



## Clinical trial results:

**Double-blind, double-dummy, multi-center, randomized parallel group trial to demonstrate therapeutic equivalence of Salmeterol/Fluticasone MDI HEXAL (25 µg/125 µg per actuation) versus Seretide™ 125 (25 µg/125 µg per actuation) over a period of 12 weeks in adolescent and adult patients with persistent moderate asthma**

### Summary

EudraCT number	2007-000134-39
Trial protocol	LT HU PL
Global end of trial date	08 January 2008

### Results information

Result version number	v2 (current)
This version publication date	24 March 2016
First version publication date	06 February 2016
Version creation reason	• Correction of full data set Information about Article 46 was not correct

### Trial information

#### Trial identification

Sponsor protocol code	2006-03-DOS-1
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#### 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	14 August 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 January 2008
Global end of trial reached?	Yes
Global end of trial date	08 January 2008
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The objective of this study is to evaluate the long-term efficacy and safety of Salmeterol/Fluticasone MDI HEXAL 25 µg/125 µg per actuation compared to Seretide™ 125 (25 µg/125 µg per actuation) in adolescent and adult patients suffering from moderate 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	30 May 2007
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	Hungary: 75
Country: Number of subjects enrolled	Lithuania: 18
Country: Number of subjects enrolled	Poland: 98
Country: Number of subjects enrolled	Ukraine: 153
Worldwide total number of subjects	344
EEA total number of subjects	191

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)	30
Adults (18-64 years)	311
From 65 to 84 years	3
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Multi-center, double-blind, randomized, parallel group study in patients in adolescent and adult patients with persistent moderate asthma

### Pre-assignment

Screening details:

A total number of 364 patients were screened and 344 patients were randomized. The study consisted of a 2-week run-in period and a 12-week blinded treatment period (14 weeks in total). A screening visit 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	364 <sup>[1]</sup>
Number of subjects completed	344

### Pre-assignment subject non-completion reasons

Reason: Number of subjects	Adverse event, non-fatal: 4
Reason: Number of subjects	Consent withdrawn by subject: 1
Reason: Number of subjects	Lost to follow-up: 3
Reason: Number of subjects	Ineligibility: 11
Reason: Number of subjects	Unsatisfactory Therapeutic Response: 1

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: 20 patients dropped out according to protocol.

### 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
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<b>Arm title</b>	Salmeterol/Fluticasone MDI HEXAL
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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/125 µg of Salmeterol/Fluticasone per actuation) 2x2 actuations per day

<b>Arm title</b>	Seretide
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Arm description: -

Arm type	Active comparator
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Investigational medicinal product name	SeretideTM 125
Investigational medicinal product code	
Other name	NA
Pharmaceutical forms	Pressurised inhalation
Routes of administration	Inhalation use

Dosage and administration details:

SeretideTM 125 (25 µg/125 µg of Salmeterol/Fluticasone per actuation) Glaxo Wellcome UK Limited, United Kingdom 2x2 actuations per day

<b>Number of subjects in period 1</b>	<b>Salmeterol/Fluticasone MDI HEXAL</b>	<b>Seretide</b>
Started	171	173
Completed	168	164
Not completed	3	9
Consent withdrawn by subject	-	2
Adverse event, non-fatal	2	-
Adverse event, serious non-fatal	-	2
Lost to follow-up	-	3
Lack of efficacy	1	-
Protocol deviation	-	2

## Baseline characteristics

### Reporting groups

Reporting group title	Salmeterol/Fluticasone MDI HEXAL
Reporting group description: -	
Reporting group title	Seretide
Reporting group description: -	

Reporting group values	Salmeterol/Fluticasone MDI HEXAL	Seretide	Total
Number of subjects	171	173	344
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)	12	18	30
From 18 - 64 years	157	154	311
From 65 – 84 years	2	1	3
Over 85 years	0	0	0
Age Continuous			
Age Continuous Characteristic			
Units: Years			
arithmetic mean	44.2	41.6	
standard deviation	± 14.1	± 14.8	-
Gender Categorical			
Gender Categorical Characteristic			
Units: Subjects			
Female	119	114	233
Male	52	59	111

## End points

### End points reporting groups

Reporting group title	Salmeterol/Fluticasone MDI HEXAL
Reporting group description: -	
Reporting group title	Seretide
Reporting group description: -	
Subject analysis set title	Salmeterol/Fluticasone MDI HEXAL - Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description: The analysis set consists of all subjects who were randomised, received at least one dose of IP	
Subject analysis set title	Seretide - Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description: The analysis set consists of all subjects who were randomised, received at least one dose of IP	
Subject analysis set title	Salmeterol/Fluticasone MDI HEXAL - FAS
Subject analysis set type	Full analysis
Subject analysis set description: The analysis set consists of all subjects who were randomised, received at least one dose of IP and had post-baseline FEV1 measure	
Subject analysis set title	Seretide - FAS
Subject analysis set type	Full analysis
Subject analysis set description: The analysis set consists of all subjects who were randomised, received at least one dose of IP and had post-baseline FEV1 measure	
Subject analysis set title	Salmeterol/Fluticasone MDI HEXAL - PPS
Subject analysis set type	Per protocol
Subject analysis set description: The analysis set consists of all subjects who were randomised, received at least one dose of IP and had post-baseline FEV1 measure, had no major protocol deviations and for who the blind was not broken	
Subject analysis set title	Seretide - PPS
Subject analysis set type	Per protocol
Subject analysis set description: The analysis set consists of all subjects who were randomised, received at least one dose of IP and had post-baseline FEV1 measure, had no major protocol deviations and for who the blind was not broken	

### Primary: The mean change in FEV1 from baseline to the end of the 12 weeks treatment period

End point title	The mean change in FEV1 from baseline to the end of the 12 weeks treatment period
End point description: The change from baseline at the end of the 12 weeks treatment period. Missing values of the primary endpoint were replaced using the last-value-carried-forward strategy as follows: in case if the FEV1 value was missing at Visit 4, the last value observed under treatment before Visit 4 was imputed as Visit 4 value. If there is no such last value under treatment, no imputation was made.	
End point type	Primary
End point timeframe: End of 12 weeks treatment period	

End point values	Salmeterol/Fluticasone MDI HEXAL - FAS	Seretide - FAS	Salmeterol/Fluticasone MDI HEXAL - PPS	Seretide - PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	171	171	165	153
Units: Litre				
arithmetic mean (standard deviation)				
Baseline, FEV1	2.128 (± 0.511)	2.22 (± 0.507)	2.134 (± 0.503)	2.242 (± 0.518)
Endpoint, FEV1	2.482 (± 0.735)	2.609 (± 0.686)	2.499 (± 0.731)	2.639 (± 0.69)
Change from Baseline	0.354 (± 0.415)	0.39 (± 0.405)	0.364 (± 0.419)	0.397 (± 0.41)

## Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
The null hypothesis was that with respect to the change from baseline FEV1 the test formulation is inferior to the reference formulation, i.e. the difference in means is smaller than -200 mL in favor of the alternative hypothesis that the test product is equivalent to or better than the reference product. An Analysis of Covariance using treatment, pooled centre as factors and baseline FEV1 as a covariate.	
Comparison groups	Salmeterol/Fluticasone MDI HEXAL - FAS v Seretide - FAS
Number of subjects included in analysis	342
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.7283
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.025373
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	-0.107422

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
The null hypothesis was that with respect to the change from baseline FEV1 the test formulation is inferior to the reference formulation, i.e. the difference in means is smaller than -200 mL in favor of the alternative hypothesis that the test product is equivalent to or better than the reference product. An Analysis of Covariance using treatment, pooled centre as factors and baseline FEV1 as a covariate.	
Comparison groups	Salmeterol/Fluticasone MDI HEXAL - PPS v Seretide - PPS
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.6598
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.018008



Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	-0.103966

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the first intake of investigational product (IP) till the 14 days after the last intake of IP

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	9.0
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### Reporting groups

Reporting group title	Seretide - Safety Set
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Reporting group description: -

Reporting group title	Salmeterol/Fluticasone MDI HEXAL - Safety Set
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Reporting group description: -

<b>Serious adverse events</b>	Seretide - Safety Set	Salmeterol/Fluticasone MDI HEXAL - Safety Set	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 173 (1.73%)	1 / 171 (0.58%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 173 (0.00%)	1 / 171 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	1 / 173 (0.58%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	1 / 173 (0.58%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

Asthma			
subjects affected / exposed	1 / 173 (0.58%)	0 / 171 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Seretide - Safety Set	Salmeterol/Fluticasone MDI HEXAL - Safety Set	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 173 (23.12%)	50 / 171 (29.24%)	
Vascular disorders			
Arteriosclerosis			
subjects affected / exposed	1 / 173 (0.58%)	0 / 171 (0.00%)	
occurrences (all)	1	0	
Hypertension			
subjects affected / exposed	0 / 173 (0.00%)	1 / 171 (0.58%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 173 (0.58%)	1 / 171 (0.58%)	
occurrences (all)	1	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 173 (0.58%)	1 / 171 (0.58%)	
occurrences (all)	1	2	
Asthma			
subjects affected / exposed	4 / 173 (2.31%)	3 / 171 (1.75%)	
occurrences (all)	4	3	
Nasal congestion			
subjects affected / exposed	0 / 173 (0.00%)	1 / 171 (0.58%)	
occurrences (all)	0	1	
Dysphonia			
subjects affected / exposed	10 / 173 (5.78%)	11 / 171 (6.43%)	
occurrences (all)	10	12	
Nasal polyps			

subjects affected / exposed occurrences (all)	0 / 173 (0.00%) 0	1 / 171 (0.58%) 1	
Pharyngolaryngeal pain subjects affected / exposed occurrences (all)	2 / 173 (1.16%) 2	1 / 171 (0.58%) 1	
Rhinitis allergic subjects affected / exposed occurrences (all)	0 / 173 (0.00%) 0	1 / 171 (0.58%) 1	
Sneezing subjects affected / exposed occurrences (all)	1 / 173 (0.58%) 1	0 / 171 (0.00%) 0	
Psychiatric disorders Anxiety disorder subjects affected / exposed occurrences (all)	1 / 173 (0.58%) 1	0 / 171 (0.00%) 0	
Insomnia subjects affected / exposed occurrences (all)	0 / 173 (0.00%) 0	1 / 171 (0.58%) 1	
Conversion disorder subjects affected / exposed occurrences (all)	0 / 173 (0.00%) 0	1 / 171 (0.58%) 1	
Investigations Blood bilirubin increased subjects affected / exposed occurrences (all)	1 / 173 (0.58%) 1	0 / 171 (0.00%) 0	
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 173 (0.58%) 1	0 / 171 (0.00%) 0	
Blood cortisol decreased subjects affected / exposed occurrences (all)	0 / 173 (0.00%) 0	2 / 171 (1.17%) 2	
Blood pressure increased subjects affected / exposed occurrences (all)	0 / 173 (0.00%) 0	1 / 171 (0.58%) 1	
Hepatic enzyme increased			

subjects affected / exposed occurrences (all)	0 / 173 (0.00%) 0	1 / 171 (0.58%) 1	
Transaminases increased subjects affected / exposed occurrences (all)	0 / 173 (0.00%) 0	2 / 171 (1.17%) 2	
White blood cell count increased subjects affected / exposed occurrences (all)	1 / 173 (0.58%) 1	0 / 171 (0.00%) 0	
Injury, poisoning and procedural complications			
Facial bones fracture subjects affected / exposed occurrences (all)	0 / 173 (0.00%) 0	1 / 171 (0.58%) 1	
Limb injury subjects affected / exposed occurrences (all)	1 / 173 (0.58%) 1	0 / 171 (0.00%) 0	
Nervous system disorders			
Dysgeusia subjects affected / exposed occurrences (all)	1 / 173 (0.58%) 1	0 / 171 (0.00%) 0	
Headache subjects affected / exposed occurrences (all)	2 / 173 (1.16%) 2	2 / 171 (1.17%) 2	
Tremor subjects affected / exposed occurrences (all)	1 / 173 (0.58%) 2	0 / 171 (0.00%) 0	
Blood and lymphatic system disorders			
Leukocytosis subjects affected / exposed occurrences (all)	1 / 173 (0.58%) 1	0 / 171 (0.00%) 0	
Eye disorders			
Keratitis subjects affected / exposed occurrences (all)	0 / 173 (0.00%) 0	1 / 171 (0.58%) 1	
Presbyopia subjects affected / exposed occurrences (all)	0 / 173 (0.00%) 0	1 / 171 (0.58%) 1	

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 173 (0.58%)	0 / 171 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	2 / 173 (1.16%)	0 / 171 (0.00%)	
occurrences (all)	2	0	
Dyspepsia			
subjects affected / exposed	1 / 173 (0.58%)	0 / 171 (0.00%)	
occurrences (all)	1	0	
Enteritis			
subjects affected / exposed	0 / 173 (0.00%)	1 / 171 (0.58%)	
occurrences (all)	0	1	
Gastrointestinal motility disorder			
subjects affected / exposed	1 / 173 (0.58%)	0 / 171 (0.00%)	
occurrences (all)	1	0	
Hiatus hernia			
subjects affected / exposed	1 / 173 (0.58%)	0 / 171 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	0 / 173 (0.00%)	1 / 171 (0.58%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	2 / 173 (1.16%)	0 / 171 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 173 (0.00%)	1 / 171 (0.58%)	
occurrences (all)	0	1	
Dermatitis atopic			
subjects affected / exposed	1 / 173 (0.58%)	0 / 171 (0.00%)	
occurrences (all)	1	0	
Dermatitis allergic			
subjects affected / exposed	0 / 173 (0.00%)	1 / 171 (0.58%)	
occurrences (all)	0	1	
Swelling face			

subjects affected / exposed occurrences (all)	0 / 173 (0.00%) 0	1 / 171 (0.58%) 1	
Renal and urinary disorders Renal colic subjects affected / exposed occurrences (all)	1 / 173 (0.58%) 1	0 / 171 (0.00%) 0	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	0 / 173 (0.00%) 0	1 / 171 (0.58%) 1	
Musculoskeletal pain subjects affected / exposed occurrences (all)	0 / 173 (0.00%) 0	1 / 171 (0.58%) 1	
Osteoarthritis subjects affected / exposed occurrences (all)	0 / 173 (0.00%) 0	1 / 171 (0.58%) 1	
Synovial cyst subjects affected / exposed occurrences (all)	0 / 173 (0.00%) 0	1 / 171 (0.58%) 1	
Infections and infestations Acute sinusitis subjects affected / exposed occurrences (all)	1 / 173 (0.58%) 1	1 / 171 (0.58%) 2	
Acute tonsillitis subjects affected / exposed occurrences (all)	1 / 173 (0.58%) 1	0 / 171 (0.00%) 0	
Bronchitis subjects affected / exposed occurrences (all)	1 / 173 (0.58%) 1	0 / 171 (0.00%) 0	
Bronchitis acute subjects affected / exposed occurrences (all)	0 / 173 (0.00%) 0	1 / 171 (0.58%) 1	
Ear infection subjects affected / exposed occurrences (all)	1 / 173 (0.58%) 1	1 / 171 (0.58%) 1	
Candidiasis			

subjects affected / exposed	1 / 173 (0.58%)	0 / 171 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	5 / 173 (2.89%)	14 / 171 (8.19%)	
occurrences (all)	7	15	
Oral candidiasis			
subjects affected / exposed	1 / 173 (0.58%)	0 / 171 (0.00%)	
occurrences (all)	1	0	
Otitis externa			
subjects affected / exposed	0 / 173 (0.00%)	1 / 171 (0.58%)	
occurrences (all)	0	1	
Pharyngeal candidiasis			
subjects affected / exposed	1 / 173 (0.58%)	4 / 171 (2.34%)	
occurrences (all)	1	4	
Pharyngitis			
subjects affected / exposed	0 / 173 (0.00%)	1 / 171 (0.58%)	
occurrences (all)	0	1	
Respiratory tract infection			
subjects affected / exposed	6 / 173 (3.47%)	6 / 171 (3.51%)	
occurrences (all)	6	7	
Rhinitis			
subjects affected / exposed	4 / 173 (2.31%)	4 / 171 (2.34%)	
occurrences (all)	4	4	
Viral infection			
subjects affected / exposed	0 / 173 (0.00%)	1 / 171 (0.58%)	
occurrences (all)	0	1	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 173 (0.58%)	0 / 171 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	1 / 173 (0.58%)	0 / 171 (0.00%)	
occurrences (all)	1	0	



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 August 2007	Primary statistical hypothesis was changed from equivalence to non-inferiority, sample size was adjusted to reflect the change in the statistical hypothesis. Age and gender were removed from the ANCOVA model for the primary endpoint. Exclusion criteria and forbidden therapies were revised.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported