Clinical trial results:
Double-blind, double-dummy, multi-center, randomized parallel group trial to demonstrate therapeutic equivalence of Salmeterol/Fluticasone MDI HEXAL (25 g/50 g per actuation) versus Seretide 50 (25 g/50 g per actuation) over a period of 12 weeks in pediatric patients aged 4-11 years with persistent moderate asthma

Summary

EudraCT number	2007-000135-26
Trial protocol	LT
Global end of trial date	05 June 2008

Results information

Result version number	v2 (current)
This version publication date	24 March 2016
First version publication date	11 February 2016
Version creation reason	• Correction of full data set Information about Articel 46 was not correct

Trial information

Trial identification

Sponsor protocol code	2006-04-DOS-2

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	22 September 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 June 2008
Global end of trial reached?	Yes
Global end of trial date	05 June 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/50 µg per actuation compared to SeretideTM 50 (25 µg/50 µg per actuation) in pediatric patients suffering from persistent moderate asthma.

Protection of trial subjects:

The trial was conducted in accordance with the International Conference on Harmonisation (ICH), Good Clinical Practices (GCP), Good Manufacturing Practice (GMP), the ethical principles of the Declaration of Helsinki and with applicable local regulations. Adverse events were systematically collected during the trial. During the trial subjects were allowed to use reliever medications for any asthma exacerbations under close medical control by physician.

Background therapy:

-

Evidence for comparator: -

Actual start date of recruitment	24 September 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	Lithuania: 51
Country: Number of subjects enrolled	Romania: 35
Country: Number of subjects enrolled	Ukraine: 260
Worldwide total number of subjects	346
EEA total number of subjects	86

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)	346
Adolescents (12-17 years)	0

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

Subject disposition

Recruitment

Recruitment details:

Double-blind, double-dummy, multi-center, randomized parallel group trial in pediatric patients aged 4-11 years with persistent moderate asthma.

Pre-assignment

Screening details:

A total number of 360 patients where screened and 346 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 (Visit -1) was followed by a 2-week run-in period during which all asthma treatments except reliever medication were stopped.

Pre-assignment period milestones

Number of subjects started	360[1]
Number of subjects completed	346

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Adverse event, non-fatal: 1
Reason: Number of subjects	Consent withdrawn by subject: 7
Reason: Number of subjects	Ineligibility: 6

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: 14 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
Arm title	Salmeterol/Fluticasone MDI HEXAL

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/50µg of salmeterol/fluticasone per actuation), 2x2 actuations per day

Arm title	Seretide

Arm description: -

Arm type	Active comparator

Investigational medicinal product name	Seretide 50 Evohaler
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

Number of subjects in period 1	Salmeterol/Fluticasone MDI HEXAL	Seretide
Started	176	170
Completed	172	168
Not completed	4	2
Consent withdrawn by subject	3	1
Adverse event, non-fatal	-	1
Lost to follow-up	1	-

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	176	170	346
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)	176	170	346
Adolescents (12-17 year)	0	0	0
From 18 - 64 years	0	0	0
From 65 – 84 years	0	0	0
Over 85 years	0	0	0
Age Continuous			
Age Continuous Characteristic			
Units: Years			
arithmetic mean	8.3	8.4	
standard deviation	± 1.9	± 1.9	-
Gender Categorical			
Gender Categorical Characteristic			
Units: Subjects			
Female	51	59	110
Male	125	111	236

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 (4-5 years) - Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The analysis set consists of all patients who were randomized and received at least one dose of IP	
Subject analysis set title	Seretide (4-5 years) - Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The analysis set consists of all patients who were randomized and received at least one dose of IP	
Subject analysis set title	Salmeterol/Fluticasone MDI HEXAL (6-11 years) - Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The analysis set consists of all patients who were randomized and received at least one dose of IP	
Subject analysis set title	Seretide (6-11 years) - Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The analysis set consists of all patients who were randomized and received at least one dose of IP	
Subject analysis set title	Salmeterol/Fluticasone MDI HEXAL (4-5 years) - FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
The analysis set consists of all patients who were included in the Safety analysis set and had post-baseline FEV1 data	
Subject analysis set title	Seretide (4-5 years) - FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
The analysis set consists of all patients who were included in the Safety analysis set and had post-baseline FEV1 data	
Subject analysis set title	Salmeterol/Fluticasone MDI HEXAL (6-11 years) - FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
The analysis set consists of all patients who were included in the Safety analysis set and had post-baseline FEV1 data	
Subject analysis set title	Seretide (6-11 years) - FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
The analysis set consists of all patients who were included in the Safety analysis set and had post-baseline FEV1 data	
Subject analysis set title	Salmeterol/Fluticasone MDI HEXAL (6-11 years) - PPS
Subject analysis set type	Per protocol
Subject analysis set description:	
The analysis set consists of all patients who were included in the FA set and completed the study and had no major protocol violations	
Subject analysis set title	Seretide (6-11 years) - PPS

Subject analysis set type	Per protocol

Subject analysis set description:

The analysis set consists of all patients who were included in the FA set and completed the study and had no major protocol violations

Primary: FEV1 at Visit 4 compared with baseline (Visit 0)

End point title	FEV1 at Visit 4 compared with baseline (Visit 0)

End point description:

The change from baseline at the end of the 12 weeks
treatment period. Missing values of the primary endpoint 'change in FEV1' were replaced using the last-value-carried forward
strategy as follows, e.g. in case 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:

From baseline to End of 12 weeks treatment period

End point values	Salmeterol/Fluticasone MDI HEXAL (6-11 years) - FAS	Seretide (6-11 years) - FAS	Salmeterol/Fluticasone MDI HEXAL (6-11 years) - PPS	Seretide (6-11 years) - PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	162	162	154	151
Units: Litre				
arithmetic mean (standard deviation)				
Baseline, FEV1	1.415 (± 0.32)	1.468 (± 0.361)	1.42 (± 0.311)	1.457 (± 0.35)
Endpoint, FEV1	1.86 (± 0.447)	1.973 (± 0.498)	1.873 (± 0.442)	1.971 (± 0.472)
Change from Baseline	0.445 (± 0.287)	0.505 (± 0.267)	0.454 (± 0.289)	0.513 (± 0.25)

Statistical analyses

Statistical analysis title	Mean Relative Change in FEV1 (FA set)

Statistical analysis description:

Analysis of covariance (ANCOVA) was applied including treatment group and center as factors and the baseline value as a covariate in the statistical model in order to calculate a one-sided 97.5% confidence interval for the difference in treatment effects (based on the adjusted means).

Comparison groups	Salmeterol/Fluticasone MDI HEXAL (6-11 years) - FAS v Seretide (6-11 years) - FAS
Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9641
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.035051

Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	-0.073225

Statistical analysis title	Mean Relative Change in FEV1 (PP set)

Statistical analysis description:

Analysis of covariance (ANCOVA) was applied including treatment group and center as factors and the baseline value as a covariate in the statistical model in order to calculate a one-sided 97.5% confidence interval for the difference in treatment effects (based on the adjusted means).

Comparison groups	Salmeterol/Fluticasone MDI HEXAL (6-11 years) - PPS v Seretide (6-11 years) - PPS
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9632
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.035511
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	-0.074444

Primary: Area under the 4-hour serial FEV1 curve (AUC0-4) at the end of the 12-week
study period (Visit 4) relative to baseline FEV1 (Visit 0)

End point title	Area under the 4-hour serial FEV1 curve (AUC0-4) at the end of the 12-week study period (Visit 4) relative to baseline FEV1 (Visit 0)

End point description:

The area under the 4-hour serial FEV1 curve (AUC0-4)
at the end of the 12-week study period (Visit 4) relative to baseline FEV1 (Visit 0). Missing values of the second primary endpoint 'AUC0-4' were replaced using linear interpolation.

End point type	Primary

End point timeframe:

From baseline to End of 12 weeks treatment period

End point values	Salmeterol/Fluticasone MDI HEXAL (6-11 years) - FAS	Seretide (6-11 years) - FAS	Salmeterol/Fluticasone MDI HEXAL (6-11 years) - PPS	Seretide (6-11 years) - PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	162	162	154	151
Units: Litre				
arithmetic mean (standard deviation)				

FEV1 at Visit 0: Baseline	1.415 (± 0.32)	1.468 (± 0.361)	1.42 (± 0.311)	1.457 (± 0.35)
FEV1 AUC0-4/4 at Visit 4/ET	1.966 (± 0.462)	2.068 (± 0.499)	1.969 (± 0.457)	2.054 (± 0.47)
Ratio of FEV1 AUC0-4/4 and baseline FEV1	1.406 (± 0.206)	1.413 (± 0.18)	1.411 (± 0.207)	1.418 (± 0.176)
Log of Ratio of FEV1 AUC0-4/4 and baseline FEV1	0.33 (± 0.145)	0.338 (± 0.127)	0.334 (± 0.145)	0.342 (± 0.123)

Statistical analyses

Statistical analysis title	AUC0-4 at Visit 4 relative to Baseline (FA set)

Statistical analysis description:

The ANCOVA was performed on log-transformed data. Similar to the first primary efficacy variable ANCOVA was applied including treatment group and center as factors and the log-transformed baseline FEV1 value as a covariate in the statistical model in order to calculate a one-sided 97.5% confidence interval for the difference in treatment effects (based on the adjusted means).

Comparison groups	Salmeterol/Fluticasone MDI HEXAL (6-11 years) - FAS v Seretide (6-11 years) - FAS
Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.8235
Method	ANCOVA
Parameter estimate	Ratio of LS Means
Point estimate	0.986185
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	0.957553

Statistical analysis title	AUC0-4 at Visit 4 relative to Baseline (PP set)

Statistical analysis description:

The ANCOVA was performed on log-transformed data. Similar to the first primary efficacy variable ANCOVA was applied including treatment group and center as factors and the log-transformed baseline FEV1 value as a covariate in the statistical model in order to calculate a one-sided 97.5% confidence interval for the difference in treatment effects (based on the adjusted means).

Comparison groups	Salmeterol/Fluticasone MDI HEXAL (6-11 years) - PPS v Seretide (6-11 years) - PPS
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.7962
Method	ANCOVA
Parameter estimate	Ratio of LS Means
Point estimate	0.987412

Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	0.958134

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

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups

Reporting group title	Salmeterol/Fluticasone MDI HEXAL (4-5 years) - Safety Set
Reporting group description: -	
Reporting group title	Salmeterol/Fluticasone MDI HEXAL (6-11 years) - Safety Set
Reporting group description: -	
Reporting group title	Seretide (6-11 years) - Safety Set
Reporting group description: -	
Reporting group title	Seretide (4-5 years) - Safety Set

Reporting group description: -

Serious adverse events	Salmeterol/Fluticasone MDI HEXAL (4-5 years) - Safety Set	Salmeterol/Fluticasone MDI HEXAL (6-11 years) - Safety Set	Seretide (6-11 years) - Safety Set
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)	1 / 163 (0.61%)	2 / 162 (1.23%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Blood and lymphatic system disorders			
Lymphadenitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 163 (0.00%)	1 / 162 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 163 (0.61%)	0 / 162 (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
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 163 (0.00%)	1 / 162 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Seretide (4-5 years) - Safety Set		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Blood and lymphatic system disorders			
Lymphadenitis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 8 (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: 0 %

Non-serious adverse events	Salmeterol/Fluticasone MDI HEXAL (4-5 years) - Safety Set	Salmeterol/Fluticasone MDI HEXAL (6-11 years) - Safety Set	Seretide (6-11 years) - Safety Set
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 13 (38.46%)	45 / 163 (27.61%)	49 / 162 (30.25%)
Injury, poisoning and procedural complications			
Joint sprain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 163 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Cardiac disorders			
Sinus arrhythmia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 163 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Nervous system disorders			

Headache			
subjects affected / exposed	0 / 13 (0.00%)	2 / 163 (1.23%)	1 / 162 (0.62%)
occurrences (all)	0	2	1
Blood and lymphatic system disorders			
Thrombocythaemia			
subjects affected / exposed	0 / 13 (0.00%)	2 / 163 (1.23%)	0 / 162 (0.00%)
occurrences (all)	0	2	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 13 (7.69%)	4 / 163 (2.45%)	2 / 162 (1.23%)
occurrences (all)	1	4	2
Immune system disorders			
Food allergy			
subjects affected / exposed	1 / 13 (7.69%)	0 / 163 (0.00%)	1 / 162 (0.62%)
occurrences (all)	1	0	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 163 (0.61%)	0 / 162 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			
subjects affected / exposed	1 / 13 (7.69%)	0 / 163 (0.00%)	1 / 162 (0.62%)
occurrences (all)	1	0	2
Diarrhoea			
subjects affected / exposed	0 / 13 (0.00%)	2 / 163 (1.23%)	1 / 162 (0.62%)
occurrences (all)	0	2	1
Gastritis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 163 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 13 (0.00%)	1 / 163 (0.61%)	0 / 162 (0.00%)
occurrences (all)	0	1	0
Cough			
subjects affected / exposed	0 / 13 (0.00%)	1 / 163 (0.61%)	1 / 162 (0.62%)
occurrences (all)	0	1	1
Pharyngolaryngeal pain			

subjects affected / exposed	0 / 13 (0.00%)	0 / 163 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Dysphonia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 163 (0.61%)	4 / 162 (2.47%)
occurrences (all)	0	1	4
Rhinitis allergic			
subjects affected / exposed	0 / 13 (0.00%)	1 / 163 (0.61%)	1 / 162 (0.62%)
occurrences (all)	0	1	1
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 13 (0.00%)	1 / 163 (0.61%)	0 / 162 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 163 (0.61%)	2 / 162 (1.23%)
occurrences (all)	0	1	2
Acute tonsillitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 163 (0.61%)	3 / 162 (1.85%)
occurrences (all)	0	1	3
Bronchitis			
subjects affected / exposed	0 / 13 (0.00%)	2 / 163 (1.23%)	2 / 162 (1.23%)
occurrences (all)	0	2	2
Bronchopneumonia			
subjects affected / exposed	0 / 13 (0.00%)	3 / 163 (1.84%)	1 / 162 (0.62%)
occurrences (all)	0	3	1
Candidiasis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 163 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Laryngitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 163 (0.61%)	0 / 162 (0.00%)
occurrences (all)	0	1	0
Ear infection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 163 (0.61%)	0 / 162 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			

subjects affected / exposed	1 / 13 (7.69%)	8 / 163 (4.91%)	11 / 162 (6.79%)
occurrences (all)	1	8	11
Oral candidiasis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 163 (0.00%)	1 / 162 (0.62%)
occurrences (all)	0	0	1
Pharyngitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 163 (0.61%)	1 / 162 (0.62%)
occurrences (all)	0	1	1
Respiratory tract infection			
subjects affected / exposed	3 / 13 (23.08%)	14 / 163 (8.59%)	14 / 162 (8.64%)
occurrences (all)	3	15	18
Respiratory tract infection viral			
subjects affected / exposed	0 / 13 (0.00%)	3 / 163 (1.84%)	1 / 162 (0.62%)
occurrences (all)	0	3	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 13 (0.00%)	3 / 163 (1.84%)	5 / 162 (3.09%)
occurrences (all)	0	3	6
Rhinitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 163 (0.61%)	2 / 162 (1.23%)
occurrences (all)	0	1	3
Viral infection			
subjects affected / exposed	0 / 13 (0.00%)	2 / 163 (1.23%)	3 / 162 (1.85%)
occurrences (all)	0	2	3

Non-serious adverse events	Seretide (4-5 years) - Safety Set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 8 (50.00%)		
Injury, poisoning and procedural complications			
Joint sprain			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Sinus arrhythmia			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Nervous system disorders			

Headache			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Thrombocythaemia			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Food allergy			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Gastritis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Cough			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Pharyngolaryngeal pain			

subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Dysphonia			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Rhinitis allergic			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Acute tonsillitis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Bronchitis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Bronchopneumonia			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Candidiasis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Laryngitis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Ear infection			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			

subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Oral candidiasis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Pharyngitis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Respiratory tract infection			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	3		
Respiratory tract infection viral			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Rhinitis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Viral infection			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 September 2007	Amendment #1 Revised text: Minor grammatical and/or administrative changes have been made. Purpose for change: To improve the readability and/or clarity of the protocol.
13 December 2007	Amendment #2 The main reason for this amendment is to include a 16-hour urine collection at the end of the treatment period for the determination of urinary free cortisol levels as an additional safety parameter.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported