



**Clinical trial results:**

**Study 201012: A Dose-Finding Study of batefenterol (GSK961081) via Dry Powder Inhaler in Patients with COPD.**

**Summary**

EudraCT number	2015-001409-15
Trial protocol	DE
Global end of trial date	06 July 2016

**Results information**

Result version number	v1 (current)
This version publication date	19 February 2017
First version publication date	19 February 2017

**Trial information**

**Trial identification**

Sponsor protocol code	201012
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**Additional study identifiers**

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

Notes:

**Sponsors**

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

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	11 October 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	06 July 2016
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the dose response, efficacy and safety of five dosage regimens of batefenterol delivered via the DPI in participants with COPD.

Protection of trial subjects:

Not Applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 November 2015
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	Germany: 89
Country: Number of subjects enrolled	South Africa: 70
Country: Number of subjects enrolled	United States: 164
Worldwide total number of subjects	323
EEA total number of subjects	89

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)	0
Adults (18-64 years)	183
From 65 to 84 years	140
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Eligible participants (par.) with an established clinical history of Chronic Obstructive Pulmonary Disease (COPD), were included in this dose-finding study of batefenterol (BAT). Of 585 par. screened, 324 par. were randomized in the study, out of which one par. was randomized in error and was not included in the Intent-to-Treat analysis.

### Pre-assignment

Screening details:

Pre-bronchodilator and post albuterol/salbutamol spirometry testing were performed at Screening visit. Post-albuterol/salbutamol (Forced expiratory Volume in One Second) FEV1 and FEV1/ (Forced Vital Capacity) FVC values were used to determine subject eligibility. Participants underwent 2 weeks run-in period.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Placebo

Arm description:

Participants received 1 actuation of placebo inhalation powder via Dry Powder Inhaler (DPI) (containing 2 strips) once daily in the morning for 42 days.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Placebo drug was administered once daily in the morning for 42 days in 2 strips via Dry Powder Inhaler (DPI)

<b>Arm title</b>	Batefenterol 37.5 µg
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Arm description:

Participants received 1 actuation of batefenterol 37.5 µg inhalation powder administered via DPI (containing 2 strips) once daily in the morning for 42 days. First strip contained lactose and second strip contained batefenterol blended with lactose.

Arm type	Experimental
Investigational medicinal product name	Batefenterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Batefenterol of strengths 37.5 µg, 75 µg, 150 µg, 300 µg or 600 µg were administered to randomized participants once daily in the morning for 42 days in 2 strips via Dry Powder Inhaler (DPI)

<b>Arm title</b>	Batefenterol 75 µg
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Arm description:

Participants received 1 actuation of batenfenterol 75 µg inhalation powder administered via DPI (containing 2 strips) once daily in the morning for 42 days. First strip contained lactose and second strip contained batenfenterol blended with lactose.

Arm type	Experimental
Investigational medicinal product name	Batenfenterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Batenfenterol of strengths 37.5 µg, 75 µg, 150 µg, 300 µg or 600 µg were administered to randomized participants once daily in the morning for 42 days in 2 strips via Dry Powder Inhaler (DPI)

<b>Arm title</b>	Batenfenterol 150 µg
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Arm description:

Participants received 1 actuation of batenfenterol 150 µg inhalation powder administered via DPI (containing 2 strips) once daily in the morning for 42 days. First strip contained lactose and second strip contained batenfenterol blended with lactose.

Arm type	Experimental
Investigational medicinal product name	Batenfenterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Batenfenterol of strengths 37.5 µg, 75 µg, 150 µg, 300 µg or 600 µg were administered to randomized participants once daily in the morning for 42 days in 2 strips via Dry Powder Inhaler (DPI)

<b>Arm title</b>	Batenfenterol 300 µg
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Arm description:

Participants received 1 actuation of batenfenterol 300 µg inhalation powder administered via DPI (containing 2 strips) once daily in the morning for 42 days. First strip contained lactose and second strip contained batenfenterol blended with lactose.

Arm type	Experimental
Investigational medicinal product name	Batenfenterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Batenfenterol of strengths 37.5 µg, 75 µg, 150 µg, 300 µg or 600 µg were administered to randomized participants once daily in the morning for 42 days in 2 strips via Dry Powder Inhaler (DPI)

<b>Arm title</b>	Batenfenterol 600 µg
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Arm description:

Participants received 1 actuation of batenfenterol 600 µg inhalation powder administered via DPI (containing 2 strips) once daily in the morning for 42 days. First strip contained lactose and second strip contained batenfenterol blended with lactose.

Arm type	Experimental
Investigational medicinal product name	Batenfenterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Batenfenterol of strengths 37.5 µg, 75 µg, 150 µg, 300 µg or 600 µg were administered to randomized

participants once daily in the morning for 42 days in 2 strips via Dry Powder Inhaler (DPI)

<b>Arm title</b>	UMEC/VI 62.5/25 µg
Arm description: Participants received 1 actuation of UMEC/VI 62.5/25 µg inhalation powder administered via DPI (containing 2 strips) once daily in the morning for 42 days. First strip contained UMEC blended with lactose and magnesium stearate. Second strip contained VI blended with lactose and magnesium stearate.	
Arm type	Active comparator
Investigational medicinal product name	UMEC/VI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

UMEC/VI (62.5/25 µg) inhalation powder was administered once daily in the morning for 42 days in 2 strips via Dry Powder Inhaler (DPI)

<b>Number of subjects in period 1</b>	Placebo	Batefenterol 37.5 µg	Batefenterol 75 µg
Started	46	46	46
Completed	44	43	41
Not completed	2	3	5
Physician decision	-	1	-
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	1	-	2
Withdrawal Request by GSK	-	-	2
Par. Reached Stopping Criteria	1	1	-
Par. did not Meet Continuation Criteria	-	-	-
Lost to follow-up	-	-	1
Lack of efficacy	-	1	-

<b>Number of subjects in period 1</b>	Batefenterol 150 µg	Batefenterol 300 µg	Batefenterol 600 µg
Started	45	47	46
Completed	40	41	44
Not completed	5	6	2
Physician decision	-	-	-
Consent withdrawn by subject	2	1	-
Adverse event, non-fatal	-	-	-
Withdrawal Request by GSK	-	-	-
Par. Reached Stopping Criteria	2	1	1

Par. did not Meet Continuation Criteria	-	-	1
Lost to follow-up	1	-	-
Lack of efficacy	-	4	-

<b>Number of subjects in period 1</b>	UMEC/VI 62.5/25 µg
Started	47
Completed	47
Not completed	0
Physician decision	-
Consent withdrawn by subject	-
Adverse event, non-fatal	-
Withdrawal Request by GSK	-
Par. Reached Stopping Criteria	-
Par. did not Meet Continuation Criteria	-
Lost to follow-up	-
Lack of efficacy	-

## Baseline characteristics

### Reporting groups

Reporting group title	Placebo
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Reporting group description:

Participants received 1 actuation of placebo inhalation powder via Dry Powder Inhaler (DPI) (containing 2 strips) once daily in the morning for 42 days.

Reporting group title	Batefenterol 37.5 µg
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Reporting group description:

Participants received 1 actuation of batefenterol 37.5 µg inhalation powder administered via DPI (containing 2 strips) once daily in the morning for 42 days. First strip contained lactose and second strip contained batefenterol blended with lactose.

Reporting group title	Batefenterol 75 µg
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Reporting group description:

Participants received 1 actuation of batefenterol 75 µg inhalation powder administered via DPI (containing 2 strips) once daily in the morning for 42 days. First strip contained lactose and second strip contained batefenterol blended with lactose.

Reporting group title	Batefenterol 150 µg
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Reporting group description:

Participants received 1 actuation of batefenterol 150 µg inhalation powder administered via DPI (containing 2 strips) once daily in the morning for 42 days. First strip contained lactose and second strip contained batefenterol blended with lactose.

Reporting group title	Batefenterol 300 µg
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Reporting group description:

Participants received 1 actuation of batefenterol 300 µg inhalation powder administered via DPI (containing 2 strips) once daily in the morning for 42 days. First strip contained lactose and second strip contained batefenterol blended with lactose.

Reporting group title	Batefenterol 600 µg
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Reporting group description:

Participants received 1 actuation of batefenterol 600 µg inhalation powder administered via DPI (containing 2 strips) once daily in the morning for 42 days. First strip contained lactose and second strip contained batefenterol blended with lactose.

Reporting group title	UMEC/VI 62.5/25 µg
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Reporting group description:

Participants received 1 actuation of UMEC/VI 62.5/25 µg inhalation powder administered via DPI (containing 2 strips) once daily in the morning for 42 days. First strip contained UMEC blended with lactose and magnesium stearate. Second strip contained VI blended with lactose and magnesium stearate.

Reporting group values	Placebo	Batefenterol 37.5 µg	Batefenterol 75 µg
Number of subjects	46	46	46
Age categorical Units: Subjects			

Age continuous			
Age continuous description			
Units: years			
arithmetic mean	61.1	61.9	63
standard deviation	± 6.6	± 8.16	± 7.21
Gender categorical			
Gender categorical description			
Units: Subjects			

Female	19	19	13
Male	27	27	33

Race/Ethnicity, Customized Units: Subjects			
African American/African Heritage	6	3	3
White	38	35	40
Multiple Geographic Ancestries	2	8	3

<b>Reporting group values</b>	Batefenterol 150 µg	Batefenterol 300 µg	Batefenterol 600 µg
Number of subjects	45	47	46
Age categorical Units: Subjects			

Age continuous			
Age continuous description			
Units: years			
arithmetic mean	63.6	61.9	63.7
standard deviation	± 8.11	± 8.7	± 7.06
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	26	20	25
Male	19	27	21
Race/Ethnicity, Customized Units: Subjects			
African American/African Heritage	2	4	3
White	35	40	38
Multiple Geographic Ancestries	8	3	5

<b>Reporting group values</b>	UMEC/VI 62.5/25 µg	Total	
Number of subjects	47	323	
Age categorical Units: Subjects			

Age continuous			
Age continuous description			
Units: years			
arithmetic mean	62.8		
standard deviation	± 8.46	-	
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	21	143	
Male	26	180	
Race/Ethnicity, Customized Units: Subjects			
African American/African Heritage	2	23	

White	39	265	
Multiple Geographic Ancestries	6	35	

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## End points

### End points reporting groups

Reporting group title	Placebo
Reporting group description: Participants received 1 actuation of placebo inhalation powder via Dry Powder Inhaler (DPI) (containing 2 strips) once daily in the morning for 42 days.	
Reporting group title	Batefenterol 37.5 µg
Reporting group description: Participants received 1 actuation of batefenterol 37.5 µg inhalation powder administered via DPI (containing 2 strips) once daily in the morning for 42 days. First strip contained lactose and second strip contained batefenterol blended with lactose.	
Reporting group title	Batefenterol 75 µg
Reporting group description: Participants received 1 actuation of batefenterol 75 µg inhalation powder administered via DPI (containing 2 strips) once daily in the morning for 42 days. First strip contained lactose and second strip contained batefenterol blended with lactose.	
Reporting group title	Batefenterol 150 µg
Reporting group description: Participants received 1 actuation of batefenterol 150 µg inhalation powder administered via DPI (containing 2 strips) once daily in the morning for 42 days. First strip contained lactose and second strip contained batefenterol blended with lactose.	
Reporting group title	Batefenterol 300 µg
Reporting group description: Participants received 1 actuation of batefenterol 300 µg inhalation powder administered via DPI (containing 2 strips) once daily in the morning for 42 days. First strip contained lactose and second strip contained batefenterol blended with lactose.	
Reporting group title	Batefenterol 600 µg
Reporting group description: Participants received 1 actuation of batefenterol 600 µg inhalation powder administered via DPI (containing 2 strips) once daily in the morning for 42 days. First strip contained lactose and second strip contained batefenterol blended with lactose.	
Reporting group title	UMEC/VI 62.5/25 µg
Reporting group description: Participants received 1 actuation of UMEC/VI 62.5/25 µg inhalation powder administered via DPI (containing 2 strips) once daily in the morning for 42 days. First strip contained UMEC blended with lactose and magnesium stearate. Second strip contained VI blended with lactose and magnesium stearate.	

### Primary: Change from Baseline in Weighted Mean FEV1 over 0 to 6 hours post-dose at Day 42

End point title	Change from Baseline in Weighted Mean FEV1 over 0 to 6 hours post-dose at Day 42
End point description: FEV1 is defined as the volume of air that can be forced out in one second after taking a deep breath. Weighted-mean change from Baseline was the weighted-mean FEV1 on Day 42 minus Baseline where Baseline is defined as the average of Day1 pre-dose FEV1 measured at -30 minutes and 0 minutes. The 0-6 hour (Hr.) serial FEV1 was collected at Day 1 (Visit 2) and Day 42 (Visit 6). The weighted-mean was derived by calculating the area under the curve (AUC) of FEV1 over the 6 hour period, and then dividing it by the 6-hour time interval. Batefenterol dose for each individual was compared with placebo or UMEC/VI. The change from Baseline in FEV1 was statistically analyzed using Bayesian Emax modeling of the dose response curve. Intent-to-Treat (ITT) Population comprised of all participants randomized to treatment and who received at least one dose of study medication. Participants with FEV1 values available at Baseline and Day 42 were analyzed.	
End point type	Primary

End point timeframe:

Baseline and Day 42

<b>End point values</b>	Placebo	Batefenterol 37.5 µg	Batefenterol 75 µg	Batefenterol 150 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	44 <sup>[1]</sup>	42 <sup>[2]</sup>	41 <sup>[3]</sup>	39 <sup>[4]</sup>
Units: Milliliters (mL)				
arithmetic mean (standard error)	-9.9 (± 31.21)	181.2 (± 30.85)	221.68 (± 21.09)	251.87 (± 16.3)

Notes:

[1] - ITT Population.

[2] - ITT Population.

[3] - ITT Population.

[4] - ITT Population.

<b>End point values</b>	Batefenterol 300 µg	Batefenterol 600 µg	UMEC/VI 62.5/25 µg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41 <sup>[5]</sup>	44 <sup>[6]</sup>	47 <sup>[7]</sup>	
Units: Milliliters (mL)				
arithmetic mean (standard error)	271.47 (± 19.49)	282.94 (± 24.2)	275.43 (± 29.91)	

Notes:

[5] - ITT Population.

[6] - ITT Population.

[7] - ITT Population.

## Statistical analyses

<b>Statistical analysis title</b>	Statistical analysis 1
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Statistical analysis description:

The 95% Bayesian credible interval for the mean difference between batefenterol 37.5 µg dose and placebo (batefenterol 37.5 µg minus placebo) was estimated.

Comparison groups	Batefenterol 37.5 µg v Placebo
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	191.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	101.07
upper limit	284.26

<b>Statistical analysis title</b>	Statistical analysis 2
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**Statistical analysis description:**

The 95% Bayesian credible interval for differences between each individual batedfenterol 75 µg dose and placebo was estimated.

Comparison groups	Placebo v Batedfenterol 75 µg
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	231.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	149.31
upper limit	310.02

**Statistical analysis title** | Statistical analysis 3**Statistical analysis description:**

The 95% Bayesian credible interval for differences between each individual batedfenterol 150 µg dose and placebo was estimated.

Comparison groups	Placebo v Batedfenterol 150 µg
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	261.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	189.85
upper limit	332.25

**Statistical analysis title** | Statistical analysis 4**Statistical analysis description:**

The 95% Bayesian credible interval for differences between each individual batedfenterol 300 µg dose and placebo was estimated.

Comparison groups	Placebo v Batedfenterol 300 µg
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	281.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	212.35
upper limit	351.3

<b>Statistical analysis title</b>	Statistical analysis 5
Statistical analysis description: The 95% Bayesian credible interval for differences between each individual batefenterol 600 µg dose and placebo was estimated.	
Comparison groups	Placebo v Batefenterol 600 µg
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	292.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	223.02
upper limit	364.42

### Secondary: Change from Baseline in Trough FEV1 at Day 42

End point title	Change from Baseline in Trough FEV1 at Day 42
End point description: Trough FEV1 at Day 42 is the mean volume of air that can be forced out in one second after taking a deep breath at the approximately 23 Hrs and 24 Hrs assessments after the last administration of study drug. Batefenterol dose for each individual was compared with placebo or UMEC/VI. Change from Baseline was calculated as trough FEV1 on Day 42 minus baseline, where Baseline is defined as the average of Day1 pre-dose FEV1 measured at -30 minutes and 0 minutes. The Maximum Likelihood Estimation (MLE) method of dose response modeling with Emax modeling without Bayesian priors was used. Participants with FEV1 values available at Baseline and Day 42 after 24 hrs after the last administration of study drug were analyzed.	
End point type	Secondary
End point timeframe: Baseline and Day 42	

End point values	Placebo	Batefenterol 37.5 µg	Batefenterol 75 µg	Batefenterol 150 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	44 <sup>[8]</sup>	43 <sup>[9]</sup>	41 <sup>[10]</sup>	40 <sup>[11]</sup>
Units: mL				
arithmetic mean (standard error)	-35.7 (± 30.8)	146.5 (± 28.3)	160.8 (± 15.6)	168.9 (± 15)

Notes:

- [8] - ITT Population
- [9] - ITT Population
- [10] - ITT Population
- [11] - ITT Population

End point values	Batefenterol 300 µg	Batefenterol 600 µg	UMEC/VI 62.5/25 µg	

Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41 <sup>[12]</sup>	44 <sup>[13]</sup>	47 <sup>[14]</sup>	
Units: mL				
arithmetic mean (standard error)	173.2 (± 18.2)	175.4 (± 20.5)	209 (± 29.8)	

Notes:

[12] - ITT Population

[13] - ITT Population

[14] - ITT Population

## Statistical analyses

<b>Statistical analysis title</b>	Statistical analysis 1
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Statistical analysis description:

The 95% confidence interval for the difference between 37.5 µg Batefenterol and Placebo was estimated.

Comparison groups	Batefenterol 37.5 µg v Placebo
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	182.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	99.8
upper limit	264.6

<b>Statistical analysis title</b>	Statistical analysis 2
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Statistical analysis description:

The 95% confidence interval for the difference between 75 µg Batefenterol and Placebo was estimated.

Comparison groups	Batefenterol 75 µg v Placebo
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	196.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	128.4
upper limit	264.8

<b>Statistical analysis title</b>	Statistical analysis 3
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Statistical analysis description:

The 95% confidence interval for the difference between 150 µg Batefenterol and Placebo was estimated.

Comparison groups	Batefenterol 150 µg v Placebo
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Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	204.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	137.2
upper limit	272.1

<b>Statistical analysis title</b>	Statistical analysis 4
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Statistical analysis description:

The 95% confidence interval for the difference between 300 µg Batefenterol and Placebo was estimated.

Comparison groups	Batefenterol 300 µg v Placebo
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	208.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	138.7
upper limit	279.2

<b>Statistical analysis title</b>	Statistical analysis 5
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Statistical analysis description:

The 95% confidence interval for the difference between 600 µg Batefenterol and Placebo was estimated.

Comparison groups	Batefenterol 600 µg v Placebo
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	211.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	138.6
upper limit	283.7

## Adverse events

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### Adverse events information

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Timeframe for reporting adverse events:

Serious Adverse Events (SAEs) were collected from start of study until follow-up contact (Visit7[Visit 6/EW+7days]). Non-serious AEs were collected from start of study treatment (Visit2) until follow-up contact (Visit7[Visit 6/EW+7days]).

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Adverse event reporting additional description:

AE and SAE analysis was based on ITT Population consisting of all participants randomized to treatment and who received at least one dose of study medication. On-treatment AEs and SAEs were defined as those with onset between treatment start date and treatment stop date +1.

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Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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### Reporting groups

Reporting group title	Placebo
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Reporting group description:

Participants received 1 actuation of placebo inhalation powder via Dry Powder Inhaler (DPI) (containing 2 strips) once daily in the morning for 42 days.

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Reporting group title	Batefenterol 75 µg
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Reporting group description:

Participants received 1 actuation of batefenterol 75 µg inhalation powder administered via DPI (containing 2 strips) once daily in the morning for 42 days. First strip contained lactose and second strip contained batefenterol blended with lactose.

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Reporting group title	Batefenterol 37.5 µg
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Reporting group description:

Participants received 1 actuation of batefenterol 37.5 µg inhalation powder administered via DPI (containing 2 strips) once daily in the morning for 42 days. First strip contained lactose and second strip contained batefenterol blended with lactose.

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Reporting group title	Batefenterol 150 µg
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Reporting group description:

Participants received 1 actuation of batefenterol 150 µg inhalation powder administered via DPI (containing 2 strips) once daily in the morning for 42 days. First strip contained lactose and second strip contained batefenterol blended with lactose.

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Reporting group title	Batefenterol 300 µg
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Reporting group description:

Participants received 1 actuation of batefenterol 300 µg inhalation powder administered via DPI (containing 2 strips) once daily in the morning for 42 days. First strip contained lactose and second strip contained batefenterol blended with lactose.

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Reporting group title	Batefenterol 600 µg
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Reporting group description:

Participants received 1 actuation of batefenterol 600 µg inhalation powder administered via DPI (containing 2 strips) once daily in the morning for 42 days. First strip contained lactose and second strip contained batefenterol blended with lactose.

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Reporting group title	UMEC/VI 62.5/25 µg
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Reporting group description:

Participants received 1 actuation of UMEC/VI 62.5/25 µg inhalation powder administered via DPI (containing 2 strips) once daily in the morning for 42 days. First strip contained UMEC blended with lactose and magnesium stearate. Second strip contained VI blended with lactose and magnesium stearate.

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<b>Serious adverse events</b>	Placebo	Batefenterol 75 µg	Batefenterol 37.5 µg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 46 (0.00%)	2 / 46 (4.35%)	0 / 46 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 46 (0.00%)	0 / 46 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 46 (0.00%)	1 / 46 (2.17%)	0 / 46 (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
Pulmonary embolism			
subjects affected / exposed	0 / 46 (0.00%)	0 / 46 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Scrotal abscess			
subjects affected / exposed	0 / 46 (0.00%)	1 / 46 (2.17%)	0 / 46 (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

<b>Serious adverse events</b>	Batefenterol 150 µg	Batefenterol 300 µg	Batefenterol 600 µg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 45 (0.00%)	1 / 47 (2.13%)	1 / 46 (2.17%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 45 (0.00%)	0 / 47 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal			

disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 45 (0.00%)	1 / 47 (2.13%)	0 / 46 (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
Pulmonary embolism			
subjects affected / exposed	0 / 45 (0.00%)	0 / 47 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Scrotal abscess			
subjects affected / exposed	0 / 45 (0.00%)	0 / 47 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

<b>Serious adverse events</b>	UMEC/VI 62.5/25 µg		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 47 (2.13%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 47 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	0 / 47 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			

Scrotal abscess			
subjects affected / exposed	0 / 47 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 3 %

<b>Non-serious adverse events</b>	Placebo	Batefenterol 75 µg	Batefenterol 37.5 µg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 46 (4.35%)	8 / 46 (17.39%)	3 / 46 (6.52%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 46 (0.00%)	2 / 46 (4.35%)	1 / 46 (2.17%)
occurrences (all)	0	2	1
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 46 (0.00%)	0 / 46 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	0 / 46 (0.00%)	0 / 46 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 46 (0.00%)	2 / 46 (4.35%)	1 / 46 (2.17%)
occurrences (all)	0	2	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 46 (4.35%)	3 / 46 (6.52%)	1 / 46 (2.17%)
occurrences (all)	2	3	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 46 (0.00%)	1 / 46 (2.17%)	0 / 46 (0.00%)
occurrences (all)	0	1	0
Viral pharyngitis			
subjects affected / exposed	0 / 46 (0.00%)	0 / 46 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			

Diabetes mellitus subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0	0 / 46 (0.00%) 0	0 / 46 (0.00%) 0
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<b>Non-serious adverse events</b>	Batefenterol 150 µg	Batefenterol 300 µg	Batefenterol 600 µg
Total subjects affected by non-serious adverse events subjects affected / exposed	5 / 45 (11.11%)	7 / 47 (14.89%)	18 / 46 (39.13%)
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	1 / 47 (2.13%) 1	0 / 46 (0.00%) 0
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	0 / 47 (0.00%) 0	0 / 46 (0.00%) 0
Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all)	2 / 45 (4.44%) 2	1 / 47 (2.13%) 1	6 / 46 (13.04%) 6
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	2 / 45 (4.44%) 2	4 / 47 (8.51%) 4	5 / 46 (10.87%) 5
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	0 / 47 (0.00%) 0	3 / 46 (6.52%) 3
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	0 / 47 (0.00%) 0	2 / 46 (4.35%) 2
Viral pharyngitis subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	0 / 47 (0.00%) 0	2 / 46 (4.35%) 2
Metabolism and nutrition disorders Diabetes mellitus subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	1 / 47 (2.13%) 1	2 / 46 (4.35%) 2

<b>Non-serious adverse events</b>	UMEC/VI 62.5/25 µg		
Total subjects affected by non-serious adverse events subjects affected / exposed	4 / 47 (8.51%)		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0		
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	2 / 47 (4.26%) 2		
Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	1 / 47 (2.13%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)  Upper respiratory tract infection subjects affected / exposed occurrences (all)  Viral pharyngitis subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0  1 / 47 (2.13%) 1  0 / 47 (0.00%) 0		
Metabolism and nutrition disorders Diabetes mellitus subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 May 2015	To correct IND number on the Sponsor Information page.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported