Clinical trial results:
A 24-week, multicenter, multinational, randomized, double-blind, triple-dummy, 3-arm parallel group study comparing the efficacy and safety of CHF 1535 200/6 (beclomethasone dipropionate 200 g plus formoterol 6 g/actuation), 2 puffs b.i.d., versus beclomethasone diproprionate HFA (250 g/actuation), 4 puffs b.i.d., versus Seretide® 500/50 (fluticasone 500 g plus salmeterol 50 g/actuation), 1 inhalation b.i.d., in patients with severe asthma.

Summary

EudraCT number	2007-002587-99
Trial protocol	LT SI CZ EE DE LV FR ES IT BG
Global end of trial date	10 September 2009

Results information

Result version number	v1 (current)
This version publication date	14 October 2017
First version publication date	14 October 2017

Trial information

Trial identification

Sponsor protocol code	CCD-0605-PR-0021

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Chiesi Farmaceutici SpA
Sponsor organisation address	Via Palermo 26/A, Parma, Italy, 43122
Public contact	Clinical Trial Transparency, Chiesi Farmaceutici SpA, Chiesi Farmaceutici SpA, 0521 2791, ClinicalTrial_info@chiesi.com
Scientific contact	Clinical Trial Transparency, Chiesi Farmaceutici SpA, Chiesi Farmaceutici SpA, 0521 2791, ClinicalTrial_info@chiesi.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 November 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 September 2009
Global end of trial reached?	Yes
Global end of trial date	10 September 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

In severe asthma patients, with forced expiratory volume in the first second (FEV1) <80% of predicted normal value and symptomatic on high-doses of inhaled corticosteroid (ICS) as monotherapy or medium doses of ICS + long-acting β2-agonist (LABA),, to demonstrate:
- the superiority of CHF 1535 200/6 (two puffs b.i.d.) versus a high dose of BDP (beclomethasone diproprionate 2000 µg/day) given as monotherapy, in terms of:
  - pulmonary function (change from baseline in pre-dose morning FEV1 measured at clinic) and
  - asthma control (change from baseline in percentage of complete days without asthma symptoms), and
- the non-inferiority versus Seretide® 500/50 (one inhalation b.i.d.), in terms of pulmonary function (change from baseline in pre-dose morning FEV1 measured at clinic) during a 24-week treatment period.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines and local law requirements. Other than routine care, no specific measures for protection of trial subjects were implemented.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 February 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	Poland: 112
Country: Number of subjects enrolled	Slovenia: 3
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Bulgaria: 64
Country: Number of subjects enrolled	Czech Republic: 19
Country: Number of subjects enrolled	Estonia: 25
Country: Number of subjects enrolled	France: 20
Country: Number of subjects enrolled	Germany: 49
Country: Number of subjects enrolled	Hungary: 38
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Latvia: 22
Country: Number of subjects enrolled	Lithuania: 14
Country: Number of subjects enrolled	Belarus: 8
Country: Number of subjects enrolled	Croatia: 37

Country: Number of subjects enrolled	Romania: 47
Country: Number of subjects enrolled	Russian Federation: 145
Country: Number of subjects enrolled	Ukraine: 113
Worldwide total number of subjects	721
EEA total number of subjects	455

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)	12
Adults (18-64 years)	649
From 65 to 84 years	60
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Male and female outpatients aged 12 to 70 inclusive (except for sites in Russia, Belarus, Estonia, Lithuania, France, Czech Republic, Hungary and Slovenia, where only patients aged ≥18 and ≤70 were enrolled) with severe persistent symptomatic (verified at screening and at randomisation) asthma diagnosed according to GINA guidance (revised 2006).

Pre-assignment

Screening details:

845 patients were screened, 818 were included in the run-in period and received at least one dose of single-blind treatment; 721 were randomised (237 in the CHF 1535 group, 242 in the BDP monotherapy group and 242 in the Seretide® group) and received at least one dose of randomised study drug.

Period 1

Period 1 title	Overall Trial by treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

This was a double-blind study except for the 2-week single-blind run-in period before randomisation. Each test and reference treatment was identical in appearance with its corresponding placebo in order to maintain the blind.

Arms

Are arms mutually exclusive?	Yes
Arm title	CHF 1535

Arm description:

CHF 1535 hydroflouroalkane (HFA)-134a pressurised metered dose (pMDI) inhaler (fixed combination of beclomethasone dipropionate 200 µg plus formoterol 6 µg/unit dose).

Arm type	Experimental
Investigational medicinal product name	CHF 1535
Investigational medicinal product code	
Other name	fixed combination of beclomethasone dipropionate and formoterol
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

CHF 1535 hydroflouroalkane (HFA)-134a pressurised metered dose (pMDI) inhaler (fixed combination of beclomethasone dipropionate 200 µg plus formoterol 6 µg/unit dose), 2 inhalations of CHF 1535 HFA pMDI b.i.d.

Administration scheme:
- 2 inhalations of CHF 1535 HFA pMDI b.i.d.
- 4 inhalations of BDP HFA pMDI placebo b.i.d.
- 1 inhalation of Seretide Accuhaler placebo b.i.d.

Investigational medicinal product name	BDP HFA pMDI placebo
Investigational medicinal product code	
Other name	beclomethasone dipropionate
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

BDP HFA pMDI placebo, 4 inhalations b.i.d.

Administration scheme:
- 2 inhalations of CHF 1535 HFA pMDI b.i.d.
- 4 inhalations of BDP HFA pMDI placebo b.i.d.
- 1 inhalation of Seretide Accuhaler placebo b.i.d.

Investigational medicinal product name	Seretide® Accuhaler® placebo
Investigational medicinal product code	
Other name	Fluticasone plus salmeterol
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Seretide® Accuhaler® placebo, 1 inhalation b.i.d.

Administration scheme:
- 2 inhalations of CHF 1535 HFA pMDI b.i.d.
- 4 inhalations of BDP HFA pMDI placebo b.i.d.
- 1 inhalation of Seretide Accuhaler placebo b.i.d.

Arm title	BDP monotherapy

Arm description:

BDP HFA-134a pMDI (beclomethasone dipropionate 250 µg/unit dose: Clenil®Modulite® 250).

Arm type	Active comparator
Investigational medicinal product name	BDP HFA
Investigational medicinal product code	
Other name	beclomethasone dipropionate
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Beclomethasone dipropionate HFA pMDI 250 µg/unit dose (Clenil® 250) (daily dose of BDP "non extrafine" 2000 µg BDP); 4 inhalations b.i.d.

Administration scheme:
- 2 inhalations of CHF 1535 HFA pMDI placebo b.i.d.
- 4 inhalations of BDP HFA pMDI b.i.d.
- 1 inhalation of Seretide Accuhaler placebo b.i.d.

Investigational medicinal product name	CHF 1535 HFA pMDI placebo
Investigational medicinal product code	
Other name	fixed combination of beclomethasone dipropionate plus formoterol
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

2 inhalations of CHF 1535 HFA pMDI placebo b.i.d.

Administration scheme:
- 2 inhalations of CHF 1535 HFA pMDI placebo b.i.d.
- 4 inhalations of BDP HFA pMDI b.i.d.
- 1 inhalation of Seretide Accuhaler placebo b.i.d.

Investigational medicinal product name	Seretide® Accuhaler® placebo
Investigational medicinal product code	
Other name	Fluticasone plus salmeterol
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

1 inhalation of Seretide Accuhaler placebo b.i.d.

Administration scheme:
- 2 inhalations of CHF 1535 HFA pMDI placebo b.i.d.
- 4 inhalations of BDP HFA pMDI b.i.d.
- 1 inhalation of Seretide Accuhaler placebo b.i.d.

Arm title	Seretide

Arm description:

Seretide® Accuhaler® (fluticasone propionate 500 µg plus salmeterol xinafoate 50 µg/actuation).

Arm type	Active comparator
Investigational medicinal product name	Seretide
Investigational medicinal product code	
Other name	Fluticasone plus salmeterol
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Seretide® Accuhaler® 500/50 µg/actuation (daily dose of fluticasone 1000 µg plus salmeterol 100 µg): 1 inhalation b.i.d.

Administration scheme:
- 2 inhalations of CHF 1535 HFA pMDI placebo b.i.d.
- 4 inhalations of BDP HFA pMDI placebo b.i.d.
- 1 inhalation of Seretide Accuhaler b.i.d.

Investigational medicinal product name	CHF 1535 HFA pMDI placebo
Investigational medicinal product code	
Other name	fixed combination of beclomethasone dipropionate plus formoterol
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

2 inhalations of CHF 1535 HFA pMDI placebo b.i.d.

Administration scheme:
- 2 inhalations of CHF 1535 HFA pMDI placebo b.i.d.
- 4 inhalations of BDP HFA pMDI placebo b.i.d.
- 1 inhalation of Seretide Accuhaler b.i.d.

Investigational medicinal product name	BDP HFA pMDI placebo
Investigational medicinal product code	
Other name	beclomethasone dipropionate
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

4 inhalations of BDP HFA pMDI placebo b.i.d.

Administration scheme:
- 2 inhalations of CHF 1535 HFA pMDI placebo b.i.d.
- 4 inhalations of BDP HFA pMDI placebo b.i.d.
- 1 inhalation of Seretide Accuhaler b.i.d.

Number of subjects in period 1	CHF 1535	BDP monotherapy	Seretide
Started	237	242	242
Completed	197	204	202
Not completed	40	38	40
Consent withdrawn by subject	10	11	13
Adverse event, non-fatal	3	6	2

inclusion/exclusion criteria not met	20	15	20
Lost to follow-up	1	2	-
Protocol deviation	3	4	2
not specified	3	-	3

Baseline characteristics

Reporting groups	
Reporting group title	CHF 1535
Reporting group description:	
CHF 1535 hydroflouroalkane (HFA)-134a pressurised metered dose (pMDI) inhaler (fixed combination of beclomethasone dipropionate 200 µg plus formoterol 6 µg/unit dose).	

Reporting group title	BDP monotherapy
Reporting group description:	
BDP HFA-134a pMDI (beclomethasone dipropionate 250 µg/unit dose: Clenil®Modulite® 250).	

Reporting group title	Seretide
Reporting group description:	
Seretide® Accuhaler® (fluticasone propionate 500 µg plus salmeterol xinafoate 50 µg/actuation).	

Reporting group values	CHF 1535	BDP monotherapy	Seretide
Number of subjects	237	242	242
Age categorical Units: Subjects			
Adolescents (12-17 years)	2	5	5
Adults (18-64 years)	215	216	218
From 65-84 years	20	21	19
Gender categorical Units: Subjects			
Female	129	140	141
Male	108	102	101

Reporting group values	Total		
Number of subjects	721		
Age categorical Units: Subjects			
Adolescents (12-17 years)	12		
Adults (18-64 years)	649		
From 65-84 years	60		
Gender categorical Units: Subjects			
Female	410		
Male	311		

Subject analysis sets	
Subject analysis set title	CHF1535 ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomised patients who received at least one administration of randomised study treatment and with at least one available efficacy evaluation after baseline. According to the ITT principle, the treatment groups for the ITT population were determined by the treatments to which the patients were randomised.	
Subject analysis set title	BDP monotherapy ITT

Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomised patients who received at least one administration of randomised study treatment and with at least one available efficacy evaluation after baseline. According to the ITT principle, the treatment groups for the ITT population were determined by the treatments to which the patients were randomised.

Subject analysis set title	Seretide ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomised patients who received at least one administration of randomised study treatment and with at least one available efficacy evaluation after baseline. According to the ITT principle, the treatment groups for the ITT population were determined by the treatments to which the patients were randomised.

Reporting group values	CHF1535 ITT	BDP monotherapy ITT	Seretide ITT
Number of subjects	234	241	241
Age categorical Units: Subjects			
Adolescents (12-17 years)	2	5	5
Adults (18-64 years)	213	215	217
From 65-84 years	19	21	19
Gender categorical Units: Subjects			
Female	128	139	141
Male	106	102	100

End points

End points reporting groups

Reporting group title	CHF 1535

Reporting group description:

CHF 1535 hydroflouroalkane (HFA)-134a pressurised metered dose (pMDI) inhaler (fixed combination of beclomethasone dipropionate 200 µg plus formoterol 6 µg/unit dose).

Reporting group title	BDP monotherapy

Reporting group description:

BDP HFA-134a pMDI (beclomethasone dipropionate 250 µg/unit dose: Clenil®Modulite® 250).

Reporting group title	Seretide

Reporting group description:

Seretide® Accuhaler® (fluticasone propionate 500 µg plus salmeterol xinafoate 50 µg/actuation).

Subject analysis set title	CHF1535 ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomised patients who received at least one administration of randomised study treatment and with at least one available efficacy evaluation after baseline. According to the ITT principle, the treatment groups for the ITT population were determined by the treatments to which the patients were randomised.

Subject analysis set title	BDP monotherapy ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomised patients who received at least one administration of randomised study treatment and with at least one available efficacy evaluation after baseline. According to the ITT principle, the treatment groups for the ITT population were determined by the treatments to which the patients were randomised.

Subject analysis set title	Seretide ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomised patients who received at least one administration of randomised study treatment and with at least one available efficacy evaluation after baseline. According to the ITT principle, the treatment groups for the ITT population were determined by the treatments to which the patients were randomised.

Primary: Change from baseline to end of treatment in pre-dose morning FEV1

End point title	Change from baseline to end of treatment in pre-dose morning FEV1

End point description:

Pre-dose morning FEV1 was measured at clinic visit.

End point type	Primary

End point timeframe:

At each single visit, from Visit 1 (run-in), through Visit 2 (baseline), to Visit 7 (end of treatment)

End point values	CHF1535 ITT	BDP monotherapy ITT	Seretide ITT	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	234	241	241	
Units: Liters				
least squares mean (confidence interval 95%)	0.2 (0.14 to 0.25)	0.16 (0.11 to 0.21)	0.22 (0.17 to 0.28)	

Statistical analyses

Statistical analysis title	CHF1535 ITT vs BDP monotherapy ITT
Comparison groups	CHF1535 ITT v BDP monotherapy ITT
Number of subjects included in analysis	475
Analysis specification	Pre-specified
Analysis type	superiority[1]
Parameter estimate	least square mean difference
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.11

Notes:

[1] - The two co-primary efficacy variables were analysed using a repeated measurements analysis of covariance (ANCOVA) model including baseline as covariate and terms for treatment and country

Statistical analysis title	CHF1535 ITT vs Seretide ITT
Comparison groups	CHF1535 ITT v Seretide ITT
Number of subjects included in analysis	475
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	least square mean difference
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.05

Primary: Change from baseline to end of treatment in % of complete days without asthma symptoms

End point title	Change from baseline to end of treatment in % of complete days without asthma symptoms

End point description:

A complete day without asthma symptoms is considered a day with all 4 asthma symptom scores (cough, wheeze, chest tightness, breathlessness) recorded as 0 (“No Symptoms”), both in the evening and in the following morning.

End point type	Primary

End point timeframe:

Asthma symptom scores were recorded daily at home with electronic peak-flow meter which allows symptoms and use of "rescue" medication to be recorded

End point values	CHF1535 ITT	BDP monotherapy ITT	Seretide ITT	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	234	241	241	
Units: Percentage				
least squares mean (confidence interval 95%)	24.64 (19.05 to 30.24)	21.95 (16.39 to 27.52)	26.57 (21.13 to 32.01)	

Statistical analyses

Statistical analysis title	CHF1535 ITT vs BDP ITT
Comparison groups	CHF1535 ITT v BDP monotherapy ITT
Number of subjects included in analysis	475
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.505
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	2.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.22
upper limit	10.6

Notes:

[2] - The two co-primary efficacy variables were analysed using a repeated measurements analysis of covariance (ANCOVA) model including baseline as covariate and terms for treatment and country.

Statistical analysis title	CHF1535 ITT vs Seretide ITT
Comparison groups	CHF1535 ITT v Seretide ITT
Number of subjects included in analysis	475
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	= 0.628
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-1.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.74
upper limit	5.89

Notes:

[3] - The two co-primary efficacy variables were analysed using a repeated measurements analysis of covariance (ANCOVA) model including baseline as covariate and terms for treatment and country.

Secondary: Morning PEF

End point title	Morning PEF

End point description:

Pre-dose morning PEF was measured daily at home by a portable electronic peak flow meter.

End point type	Secondary

End point timeframe:

Pre-dose morning PEF was measured daily. Data are available for the run-in period and for 2-week periods from week 1 to week 22 and also last 2 weeks bef V7. Only data from last 2 weeks bef. V7 are reported here.

End point values	CHF1535 ITT	BDP monotherapy ITT	Seretide ITT	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	128[4]	123[5]	133[6]	
Units: L/min				
arithmetic mean (standard deviation)	330.83 (± 104.01)	315.54 (± 98.06)	334.5 (± 108.57)	

Notes:

[4] - This is the actual number of patients analysed.

[5] - This is the actual number of patients analysed.

[6] - This is the actual number of patients analysed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in morning PEF

End point title	Change from baseline in morning PEF

End point description:

Pre-dose morning PEF was measured daily at home by a portable electronic peak flow meter.

End point type	Secondary

End point timeframe:

Pre-dose morning PEF was measured daily. Data are available for the run-in period and for 2-week periods from week 1 to week 22 and also last 2 weeks bef V7. Only data on change from baseline to last 2 weeks bef. V7 are reported here.

End point values	CHF1535 ITT	BDP monotherapy ITT	Seretide ITT	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	99[7]	100[8]	105[9]	
Units: L/min				
least squares mean (confidence interval	12.28 (2.96 to	-9.06 (-17.96	13.72 (4.95 to	

95%)	21.61)	to -0.15)	22.48)

Notes:

[7] - This is the actual number of patients analysed.

[8] - This is the actual number of patients analysed.

[9] - This is the actual number of patients analysed.

Statistical analyses

Statistical analysis title	CHF1535 vs BDP monotherapy
Comparison groups	CHF1535 ITT v BDP monotherapy ITT
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.001
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	21.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.43
upper limit	34.25

Notes:

[10] - Changes from baseline in morning PEF, evening PEF and PEF variability were analysed using the same repeated measurements ANCOVA as for the change in % of days without asthma symptoms.

Statistical analysis title	CHF1535 vs Seretide
Comparison groups	CHF1535 ITT v Seretide ITT
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	non-inferiority[11]
P-value	= 0.826
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.26
upper limit	11.39

Notes:

[11] - Changes from baseline in morning PEF, evening PEF and PEF variability were analysed using the same repeated measurements ANCOVA as for the change in % of days without asthma symptoms.

Secondary: Daily total number of rescue medication puffs

End point title	Daily total number of rescue medication puffs

End point description:

The daily use of rescue medication were recorded in the SpirotelTM as follows: the number of puffs taken during the day were recorded each evening before taking the study drug, while the number of puffs taken during the night will be recorded each
morning on awakening.

End point type	Secondary

End point timeframe:

Throughout the study. Data are available for the run-in period and for 2-week periods from week 1 to week 22 and also last 2 weeks bef V7. Only data from last 2 weeks bef. V7 are reported here.

End point values	CHF1535 ITT	BDP monotherapy ITT	Seretide ITT	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	166[12]	162[13]	178[14]	
Units: Puffs				
arithmetic mean (standard deviation)	-0.84 (± 2.63)	-0.72 (± 2.38)	-1.05 (± 2.03)	

Notes:

[12] - This is the actual number of patients analysed

[13] - This is the actual number of patients analysed

[14] - This is the actual number of patients analysed

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were assessed at each visit, from Visit 1 (run-in) to Visit 7 (of the treatment period)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	10.1

Reporting groups	
Reporting group title	CHF1535 - Safety
Reporting group description:	
Safety population: all randomised patients who received at least one administration of randomised study treatment. Patients were included in the analysis according to the treatment actually received.	
Reporting group title	BDP monotherapy - safety
Reporting group description:	
Safety population: all randomised patients who received at least one administration of randomised study treatment. Patients were included in the analysis according to the treatment actually received	
Reporting group title	Seretide - safety
Reporting group description:	
Safety population: all randomised patients who received at least one administration of randomised study treatment. Patients were included in the analysis according to the treatment actually received	

Serious adverse events	CHF1535 - Safety	BDP monotherapy - safety	Seretide - safety
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 239 (2.09%)	9 / 244 (3.69%)	4 / 242 (1.65%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bowen's disease			
subjects affected / exposed	0 / 239 (0.00%)	1 / 244 (0.41%)	0 / 242 (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
Uterine cancer			
subjects affected / exposed	0 / 239 (0.00%)	1 / 244 (0.41%)	0 / 242 (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
Injury, poisoning and procedural complications			

Femoral neck fracture			
subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dislocation of vertebra			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Thrombophlebitis superficial			
subjects affected / exposed	0 / 239 (0.00%)	1 / 244 (0.41%)	0 / 242 (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
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 239 (0.00%)	1 / 244 (0.41%)	0 / 242 (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
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 239 (0.42%)	3 / 244 (1.23%)	1 / 242 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Calculus urinary			
subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	1 / 242 (0.41%)
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			
Urinary retention			
subjects affected / exposed	0 / 239 (0.00%)	1 / 244 (0.41%)	0 / 242 (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
Urosepsis	Additional description: SAE occurred during the run-in period		
subjects affected / exposed	0 / 239 (0.00%)	1 / 244 (0.41%)	0 / 242 (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
Pneumonia			
subjects affected / exposed	0 / 239 (0.00%)	1 / 244 (0.41%)	0 / 242 (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
Postoperative wound infection			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0.4 %

Non-serious adverse events	CHF1535 - Safety	BDP monotherapy - safety	Seretide - safety
Total subjects affected by non-serious adverse events			
subjects affected / exposed	87 / 239 (36.40%)	90 / 244 (36.89%)	87 / 242 (35.95%)
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 239 (0.84%)	3 / 244 (1.23%)	1 / 242 (0.41%)
occurrences (all)	2	3	1
Hypertensive crisis			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences (all)	0	0	1
Pallor			
subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 239 (0.00%)	3 / 244 (1.23%)	0 / 242 (0.00%)
occurrences (all)	0	3	0
Asthenia			
subjects affected / exposed	0 / 239 (0.00%)	1 / 244 (0.41%)	1 / 242 (0.41%)
occurrences (all)	0	1	1
Pyrexia			
subjects affected / exposed	1 / 239 (0.42%)	1 / 244 (0.41%)	0 / 242 (0.00%)
occurrences (all)	1	1	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 239 (0.00%)	1 / 244 (0.41%)	0 / 242 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Breast mass			
subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences (all)	1	0	0
Urogenital prolapse			
subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences (all)	1	0	0
Uterine cervical erosion			

subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	20 / 239 (8.37%)	22 / 244 (9.02%)	20 / 242 (8.26%)
occurrences (all)	21	24	29
Cough			
subjects affected / exposed	6 / 239 (2.51%)	7 / 244 (2.87%)	8 / 242 (3.31%)
occurrences (all)	6	8	8
Dysphonia			
subjects affected / exposed	4 / 239 (1.67%)	2 / 244 (0.82%)	7 / 242 (2.89%)
occurrences (all)	4	2	7
Pharyngolaryngeal pain			
subjects affected / exposed	3 / 239 (1.26%)	1 / 244 (0.41%)	1 / 242 (0.41%)
occurrences (all)	3	1	1
Throat irritation			
subjects affected / exposed	2 / 239 (0.84%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences (all)	2	0	1
Dyspnoea			
subjects affected / exposed	0 / 239 (0.00%)	1 / 244 (0.41%)	1 / 242 (0.41%)
occurrences (all)	0	11	1
Rhinitis allergic			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	2 / 242 (0.83%)
occurrences (all)	0	0	2
Nasal polyps			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences (all)	0	0	1
Pharyngeal erythema			
subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences (all)	1	0	0
Postnasal drip			
subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences (all)	1	0	0
Respiratory disorder			

subjects affected / exposed	0 / 239 (0.00%)	1 / 244 (0.41%)	0 / 242 (0.00%)
occurrences (all)	0	1	0
Rhinorrhoea			
subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences (all)	1	0	0
Sneezing			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences (all)	0	0	1
Wheezing			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences (all)	0	0	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	3 / 242 (1.24%)
occurrences (all)	0	0	3
Restlessness			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences (all)	0	0	1
Investigations			
Blood cortisol decreased			
subjects affected / exposed	0 / 239 (0.00%)	2 / 244 (0.82%)	1 / 242 (0.41%)
occurrences (all)	0	2	1
Blood pressure increased			
subjects affected / exposed	2 / 239 (0.84%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences (all)	2	0	1
C-reactive protein increased			
subjects affected / exposed	0 / 239 (0.00%)	2 / 244 (0.82%)	0 / 242 (0.00%)
occurrences (all)	0	2	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 239 (0.00%)	2 / 244 (0.82%)	0 / 242 (0.00%)
occurrences (all)	0	2	0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 239 (0.00%)	1 / 244 (0.41%)	0 / 242 (0.00%)
occurrences (all)	0	1	0
Aspartate aminotransferase increased			

subjects affected / exposed	0 / 239 (0.00%)	1 / 244 (0.41%)	0 / 242 (0.00%)
occurrences (all)	0	1	0
Blood cholesterol increased			
subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences (all)	1	0	0
Blood cortisol increased			
subjects affected / exposed	0 / 239 (0.00%)	1 / 244 (0.41%)	0 / 242 (0.00%)
occurrences (all)	0	1	0
Blood glucose increased			
subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences (all)	1	0	0
Blood potassium increased			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences (all)	0	0	1
Blood pressure diastolic increased			
subjects affected / exposed	0 / 239 (0.00%)	1 / 244 (0.41%)	0 / 242 (0.00%)
occurrences (all)	0	1	0
Electrocardiogram ST segment abnormal			
subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences (all)	1	0	0
QRS axis abnormal			
subjects affected / exposed	0 / 239 (0.00%)	1 / 244 (0.41%)	0 / 242 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	2 / 242 (0.83%)
occurrences (all)	0	0	2
Joint dislocation			
subjects affected / exposed	0 / 239 (0.00%)	1 / 244 (0.41%)	1 / 242 (0.41%)
occurrences (all)	0	1	1
Joint sprain			
subjects affected / exposed	0 / 239 (0.00%)	1 / 244 (0.41%)	0 / 242 (0.00%)
occurrences (all)	0	1	0
Muscle strain			

subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences (all)	0	0	1
Rib fracture			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences (all)	0	0	1
Skin laceration			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences (all)	0	0	1
Cardiac disorders			
Ventricular extrasystoles			
subjects affected / exposed	0 / 239 (0.00%)	2 / 244 (0.82%)	1 / 242 (0.41%)
occurrences (all)	0	2	1
Palpitations			
subjects affected / exposed	0 / 239 (0.00%)	2 / 244 (0.82%)	0 / 242 (0.00%)
occurrences (all)	0	3	0
Sinus arrhythmia			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	2 / 242 (0.83%)
occurrences (all)	0	0	2
Supraventricular extrasystoles			
subjects affected / exposed	1 / 239 (0.42%)	1 / 244 (0.41%)	0 / 242 (0.00%)
occurrences (all)	1	1	0
Tachycardia			
subjects affected / exposed	2 / 239 (0.84%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences (all)	2	0	0
Angina pectoris			
subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences (all)	1	0	0
Aortic valve disease			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences (all)	0	0	1
Bundle branch block left			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences (all)	0	0	1
Bundle branch block			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences (all)	0	0	1

Cardiac discomfort			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences (all)	0	0	1
Cardiac failure chronic			
subjects affected / exposed	0 / 239 (0.00%)	1 / 244 (0.41%)	0 / 242 (0.00%)
occurrences (all)	0	1	0
Cardiac failure			
subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences (all)	1	0	0
Ischaemic cardiomyopathy			
subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences (all)	1	0	0
Right ventricular hypertrophy			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences (all)	0	0	1
Sinus bradycardia			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 239 (3.77%)	8 / 244 (3.28%)	6 / 242 (2.48%)
occurrences (all)	17	8	14
Dizziness			
subjects affected / exposed	0 / 239 (0.00%)	1 / 244 (0.41%)	3 / 242 (1.24%)
occurrences (all)	0	1	3
Carpal tunnel syndrome			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences (all)	0	0	1
Convulsions local			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences (all)	0	0	1
Facial nerve disorder			
subjects affected / exposed	0 / 239 (0.00%)	1 / 244 (0.41%)	0 / 242 (0.00%)
occurrences (all)	0	1	0
Hypotonia			

subjects affected / exposed	0 / 239 (0.00%)	1 / 244 (0.41%)	0 / 242 (0.00%)
occurrences (all)	0	1	0
MIgrane			
subjects affected / exposed	0 / 239 (0.00%)	1 / 244 (0.41%)	0 / 242 (0.00%)
occurrences (all)	0	1	0
Radiculitis			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences (all)	0	0	1
Syncope			
subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences (all)	1	0	0
Tremor			
subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	2 / 242 (0.83%)
occurrences (all)	0	0	2
Thrombocytopenia			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	2 / 242 (0.83%)
occurrences (all)	0	0	2
Iron deficiency anaemia			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences (all)	0	0	1
Leukocytosis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 244 (0.41%)	0 / 242 (0.00%)
occurrences (all)	0	1	0
Leukopenia			
subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences (all)	1	0	0
Eye disorders			

Conjunctivitis allergic			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences (all)	0	0	2
Conjunctivitis			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences (all)	0	0	1
Eye irritation			
subjects affected / exposed	0 / 239 (0.00%)	1 / 244 (0.41%)	0 / 242 (0.00%)
occurrences (all)	0	1	0
Scleral haemorrhage			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 239 (0.84%)	1 / 244 (0.41%)	3 / 242 (1.24%)
occurrences (all)	2	1	3
Diarrhoea			
subjects affected / exposed	2 / 239 (0.84%)	1 / 244 (0.41%)	0 / 242 (0.00%)
occurrences (all)	2	1	0
Food poisoning			
subjects affected / exposed	3 / 239 (1.26%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences (all)	3	0	0
Vomiting			
subjects affected / exposed	1 / 239 (0.42%)	2 / 244 (0.82%)	0 / 242 (0.00%)
occurrences (all)	1	2	0
Abdominal pain upper			
subjects affected / exposed	0 / 239 (0.00%)	1 / 244 (0.41%)	1 / 242 (0.41%)
occurrences (all)	0	1	1
Glossodynia			
subjects affected / exposed	0 / 239 (0.00%)	1 / 244 (0.41%)	1 / 242 (0.41%)
occurrences (all)	0	1	1
Abdominal distension			
subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences (all)	1	0	0
Dry mouth			

subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences (all)	0	0	1
Duodenal ulcer			
subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences (all)	1	0	0
Dyspepsia			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences (all)	0	0	1
Dysphagia			
subjects affected / exposed	0 / 239 (0.00%)	1 / 244 (0.41%)	0 / 242 (0.00%)
occurrences (all)	0	1	0
Gastric ulcer			
subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences (all)	1	0	0
Gastritis atrophic			
subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences (all)	1	0	0
Gastritis			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences (all)	0	0	1
Oesophageal disorder			
subjects affected / exposed	0 / 239 (0.00%)	1 / 244 (0.41%)	0 / 242 (0.00%)
occurrences (all)	0	1	0
Pancreatitis			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences (all)	0	0	1
Stomatitis			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences (all)	0	0	1
Tongue coated			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences (all)	0	0	1
Tongue disorder			
subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			

Alopecia			
subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences (all)	1	0	0
Dermatitis atopic			
subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences (all)	1	0	0
Seborrhoeic dermatitis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 244 (0.41%)	0 / 242 (0.00%)
occurrences (all)	0	1	0
Urticaria thermal			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences (all)	0	0	1
Urticaria			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 244 (0.41%)	0 / 242 (0.00%)
occurrences (all)	0	1	0
Renal colic			
subjects affected / exposed	0 / 239 (0.00%)	1 / 244 (0.41%)	0 / 242 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 239 (0.84%)	2 / 244 (0.82%)	2 / 242 (0.83%)
occurrences (all)	2	2	2
Muscle spasms			
subjects affected / exposed	4 / 239 (1.67%)	1 / 244 (0.41%)	1 / 242 (0.41%)
occurrences (all)	4	1	1
Arthralgia			
subjects affected / exposed	1 / 239 (0.42%)	1 / 244 (0.41%)	2 / 242 (0.83%)
occurrences (all)	1	2	7
Arthritis			

subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences (all)	1	0	0
Bone pain			
subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences (all)	0	0	1
Musculoskeletal pain			
subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences (all)	1	0	0
Osteochondrosis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 244 (0.41%)	0 / 242 (0.00%)
occurrences (all)	0	1	0
Osteopenia			
subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences (all)	0	0	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	9 / 239 (3.77%)	14 / 244 (5.74%)	16 / 242 (6.61%)
occurrences (all)	10	15	17
Respiratory tract infection			
subjects affected / exposed	2 / 239 (0.84%)	5 / 244 (2.05%)	5 / 242 (2.07%)
occurrences (all)	2	5	6
Bronchitis			
subjects affected / exposed	4 / 239 (1.67%)	6 / 244 (2.46%)	1 / 242 (0.41%)
occurrences (all)	4	6	1
Respiratory tract infection viral			
subjects affected / exposed	1 / 239 (0.42%)	5 / 244 (2.05%)	5 / 242 (2.07%)
occurrences (all)	1	6	7
Upper respiratory tract infection			
subjects affected / exposed	3 / 239 (1.26%)	3 / 244 (1.23%)	4 / 242 (1.65%)
occurrences (all)	3	3	6

Influenza			
subjects affected / exposed	2 / 239 (0.84%)	4 / 244 (1.64%)	3 / 242 (1.24%)
occurrences (all)	2	6	3
Pharyngitis			
subjects affected / exposed	3 / 239 (1.26%)	3 / 244 (1.23%)	2 / 242 (0.83%)
occurrences (all)	3	3	2
Oral candidiasis			
subjects affected / exposed	1 / 239 (0.42%)	5 / 244 (2.05%)	1 / 242 (0.41%)
occurrences (all)	1	7	1
Acute tonsillitis			
subjects affected / exposed	1 / 239 (0.42%)	3 / 244 (1.23%)	2 / 242 (0.83%)
occurrences (all)	1	3	2
Viral infection			
subjects affected / exposed	4 / 239 (1.67%)	1 / 244 (0.41%)	1 / 242 (0.41%)
occurrences (all)	4	1	1
Rhinitis			
subjects affected / exposed	1 / 239 (0.42%)	1 / 244 (0.41%)	2 / 242 (0.83%)
occurrences (all)	1	1	2
Sinusitis			
subjects affected / exposed	0 / 239 (0.00%)	2 / 244 (0.82%)	2 / 242 (0.83%)
occurrences (all)	0	2	2
Laryngitis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences (all)	1	0	1
Pneumonia			
subjects affected / exposed	0 / 239 (0.00%)	1 / 244 (0.41%)	1 / 242 (0.41%)
occurrences (all)	0	1	1
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 239 (0.00%)	1 / 244 (0.41%)	1 / 242 (0.41%)
occurrences (all)	0	1	1
Bronchitis bacterial			
subjects affected / exposed	0 / 239 (0.00%)	1 / 244 (0.41%)	0 / 242 (0.00%)
occurrences (all)	0	1	0
Cervicitis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences (all)	1	0	0

Cystitis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 244 (0.41%)	0 / 242 (0.00%)
occurrences (all)	0	2	0
Gastroenteritis			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences (all)	0	0	1
Pyelonephritis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 244 (0.41%)	0 / 242 (0.00%)
occurrences (all)	0	1	0
Tracheitis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection bacterial			
subjects affected / exposed	0 / 239 (0.00%)	0 / 244 (0.00%)	1 / 242 (0.41%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	4 / 239 (1.67%)	2 / 244 (0.82%)	1 / 242 (0.41%)
occurrences (all)	4	2	1
Hypercholesterolaemia			
subjects affected / exposed	1 / 239 (0.42%)	2 / 244 (0.82%)	0 / 242 (0.00%)
occurrences (all)	1	2	0
Diabetes mellitus			
subjects affected / exposed	2 / 239 (0.84%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences (all)	2	0	0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 239 (0.00%)	2 / 244 (0.82%)	0 / 242 (0.00%)
occurrences (all)	0	2	0
Dyslipidaemia			
subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences (all)	1	0	0
Hyperglycaemia			
subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences (all)	1	0	0
Hypernatraemia			

subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences (all)	1	0	0
Hypocalcaemia			
subjects affected / exposed	1 / 239 (0.42%)	0 / 244 (0.00%)	0 / 242 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 July 2007	Changes were made to improve some safety measures of the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

There are no limitation or caveats applicable to this summary of results.

Notes: