Clinical trial results:
Efficacy and safety of Salmeterol/Fluticasone MDI HEXAL versus SeretideTM EvohalerTM in adolescent and adult patients with moderate-to-severe persistent asthma: A 12-week, multicenter, randomized, double-blind, double-dummy, parallel group study

Summary

EudraCT number	2007-005235-29
Trial protocol	HU CZ PL
Global end of trial date	27 April 2009

Results information

Result version number	v3 (current)
This version publication date	14 April 2016
First version publication date	06 February 2016
Version creation reason	• Correction of full data set Article 46 was not correct.

Trial information

Trial identification

Sponsor protocol code	2007-41-DOS-3

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	HEXAL AG
Sponsor organisation address	Industriestraße 25, Holzkirchen, Germany, 83607
Public contact	Head of Clinical Research Department, Hexal AG, 0049 80249080,
Scientific contact	Head of Clinical Research Department, Hexal AG, 0049 80249080,

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 August 2009
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 April 2009
Global end of trial reached?	Yes
Global end of trial date	27 April 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study was to evaluate the long-term efficacy and safety of Salmeterol/Fluticasone MDI HEXAL compared to Seretide Evohaler in adolescent and adult patients suffering from moderate-to-severe persistent asthma.

Protection of trial subjects:

Safety assessments included adverse events (AEs), physical examination, ECG, vital signs and clinical laboratory data. This study was conducted in accordance with International Conference on Harmonisation of Good Clinical Practice, the principles of the Declaration of Helsinki, as well as other applicable local ethical and legal requirements.

Background therapy:

-

Evidence for comparator: -

Actual start date of recruitment	13 October 2008
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	Czech Republic: 29
Country: Number of subjects enrolled	Hungary: 49
Country: Number of subjects enrolled	Poland: 175
Country: Number of subjects enrolled	Romania: 40
Country: Number of subjects enrolled	Ukraine: 279
Worldwide total number of subjects	572
EEA total number of subjects	293

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)	94
Adults (18-64 years)	477
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Double-blind, double-dummy, multicenter, multinational, randomized parallel group study in adolescent and adult patients suffering from moderate-to-severe asthma

Pre-assignment

Screening details:

A total number of 610 patients where screened and 572 patients were randomized. A 2-week run-in period followed by a 12-week blinded treatment period. The screening visit (Visit -1) was followed by a 2-week run-in period during which all asthma treatments except reliever medication were to be stopped.

Pre-assignment period milestones

Number of subjects started	610[1]
Number of subjects completed	572

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Adverse event, serious non-fatal: 1
Reason: Number of subjects	Consent withdrawn by subject: 4
Reason: Number of subjects	Adverse event, non-fatal: 1
Reason: Number of subjects	Physician decision: 1
Reason: Number of subjects	Pregnancy: 1
Reason: Number of subjects	Lost to follow-up: 3
Reason: Number of subjects	Ineligibility: 24
Reason: Number of subjects	Sponsor decision: 3

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Patients didn't complete the study due to various reasons.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg)

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Salmeterol/Fluticasone MDI HEXAL
Investigational medicinal product code	
Other name	NA
Pharmaceutical forms	Pressurised inhalation
Routes of administration	Inhalation use

Dosage and administration details:

Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg of salmeterol/fluticasone per actuation), 2x2 actuations per day

Arm title	Seretide 50 Evohaler
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Seretide 50
Investigational medicinal product code	
Other name	NA
Pharmaceutical forms	Pressurised inhalation
Routes of administration	Inhalation use

Dosage and administration details:

Seretide 50 Evohaler (25 µg/50 µg per actuation), 2x2 actuations per day

Arm title	Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg)
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Salmeterol/Fluticasone MDI HEXAL
Investigational medicinal product code	
Other name	NA
Pharmaceutical forms	Pressurised inhalation
Routes of administration	Inhalation use

Dosage and administration details:

Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg of salmeterol/fluticasone per actuation), 2x2 actuations per day

Arm title	Seretide 250 Evohaler
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Seretide 250
Investigational medicinal product code	
Other name	NA
Pharmaceutical forms	Pressurised inhalation
Routes of administration	Inhalation use

Dosage and administration details:

Seretide 250 Evohaler (25 µg/250 µg per actuation), 2x2 actuations per day

Number of subjects in period 1	Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg)	Seretide 50 Evohaler	Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg)
Started	195	192	96
Completed	185	180	91
Not completed	10	12	5
Consent withdrawn by subject	4	8	4
Envelope opened	-	1	-
Adverse event, non-fatal	1	1	-
Lost to follow-up	3	-	1
Sponsor decision	1	1	-
Protocol deviation	1	-	-
Lack of efficacy	-	1	-

Number of subjects in period 1	Seretide 250 Evohaler
Started	89
Completed	81
Not completed	8
Consent withdrawn by subject	5
Envelope opened	-
Adverse event, non-fatal	2
Lost to follow-up	1
Sponsor decision	-
Protocol deviation	-
Lack of efficacy	-

Baseline characteristics

Reporting groups	
Reporting group title	Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg)
Reporting group description: -	
Reporting group title	Seretide 50 Evohaler
Reporting group description: -	
Reporting group title	Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg)
Reporting group description: -	
Reporting group title	Seretide 250 Evohaler
Reporting group description: -	

Reporting group values	Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg)	Seretide 50 Evohaler	Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg)
Number of subjects	195	192	96
Age Categorical			
Age Categorical Characteristic			
Units: Subjects			
In Utero	0	0	0
Preterm newborn- gestational age < 37 wk	0	0	0
Newborns (0-27days)	0	0	0
Infants and toddlers (28days – 23months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 year)	30	34	18
From 18 - 64 years	164	158	78
From 65 – 84 years	1	0	0
Over 85 years	0	0	0
Age Continuous			
Age Continuous Characteristic			
Units: Years			
arithmetic mean	39.9	41	40
standard deviation	± 15.8	± 17.2	± 17.3
Gender Categorical			
Gender Categorical Characteristic			
Units: Subjects			
Female	118	115	55
Male	77	77	41

Reporting group values	Seretide 250 Evohaler	Total	
Number of subjects	89	572	
Age Categorical			
Age Categorical Characteristic			
Units: Subjects			
In Utero	0	0	
Preterm newborn- gestational age < 37 wk	0	0	
Newborns (0-27days)	0	0	

Infants and toddlers (28days – 23months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 year)	12	94	
From 18 - 64 years	77	477	
From 65 – 84 years	0	1	
Over 85 years	0	0	
Age Continuous			
Age Continuous Characteristic			
Units: Years			
arithmetic mean	39.3		
standard deviation	± 16.3	-	
Gender Categorical			
Gender Categorical Characteristic			
Units: Subjects			
Female	49	337	
Male	40	235	

End points

End points reporting groups

Reporting group title	Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg)
Reporting group description: -	
Reporting group title	Seretide 50 Evohaler
Reporting group description: -	
Reporting group title	Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg)
Reporting group description: -	
Reporting group title	Seretide 250 Evohaler
Reporting group description: -	
Subject analysis set title	Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg) - Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description: The analysis consist of all patients who - were randomized - received at least one dose of IP	
Subject analysis set title	Seretide 50 Evohaler - Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description: The analysis consist of all patients who - were randomized - received at least one dose of IP	
Subject analysis set title	Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg) - Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description: The analysis consist of all patients who - were randomized - received at least one dose of IP	
Subject analysis set title	Seretide 250 Evohaler - Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description: The analysis consist of all patients who - were randomized - received at least one dose of IP	
Subject analysis set title	Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg) - FAS
Subject analysis set type	Full analysis
Subject analysis set description: The analysis consist of all patients who - are included in the Safety analysis set - had FEV1 data after the baseline visit	
Subject analysis set title	Seretide 50 Evohaler - FAS
Subject analysis set type	Full analysis
Subject analysis set description: The analysis consist of all patients who - are included in the Safety analysis set - had FEV1 data after the baseline visit	
Subject analysis set title	Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg) - FAS
Subject analysis set type	Full analysis
Subject analysis set description: The analysis consist of all patients who - are included in the Safety analysis set - had FEV1 data after the baseline visit	
Subject analysis set title	Seretide 250 Evohaler - FAS
Subject analysis set type	Full analysis

Subject analysis set description:

The analysis consist of all patients who
- are included in the Safety analysis set
- had FEV1 data after the baseline visit

Subject analysis set title	Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg) - PPS
Subject analysis set type	Per protocol

Subject analysis set description:

The analysis consist of all patients who
- are included in the FA set
- completed the study
- had no major protocol violations

Subject analysis set title	Seretide 50 Evohaler - PPS
Subject analysis set type	Per protocol

Subject analysis set description:

The analysis consist of all patients who
- are included in the FA set
- completed the study
- had no major protocol violations

Subject analysis set title	Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg) - PPS
Subject analysis set type	Per protocol

Subject analysis set description:

The analysis consist of all patients who
- are included in the FA set
- completed the study
- had no major protocol violations

Subject analysis set title	Seretide 250 Evohaler - PPS
Subject analysis set type	Per protocol

Subject analysis set description:

The analysis consist of all patients who
- are included in the FA set
- completed the study
- had no major protocol violations

Primary: The mean change in FEV1 from baseline to the end of 12-week study period (Visit 6)

End point title	The mean change in FEV1 from baseline to the end of 12-week study period (Visit 6)

End point description:

The change from baseline at the end of the 12-week treatment period. Missing values of the primary endpoint 'change in FEV1' were replaced using the last-value-carried-forward strategy as follows: in case if both pre–dose FEV1 values were missing at Visit 6/ET, the last value observed under treatment before Visit 6/ET was imputed as Visit 6/ET value. If there is no such last value under treatment, no imputation was made. If there is only one assessment of FEV1 pre-dose values at Visit 0 or Visit 6/ET is done, the available value was used for analysis.

End point type	Primary

End point timeframe:

From baseline (Visit 0) to end of 12 weeks study period (Visit 6)

End point values	Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg) - FAS	Seretide 50 Evohaler - FAS	Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg) - FAS	Seretide 250 Evohaler - FAS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	192	190	95	88
Units: Litre				

arithmetic mean (standard deviation)				
Baseline, FEV1	2.218 (± 0.544)	2.127 (± 0.521)	2.158 (± 0.597)	2.221 (± 0.548)
Endpoint, FEV1	2.595 (± 0.814)	2.57 (± 0.791)	2.574 (± 0.884)	2.742 (± 0.762)
Change from Baseline	0.377 (± 0.472)	0.443 (± 0.475)	0.416 (± 0.477)	0.522 (± 0.486)

End point values	Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg) - PPS	Seretide 50 Evohaler - PPS	Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg) - PPS	Seretide 250 Evohaler - PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	183	177	89	81
Units: Litre				
arithmetic mean (standard deviation)				
Baseline, FEV1	2.226 (± 0.545)	2.127 (± 0.513)	2.154 (± 0.576)	2.239 (± 0.54)
Endpoint, FEV1	2.611 (± 0.808)	2.541 (± 0.765)	2.587 (± 0.858)	2.752 (± 0.768)
Change from Baseline	0.385 (± 0.47)	0.414 (± 0.458)	0.433 (± 0.478)	0.512 (± 0.491)

Statistical analyses

Statistical analysis title	Statistical analysis 1: ANCOVA

Statistical analysis description:

An Analysis of Covariance (ANCOVA) using treatment and centre as factors and baseline FEV1 and age as co-variables.
The first null hypothesis was that with respect to the change from baseline FEV1 (mean of the 2 pre-dose values at Visit 0) the test formulation is inferior to the reference formulation (the difference in means, µtest - µref is smaller than -200mL) in favour of the alternative hypothesis that the test product is equivalent to or better than the reference product.

Comparison groups	Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg) - FAS v Seretide 50 Evohaler - FAS
Number of subjects included in analysis	382
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9739
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.080611
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	-0.161974

Statistical analysis title	Statistical analysis 2: ANCOVA

Statistical analysis description:

An Analysis of Covariance (ANCOVA) using treatment and centre as factors and baseline FEV1 and age as co-variables.
The first null hypothesis was that with respect to the change from baseline FEV1 (mean of the 2 pre-dose values at Visit 0) the test formulation is inferior to the reference formulation (the difference in means, µtest - µref is smaller than -200mL) in favour of the alternative hypothesis that the test product is equivalent to or better than the reference product.

Comparison groups	Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg) - PPS v Seretide 50 Evohaler - PPS
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9104
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.056504
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	-0.139088

Statistical analysis title	Statistical analysis 3: ANCOVA

Statistical analysis description:

An Analysis of Covariance (ANCOVA) using treatment and centre as factors and baseline FEV1 and age as co-variables.
The first null hypothesis was that with respect to the change from baseline FEV1 (mean of the 2 pre-dose values at Visit 0) the test formulation is inferior to the reference formulation (the difference in means, µtest - µref is smaller than -200mL) in favour of the alternative hypothesis that the test product is equivalent to or better than the reference product.

Comparison groups	Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg) - FAS v Seretide 250 Evohaler - FAS
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9489
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.102292
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	-0.225175

Statistical analysis title	Statistical analysis 4: ANCOVA

Statistical analysis description:

An Analysis of Covariance (ANCOVA) using treatment and centre as factors and baseline FEV1 and age as co-variables.
The first null hypothesis was that with respect to the change from baseline FEV1 (mean of the 2 pre-dose values at Visit 0) the test formulation is inferior to the reference formulation (the difference in means, µtest - µref is smaller than -200mL) in favour of the alternative hypothesis that the test product is equivalent to or better than the reference product.

Comparison groups	Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg) - PPS v Seretide 250 Evohaler - PPS
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.8427
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.066329
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	-0.196239

Primary: AUC(0—12)/12 at the end of 12-week study period (Visit 6) relative to baseline

End point title	AUC(0—12)/12 at the end of 12-week study period (Visit 6) relative to baseline

End point description:

The area under the 12-hour serial FEV1 curve
(AUC0-12) at the end of the 12-week treatment period (Visit 6) relative to baseline FEV1 (mean of the 2 pre-dose values at Visit 0). Missing values of the second primary endpoint 'FEV1 AUC(0-12)' were replaced using linear interpolation.

End point type	Primary

End point timeframe:

From baseline (Visit 0) to end of 12 weeks study period (Visit 6)

End point values	Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg) - FAS	Seretide 50 Evohaler - FAS	Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg) - FAS	Seretide 250 Evohaler - FAS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	192	190	95	88
Units: Litre				
arithmetic mean (standard deviation)				
Baseline, FEV1	2.218 (± 0.544)	2.127 (± 0.521)	2.158 (± 0.597)	2.221 (± 0.548)
AUC(0—12)/12 (L) at V6/ET	2.733 (± 0.825)	2.702 (± 0.813)	2.682 (± 0.868)	2.896 (± 0.849)
Ratio of AUC(0—12)/12 and Baseline	1.225 (± 0.21)	1.262 (± 0.227)	1.246 (± 0.221)	1.303 (± 0.229)
Log of Ratio of AUC(0—12)/12 and Baseline	0.189 (± 0.165)	0.217 (± 0.179)	0.205 (± 0.168)	0.25 (± 0.17)

End point values	Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg) -	Seretide 50 Evohaler - PPS	Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg) -	Seretide 250 Evohaler - PPS

	PPS		PPS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	183	177	89	81
Units: Litre				
arithmetic mean (standard deviation)				
Baseline, FEV1	2.226 (± 0.545)	2.127 (± 0.513)	2.154 (± 0.576)	2.239 (± 0.54)
AUC(0—12)/12 (L) at V6/ET	2.732 (± 0.829)	2.677 (± 0.792)	2.693 (± 0.865)	2.899 (± 0.854)
Ratio of AUC(0—12)/12 and Baseline	1.223 (± 0.209)	1.255 (± 0.223)	1.248 (± 0.222)	1.299 (± 0.228)
Log of Ratio of AUC(0—12)/12 and Baseline	0.187 (± 0.165)	0.212 (± 0.177)	0.207 (± 0.169)	0.247 (± 0.169)

Statistical analyses

Statistical analysis title	Statistical analysis 5: ANCOVA

Statistical analysis description:

Analysis of Covariance (ANCOVA) using treatment and centre as factors and log transformed baseline FEV1 and age as co-variables.
The second null hypothesis was that with respect to the FEV1 AUC(0-12) after 12 weeks of treatment relative to baseline FEV1 the test formulation is inferior to the reference formulation (the ratio in means, µtest/µref, is smaller than 80%) in favour of the alternative hypothesis that the test formulation is equivalent to or better than the reference formulation.

Comparison groups	Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg) - FAS v Seretide 50 Evohaler - FAS
Number of subjects included in analysis	382
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9818
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.968004
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	0.938962

Statistical analysis title	Statistical analysis 6: ANCOVA

Statistical analysis description:

Analysis of Covariance (ANCOVA) using treatment and centre as factors and log transformed baseline FEV1 and age as co-variables.
The second null hypothesis was that with respect to the FEV1 AUC(0-12) after 12 weeks of treatment relative to baseline FEV1 the test formulation is inferior to the reference formulation (the ratio in means, µtest/µref, is smaller than 80%) in favour of the alternative hypothesis that the test formulation is equivalent to or better than the reference formulation.

Comparison groups	Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg) - PPS v Seretide 50 Evohaler - PPS

Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9721
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.970518
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	0.941211

Statistical analysis title	Statistical analysis 7: ANCOVA

Statistical analysis description:

Analysis of Covariance (ANCOVA) using treatment and centre as factors and log transformed baseline FEV1 and age as co-variables.
The second null hypothesis was that with respect to the FEV1 AUC(0-12) after 12 weeks of treatment relative to baseline FEV1 the test formulation is inferior to the reference formulation (the ratio in means, µtest/µref, is smaller than 80%) in favour of the alternative hypothesis that the test formulation is equivalent to or better than the reference formulation.

Comparison groups	Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg) - FAS v Seretide 250 Evohaler - FAS
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9822
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.952911
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	0.911031

Statistical analysis title	Statistical analysis 8: ANCOVA

Statistical analysis description:

Analysis of Covariance (ANCOVA) using treatment and centre as factors and log transformed baseline FEV1 and age as co-variables.
The second null hypothesis was that with respect to the FEV1 AUC(0-12) after 12 weeks of treatment relative to baseline FEV1 the test formulation is inferior to the reference formulation (the ratio in means, µtest/µref, is smaller than 80%) in favour of the alternative hypothesis that the test formulation is equivalent to or better than the reference formulation.

Comparison groups	Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg) - PPS v Seretide 250 Evohaler - PPS

Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9621
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.960046
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	0.917738

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From the first intake of investigational product (IP) till the 28 days after the last intake of IP	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups	
Reporting group title	Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg) - Safety Set
Reporting group description: -	
Reporting group title	Seretide 50 Evohaler - Safety Set
Reporting group description: -	
Reporting group title	Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg) - Safety Set
Reporting group description: -	
Reporting group title	Seretide 250 Evohaler - Safety Set
Reporting group description: -	

Serious adverse events	Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg) - Safety Set	Seretide 50 Evohaler - Safety Set	Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg) - Safety Set
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 195 (0.00%)	0 / 192 (0.00%)	0 / 96 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Seretide 250 Evohaler - Safety Set		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 89 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg) - Safety Set	Seretide 50 Evohaler - Safety Set	Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg) - Safety Set
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 195 (30.77%)	41 / 192 (21.35%)	22 / 96 (22.92%)
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 195 (0.00%)	1 / 192 (0.52%)	0 / 96 (0.00%)
occurrences (all)	0	1	0
Chills			
subjects affected / exposed	0 / 195 (0.00%)	0 / 192 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Oedema			
subjects affected / exposed	0 / 195 (0.00%)	0 / 192 (0.00%)	0 / 96 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	1 / 195 (0.51%)	0 / 192 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	3 / 195 (1.54%)	2 / 192 (1.04%)	2 / 96 (2.08%)
occurrences (all)	3	2	2
Dysphonia			
subjects affected / exposed	7 / 195 (3.59%)	2 / 192 (1.04%)	3 / 96 (3.13%)
occurrences (all)	7	3	3
Epistaxis			
subjects affected / exposed	1 / 195 (0.51%)	1 / 192 (0.52%)	1 / 96 (1.04%)
occurrences (all)	1	1	1
Pharyngolaryngeal pain			
subjects affected / exposed	2 / 195 (1.03%)	0 / 192 (0.00%)	0 / 96 (0.00%)
occurrences (all)	2	0	0
Rhinitis allergic			
subjects affected / exposed	0 / 195 (0.00%)	0 / 192 (0.00%)	0 / 96 (0.00%)
occurrences (all)	0	0	0
Sneezing			

subjects affected / exposed	1 / 195 (0.51%)	0 / 192 (0.00%)	0 / 96 (0.00%)
occurrences (all)	2	0	0
Wheezing			
subjects affected / exposed	0 / 195 (0.00%)	1 / 192 (0.52%)	0 / 96 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Nervousness			
subjects affected / exposed	0 / 195 (0.00%)	0 / 192 (0.00%)	0 / 96 (0.00%)
occurrences (all)	0	0	0
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 195 (0.51%)	0 / 192 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Alanine aminotransferase increased			
subjects affected / exposed	1 / 195 (0.51%)	0 / 192 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 195 (0.51%)	0 / 192 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Cortisol free urine increased			
subjects affected / exposed	1 / 195 (0.51%)	0 / 192 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Electrocardiogram t wave inversion			
subjects affected / exposed	1 / 195 (0.51%)	0 / 192 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Weight increased			
subjects affected / exposed	2 / 195 (1.03%)	1 / 192 (0.52%)	0 / 96 (0.00%)
occurrences (all)	2	1	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 195 (0.00%)	0 / 192 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Fibula fracture			
subjects affected / exposed	1 / 195 (0.51%)	0 / 192 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Hand fracture			

subjects affected / exposed	1 / 195 (0.51%)	0 / 192 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Joint sprain			
subjects affected / exposed	0 / 195 (0.00%)	0 / 192 (0.00%)	0 / 96 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 195 (0.00%)	1 / 192 (0.52%)	0 / 96 (0.00%)
occurrences (all)	0	1	0
Extrasystoles			
subjects affected / exposed	1 / 195 (0.51%)	0 / 192 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Supraventricular extrasystoles			
subjects affected / exposed	0 / 195 (0.00%)	0 / 192 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	0 / 195 (0.00%)	1 / 192 (0.52%)	0 / 96 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	4 / 195 (2.05%)	1 / 192 (0.52%)	1 / 96 (1.04%)
occurrences (all)	4	3	3
Intercostal neuralgia			
subjects affected / exposed	0 / 195 (0.00%)	1 / 192 (0.52%)	0 / 96 (0.00%)
occurrences (all)	0	1	0
Somnolence			
subjects affected / exposed	1 / 195 (0.51%)	0 / 192 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Tremor			
subjects affected / exposed	0 / 195 (0.00%)	1 / 192 (0.52%)	0 / 96 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 195 (0.51%)	0 / 192 (0.00%)	1 / 96 (1.04%)
occurrences (all)	1	0	1
Gastrointestinal disorders			

Cheilitis			
subjects affected / exposed	0 / 195 (0.00%)	0 / 192 (0.00%)	0 / 96 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 195 (0.00%)	1 / 192 (0.52%)	1 / 96 (1.04%)
occurrences (all)	0	1	1
Duodenitis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 192 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Enterocolitis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 192 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Gastritis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 192 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	1 / 195 (0.51%)	0 / 192 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Toothache			
subjects affected / exposed	0 / 195 (0.00%)	0 / 192 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	1 / 195 (0.51%)	0 / 192 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Photodermatosis			
subjects affected / exposed	0 / 195 (0.00%)	0 / 192 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Rash pruritic			
subjects affected / exposed	0 / 195 (0.00%)	0 / 192 (0.00%)	0 / 96 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Toxic nodular goitre			
subjects affected / exposed	0 / 195 (0.00%)	1 / 192 (0.52%)	0 / 96 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	3 / 195 (1.54%)	1 / 192 (0.52%)	0 / 96 (0.00%)
occurrences (all)	3	1	0
Intervertebral disc disorder			
subjects affected / exposed	1 / 195 (0.51%)	0 / 192 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Limb discomfort			
subjects affected / exposed	1 / 195 (0.51%)	1 / 192 (0.52%)	0 / 96 (0.00%)
occurrences (all)	4	1	0
Muscle spasms			
subjects affected / exposed	1 / 195 (0.51%)	1 / 192 (0.52%)	0 / 96 (0.00%)
occurrences (all)	1	3	0
Muscular weakness			
subjects affected / exposed	0 / 195 (0.00%)	1 / 192 (0.52%)	0 / 96 (0.00%)
occurrences (all)	0	1	0
Spinal osteoarthritis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 192 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	0 / 195 (0.00%)	0 / 192 (0.00%)	0 / 96 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 195 (0.00%)	0 / 192 (0.00%)	0 / 96 (0.00%)
occurrences (all)	0	0	0
Acute tonsillitis			
subjects affected / exposed	2 / 195 (1.03%)	0 / 192 (0.00%)	0 / 96 (0.00%)
occurrences (all)	2	0	0
Bronchitis			
subjects affected / exposed	4 / 195 (2.05%)	1 / 192 (0.52%)	1 / 96 (1.04%)
occurrences (all)	4	1	1
Candidiasis			
subjects affected / exposed	2 / 195 (1.03%)	2 / 192 (1.04%)	0 / 96 (0.00%)
occurrences (all)	2	2	0
Cystitis			

subjects affected / exposed	0 / 195 (0.00%)	0 / 192 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	4 / 195 (2.05%)	1 / 192 (0.52%)	0 / 96 (0.00%)
occurrences (all)	4	1	0
Laryngitis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 192 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	10 / 195 (5.13%)	7 / 192 (3.65%)	3 / 96 (3.13%)
occurrences (all)	10	8	3
Oral candidiasis			
subjects affected / exposed	0 / 195 (0.00%)	1 / 192 (0.52%)	0 / 96 (0.00%)
occurrences (all)	0	1	0
Oral herpes			
subjects affected / exposed	0 / 195 (0.00%)	1 / 192 (0.52%)	0 / 96 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal candidiasis			
subjects affected / exposed	0 / 195 (0.00%)	1 / 192 (0.52%)	0 / 96 (0.00%)
occurrences (all)	0	1	0
Paronychia			
subjects affected / exposed	0 / 195 (0.00%)	1 / 192 (0.52%)	0 / 96 (0.00%)
occurrences (all)	0	1	0
Pharyngitis			
subjects affected / exposed	1 / 195 (0.51%)	3 / 192 (1.56%)	0 / 96 (0.00%)
occurrences (all)	1	3	0
Pneumonia			
subjects affected / exposed	1 / 195 (0.51%)	0 / 192 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Respiratory tract infection			
subjects affected / exposed	12 / 195 (6.15%)	12 / 192 (6.25%)	6 / 96 (6.25%)
occurrences (all)	14	12	7
Respiratory tract infection viral			
subjects affected / exposed	7 / 195 (3.59%)	6 / 192 (3.13%)	5 / 96 (5.21%)
occurrences (all)	9	6	6
Rhinitis			

subjects affected / exposed	2 / 195 (1.03%)	1 / 192 (0.52%)	2 / 96 (2.08%)
occurrences (all)	2	1	2
Tracheitis			
subjects affected / exposed	0 / 195 (0.00%)	0 / 192 (0.00%)	0 / 96 (0.00%)
occurrences (all)	0	0	0
Tonsillitis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 192 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Tracheobronchitis			
subjects affected / exposed	0 / 195 (0.00%)	0 / 192 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	2 / 195 (1.03%)	3 / 192 (1.56%)	2 / 96 (2.08%)
occurrences (all)	2	3	2
Viral infection			
subjects affected / exposed	1 / 195 (0.51%)	1 / 192 (0.52%)	1 / 96 (1.04%)
occurrences (all)	1	1	1
Viral rhinitis			
subjects affected / exposed	0 / 195 (0.00%)	1 / 192 (0.52%)	0 / 96 (0.00%)
occurrences (all)	0	1	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 195 (0.00%)	0 / 192 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1

Non-serious adverse events	Seretide 250 Evohaler - Safety Set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 89 (26.97%)		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Chills			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Oedema			

subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Dysphonia			
subjects affected / exposed	3 / 89 (3.37%)		
occurrences (all)	3		
Epistaxis			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Pharyngolaryngeal pain			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Rhinitis allergic			
subjects affected / exposed	2 / 89 (2.25%)		
occurrences (all)	6		
Sneezing			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Wheezing			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Nervousness			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Alanine aminotransferase increased			

subjects affected / exposed	2 / 89 (2.25%)		
occurrences (all)	2		
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Cortisol free urine increased			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Electrocardiogram t wave inversion			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Weight increased			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Fibula fracture			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Hand fracture			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Joint sprain			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Extrasystoles			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Supraventricular extrasystoles			

subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Intercostal neuralgia			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Somnolence			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Tremor			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Cheilitis			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Duodenitis			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Enterocolitis			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Gastritis			

subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Toothache			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Photodermatosis			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Rash pruritic			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Endocrine disorders			
Toxic nodular goitre			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Intervertebral disc disorder			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Limb discomfort			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Muscle spasms			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Muscular weakness			

subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Spinal osteoarthritis			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Acute tonsillitis			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Bronchitis			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Candidiasis			
subjects affected / exposed	2 / 89 (2.25%)		
occurrences (all)	2		
Cystitis			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Laryngitis			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Oral candidiasis			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		

Oral herpes				
subjects affected / exposed	0 / 89 (0.00%)			
occurrences (all)	0			
Oropharyngeal candidiasis				
subjects affected / exposed	0 / 89 (0.00%)			
occurrences (all)	0			
Paronychia				
subjects affected / exposed	0 / 89 (0.00%)			
occurrences (all)	0			
Pharyngitis				
subjects affected / exposed	4 / 89 (4.49%)			
occurrences (all)	4			
Pneumonia				
subjects affected / exposed	0 / 89 (0.00%)			
occurrences (all)	0			
Respiratory tract infection				
subjects affected / exposed	5 / 89 (5.62%)			
occurrences (all)	5			
Respiratory tract infection viral				
subjects affected / exposed	2 / 89 (2.25%)			
occurrences (all)	2			
Rhinitis				
subjects affected / exposed	0 / 89 (0.00%)			
occurrences (all)	0			
Tracheitis				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences (all)	1			
Tonsillitis				
subjects affected / exposed	0 / 89 (0.00%)			
occurrences (all)	0			
Tracheobronchitis				
subjects affected / exposed	0 / 89 (0.00%)			
occurrences (all)	0			
Upper respiratory tract infection				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences (all)	1			

Viral infection subjects affected / exposed occurrences (all)	0 / 89 (0.00%) 0		
Viral rhinitis subjects affected / exposed occurrences (all)	0 / 89 (0.00%) 0		
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 89 (0.00%) 0		

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