 v BUD 160
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.105
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.056
upper limit	0.155
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	FEV1 at 12 hours after study medication
Statistical analysis description:	
Factors in the ANCOVA model included: patient, visit, treatment, and the covariate pre-dose FEV1 from	

each visit. LOCF imputation method used.

Comparison groups	BUD 160/FM 4.5 v BUD 160
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0092
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.066
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.017
upper limit	0.116
Variability estimate	Standard error of the mean
Dispersion value	0.0252

Statistical analysis title	FEV1 at 12 hours after study medication

Statistical analysis description:

Factors in the ANCOVA model included: patient, visit, treatment, and the covariate pre-dose FEV1 from each visit. LOCF imputation method used.

Comparison groups	BUD 160/FM 2.25 v BUD 160
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5509
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.015
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.035
upper limit	0.065
Variability estimate	Standard error of the mean
Dispersion value	0.0252

Statistical analysis title	FEV1 at 12 hours after study medication

Statistical analysis description:

Factors in the ANCOVA model included: patient, visit, treatment, and the covariate pre-dose FEV1 from each visit. LOCF imputation method used.

Comparison groups	BUD 160/FM 4.5 v BUD 160/FM 9.0

Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1163
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.039
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.088
upper limit	0.01
Variability estimate	Standard error of the mean
Dispersion value	0.0249

Statistical analysis title	FEV1 at 12 hours after study medication
Statistical analysis description:	
Factors in the ANCOVA model included: patient, visit, treatment, and the covariate pre-dose FEV1 from each visit. LOCF imputation method used.	
Comparison groups	BUD 160/FM 2.25 v BUD 160/FM 9.0
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0004
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	-0.041
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	FEV1 at 12 hours after study medication
Statistical analysis description:	
Factors in the ANCOVA model included: patient, visit, treatment, and the covariate pre-dose FEV1 from each visit. LOCF imputation method used.	
Comparison groups	BUD 160/FM 2.25 v BUD 160/FM 4.5
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.04
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.051

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	-0.002
Variability estimate	Standard error of the mean
Dispersion value	0.0247

Statistical analysis title	FEV1 at 12 hours after study medication
Statistical analysis description:	
Factors in the ANCOVA model included: patient, visit, treatment, and the covariate pre-dose FEV1 from each visit. LOCF imputation method used.	
Comparison groups	BUD 160 v BUD 160/Foradil 12.0
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0011
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.083
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.133
upper limit	-0.034
Variability estimate	Standard error of the mean
Dispersion value	0.0252

Statistical analysis title	FEV1 at 12 hours after study medication
Statistical analysis description:	
Factors in the ANCOVA model included: patient, visit, treatment, and the covariate pre-dose FEV1 from each visit. LOCF imputation method used.	
Comparison groups	BUD 160/FM 2.25 v BUD 160/Foradil 12.0
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0077
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.068
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.118
upper limit	-0.018
Variability estimate	Standard error of the mean
Dispersion value	0.0254

Statistical analysis title	FEV1 at 12 hours after study medication
Statistical analysis description: Factors in the ANCOVA model included: patient, visit, treatment, and the covariate pre-dose FEV1 from each visit. LOCF imputation method used.	
Comparison groups	BUD 160/FM 4.5 v BUD 160/Foradil 12.0
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4957
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.017
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.067
upper limit	0.033
Variability estimate	Standard error of the mean
Dispersion value	0.0252

Statistical analysis title	FEV1 at 12 hours after study medication
Statistical analysis description: Factors in the ANCOVA model included: patient, visit, treatment, and the covariate pre-dose FEV1 from each visit. LOCF imputation method used.	
Comparison groups	BUD 160/FM 9.0 v BUD 160/Foradil 12.0
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.38
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.022
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.027
upper limit	0.071
Variability estimate	Standard error of the mean
Dispersion value	0.025

Secondary: Maximal FEV1 during the 12-hour study period	
End point title	Maximal FEV1 during the 12-hour study period

End point description:

Pulmonary function tests consisted of 3 forced expiratory maneuvers in which the patient expired forcefully from total lung capacity to residual volume, recorded using a spirometer. FEV1 was measured at 3, 9, 15, 60, 120, 180, 240, 360, 480, 600 and 720 minutes post administration of randomized study medication. The maximum FEV1 value was defined as the largest observed FEV1 value recorded during each 12-hour serial spirometry procedure. One subject was incorrectly administered BUD 160/ formoterol (FM) 9.0 rather than BUD 160/ Foradil 12.0 at Period 4. Hence this subject is included in the Efficacy Analysis Set, but not the Safety Analysis Set for BUD 160/ Foradil 12.0.

End point type	Secondary

End point timeframe:

at 3, 9, 15, 60, 120, 180, 240, 360, 480, 600 and 720 minutes postdose

End point values	BUD 160/FM 2.25	BUD 160/FM 4.5	BUD 160/FM 9.0	BUD 160
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	54	53	53	51
Units: liters				
least squares mean (standard error)	1.833 (± 0.0119)	1.889 (± 0.012)	1.884 (± 0.012)	1.777 (± 0.0123)

End point values	BUD 160/Foradil 12.0			
Subject group type	Reporting group			
Number of subjects analysed	51			
Units: liters				
least squares mean (standard error)	1.892 (± 0.0123)			

Statistical analyses

Statistical analysis title	Maximal FEV1 during the 12-hour study period

Statistical analysis description:

Factors in the Analysis of Covariance model included: patient, visit, treatment, and the covariate pre-dose FEV1 from each visit.

Comparison groups	BUD 160/FM 9.0 v BUD 160
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.107

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.073
upper limit	0.14
Variability estimate	Standard error of the mean
Dispersion value	0.017

Statistical analysis title	Maximal FEV1 during the 12-hour study period
Statistical analysis description:	
Factors in the Analysis of Covariance model included: patient, visit, treatment, and the covariate pre-dose FEV1 from each visit.	
Comparison groups	BUD 160/FM 4.5 v BUD 160
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.112
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.078
upper limit	0.146
Variability estimate	Standard error of the mean
Dispersion value	0.0171

Statistical analysis title	Maximal FEV1 during the 12-hour study period
Statistical analysis description:	
Factors in the Analysis of Covariance model included: patient, visit, treatment, and the covariate pre-dose FEV1 from each visit.	
Comparison groups	BUD 160/FM 2.25 v BUD 160
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0011
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.057
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.023
upper limit	0.09
Variability estimate	Standard error of the mean
Dispersion value	0.0172

Statistical analysis title	Maximal FEV1 during the 12-hour study period
Statistical analysis description:	
Factors in the Analysis of Covariance model included: patient, visit, treatment, and the covariate pre-dose FEV1 from each visit.	
Comparison groups	BUD 160/FM 4.5 v BUD 160/FM 9.0
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7589
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.005
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.028
upper limit	0.039
Variability estimate	Standard error of the mean
Dispersion value	0.0169

Statistical analysis title	Maximal FEV1 during the 12-hour study period
Statistical analysis description:	
Factors in the Analysis of Covariance model included: patient, visit, treatment, and the covariate pre-dose FEV1 from each visit.	
Comparison groups	BUD 160/FM 2.25 v BUD 160/FM 9.0
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0035
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.084
upper limit	-0.017
Variability estimate	Standard error of the mean
Dispersion value	0.017

Statistical analysis title	Maximal FEV1 during the 12-hour study period
Statistical analysis description:	
Factors in the Analysis of Covariance model included: patient, visit, treatment, and the covariate pre-dose FEV1 from each visit.	

Comparison groups	BUD 160/FM 2.25 v BUD 160/FM 4.5
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0011
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.055
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.089
upper limit	-0.022
Variability estimate	Standard error of the mean
Dispersion value	0.0168

Statistical analysis title	Maximal FEV1 during the 12-hour study period

Statistical analysis description:

Factors in the Analysis of Covariance model included: patient, visit, treatment, and the covariate pre-dose FEV1 from each visit.

Comparison groups	BUD 160 v BUD 160/Foradil 12.0
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.115
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.149
upper limit	-0.081
Variability estimate	Standard error of the mean
Dispersion value	0.0171

Statistical analysis title	Maximal FEV1 during the 12-hour study period

Statistical analysis description:

Factors in the Analysis of Covariance model included: patient, visit, treatment, and the covariate pre-dose FEV1 from each visit.

Comparison groups	BUD 160/FM 2.25 v BUD 160/Foradil 12.0

Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0008
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.058
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.092
upper limit	-0.024
Variability estimate	Standard error of the mean
Dispersion value	0.0172

Statistical analysis title	Maximal FEV1 during the 12-hour study period
Statistical analysis description:	
Factors in the Analysis of Covariance model included: patient, visit, treatment, and the covariate pre-dose FEV1 from each visit.	
Comparison groups	BUD 160/FM 4.5 v BUD 160/Foradil 12.0
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8582
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.003
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.037
upper limit	0.031
Variability estimate	Standard error of the mean
Dispersion value	0.0172

Statistical analysis title	Maximal FEV1 during the 12-hour study period
Statistical analysis description:	
Factors in the Analysis of Covariance model included: patient, visit, treatment, and the covariate pre-dose FEV1 from each visit.	
Comparison groups	BUD 160/FM 9.0 v BUD 160/Foradil 12.0
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6276
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.008

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.042
upper limit	0.025
Variability estimate	Standard error of the mean
Dispersion value	0.017

Secondary: Urinary excretion of formoterol during the 12 hours following inhalation of study drug

End point title	Urinary excretion of formoterol during the 12 hours following inhalation of study drug

End point description:

The amount of formoterol excreted unchanged in urine over the 12-hour period after administration [Ae(0-12h)] was calculated from the concentration of formoterol in urine multiplied by the total volume of urine collected. Volume was determined from the weight of the collected urine times an assumed urine density of 1020 g/L. The data for six patients who did not have measurable formoterol in their urine on the Foradil 12 µg treatment day was excluded from the analysis. All other urine concentrations below the lower limit of quantification were set to zero. One subject was incorrectly administered BUD 160/ formoterol (FM) 9.0 rather than BUD 160/ Foradil 12.0 at Period 4. Hence this subject is included in the Efficacy Analysis Set, but not the Safety Analysis Set for BUD 160/ Foradil 12.0.

End point type	Secondary

End point timeframe:

0 to 12 hours

End point values	BUD 160/FM 2.25	BUD 160/FM 4.5	BUD 160/FM 9.0	BUD 160/Foradil 12.0
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	52	51	43
Units: pmol				
arithmetic mean (standard deviation)	278.39 (± 204.52)	532.65 (± 416.762)	1090.88 (± 681.941)	980.47 (± 789.274)

Statistical analyses

Statistical analysis title	Amount of urinary excretion of formoterol

Statistical analysis description:

Factors in the ANOVA model included: patient, period and treatment.

Comparison groups	BUD 160/FM 2.25 v BUD 160/FM 4.5
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	0.52

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.393
upper limit	0.7

Statistical analysis title	Urinary excretion of formoterol
Statistical analysis description:	
Factors in the ANOVA model included: patient, period and treatment.	
Comparison groups	BUD 160/FM 2.25 v BUD 160/FM 9.0
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.194
upper limit	0.347

Statistical analysis title	Urinary excretion of formoterol
Statistical analysis description:	
Factors in the ANOVA model included: patient, period and treatment.	
Comparison groups	BUD 160/FM 2.25 v BUD 160/Foradil 12.0
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.214
upper limit	0.396

Statistical analysis title	Urinary excretion of formoterol
Statistical analysis description:	
Factors in the ANOVA model included: patient, period and treatment.	
Comparison groups	BUD 160/FM 4.5 v BUD 160/FM 9.0

Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.371
upper limit	0.659

Statistical analysis title	Urinary excretion of formoterol
Statistical analysis description: Factors in the ANOVA model included: patient, period and treatment.	
Comparison groups	BUD 160/FM 9.0 v BUD 160/Foradil 12.0
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4512
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.827
upper limit	1.528

Statistical analysis title	Urinary excretion of formoterol
Statistical analysis description: Factors in the ANOVA model included: patient, period and treatment.	
Comparison groups	BUD 160/FM 4.5 v BUD 160/Foradil 12.0
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0002
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.409
upper limit	0.755

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were collected from the enrollment visit until visit 7(5 weeks after randomization). AEs occuring on or after the first dose of medication are included in the summaries below.

Adverse event reporting additional description:

One subject was incorrectly administered BUD 160/ formoterol (FM) 9.0 rather than BUD 160/ Foradil 12.0 at Period 4. Hence this subject is included in the Efficacy Analysis Set, but not the Safety Analysis Set for BUD 160/ Foradil 12.0.

A total of 13 patients reported non-serious AEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	BUD 160/FM 2.25
Reporting group description:	
2.25 µg formoterol (as 80/2.25 µg Symbicort pMDI x 1 inhalation) + 40 µg budesonide HFA pMDI × 2 inhalations	
Reporting group title	BUD 160/FM 4.5
Reporting group description:	
placebo HFA pMDI x 1 inhalation + 4.5 µg formoterol (as 80/2.25 µg Symbicort pMDI x 2 inhalations)	
Reporting group title	BUD 160
Reporting group description:	
placebo HFA pMDI x 1 inhalation + 80 µg budesonide HFA pMDI x 2 inhalations	
Reporting group title	BUD 160/ Foradil 12.0
Reporting group description:	
Foradil Aerolizer 12 µg x 1 inhalation + 80 µg budesonide HFA pMDI × 2 inhalations	
Reporting group title	BUD 160/FM 9.0
Reporting group description:	
placebo HFA pMDI x 1 inhalation + 9 µg formoterol (as 80/4.5 µg Symbicort pMDI x 2 inhalations)	

Serious adverse events	BUD 160/FM 2.25	BUD 160/FM 4.5	BUD 160
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 54 (0.00%)	0 / 53 (0.00%)	0 / 51 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	BUD 160/ Foradil 12.0	BUD 160/FM 9.0	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 50 (0.00%)	0 / 53 (0.00%)	

number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	BUD 160/FM 2.25	BUD 160/FM 4.5	BUD 160
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 54 (1.85%)	1 / 53 (1.89%)	2 / 51 (3.92%)
Nervous system disorders			
Headache			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 54 (1.85%)	1 / 53 (1.89%)	2 / 51 (3.92%)
occurrences (all)	1	2	4
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 54 (0.00%)	1 / 53 (1.89%)	0 / 51 (0.00%)
occurrences (all)	0	2	0

Non-serious adverse events	BUD 160/ Foradil 12.0	BUD 160/FM 9.0	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 50 (2.00%)	5 / 53 (9.43%)	
Nervous system disorders			
Headache			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	0 / 50 (0.00%)	5 / 53 (9.43%)	
occurrences (all)	0	5	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 50 (2.00%)	1 / 53 (1.89%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported