Clinical trial results:
A 12-week, multinational, randomised, double blind, double dummy, 4-arm parallel-group study comparing the efficacy and safety of CHF 1535 (fixed combination of beclomethasone dipropionate + formoterol fumarate) 100 + 6 g/actuation inhalation powder, administered via the NEXT™ inhaler, versus CHF 1535 (fixed combination of beclomethasone dipropionate + formoterol fumarate) 100 + 6 g/actuation, via HFA pressurised inhalation solution, in moderate to severe symptomatic asthmatic patients aged 12 years under treatment with inhaled corticosteroids.

Summary

EudraCT number	2008-000401-11
Trial protocol	DE CZ HU BG
Global end of trial date	19 October 2009

Results information

Result version number	v1 (current)
This version publication date	15 July 2017
First version publication date	15 July 2017

Trial information

Trial identification

Sponsor protocol code	CCD-0705-PR-0027

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00862394
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, 0521 2791, ClinicalTrial_info@chiesi.com
Scientific contact	Clinical Trial Transparency , Chiesi Farmaceutici SpA, 0521 2791, ClinicalTrial_info@chiesi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000548-PIP01-09
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	19 October 2009
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 October 2009
Global end of trial reached?	Yes
Global end of trial date	19 October 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that CHF 1535 via NEXT™DPI (beclomethasone dipropionate + formoterol fumarate 100 + 6 µg), 1 inhalation or 2 inhalations twice daily, for 12 weeks is non-inferior to the corresponding dose of CHF 1535 via HFA-134a "extrafine" pMDI in terms of pulmonary function (change from baseline in pre-dose morning FEV1) in moderate to severe symptomatic asthmatic patients aged ≥ 12 years under treatment with inhaled corticosteroids (< 2000 µg BDP or equivalent).

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:

No background therapy is concerned.

Evidence for comparator: -	
Actual start date of recruitment	19 February 2009
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	Romania: 67
Country: Number of subjects enrolled	Russian Federation: 101
Country: Number of subjects enrolled	Ukraine: 193
Country: Number of subjects enrolled	Bulgaria: 96
Country: Number of subjects enrolled	Czech Republic: 43
Country: Number of subjects enrolled	Germany: 93
Country: Number of subjects enrolled	Hungary: 103
Worldwide total number of subjects	696
EEA total number of subjects	402

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)	162
Adults (18-64 years)	481
From 65 to 84 years	53
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients of both sexes, aged > 12 years, non/ex-smokers, with a diagnosis of moderate to severe symptomatic asthma treated with a stable daily dose of inhaled corticosteroids < 2000 µg BDP or equivalent for at least 4 weeks prior to inclusion (plus additional criteria) were considered for recruitment.

Pre-assignment

Screening details:

A total of 783 patients were screened, 87 (11.1%) patients were withdrawn before randomisation and were considered as screen failures.
The study entailed a 2-week run-in period followed by a 12-week randomised active treatment.
A total of 696 patients were randomised to receive one of the four study treatments between 05 March and 22 July 2009.

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:

The study was double-blind and double-dummy with respect to the formulations of the test product CHF 1535, NEXT DPI® and pMDI. No blinding was applied with respect to the dose intake.
The randomisation list was provided to the labelling facility but was not available to patients, investigators, monitors or employees of the centres involved in the management of the trial before unblinding of the data, unless in case of emergency.

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

CHF 1535 NEXT DPI®, 1 inhalation bid + placebo pMDI, 1 inhalation bid

Arm type	Experimental
Investigational medicinal product name	CHF 1535 NEXT DPI
Investigational medicinal product code	
Other name	beclomethasone dipropionate, formoterol fumarate
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

1 inhalation bid
Daily dose: beclomethasone dipropionate (BDP) 200 µg/formoterol fumarate (FF) 12 µg

Investigational medicinal product name	placebo pMDI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Pressurised inhalation, solution
Routes of administration	Inhalation use

Dosage and administration details:

1 inhalation bid

Arm title	Arm B

Arm description:

CHF 1535 pMDI, 1 inhalation bid + placebo NEXT DPI®, 1 inhalation bid.

Arm type	Active comparator
Investigational medicinal product name	CHF 1535 pMDI
Investigational medicinal product code	
Other name	beclomethasone dipropionate, formoterol fumarate
Pharmaceutical forms	Pressurised inhalation, solution
Routes of administration	Inhalation use

Dosage and administration details:

1 inhalation bid
Daily dose: beclometasone (BDP) 200 µg/formoterol fumarate (FF) 12 µg

Investigational medicinal product name	placebo NEXT DPI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

1 inhalation bid

Arm title	Arm C

Arm description:

CHF 1535 NEXT DPI®, 2 inhalations bid + placebo pMDI, 2 inhalations bid

Arm type	Experimental
Investigational medicinal product name	CHF 1535 NEXT DPI
Investigational medicinal product code	
Other name	beclomethasone dipropionate, formoterol fumarate
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

2 inhalations bid
Daily dose: beclomethasone dipropionate (BDP) 400 µg/formoterol fumarate (FF) 24 µg

Investigational medicinal product name	placebo pMDI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Pressurised inhalation, solution
Routes of administration	Inhalation use

Dosage and administration details:

2 inhalations bid

Arm title	Arm D

Arm description:

CHF 1535 pMDI, 2 inhalations bid + placebo NEXT DPI®, 2 inhalations bid

Arm type	Active comparator
Investigational medicinal product name	CHF 1535 pMDI
Investigational medicinal product code	
Other name	beclomethasone dipropionate (BDP) 400 µg/formoterol fumarate
Pharmaceutical forms	Pressurised inhalation, solution
Routes of administration	Inhalation use

Dosage and administration details:

2 inhalations bid
Daily dose: beclomethasone dipropionate (BDP) 400 µg/formoterol fumarate (FF) 24 µg

Investigational medicinal product name	placebo NEXT DPI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder

Routes of administration	Inhalation use

Dosage and administration details:

2 inhalations bid

Number of subjects in period 1	Arm A	Arm B	Arm C
Started	173	173	176
Completed	161	159	163
Not completed	12	14	13
Consent withdrawn by subject	3	-	1
Adverse event, non-fatal	3	4	3
Non compliance	1	1	-
Unspecified	2	3	6
Discontinuation criteria	-	6	-
Protocol deviation	3	-	3

Number of subjects in period 1	Arm D
Started	174
Completed	160
Not completed	14
Consent withdrawn by subject	1
Adverse event, non-fatal	2
Non compliance	-
Unspecified	3
Discontinuation criteria	-
Protocol deviation	8

Baseline characteristics

Reporting groups	
Reporting group title	Arm A
Reporting group description:	
CHF 1535 NEXT DPI®, 1 inhalation bid + placebo pMDI, 1 inhalation bid	
Reporting group title	Arm B
Reporting group description:	
CHF 1535 pMDI, 1 inhalation bid + placebo NEXT DPI®, 1 inhalation bid.	

Reporting group title	Arm C
Reporting group description:	
CHF 1535 NEXT DPI®, 2 inhalations bid + placebo pMDI, 2 inhalations bid	
Reporting group title	Arm D
Reporting group description:	
CHF 1535 pMDI, 2 inhalations bid + placebo NEXT DPI®, 2 inhalations bid	

Reporting group values	Arm A	Arm B	Arm C
Number of subjects	173	173	176
Age categorical Units: Subjects			
12 ≤ Age < 18	42	38	47
Age ≥ 18	131	135	129
Gender categorical Units: Subjects			
Female	111	101	91
Male	62	72	85

Reporting group values	Arm D	Total	
Number of subjects	174	696	
Age categorical Units: Subjects			
12 ≤ Age < 18	35	162	
Age ≥ 18	139	534	
Gender categorical Units: Subjects			
Female	100	403	
Male	74	293	

Subject analysis sets	
Subject analysis set title	Arm A - ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects randomised to Arm A who received at least one dose of the study medications and with at least one post-baseline evaluation for any efficacy variable.	
Subject analysis set title	Arm B - ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects randomised to Arm B who received at least one dose of the study medications and with at least one post-baseline evaluation for any efficacy variable.

Subject analysis set title	Arm C - ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects randomised to Arm C who received at least one dose of the study medications and with at least one post-baseline evaluation for any efficacy variable.

Subject analysis set title	Arm D - ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects randomised to Arm D who received at least one dose of the study medications and with at least one post-baseline evaluation for any efficacy variable.

Subject analysis set title	Arm A - Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects randomised to Arm A who took at least one dose of study medication

Subject analysis set title	Arm B - Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects randomised to Arm B who took at least one dose of study medication

Subject analysis set title	Arm C - Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects randomised to Arm C who took at least one dose of study medication

Subject analysis set title	Arm D - Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects randomised to Arm D who took at least one dose of study medication

Subject analysis set title	Arm A - PP population
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects randomised to Arm A included in the ITT population who also met all inclusion/exclusion criteria and who did not have any major protocol deviations.

Subject analysis set title	Arm B - PP population
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects randomised to Arm B included in the ITT population who also met all inclusion/exclusion criteria and who did not have any major protocol deviations.

Subject analysis set title	Arm C - PP population
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects randomised to Arm C included in the ITT population who also met all inclusion/exclusion criteria and who did not have any major protocol deviations.

Subject analysis set title	Arm D - PP population
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects randomised to Arm D included in the ITT population who also met all inclusion/exclusion criteria and who did not have any major protocol deviations.

Reporting group values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population
Number of subjects	173	173	176

Age categorical Units: Subjects			
12 ≤ Age < 18	42	38	47
Age ≥ 18	131	135	129
Gender categorical Units: Subjects			
Female	111	101	91
Male	62	72	85

Reporting group values	Arm D - ITT population	Arm A - Safety population	Arm B - Safety population
Number of subjects	172	172	173
Age categorical Units: Subjects			
12 ≤ Age < 18	35	42	38
Age ≥ 18	137	130	135
Gender categorical Units: Subjects			
Female	99	111	100
Male	73	62	72

Reporting group values	Arm C - Safety population	Arm D - Safety population	Arm A - PP population
Number of subjects	177	173	159
Age categorical Units: Subjects			
12 ≤ Age < 18	47	35	41
Age ≥ 18	130	138	118
Gender categorical Units: Subjects			
Female	92	99	100
Male	85	74	59

Reporting group values	Arm B - PP population	Arm C - PP population	Arm D - PP population
Number of subjects	154	161	158
Age categorical Units: Subjects			
12 ≤ Age < 18	34	44	34
Age ≥ 18	120	117	124
Gender categorical Units: Subjects			
Female	87	81	91
Male	67	80	67

End points

End points reporting groups

Reporting group title	Arm A
Reporting group description:	
CHF 1535 NEXT DPI®, 1 inhalation bid + placebo pMDI, 1 inhalation bid	
Reporting group title	Arm B
Reporting group description:	
CHF 1535 pMDI, 1 inhalation bid + placebo NEXT DPI®, 1 inhalation bid.	

Reporting group title	Arm C
Reporting group description:	
CHF 1535 NEXT DPI®, 2 inhalations bid + placebo pMDI, 2 inhalations bid	
Reporting group title	Arm D
Reporting group description:	
CHF 1535 pMDI, 2 inhalations bid + placebo NEXT DPI®, 2 inhalations bid	
Subject analysis set title	Arm A - ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects randomised to Arm A who received at least one dose of the study medications and with at least one post-baseline evaluation for any efficacy variable.	
Subject analysis set title	Arm B - ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects randomised to Arm B who received at least one dose of the study medications and with at least one post-baseline evaluation for any efficacy variable.	
Subject analysis set title	Arm C - ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects randomised to Arm C who received at least one dose of the study medications and with at least one post-baseline evaluation for any efficacy variable.	
Subject analysis set title	Arm D - ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects randomised to Arm D who received at least one dose of the study medications and with at least one post-baseline evaluation for any efficacy variable.	
Subject analysis set title	Arm A - Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects randomised to Arm A who took at least one dose of study medication	
Subject analysis set title	Arm B - Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects randomised to Arm B who took at least one dose of study medication	
Subject analysis set title	Arm C - Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects randomised to Arm C who took at least one dose of study medication	
Subject analysis set title	Arm D - Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects randomised to Arm D who took at least one dose of study medication

Subject analysis set title	Arm A - PP population
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects randomised to Arm A included in the ITT population who also met all inclusion/exclusion criteria and who did not have any major protocol deviations.

Subject analysis set title	Arm B - PP population
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects randomised to Arm B included in the ITT population who also met all inclusion/exclusion criteria and who did not have any major protocol deviations.

Subject analysis set title	Arm C - PP population
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects randomised to Arm C included in the ITT population who also met all inclusion/exclusion criteria and who did not have any major protocol deviations.

Subject analysis set title	Arm D - PP population
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects randomised to Arm D included in the ITT population who also met all inclusion/exclusion criteria and who did not have any major protocol deviations.

Primary: Change in Pre-Dose FEV1 from Baseline to End of Treatment - ITT population

End point title	Change in Pre-Dose FEV1 from Baseline to End of Treatment - ITT population

End point description:

Change from baseline measured at clinic visit V2 (end of run-in) to the end of treatment period (V5) in pre-dose morning Forced Expiratory Volume in the 1st second (FEV1) measured at clinic.

End point type	Primary

End point timeframe:

From visit 2 (end of run-in) to Visit 5 (end of treatment period)

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	170[1]	166[2]	175[3]	170[4]
Units: liters				
arithmetic mean (standard deviation)	0.29 (± 0.41)	0.39 (± 0.5)	0.38 (± 0.42)	0.45 (± 0.46)

Notes:

[1] - The one reported is the real number of patients analyzed

[2] - The one reported is the real number of patients analyzed

[3] - The one reported is the real number of patients analyzed

[4] - The one reported is the real number of patients analyzed

Statistical analyses

Statistical analysis title	Arm A vs Arm B

Statistical analysis description:

Non-inferiority comparison of CHF 1535 NEXT DPI® versus the corresponding dose (1 inhalation bid) of CHF 1535 pMDI

Comparison groups	Arm B - ITT population v Arm A - ITT population
Number of subjects included in analysis	336
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
Parameter estimate	least square means difference
Point estimate	-0.109
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	-0.017
Variability estimate	Standard error of the mean
Dispersion value	0.047

Notes:

[5] - The primary efficacy variable was submitted to an ANCOVA model, including terms for country and treatment as factors and baseline value as a covariate.

Statistical analysis title	Arm C vs Arm D

Statistical analysis description:

Non-inferiority comparison of CHF 1535 NEXT DPI® versus the corresponding dose (2 inhalations bid) of CHF 1535 pMDI

Comparison groups	Arm C - ITT population v Arm D - ITT population
Number of subjects included in analysis	345
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
Parameter estimate	least square means difference
Point estimate	-0.076
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.166
upper limit	0.014
Variability estimate	Standard error of the mean
Dispersion value	0.046

Notes:

[6] - The primary efficacy variable was submitted to an ANCOVA model, including terms for country and treatment as factors and baseline value as a covariate

Statistical analysis title	Arm C vs Arm A
Comparison groups	Arm A - ITT population v Arm C - ITT population
Number of subjects included in analysis	345
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
P-value	= 0.069
Method	ANCOVA
Parameter estimate	least square means difference
Point estimate	0.084
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.007
upper limit	0.174

Notes:

[7] - The primary efficacy variable was submitted to an ANCOVA model, including terms for country and treatment as factors and baseline value as a covariate.

Statistical analysis title	Arm D vs Arm B
Comparison groups	Arm D - ITT population v Arm B - ITT population
Number of subjects included in analysis	336
Analysis specification	Pre-specified
Analysis type	non-inferiority[8]
P-value	= 0.272
Method	ANCOVA
Parameter estimate	least square means difference
Point estimate	0.051
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.143

Notes:

[8] - The primary efficacy variable was submitted to an ANCOVA model, including terms for country and treatment as factors and baseline value as a covariate.

Primary: Change in Pre-Dose FEV1 from Baseline to End of Treatment - PP population

End point title	Change in Pre-Dose FEV1 from Baseline to End of Treatment - PP population

End point description:

Change from baseline measured at clinic visit V2 (end of run-in) to the end of treatment period (V5) in pre-dose morning Forced Expiratory Volume in the 1st second (FEV1) measured at clinic.

End point type	Primary

End point timeframe:

From visit 2 (end of run-in) to Visit 5 (end of treatment period)

End point values	Arm A - PP population	Arm B - PP population	Arm C - PP population	Arm D - PP population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	159[9]	154[10]	161[11]	158[12]
Units: liters				
least squares mean (standard error)	0.26 (± 0.03)	0.36 (± 0.04)	0.34 (± 0.03)	0.43 (± 0.04)

Notes:

[9] - The one reported is the real number of patients analyzed

[10] - The one reported is the real number of patients analyzed

[11] - The one reported is the real number of patients analyzed

[12] - The one reported is the real number of patients analyzed

Statistical analyses

Statistical analysis title	Arm A vs Arm B - PP population

Statistical analysis description:

Non-inferiority comparison of CHF 1535 NEXT DPI® versus the corresponding dose (1 inhalation bid) of CHF 1535 pMDI

Comparison groups	Arm A - PP population v Arm B - PP population
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	non-inferiority[13]
Parameter estimate	least square means difference
Point estimate	-0.104
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.199
upper limit	-0.009
Variability estimate	Standard error of the mean
Dispersion value	0.048

Notes:

[13] - The primary efficacy variable was submitted to an ANCOVA model, including terms for country and treatment as factors and baseline value as a covariate.

Statistical analysis title	Arm C vs Arm D - PP population

Statistical analysis description:

Non-inferiority comparison of CHF 1535 NEXT DPI® versus the corresponding dose (2 inhalations bid) of CHF 1535 pMDI

Comparison groups	Arm C - PP population v Arm D - PP population
Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	non-inferiority[14]
Parameter estimate	least square means difference
Point estimate	-0.082
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.176
upper limit	0.011
Variability estimate	Standard error of the mean
Dispersion value	0.048

Notes:

[14] - The primary efficacy variable was submitted to an ANCOVA model, including terms for country and treatment as factors and baseline value as a covariate.

Secondary: Pre-dose FEV1 at Visit 2

End point title	Pre-dose FEV1 at Visit 2

End point description:

End point type	Secondary

End point timeframe:

Lung Function Tests – FEV1, FVC, FEF25-75% – were measured pre-dose at each clinic visit: Visit 1 (Week –2), Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8), Visit 5 (Week 12). Data from Visit 2 are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	173	173	176	172
Units: liters				
arithmetic mean (standard deviation)	2.03 (± 0.59)	2.03 (± 0.53)	2.12 (± 0.55)	2.06 (± 0.59)

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose FEV1 at Visit 3

End point title	Pre-dose FEV1 at Visit 3

End point description:

End point type	Secondary

End point timeframe:

Lung Function Tests – FEV1, FVC, FEF25-75% – were measured pre-dose at each clinic visit: Visit 1 (Week –2), Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8), Visit 5 (Week 12). Data from Visit 3 are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	167[15]	164[16]	170[17]	166[18]
Units: liters				
arithmetic mean (standard deviation)	2.33 (± 0.77)	2.37 (± 0.79)	2.46 (± 0.73)	2.46 (± 0.72)

Notes:

[15] - The one reported is the real number of patients analyzed

[16] - The one reported is the real number of patients analyzed

[17] - The one reported is the real number of patients analyzed

[18] - The one reported is the real number of patients analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose FEV1 at Visit 4

End point title	Pre-dose FEV1 at Visit 4

End point description:

End point type	Secondary

End point timeframe:

Lung Function Tests – FEV1, FVC, FEF25-75% – were measured pre-dose at each clinic visit: Visit 1 (Week –2), Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8), Visit 5 (Week 12). Data from Visit 4 are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	167[19]	165[20]	170[21]	166[22]
Units: liters				
arithmetic mean (standard deviation)	2.32 (± 0.77)	2.41 (± 0.8)	2.51 (± 0.71)	2.54 (± 0.76)

Notes:

[19] - The one reported is the real number of patients analyzed

[20] - The one reported is the real number of patients analyzed

[21] - The one reported is the real number of patients analyzed

[22] - The one reported is the real number of patients analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose FEV1 at Visit 5

End point title	Pre-dose FEV1 at Visit 5

End point description:

End point type	Secondary

End point timeframe:

Lung Function Tests – FEV1, FVC, FEF25-75% – were measured pre-dose at each clinic visit: Visit 1 (Week –2), Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8), Visit 5 (Week 12). Data from Visit 5 are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	170[23]	166[24]	175[25]	170[26]
Units: liters				
arithmetic mean (standard deviation)	2.31 (± 0.78)	2.43 (± 0.82)	2.5 (± 0.7)	2.51 (± 78)

Notes:

[23] - The one reported is the real number of patients analyzed

[24] - The one reported is the real number of patients analyzed

[25] - The one reported is the real number of patients analyzed

[26] - The one reported is the real number of patients analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Post-dose FEV1 AUC0-8 h at Visit 2

End point title	Post-dose FEV1 AUC0-8 h at Visit 2

End point description:

Area under the curve was calculated using the linear trapezoidal rule in the subgroup of patients performing spirometry until 8 hours post-dose.

End point type	Secondary

End point timeframe:

Post-dose FEV1 AUC0-8 h standardised by time (FEV1 at 10 min, 30 min, 1, 2, 3 , 4 , 6 and 8 h) was measured at Visit 2 (Week 0) and Visit 5 (End of treatment period). Data from Visit 2 are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	61[27]	56[28]	60[29]	63[30]
Units: ng*h/mL				
arithmetic mean (standard deviation)	2.35 (± 0.73)	2.55 (± 0.68)	2.62 (± 0.67)	2.65 (± 0.78)

Notes:

[27] - The real number of patients analyzed out of 67 who underwent serial spirometry until 8 hr post-dose.
[28] - The real number of patients analyzed out of 65 who underwent serial spirometry until 8 hr post-dose.
[29] - The real number of patients analyzed out of 63 who underwent serial spirometry until 8 hr post-dose.
[30] - The real number of patients analyzed out of 66 who underwent serial spirometry until 8 hr post-dose.

Statistical analyses

Statistical analysis title	Arm A vs Arm B
Comparison groups	Arm A - ITT population v Arm C - ITT population
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	other[31]
P-value	= 0.009
Method	ANCOVA
Parameter estimate	least square means difference
Point estimate	-0.167
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.292
upper limit	-0.043

Notes:

[31] - AUCs were compared between treatments at both V2 and V5 using ANCOVA with baseline FEV1 (pre-dose at visit 2) as covariate and country as factor.
Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Statistical analysis title	Arm B vs Arm D
Comparison groups	Arm B - ITT population v Arm D - ITT population
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	other[32]
P-value	= 0.242
Method	ANCOVA
Parameter estimate	least square means difference
Point estimate	-0.073

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.195
upper limit	0.049

Notes:

[32] - AUCs were compared between treatments at both V2 and V5 using ANCOVA with baseline FEV1 (pre-dose at visit 2) as covariate and country as factor.
Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Secondary: Post-dose FEV1 AUC0-8 h at Visit 5

End point title	Post-dose FEV1 AUC0-8 h at Visit 5

End point description:

Area under the curve was calculated using the linear trapezoidal rule in the subgroup of patients performing spirometry until 8 hours post-dose.

End point type	Secondary

End point timeframe:

Post-dose FEV1 AUC0-8 h standardised by time (FEV1 at 10 min, 30 min, 1 hour, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours) was measured at Visit V2 (Wek 0) and Visit 5 (End of treatment period). data from Visit 5 are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	62[33]	53[34]	60[35]	61[36]
Units: ng*h/mL				
arithmetic mean (standard deviation)	2.5 (± 0.81)	2.8 (± 0.8)	2.74 (± 0.64)	2.78 (± 0.7)

Notes:

[33] - The real number of patients analyzed out of 67 who underwent serial spirometry until 8 hr post-dose.
[34] - The real number of patients analyzed out of 65 who underwent serial spirometry until 8 hr post-dose.
[35] - The real number of patients analyzed out of 63 who underwent serial spirometry until 8 hr post-dose.
[36] - The real number of patients analyzed out of 66 who underwent serial spirometry until 8 hr post-dose.

Statistical analyses

Statistical analysis title	Arm A vs Arm B
Comparison groups	Arm A - ITT population v Arm B - ITT population
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	other[37]
P-value	= 0.206
Method	ANCOVA
Parameter estimate	least square means difference
Point estimate	-0.054

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.139
upper limit	0.03

Notes:

[37] - AUCs were compared between treatments at both V2 and V5 using ANCOVA with baseline FEV1 (pre-dose at visit 2) as covariate and country as factor.
Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Statistical analysis title	Arm C vs Arm D
Comparison groups	Arm C - ITT population v Arm D - ITT population
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	non-inferiority[38]
P-value	= 0.568
Method	ANCOVA
Parameter estimate	least square means difference
Point estimate	-0.024
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.106
upper limit	0.058

Notes:

[38] - AUCs were compared between treatments at both V2 and V5 using ANCOVA with baseline FEV1 (pre-dose at visit 2) as covariate and country as factor.
Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Secondary: Pre-dose FVC at Visit 2

End point title	Pre-dose FVC at Visit 2

End point description:

End point type	Secondary

End point timeframe:

Lung Function Tests – FEV1, FVC, FEF25-75% – were measured pre-dose at each clinic visit: Visit 1 (Week –2), Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8), Visit 5 (Week 12). Data from Visit 2 are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	173	173	176	172
Units: liters				
arithmetic mean (standard deviation)	2.87 (± 0.81)	2.94 (± 0.77)	3 (± 0.86)	2.96 (± 0.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose FVC at Visit 3

End point title	Pre-dose FVC at Visit 3

End point description:

End point type	Secondary

End point timeframe:

Lung Function Tests – FEV1, FVC, FEF25-75% – were measured pre-dose at each clinic visit: Visit 1 (Week –2), Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8), Visit 5 (Week 12). Data from Visit 3 are reported here

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	167[39]	164[40]	170[41]	166[42]
Units: liters				
arithmetic mean (standard deviation)	3.15 (± 0.95)	3.24 (± 0.93)	3.31 (± 0.88)	3.34 (± 0.93)

Notes:

[39] - This is the real number of patients analyzed.

[40] - This is the real number of patients analyzed.

[41] - This is the real number of patients analyzed.

[42] - This is the real number of patients analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose FVC at Visit 4

End point title	Pre-dose FVC at Visit 4

End point description:

End point type	Secondary

End point timeframe:

Lung Function Tests – FEV1, FVC, FEF25-75% – were measured pre-dose at each clinic visit: Visit 1 (Week –2), Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8), Visit 5 (Week 12). Data from Visit 4 are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	167[43]	165[44]	170[45]	166[46]
Units: liters				
arithmetic mean (standard deviation)	3.16 (± 0.88)	3.32 (± 1.05)	3.39 (± 0.89)	3.46 (± 0.99)

Notes:

[43] - This is the real number of patients analyzed.

[44] - This is the real number of patients analyzed.

[45] - This is the real number of patients analyzed.

[46] - This is the real number of patients analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose FVC at Visit 5

End point title	Pre-dose FVC at Visit 5

End point description:

End point type	Secondary

End point timeframe:

Lung Function Tests – FEV1, FVC, FEF25-75% – were measured pre-dose at each clinic visit: Visit 1 (Week –2), Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8), Visit 5 (Week 12). Data from Visit 5 are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	170[47]	166[48]	175[49]	170[50]
Units: liters				
arithmetic mean (standard deviation)	3.17 (± 0.94)	3.32 (± 0.96)	3.37 (± 0.86)	3.42 (± 0.94)

Notes:

[47] - This is the real number of patients analyzed.

[48] - This is the real number of patients analyzed.

[49] - This is the real number of patients analyzed.

[50] - This is the real number of patients analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Pre-Dose FVC from Baseline to End of Treatment

End point title	Change in Pre-Dose FVC from Baseline to End of Treatment

End point description:

End point type	Secondary

End point timeframe:

Lung Function Tests – FEV1, FVC, FEF25-75% – were measured pre-dose at each clinic visit: Visit 1 (Week –2), Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8), Visit 5 (Week 12).

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	170[51]	166[52]	175[53]	170[54]
Units: liters				
arithmetic mean (standard deviation)	0.3 (± 0.49)	0.38 (± 0.61)	0.37 (± 0.46)	0.47 (± 0.55)

Notes:

[51] - This is the real number of patients analyzed.

[52] - This is the real number of patients analyzed.

[53] - This is the real number of patients analyzed.

[54] - This is the real number of patients analyzed.

Statistical analyses

Statistical analysis title	Arm A vs Arm B
Comparison groups	Arm A - ITT population v Arm B - ITT population
Number of subjects included in analysis	336
Analysis specification	Pre-specified
Analysis type	other[55]
P-value	= 0.127
Method	ANCOVA
Parameter estimate	least square means difference
Point estimate	-0.086
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.197
upper limit	0.024

Notes:

[55] - Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Statistical analysis title	Arm C vs Arm D
Comparison groups	Arm C - ITT population v Arm D - ITT population
Number of subjects included in analysis	345
Analysis specification	Pre-specified
Analysis type	other[56]
P-value	= 0.076
Method	ANCOVA
Parameter estimate	least square means difference
Point estimate	-0.098
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.207
upper limit	0.01

Notes:

[56] - Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Secondary: Pre-dose FEF25-75% at Visit 2

End point title	Pre-dose FEF25-75% at Visit 2

End point description:

End point type	Secondary

End point timeframe:

Lung Function Tests – FEV1, FVC, FEF25-75% – were measured pre-dose at each clinic visit: Visit 1 (Week –2), Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8), Visit 5 (Week 12). Data from Visit 2 are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	173			
Units: L/sec				
arithmetic mean (standard deviation)	1.74 (± 1.16)	1.61 (± 0.95)	1.68 (± 0.81)	1.69 (± 0.98)

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose FEF25-75% at Visit 3

End point title	Pre-dose FEF25-75% at Visit 3

End point description:

End point type	Secondary

End point timeframe:

Lung Function Tests – FEV1, FVC, FEF25-75% – were measured pre-dose at each clinic visit: Visit 1 (Week –2), Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8), Visit 5 (Week 12). Data from Visit 3 are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	167[57]	164[58]	170[59]	166[60]
Units: L/sec				
arithmetic mean (standard deviation)	2.12 (± 1.41)	2.07 (± 1.32)	2.15 (± 1.24)	2.17 (± 1.25)

Notes:

[57] - This is the real number of patients analyzed.

[58] - This is the real number of patients analyzed.

[59] - This is the real number of patients analyzed.

[60] - This is the real number of patients analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose FEF25-75% at Visit 4

End point title	Pre-dose FEF25-75% at Visit 4

End point description:

End point type	Secondary

End point timeframe:

Lung Function Tests – FEV1, FVC, FEF25-75% – were measured pre-dose at each clinic visit: Visit 1 (Week –2), Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8), Visit 5 (Week 12). Data from Visit 4 are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	167[61]	165[62]	170[63]	166[64]
Units: L/sec				
arithmetic mean (standard deviation)	2.1 (± 1.39)	2.12 (± 1.33)	2.17 (± 1.2)	2.21 (± 1.28)

Notes:

[61] - This is the real number of patients analyzed.

[62] - This is the real number of patients analyzed.

[63] - This is the real number of patients analyzed.

[64] - This is the real number of patients analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose FEF25-75% at Visit 5

End point title	Pre-dose FEF25-75% at Visit 5

End point description:

End point type	Secondary

End point timeframe:

Lung Function Tests – FEV1, FVC, FEF25-75% – were measured pre-dose at each clinic visit: Visit 1 (Week –2), Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8), Visit 5 (Week 12). Data from Visit 5 are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	170[65]	166[66]	175[67]	170[68]
Units: L/sec				
arithmetic mean (standard deviation)	2.06 (± 1.28)	2.11 (± 1.35)	2.18 (± 1.24)	2.18 (± 1.29)

Notes:

[65] - This is the real number of patients analyzed.

[66] - This is the real number of patients analyzed.

[67] - This is the real number of patients analyzed.

[68] - This is the real number of patients analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Pre-Dose FEF25-75% from Baseline to End of Treatment

End point title	Change in Pre-Dose FEF25-75% from Baseline to End of Treatment

End point description:

End point type	Secondary

End point timeframe:

Lung Function Tests – FEV1, FVC, FEF25-75% – were measured pre-dose at each clinic visit: Visit 1 (Week –2), Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8), Visit 5 (Week 12).

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	170[69]	166[70]	175[71]	170[72]
Units: L/sec				
arithmetic mean (standard deviation)	0.32 (± 0.99)	0.51 (± 0.78)	0.49 (± 0.89)	0.48 (± 0.74)

Notes:

[69] - This is the real number of patients analyzed.

[70] - This is the real number of patients analyzed.

[71] - This is the real number of patients analyzed.

[72] - This is the real number of patients analyzed.

Statistical analyses

Statistical analysis title	Arm A vs Arm B
Comparison groups	Arm A - ITT population v Arm B - ITT population
Number of subjects included in analysis	336
Analysis specification	Pre-specified
Analysis type	other[73]
P-value	= 0.042
Method	ANCOVA
Parameter estimate	least square means difference
Point estimate	-0.188
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.369
upper limit	-0.007

Notes:

[73] - Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Statistical analysis title	Arm C vs Arm D
Comparison groups	Arm C - ITT population v Arm D - ITT population

Number of subjects included in analysis	345
Analysis specification	Pre-specified
Analysis type	other[74]
P-value	= 0.884
Method	ANCOVA
Parameter estimate	Least square means difference
Point estimate	0.013
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.165
upper limit	0.192

Notes:

[74] - Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Secondary: Post-dose FVC AUC0-8 h at Visit 2

End point title	Post-dose FVC AUC0-8 h at Visit 2

End point description:

Area under the curve was calculated using the linear trapezoidal rule in the subgroup of patients performing spirometry until 8 hours post-dose.

End point type	Secondary

End point timeframe:

Post-dose FVC AUC0-8 h standardised by time (FEV1 at 10 min, 30 min, 1, 2, 3 , 4 , 6 and 8 h) was measured at Visit 2 (Week 0) and Visit 5 (End of treatment period). Data from Visit 2 are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	61[75]	56[76]	60[77]	63[78]
Units: ng*h/mL				
arithmetic mean (standard deviation)	3.18 (± 0.94)	3.4 (± 0.84)	3.54 (± 0.92)	3.56 (± 1.04)

Notes:

[75] - The real number of patients analyzed out of 67 who underwent serial spirometry until 8 hr post-dose.
[76] - The real number of patients analyzed out of 65 who underwent serial spirometry until 8 hr post-dose.
[77] - The real number of patients analyzed out of 63 who underwent serial spirometry until 8 hr post-dose.
[78] - The real number of patients analyzed out of 66 who underwent serial spirometry until 8 hr post-dose.

Statistical analyses

Statistical analysis title	Arm A vs Arm B
Comparison groups	Arm A - ITT population v Arm B - ITT population

Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	other[79]
P-value	= 0.183
Method	ANCOVA
Parameter estimate	least square means difference
Point estimate	-0.108
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.268
upper limit	0.052

Notes:

[79] - AUCs were compared between treatments at both V2 and V5 using ANCOVA with baseline FVC (pre-dose at visit 2) as covariate and country as factor.
Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Statistical analysis title	Arm C vs Arm D
Comparison groups	Arm C - ITT population v Arm D - ITT population
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	other[80]
P-value	= 0.352
Method	ANCOVA
Parameter estimate	Least square means difference
Point estimate	-0.074
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.231
upper limit	0.083

Notes:

[80] - AUCs were compared between treatments at both V2 and V5 using ANCOVA with baseline FVC (pre-dose at visit 2) as covariate and country as factor.
Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Secondary: Post-dose FVC AUC0-8 h at Visit 5

End point title	Post-dose FVC AUC0-8 h at Visit 5

End point description:

Area under the curve was calculated using the linear trapezoidal rule in the subgroup of patients performing spirometry until 8 hours post-dose.

End point type	Secondary

End point timeframe:

Post-dose FVC AUC0-8 h standardised by time (FEV1 at 10 min, 30 min, 1, 2, 3 , 4 , 6 and 8 h) was measured at Visit 2 (Week 0) and Visit 5 (End of treatment period). Data from Visit 5 are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	62[81]	53[82]	60[83]	61[84]
Units: ng*h/mL				
arithmetic mean (standard deviation)	3.31 (± 0.91)	3.6 (± 0.88)	3.64 (± 0.87)	3.62 (± 0.9)

Notes:

[81] - The real number of patients analyzed out of 67 who underwent serial spirometry until 8 hr post-dose.
[82] - The real number of patients analyzed out of 65 who underwent serial spirometry until 8 hr post-dose.
[83] - The real number of patients analyzed out of 63 who underwent serial spirometry until 8 hr post-dose.
[84] - The real number of patients analyzed out of 66 who underwent serial spirometry until 8 hr post-dose.

Statistical analyses

Statistical analysis title	Arm A vs Arm B
Comparison groups	Arm A - ITT population v Arm B - ITT population
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	other[85]
P-value	= 0.647
Method	ANCOVA
Parameter estimate	Least square means difference
Point estimate	-0.023
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.121
upper limit	0.075

Notes:

[85] - AUCs were compared between treatments at both V2 and V5 using ANCOVA with baseline FVC (pre-dose at visit 2) as covariate and country as factor.
Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Statistical analysis title	Arm C vs arm D
Comparison groups	Arm C - ITT population v Arm D - ITT population
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	other[86]
P-value	= 0.843
Method	ANCOVA
Parameter estimate	Least square means difference
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.105
upper limit	0.086

Notes:

[86] - AUCs were compared between treatments at both V2 and V5 using ANCOVA with baseline FVC (pre-dose at visit 2) as covariate and country as factor.
Comparisons between treatments were done using the same ANCOVA model as for the primary analysis

without testing for non-inferiority.

Secondary: Pre-dose morning PEF - Run-in period

End point title	Pre-dose morning PEF - Run-in period

End point description:

PEF was measured 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 over the 12-week treatment.
Data for the Run-in period are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	112[87]	100[88]	107[89]	108
Units: L/min				
arithmetic mean (standard deviation)	307.18 (± 81.71)	322.18 (± 94.95)	331.9 (± 96.22)	336.79 (± 95.13)

Notes:

[87] - This is the real number of patients analyzed.

[88] - This is the real number of patients analyzed.

[89] - This is the real number of patients analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose morning PEF - End-of-treatment period

End point title	Pre-dose morning PEF - End-of-treatment period

End point description:

PEF was measured at home by a portable electronic peak flow meter.
End-of-treatment period is the last 14 days of treatment.

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 over the 12-week treatment.
Data for the End-of-treatment period are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	111[90]	105[91]	104[92]	107[93]
Units: L/min				
arithmetic mean (standard deviation)	313.96 (± 92.48)	339.79 (± 106.57)	352.78 (± 98.37)	361.99 (± 103.07)

Notes:

[90] - This is the real number of patients analyzed.

[91] - This is the real number of patients analyzed.

[92] - This is the real number of patients analyzed.

[93] - This is the real number of patients analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose morning PEF - Overall treatment period

End point title	Pre-dose morning PEF - Overall treatment period

End point description:

PEF was measured at home by a portable electronic peak flow meter.
Overall treatment period is from Day 1 to Last day of treatment.

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 over the 12-week treatment.
Data for the Overall treatment period are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	166[94]	163[95]	170[96]	168[97]
Units: L/min				
arithmetic mean (standard deviation)	313.34 (± 92.81)	328.15 (± 106.01)	336.37 (± 96.5)	351.12 (± 100.35)

Notes:

[94] - This is the real number of patients analyzed.

[95] - This is the real number of patients analyzed.

[96] - This is the real number of patients analyzed.

[97] - This is the real number of patients analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose morning PEF - Change from Run-in period to End-of-treatment period

End point title	Pre-dose morning PEF - Change from Run-in period to End-of-treatment period

End point description:

PEF was measured at home by a portable electronic peak flow meter.
End-of-treatment period is the last 14 days of treatment.

End point type	Secondary

End point timeframe:

Pre-dose morning PEF was measured daily at home.
Data are available for the Run-in period and for 2-week periods over the 12-week treatment.
Data for the change from Run-in period to End-of-treatment period are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	84[98]	75[99]	80[100]	80
Units: L/min				
arithmetic mean (standard deviation)	9.3 (± 55.24)	19 (± 47.63)	27.77 (± 54.76)	29.19 (± 56.82)

Notes:

[98] - This is the real number of patients analyzed.

[99] - This is the real number of patients analyzed.

[100] - This is the real number of patients analyzed.

Statistical analyses

Statistical analysis title	Arm A vs Arm B
Comparison groups	Arm A - ITT population v Arm B - ITT population
Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	other[101]
P-value	= 0.301
Method	ANCOVA
Parameter estimate	Least square means ratio
Point estimate	-8.623
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.983
upper limit	7.738

Notes:

[101] - Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Statistical analysis title	Arm C vs Arm D
Comparison groups	Arm C - ITT population v Arm D - ITT population
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	other[102]
P-value	= 0.806
Method	ANCOVA
Parameter estimate	Leats square means difference
Point estimate	-2.032
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.266
upper limit	14.203

Notes:

[102] - Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Secondary: Pre-dose morning PEF - Change from Run-in periodo to Overall treatment period

End point title	Pre-dose morning PEF - Change from Run-in periodo to Overall treatment period

End point description:

PEF was measured daily at home by a portable electronic peak flow meter.
Overall treatment period is from Day 1 to Last day of treatment.

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 over the 12-week treatment.
Data for change from Run-in period to Overall treatment period are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	111[103]	98[104]	105[105]	107[106]
Units: L/min				
arithmetic mean (standard deviation)	10.47 (± 47.38)	9.87 (± 38.34)	25.68 (± 42.92)	27.77 (± 44.9)

Notes:

[103] - This is the real number of patients analyzed.

[104] - This is the real number of patients analyzed.

[105] - This is the real number of patients analyzed.

[106] - This is the real number of patients analyzed.

Statistical analyses

Statistical analysis title	Arm A vs Arm B

Statistical analysis description:

Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Comparison groups	Arm A - ITT population v Arm B - ITT population
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	other[107]
P-value	= 0.864
Method	ANCOVA
Parameter estimate	Least square means difference
Point estimate	1.006
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.568
upper limit	12.581

Notes:

[107] - Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Statistical analysis title	Arm C vs Arm D
Comparison groups	Arm C - ITT population v Arm D - ITT population

Number of subjects included in analysis	212
Analysis specification	Pre-specified
Analysis type	other[108]
P-value	= 0.656
Method	ANCOVA
Parameter estimate	Least square means difference
Point estimate	-2.592
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.026
upper limit	8.842

Notes:

[108] - Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Secondary: Pre-dose evening PEF - Run-in period

End point title	Pre-dose evening PEF - Run-in period

End point description:

PEF was measured at home by a portable electronic peak flow meter.

End point type	Secondary

End point timeframe:

Pre-dose evening PEF was measured daily.
Data are available for the Run-in period and for 2-week periods over the 12-week treatment.
Data for the Run-in period are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	102[109]	108[110]	100[111]	100[112]
Units: L/min				
arithmetic mean (standard deviation)	321.14 (± 88.74)	334.75 (± 106.46)	343.24 (± 104.77)	352.22 (± 101.96)

Notes:

[109] - This is the real number of patients analyzed.

[110] - This is the real number of patients analyzed.

[111] - This is the real number of patients analyzed.

[112] - This is the real number of patients analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose evening PEF - End-of-treatment period

End point title	Pre-dose evening PEF - End-of-treatment period

End point description:

PEF was measured at home by a portable electronic peak flow meter.
End-of-treatment period is the last 14 days of treatment

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 over the 12-week treatment.
Data for the End-of-treatment period are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	103[113]	104[114]	94[115]	97[116]
Units: L/min				
arithmetic mean (standard deviation)	319.33 (± 88.86)	352.3 (± 106.42)	356.07 (± 92.95)	367.31 (± 98.03)

Notes:

[113] - This is the real number of patients analyzed.

[114] - This is the real number of patients analyzed.

[115] - This is the real number of patients analyzed.

[116] - This is the real number of patients analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose evening PEF - Overall treatment period

End point title	Pre-dose evening PEF - Overall treatment period

End point description:

PEF was measured at home by a portable electronic peak flow meter.
Overall treatment period is from Day 1 to Last day of treatment.

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 over the 12-week treatment.
Data for the Overall treatment period are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	166[117]	166[118]	169[119]	166[120]
Units: L/min				
arithmetic mean (standard deviation)	322.43 (± 95.17)	340.29 (± 104.84)	347.17 (± 97.59)	359.71 (± 101.51)

Notes:

[117] - This is the real number of patients analyzed.

[118] - This is the real number of patients analyzed.

[119] - This is the real number of patients analyzed.

[120] - This is the real number of patients analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose evening PEF - Change from Run-in period to End-of-treatment period

End point title	Pre-dose evening PEF - Change from Run-in period to End-of-treatment period

End point description:

PEF was measured at home by a portable electronic peak flow meter.
End-of-treatment period is the last 14 days of treatment.

End point type	Secondary

End point timeframe:

Pre-dose evening PEF was measured daily.
Data are available for the Run-in period and for 2-week periods over the 12-week treatment.
Data for the change from Run-in period to End-of-treatment period are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	73[121]	76[122]	65[123]	69[124]
Units: L/min				
arithmetic mean (standard deviation)	4.51 (± 38.19)	17.18 (± 47.79)	16.43 (± 45.81)	23.17 (± 55.32)

Notes:

[121] - This is the real number of patients analyzed.

[122] - This is the real number of patients analyzed.

[123] - This is the real number of patients analyzed.

[124] - This is the real number of patients analyzed.

Statistical analyses

Statistical analysis title	Arm A vs Arm B
Comparison groups	Arm A - ITT population v Arm B - ITT population
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	other[125]
P-value	= 0.076
Method	ANCOVA
Parameter estimate	Least square means difference
Point estimate	-13.428
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.287
upper limit	1.431

Notes:

[125] - Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Statistical analysis title	Arm C vs Arm D
Comparison groups	Arm C - ITT population v Arm D - ITT population

Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	other[126]
P-value	= 0.484
Method	ANCOVA
Parameter estimate	Least square means difference
Point estimate	-5.582
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.255
upper limit	10.091

Notes:

[126] - Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Secondary: Pre-dose evening PEF - Change from Run-in period to Overall treatment period

End point title	Pre-dose evening PEF - Change from Run-in period to Overall treatment period

End point description:

Evening PEF was measured at home by a portable electronic peak flow meter.
Overall treatment period is from Day 1 to Last day of treatment.

End point type	Secondary

End point timeframe:

Pre-dose evening PEF was measured daily.
Data are available for the Run-in period and for 2-week periods over the 12-week treatment.
Data for change from Run-in period to Overall treatment period are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	101[127]	107[128]	100[129]	99[130]
Units: L/min				
arithmetic mean (standard deviation)	8.33 (± 40.74)	12.53 (± 42.23)	16.8 (± 37.34)	24.21 (± 46.17)

Notes:

[127] - This is the real number of patients analyzed.

[128] - This is the real number of patients analyzed.

[129] - This is the real number of patients analyzed.

[130] - This is the real number of patients analyzed.

Statistical analyses

Statistical analysis title	Arm A vs Arm B
Comparison groups	Arm A - ITT population v Arm B - ITT population

Number of subjects included in analysis	208
Analysis specification	Pre-specified
Analysis type	other[131]
P-value	= 0.384
Method	ANCOVA
Parameter estimate	Least square means difference
Point estimate	-4.917
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.998
upper limit	6.164

Notes:

[131] - Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Statistical analysis title	Arm C vs Arm D
Comparison groups	Arm C - ITT population v Arm D - ITT population
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other[132]
P-value	= 0.171
Method	ANCOVA
Parameter estimate	Least square means difference
Point estimate	-7.872
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.163
upper limit	3.419

Notes:

[132] - Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Secondary: Daily PEF variability - Run-in period

End point title	Daily PEF variability - Run-in period

End point description:

During each measurement session (morning or evening before the intake of the study medication) the patient had to perform 3 blows and only the best PEF parameter was saved into the peak flow meter memory. The device automatically calculated the daily PEF variability.

End point type	Secondary

End point timeframe:

Morning and evening PEF was measured daily at home by a portable electronic peak flow meter.
Data are available for the Run-in period and for 2-week periods over the 12-week treatment.
Data for the Run-in period are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	94[133]	95[134]	98[135]	100[136]
Units: L/min				
arithmetic mean (standard deviation)	12.79 (± 8.61)	12.97 (± 8.74)	11.78 (± 8)	12.14 (± 7.74)

Notes:

[133] - This is the real number of patients analyzed.

[134] - This is the real number of patients analyzed.

[135] - This is the real number of patients analyzed.

[136] - This is the real number of patients analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Daily PEF variability - End-of-treatment period

End point title	Daily PEF variability - End-of-treatment period

End point description:

During each measurement session (morning or evening before the intake of the study medication) the patient had to perform 3 blows and only the best PEF parameter was saved into the peak flow meter memory. The device automatically calculated the daily
PEF variability.
End-of treatment period is the last 14 days of treatment.

End point type	Secondary

End point timeframe:

Morning and evening PEF was measured daily at home by a portable electronic peak flow meter.
Data are available for the Run-in period and for 2-week periods over the 12-week treatment.
Data for the End-of-treatment period are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	97[137]	102[138]	93[139]	92[140]
Units: L/min				
arithmetic mean (standard deviation)	10.2 (± 6.47)	10.76 (± 5.83)	8.23 (± 4.63)	9.35 (± 6.27)

Notes:

[137] - This is the real number of patients analyzed.

[138] - This is the real number of patients analyzed.

[139] - This is the real number of patients analyzed.

[140] - This is the real number of patients analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Daily PEF variability - Overall treatment period

End point title	Daily PEF variability - Overall treatment period

End point description:

During each measurement session (morning or evening before the intake of the study medication) the patient had to perform 3 blows and only the best PEF parameter was saved into the peak flow meter memory. The device automatically calculated the daily PEF variability.

Overal treatment period is from Day 1 to Last day of treatment.

End point type	Secondary

End point timeframe:

Morning and evening PEF was measured daily at home by a portable electronic peak flow meter.
Data are available for the Run-in period and for 2-week periods over the 12-week treatment.
Data for the Overall treatment period are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	159[141]	157[142]	164[143]	158[144]
Units: L/min				
arithmetic mean (standard deviation)	11.11 (± 6.03)	12.87 (± 10.32)	10.83 (± 6.51)	10.74 (± 6.36)

Notes:

[141] - This is the real number of patients analyzed.

[142] - This is the real number of patients analyzed.

[143] - This is the real number of patients analyzed.

[144] - This is the real number of patients analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Daily PEF variability - Change from Run-in period to End-of-treatment period

End point title	Daily PEF variability - Change from Run-in period to End-of-treatment period

End point description:

During each measurement session (morning or evening before the intake of the study medication) the patient had to perform 3 blows and only the best PEF parameter was saved into the peak flow meter memory. The device automatically calculated the daily PEF variability.
End-of-treatment period is the last 14 days of treatment.

End point type	Secondary

End point timeframe:

Morning and evening PEF was measured daily at home.
Data are available for the Run-in period and for 2-week periods over the 12-week treatment.
Data for the change from Run-in period to End-of-treatment period are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	67[145]	76[146]	69[147]	68[148]
Units: L/min				
arithmetic mean (standard deviation)	-2.18 (± 8.13)	-1.76 (± 8.92)	-3.21 (± 8.26)	-2.54 (± 8.25)

Notes:

[145] - This is the real number of patients analyzed.

[146] - This is the real number of patients analyzed.

[147] - This is the real number of patients analyzed.

[148] - This is the real number of patients analyzed.

Statistical analyses

Statistical analysis title	Arm A vs Arm B
Comparison groups	Arm A - ITT population v Arm B - ITT population
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	other[149]
P-value	= 0.488
Method	ANCOVA
Parameter estimate	Leats square means difference
Point estimate	-0.644
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.467
upper limit	1.18

Notes:

[149] - Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Statistical analysis title	Arm C vs Arm D
Comparison groups	Arm C - ITT population v Arm D - ITT population
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	other[150]
P-value	= 0.092
Method	ANCOVA
Parameter estimate	Leats square means difference
Point estimate	-1.599
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.464
upper limit	0.265

Notes:

[150] - Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Secondary: Daily PEF variability - Change from Run-in period to Overall treatment period

End point title	Daily PEF variability - Change from Run-in period to Overall treatment period

End point description:

During each measurement session (morning or evening before the intake of the study medication) the patient had to perform 3 blows and only the best PEF parameter was saved into the peak flow meter memory. The device automatically calculated the daily PEF variability.
Overall treatment period is from Day 1 to Last day of treatment.

End point type	Secondary

End point timeframe:

Morning and evening PEF was measured daily at home.
Data are available for the Run-in period and for 2-week periods over the 12-week treatment.
Data for the change from Run-in period to Overall treatment period are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	91[151]	91[152]	97[153]	98[154]
Units: L/min				
arithmetic mean (standard deviation)	-1.88 (± 7.15)	-1.76 (± 6.7)	-2.08 (± 7.09)	-2.28 (± 6.74)

Notes:

[151] - This is the real number of patients analyzed.

[152] - This is the real number of patients analyzed.

[153] - This is the real number of patients analyzed.

[154] - This is the real number of patients analyzed.

Statistical analyses

Statistical analysis title	Arm A vs Arm B
Comparison groups	Arm A - ITT population v Arm B - ITT population
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	other[155]
P-value	= 0.559
Method	ANCOVA
Parameter estimate	Least square means difference
Point estimate	-0.366
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.598
upper limit	0.866

Notes:

[155] - Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Statistical analysis title	Arm C vs Arm D
Comparison groups	Arm C - ITT population v Arm D - ITT population
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other[156]
P-value	= 0.98
Method	ANCOVA
Parameter estimate	Least square means difference
Point estimate	0.015

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.175
upper limit	1.204

Notes:

[156] - Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Statistical analysis title	Arm C vs Arm A
Comparison groups	Arm C - ITT population v Arm A - ITT population
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority[157]
P-value	= 0.151
Method	ANCOVA
Parameter estimate	Least square means difference
Point estimate	-0.887
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.099
upper limit	0.326

Notes:

[157] - Within-treatment comparison in the change from Run-in period to End-of-treatment period was performed using the same ANCOVA model as for the primary efficacy analysis.

Secondary: Morning Asthma Symptom Score - Run-in period

End point title	Morning Asthma Symptom Score - Run-in period

End point description:

The asthma symptom scores were recorded with a portable peak flow meter twice daily in the morning and in the evening, before PEF measurements.

End point type	Secondary

End point timeframe:

Daily before morning and evening PEF measurements.
Scores for the Run-in period are reported here.

End point values	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population	Arm A - Safety population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	169[158]	167[159]	168[160]	171[161]
Units: integer from 0 to 3				
arithmetic mean (standard deviation)	3.11 (± 2.19)	3.34 (± 2.14)	3.27 (± 2.22)	3.31 (± 2.29)

Notes:

[158] - This is the real number of patients analyzed.

[159] - This is the real number of patients analyzed.

[160] - This is the real number of patients analyzed.

[161] - This is the real number of patients analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Morning Asthma Symptom Score - End-of-treatment period

End point title	Morning Asthma Symptom Score - End-of-treatment period

End point description:

The asthma symptom scores were recorded with a portable peak flow meter twice daily in the morning and in the evening, before PEF measurements.
End-of-treatment period is the last 14 days of treatment.

End point type	Secondary

End point timeframe:

Daily before morning and evening PEF measurements.
Scores for the End-of-treatment period are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	161[162]	158[163]	158[164]	160[165]
Units: integer from 0 to 3				
arithmetic mean (standard deviation)	1.93 (± 2.23)	2.12 (± 2.45)	1.74 (± 2.3)	1.94 (± 2.29)

Notes:

[162] - This is the real number of patients analyzed.

[163] - This is the real number of patients analyzed.

[164] - This is the real number of patients analyzed.

[165] - This is the real number of patients analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Morning Asthma Symptom Score - Overall treatment period

End point title	Morning Asthma Symptom Score - Overall treatment period

End point description:

The asthma symptom scores were recorded with the above described portable peak flow meter twice daily in the morning and in the evening, before PEF measurements.
Overall treatment period is from Day 1 to Last day of treatment.

End point type	Secondary

End point timeframe:

Daily before morning and evening PEF measurements.
Scores for the Overall treatment period are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	171[166]	168[167]	175[168]	171[169]
Units: integer from 0 to 3				
arithmetic mean (standard deviation)	2.12 (± 1.99)	2.31 (± 2.21)	2.03 (± 2.19)	2.22 (± 2.1)

Notes:

[166] - This is the real number of patients analyzed.

[167] - This is the real number of patients analyzed.

[168] - This is the real number of patients analyzed.

[169] - This is the real number of patients analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Morning Asthma Symptom Score - Change from Run-in period to End-of-treatment period

End point title	Morning Asthma Symptom Score - Change from Run-in period to End-of-treatment period

End point description:

The asthma symptom scores were recorded with a portable peak flow meter twice daily in the morning and in the evening, before PEF measurements.
End-of-treatment period is the last 14 days of treatment.

End point type	Secondary

End point timeframe:

Daily before morning and evening PEF measurements.
Change in the scores from Run-in period to the End-of-treatment period are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	159[170]	156[171]	153[172]	159[173]
Units: integer from 0 to 3				
arithmetic mean (standard deviation)	-1.18 (± 2.23)	-1.16 (± 2.23)	-1.59 (± 2.08)	-1.37 (± 2.22)

Notes:

[170] - This is the real number of patients analyzed.

[171] - This is the real number of patients analyzed.

[172] - This is the real number of patients analyzed.

[173] - This is the real number of patients analyzed.

Statistical analyses

Statistical analysis title	Arm A vs Arm B
Comparison groups	Arm A - ITT population v Arm B - ITT population

Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	other[174]
P-value	= 0.632
Method	ANCOVA
Parameter estimate	Least square means difference
Point estimate	-0.101
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.517
upper limit	0.314

Notes:

[174] - Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Statistical analysis title	Arm C vs Arm D
Comparison groups	Arm C - ITT population v Arm D - ITT population
Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	other[175]
P-value	= 0.24
Method	ANCOVA
Parameter estimate	Least square means difference
Point estimate	-0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.667
upper limit	0.167

Notes:

[175] - Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Secondary: Morning Asthma Symptom Score - Change from Run-in period to Overall treatment period

End point title	Morning Asthma Symptom Score - Change from Run-in period to Overall treatment period

End point description:

End point type	Secondary

End point timeframe:

Daily before morning and evening PEF measurements.
Change in the scores from Run-in period to the Overall treatment period are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	169[176]	165[177]	168[178]	170[179]
Units: integer from 0 to 3				
arithmetic mean (standard deviation)	-0.96 (± 1.81)	-1.04 (± 1.87)	-1.38 (± 1.8)	-1.12 (± 1.94)

Notes:

[176] - This is the real number of patients analyzed.

[177] - This is the real number of patients analyzed.

[178] - This is the real number of patients analyzed.

[179] - This is the real number of patients analyzed.

Statistical analyses

Statistical analysis title	Arm A vs Arm B
Comparison groups	Arm B - ITT population v Arm A - ITT population
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	other[180]
P-value	= 0.962
Method	ANCOVA
Parameter estimate	Least square means difference
Point estimate	-0.008
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.341
upper limit	0.325

Notes:

[180] - Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Statistical analysis title	Arm C vs Arm D
Comparison groups	Arm D - ITT population v Arm C - ITT population
Number of subjects included in analysis	338
Analysis specification	Pre-specified
Analysis type	other[181]
P-value	= 0.101
Method	ANCOVA
Parameter estimate	Least square means difference
Point estimate	-0.276
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.607
upper limit	0.054

Notes:

[181] - Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Secondary: Evening Asthma Symptom Score - Run-in period

End point title	Evening Asthma Symptom Score - Run-in period

End point description:

The asthma symptom scores were recorded with a portable peak flow meter twice daily in the morning and in the evening, before PEF measurements.

End point type	Secondary

End point timeframe:

Daily before morning and evening PEF measurements.
Scores for the Run-in period are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	167[182]	161[183]	162[184]	163[185]
Units: integer from 0 to 3				
arithmetic mean (standard deviation)	3.44 (± 2.22)	3.55 (± 2.18)	3.4 (± 2.3)	3.59 (± 2.15)

Notes:

[182] - This is the real number of patients analyzed.

[183] - This is the real number of patients analyzed.

[184] - This is the real number of patients analyzed.

[185] - This is the real number of patients analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Evening Asthma Symptom Score - End-of-treatment period

End point title	Evening Asthma Symptom Score - End-of-treatment period

End point description:

The asthma symptom scores were recorded with a portable peak flow meter twice daily in the morning and in the evening, before PEF measurements.
End-of-treatment period is the last 14 days of treatment.

End point type	Secondary

End point timeframe:

Daily before morning and evening PEF measurements.
Scores for the End-of-treatment period are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	158[186]	152[187]	156[188]	152[189]
Units: integer from 0 to 3				
arithmetic mean (standard deviation)	2.08 (± 2.26)	2.21 (± 2.41)	1.91 (± 2.43)	2.12 (± 2.45)

Notes:

[186] - This is the real number of patients analyzed.

[187] - This is the real number of patients analyzed.

[188] - This is the real number of patients analyzed.

[189] - This is the real number of patients analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Evening Asthma Symptom score - Overall treatment period

End point title	Evening Asthma Symptom score - Overall treatment period

End point description:

The asthma symptom scores were recorded with a portable peak flow meter twice daily in the morning and in the evening, before PEF measurements.
Overall treatment period is from Day 1 to Last day of treatment.

End point type	Secondary

End point timeframe:

Daily before morning and evening PEF measurements.
Scores for the Overall treatment period are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	171[190]	171[191]	174[192]	171[193]
Units: integer from 0 to 3				
arithmetic mean (standard deviation)	2.32 (± 2.01)	2.46 (± 2.2)	2.15 (± 2.18)	2.35 (± 2.16)

Notes:

[190] - This is the real number of patients analyzed.

[191] - This is the real number of patients analyzed.

[192] - This is the real number of patients analyzed.

[193] - This is the real number of patients analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Evening Asthma Symptoms score - Change from Run-in period to End-of-treatment period

End point title	Evening Asthma Symptoms score - Change from Run-in period to End-of-treatment period

End point description:

The asthma symptom scores were recorded with a portable peak flow meter twice daily in the morning and in the evening, before PEF measurements.
End-of-treatment period is the last 14 days of treatment.

End point type	Secondary

End point timeframe:

Daily before morning and evening PEF measurements.
Change in the scores from Run-in period to End-of-treatment period are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	154[194]	148[195]	149[196]	147[197]
Units: integer from 0 to 3				
arithmetic mean (standard deviation)	-1.31 (± 2.24)	-1.28 (± 2.15)	-1.68 (± 2.18)	-1.48 (± 2.53)

Notes:

[194] - This is the real number of patients analyzed.

[195] - This is the real number of patients analyzed.

[196] - This is the real number of patients analyzed.

[197] - This is the real number of patients analyzed.

Statistical analyses

Statistical analysis title	Arm A vs Arm B
Comparison groups	Arm A - ITT population v Arm B - ITT population
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.665
Method	ANCOVA
Parameter estimate	Least square means difference
Point estimate	-0.097
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.535
upper limit	0.341

Statistical analysis title	Arm C vs Arm D
Comparison groups	Arm D - ITT population v Arm C - ITT population
Number of subjects included in analysis	296
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.312
Method	ANCOVA
Parameter estimate	Least square means difference
Point estimate	-0.228
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.671
upper limit	0.215

Secondary: Evening Asthma Symptom score - Change from Run-in period to Overall treatment period

End point title	Evening Asthma Symptom score - Change from Run-in period to Overall treatment period

End point description:

The asthma symptom scores were recorded with a portable peak flow meter twice daily in the morning and in the evening, before PEF measurements.
Overall treatment period is from Day 1 to Last day of treatment.

End point type	Secondary

End point timeframe:

Daily before morning and evening PEF measurements.
Change in the scores from the Run-in period to the Overall treatment period are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	167[198]	161[199]	162[200]	162[201]
Units: integer from 0 to 3				
arithmetic mean (standard deviation)	-1.11 (± 1.81)	-1.1 (± 1.78)	-1.36 (± 1.89)	-1.28 (± 2.11)

Notes:

[198] - This is the real number of patients analyzed.

[199] - This is the real number of patients analyzed.

[200] - This is the real number of patients analyzed.

[201] - This is the real number of patients analyzed.

Statistical analyses

Statistical analysis title	Arm A vs Arm B
Comparison groups	Arm A - ITT population v Arm B - ITT population
Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	other[202]
P-value	= 0.769
Method	ANCOVA
Parameter estimate	Leeast square means difference
Point estimate	-0.051
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.393
upper limit	0.291

Notes:

[202] - Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Statistical analysis title	Arm C vs Arm D
Comparison groups	Arm C - ITT population v Arm D - ITT population
Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	other[203]
P-value	= 0.414
Method	ANCOVA
Parameter estimate	Leeast square means difference
Point estimate	-0.143

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.488
upper limit	0.201

Notes:

[203] - Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Statistical analysis title	Arm C vs Arm A
Comparison groups	Arm C - ITT population v Arm A - ITT population
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	superiority[204]
P-value	= 0.123
Method	ANCOVA
Parameter estimate	Leeast square means difference
Point estimate	-0.269
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.61
upper limit	0.073

Notes:

[204] - Within-treatment comparison in the change from Run-in period to End-of-treatment period was performed using the same ANCOVA model as for the primary efficacy analysis.

Statistical analysis title	Arm D vs Arm B
Comparison groups	Arm B - ITT population v Arm D - ITT population
Number of subjects included in analysis	323
Analysis specification	Pre-specified
Analysis type	superiority[205]
P-value	= 0.315
Method	ANCOVA
Parameter estimate	Leeast square means difference
Point estimate	-0.177
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.521
upper limit	0.168

Notes:

[205] - Within-treatment comparison in the change from Run-in period to End-of-treatment period was performed using the same ANCOVA model as for the primary efficacy analysis.

Secondary: Asthma Control Questionnaire score - Baseline

End point title	Asthma Control Questionnaire score - Baseline

End point description:

End point type	Secondary

End point timeframe:

At Visit 2 (Baseline) and Visit 5 (End of treatment)
Data from Visit 2 are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	173[206]	173[207]	176[208]	172[209]
Units: digit				
arithmetic mean (standard deviation)	2.51 (± 0.56)	2.44 (± 0.6)	2.47 (± 0.58)	2.52 (± 0.59)

Notes:

[206] - This is the real number of patients analyzed.

[207] - This is the real number of patients analyzed.

[208] - This is the real number of patients analyzed.

[209] - This is the real number of patients analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Asthma Control Questionnaire score - End of treatment

End point title	Asthma Control Questionnaire score - End of treatment

End point description:

End point type	Secondary

End point timeframe:

At Visit 2 (Baseline) and Visit 5 (End of treatment)
Data from Visit 5 are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	164[210]	160[211]	168[212]	166[213]
Units: digit				
arithmetic mean (standard deviation)	1.43 (± 0.93)	1.33 (± 0.98)	1.24 (± 0.87)	1.16 (± 0.84)

Notes:

[210] - This is the real number of patients analyzed.

[211] - This is the real number of patients analyzed.

[212] - This is the real number of patients analyzed.

[213] - This is the real number of patients analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Asthma Control Questionnaire score - Change from Baseline to End of treatment

End point title	Asthma Control Questionnaire score - Change from Baseline to End of treatment

End point description:

End point type	Secondary

End point timeframe:

Asthma Control Questionnaire was administered at Visit 2 (Baseline) and Visit 5 (End of treatment) Change in score from Visit 2 (Baseline) to Visit 5 (End of treatment) is reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	164[214]	160[215]	168[216]	166[217]
Units: digit				
arithmetic mean (standard deviation)	-1.08 (± 0.91)	-1.08 (± 0.91)	-1.24 (± 0.73)	-1.36 (± 0.87)

Notes:

[214] - This is the real number of patients analyzed.

[215] - This is the real number of patients analyzed.

[216] - This is the real number of patients analyzed.

[217] - This is the real number of patients analyzed.

Statistical analyses

Statistical analysis title	Arm A vs Arm B
Comparison groups	Arm A - ITT population v Arm B - ITT population
Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	other[218]
P-value	= 0.349
Method	ANCOVA
Parameter estimate	Least square means difference
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	0.24

Notes:

[218] - Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Statistical analysis title	Arm C vs Arm D
Comparison groups	Arm C - ITT population v Arm D - ITT population
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	other[219]
P-value	= 0.276
Method	ANCOVA
Parameter estimate	Least square means difference
Point estimate	0.09

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.25

Notes:

[219] - Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Secondary: Asthma Control Days - Run-in period

End point title	Asthma Control Days - Run-in period

End point description:

Asthma control day was defined as a day with symptom score = 0 daytime and night, and no use of rescue medication.

End point type	Secondary

End point timeframe:

Daily before morning and evening PEF measurements.
Data from the Run-in period are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	162[220]	157[221]	157[222]	160[223]
Units: percentage				
arithmetic mean (standard deviation)	7.29 (± 16.35)	5.78 (± 12.69)	6.09 (± 14.36)	6.24 (± 14.28)

Notes:

[220] - This is the real number of patients analyzed.

[221] - This is the real number of patients analyzed.

[222] - This is the real number of patients analyzed.

[223] - This is the real number of patients analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Asthma Control days - End of Treatment period

End point title	Asthma Control days - End of Treatment period

End point description:

Asthma control day was defined as a day with symptom score = 0 daytime and night, and no use of rescue medication.

End point type	Secondary

End point timeframe:

Daily before morning and evening PEF measurements.
Data from the End-of-treatment period are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	138[224]	144[225]	141[226]	140[227]
Units: percentage				
arithmetic mean (standard deviation)	26.22 (± 34.09)	27.4 (± 34.77)	33.63 (± 37.83)	27.94 (± 35.56)

Notes:

[224] - This is the real number of patients analyzed.

[225] - This is the real number of patients analyzed.

[226] - This is the real number of patients analyzed.

[227] - This is the real number of patients analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Asthma Control days - Overall Treatment period

End point title	Asthma Control days - Overall Treatment period

End point description:

Asthma control day was defined as a day with symptom score = 0 daytime and night, and no use of rescue medication.

End point type	Secondary

End point timeframe:

Daily before morning and evening PEF measurements.
Data from the Overall treatment period are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	169[228]	163[229]	172[230]	169[231]
Units: percentage				
arithmetic mean (standard deviation)	20.83 (± 28.53)	22.16 (± 28.36)	24.84 (± 30.23)	21.13 (± 28.18)

Notes:

[228] - This is the real number of patients analyzed.

[229] - This is the real number of patients analyzed.

[230] - This is the real number of patients analyzed.

[231] - This is the real number of patients analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Asthma Control days - Change from Run-in period to End of Treatment period

End point title	Asthma Control days - Change from Run-in period to End of Treatment period

End point description:

The asthma symptom scores were recorded with a portable peak flow meter twice daily in the morning and in the evening, before PEF measurements.

End point type	Secondary

End point timeframe:

Daily before morning and evening PEF measurements.
Changes from Run-in period to End-of-treatment period are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	133[232]	139[233]	132[234]	133[235]
Units: percentage				
arithmetic mean (standard deviation)	18.76 (± 30.49)	21.22 (± 31.52)	28.53 (± 35.02)	21.82 (± 32.64)

Notes:

[232] - This is the real number of patients analyzed.

[233] - This is the real number of patients analyzed.

[234] - This is the real number of patients analyzed.

[235] - This is the real number of patients analyzed.

Statistical analyses

Statistical analysis title	Arm A vs Arm B
Comparison groups	Arm A - ITT population v Arm B - ITT population
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	other[236]
P-value	= 0.613
Method	ANCOVA
Parameter estimate	Least square means difference
Point estimate	-1.891
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.237
upper limit	5.455

Notes:

[236] - Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Statistical analysis title	Arm C vs Arm D
Comparison groups	Arm C - ITT population v Arm D - ITT population
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	other[237]
P-value	= 0.119
Method	ANCOVA
Parameter estimate	Least square means difference
Point estimate	5.91

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.52
upper limit	13.339

Notes:

[237] - Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Secondary: Asthma control days - Change from Run-in period to Overall Treatment period

End point title	Asthma control days - Change from Run-in period to Overall Treatment period

End point description:

Asthma control day was defined as a day with symptom score = 0 daytime and night, and no use of rescue medication

End point type	Secondary

End point timeframe:

Daily before morning and evening PEF measurements.
Changes from the Run-in period to the Overall Treatment period are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	160[238]	151[239]	155[240]	158[241]
Units: percentage				
arithmetic mean (standard deviation)	13.99 (± 24.3)	17.05 (± 24.95)	19.27 (± 26.08)	15.81 (± 25.39)

Notes:

[238] - This is the real number of patients analyzed.

[239] - This is the real number of patients analyzed.

[240] - This is the real number of patients analyzed.

[241] - This is the real number of patients analyzed.

Statistical analyses

Statistical analysis title	Arm A vs Arm B
Comparison groups	Arm A - ITT population v Arm B - ITT population
Number of subjects included in analysis	311
Analysis specification	Pre-specified
Analysis type	other[242]
P-value	= 0.205
Method	ANCOVA
Parameter estimate	Least square means difference
Point estimate	-3.461
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.819
upper limit	1.897

Notes:

[242] - Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Statistical analysis title	Arm C vs Arm D
Comparison groups	Arm C - ITT population v Arm D - ITT population
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	other[243]
P-value	= 0.233
Method	ANCOVA
Parameter estimate	Least square means difference
Point estimate	3.248
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.09
upper limit	8.585

Notes:

[243] - Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Statistical analysis title	Arm C vs Arm A
Comparison groups	Arm C - ITT population v Arm A - ITT population
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	superiority[244]
P-value	= 0.047
Method	ANCOVA
Parameter estimate	Least square means difference
Point estimate	5.385
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.064
upper limit	10.706

Notes:

[244] - Within-treatment comparison in the change from Run-in period to Overall Treatment period was performed using the same ANCOVA model as for the primary efficacy analysis.

Statistical analysis title	Arm D vs Arm B
Comparison groups	Arm D - ITT population v Arm B - ITT population
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority[245]
P-value	= 0.629
Method	ANCOVA
Parameter estimate	Least square means difference
Point estimate	-1.323

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.694
upper limit	4.047

Notes:

[245] - Within-treatment comparison in the change from Run-in period to Overall Treatment period was performed using the same ANCOVA model as for the primary efficacy analysis.

Secondary: Asthma exacerbations

End point title	Asthma exacerbations

End point description:

Moderate asthma exacerbations were defined as need for systemic corticosteroids and unscheduled medical visit, and severe asthma exacerbations were defined as emergency room attendance or hospitalisation (GINA definitions).

End point type	Secondary

End point timeframe:

Throughout the study/At each visit

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	173[246]	173[247]	176[248]	172[249]
Units: number of events				
Moderate	0	4	5	2
Severe	0	4	5	1

Notes:

[246] - No subjects experienced asthma exacerbations.

[247] - Four subjects experienced moderate asthma exacerbations.

[248] - Five subjects experienced moderate asthma exacerbations.

[249] - Two/one subjects experienced moderate/severe asthma exacerbations.

Statistical analyses

No statistical analyses for this end point

Secondary: Use of rescue salbutamol - Run-in period

End point title	Use of rescue salbutamol - Run-in period

End point description:

End point type	Secondary

End point timeframe:

Daily throughout the study.
Data are available for the Run-in period and for 2-week periods over the 12-week treatment.
Data for the Run-in period are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	170[250]	169[251]	169[252]	171[253]
Units: puffs/day				
arithmetic mean (standard deviation)	1.66 (± 1.82)	1.72 (± 2.12)	1.58 (± 1.66)	1.64 (± 1.67)

Notes:

[250] - This is the real number of patients analyzed.

[251] - This is the real number of patients analyzed.

[252] - This is the real number of patients analyzed.

[253] - This is the real number of patients analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Use of rescue salbutamol - End-of-treatment period

End point title	Use of rescue salbutamol - End-of-treatment period

End point description:

End.of-treatment period is the last 14 days of treatment.

End point type	Secondary

End point timeframe:

Daily trhoughout the study.
Data are available for the Run-in period and for 2-week periods over the 12-week treatment.
Data for the End.of-treatment period are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	166[254]	159[255]	167[256]	163[257]
Units: puffs/day				
arithmetic mean (standard deviation)	1.02 (± 1.9)	0.83 (± 1.55)	0.55 (± 1.03)	0.74 (± 1.43)

Notes:

[254] - This is the real number of patients analyzed.

[255] - This is the real number of patients analyzed.

[256] - This is the real number of patients analyzed.

[257] - This is the real number of patients analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Use of rescue salbutamol - Overall treatment period

End point title	Use of rescue salbutamol - Overall treatment period

End point description:

Overall treatment period is from Day 1 to Last day of treatment.

End point type	Secondary

End point timeframe:

Daily throughout the study.
Data are available for the Run-in period and for 2-week periods over the 12-week treatment.
Data for the Overall treatment period are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	171[258]	171[259]	175[260]	171[261]
Units: puffs/day				
arithmetic mean (standard deviation)	1.08 (± 1.56)	0.99 (± 1.49)	0.78 (± 1.39)	0.9 (± 1.42)

Notes:

[258] - This is the real number of patients analyzed.

[259] - This is the real number of patients analyzed.

[260] - This is the real number of patients analyzed.

[261] - This is the real number of patients analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Use of rescue salbutamol - Change from Run-in period to End-of-treatment period

End point title	Use of rescue salbutamol - Change from Run-in period to End-of-treatment period

End point description:

End-of-treatment period is the last 14 days of treatment.

End point type	Secondary

End point timeframe:

Daily throughout the study.
Data are available for the Run-in period and for 2-week periods over the 12-week treatment.
Data for change from Run-in period to End-of-treatment period are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	165[262]	158[263]	163[264]	162[265]
Units: puffs/day				
arithmetic mean (standard deviation)	-0.66 (± 2.04)	-0.94 (± 2.06)	-1.03 (± 1.5)	-0.95 (± 1.91)

Notes:

[262] - This is the real number of patients analyzed.

[263] - This is the real number of patients analyzed.

[264] - This is the real number of patients analyzed.

[265] - This is the real number of patients analyzed.

Statistical analyses

Statistical analysis title	Arm A vs Arm B
Comparison groups	Arm A - ITT population v Arm B - ITT population

Number of subjects included in analysis	323
Analysis specification	Pre-specified
Analysis type	other[266]
P-value	= 0.168
Method	ANCOVA
Parameter estimate	Least square means difference
Point estimate	0.208
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.088
upper limit	0.503

Notes:

[266] - Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Statistical analysis title	Arm C vs Arm D
Comparison groups	Arm C - ITT population v Arm D - ITT population
Number of subjects included in analysis	325
Analysis specification	Pre-specified
Analysis type	other[267]
P-value	= 0.39
Method	ANCOVA
Parameter estimate	Least square means difference
Point estimate	-0.129
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.424
upper limit	0.166

Notes:

[267] - Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Secondary: Use of rescue salbutamol - Change from Run-in period to Overall treatment period

End point title	Use of rescue salbutamol - Change from Run-in period to Overall treatment period

End point description:

Overall treatment period is from Day 1 to Last day of treatment.

End point type	Secondary

End point timeframe:

Daily throughout the study.
Data are available for the Run-in period and for 2-week periods over the 12-week treatment.
Data for change from Run-in period to Overall treatment period are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	170[268]	169[269]	169[270]	170[271]
Units: puffs/day				
arithmetic mean (standard deviation)	-0.58 (± 1.77)	-0.72 (± 1.84)	-0.77 (± 1.61)	-0.76 (± 1.69)

Notes:

[268] - This is the real number of patients analyzed.

[269] - This is the real number of patients analyzed.

[270] - This is the real number of patients analyzed.

[271] - This is the real number of patients analyzed.

Statistical analyses

Statistical analysis title	Arm A vs Arm B
Comparison groups	Arm A - ITT population v Arm B - ITT population
Number of subjects included in analysis	339
Analysis specification	Pre-specified
Analysis type	other[272]
P-value	= 0.518
Method	ANCOVA
Parameter estimate	Least square means difference
Point estimate	0.088
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.179
upper limit	0.355

Notes:

[272] - Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Statistical analysis title	Arm C vs Arm D
Comparison groups	Arm C - ITT population v Arm D - ITT population
Number of subjects included in analysis	339
Analysis specification	Pre-specified
Analysis type	other[273]
P-value	= 0.687
Method	ANCOVA
Parameter estimate	Least square means difference
Point estimate	-0.055
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.322
upper limit	0.212

Notes:

[273] - Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Secondary: Patients Achieving the Level of 'Controlled' Asthma - Baseline

End point title	Patients Achieving the Level of 'Controlled' Asthma - Baseline

End point description:

End point type	Secondary

End point timeframe:

At Baseline and at the End-of-treatment period.
Data are available as number of patients and percentage.
Number of patients with controlled asthma at Baseline are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	170[274]	168[275]	170[276]	169[277]
Units: number of patients	0	0	0	0

Notes:

[274] - This is the real number of patients analyzed.

[275] - This is the real number of patients analyzed.

[276] - This is the real number of patients analyzed.

[277] - This is the real number of patients analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Patients Achieving the Level of 'Controlled' Asthma - End of treatment

End point title	Patients Achieving the Level of 'Controlled' Asthma - End of treatment

End point description:

End point type	Secondary

End point timeframe:

At Baseline and at the End-of-treatment period.
Data are available as number of patients and percentage.
Number of patients achieving a total control of asthma at the End of treatment are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	156[278]	151[279]	160[280]	156[281]
Units: number of patients	15	22	13	16

Notes:

[278] - This is the real number of patients analyzed.

[279] - This is the real number of patients analyzed.

[280] - This is the real number of patients analyzed.

[281] - This is the real number of patients analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Induced Sputum Eosinophils Count - Baseline

End point title	Induced Sputum Eosinophils Count - Baseline

End point description:

End point type	Secondary

End point timeframe:

Induced sputum eosinophil count was performed locally in a subgroup of 48 patients (at Visiit 2 and Visit 5) at selected sites.
Data for Visit 2 (Baseline, i.e. the last available value before first inhalation of study drug) are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11[282]	11[283]	9[284]	10[285]
Units: percentage				
arithmetic mean (standard deviation)	5 (± 5.85)	5.36 (± 5.18)	6.22 (± 8.01)	7.6 (± 9.07)

Notes:

[282] - This is the real number of patients analyzed.

[283] - This is the real number of patients analyzed.

[284] - This is the real number of patients analyzed.

[285] - This is the real number of patients analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Induced sputum eosinophil count - End of treatment

End point title	Induced sputum eosinophil count - End of treatment

End point description:

End point type	Secondary

End point timeframe:

Induced sputum eosinophil count was performed locally in a subgroup of 48 patients (at Visiit 2 and Visit 5) at selected sites.
Data for Visit 5 (End of treatment, i.e. the last available post-baseline value) are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10[286]	10[287]	7[288]	10[289]
Units: percentage				
arithmetic mean (standard deviation)	4.4 (± 8.19)	8.9 (± 14.44)	8.14 (± 5.84)	5 (± 11.73)

Notes:
[286] - This is the real number of patients analyzed.
[287] - This is the real number of patients analyzed.
[288] - This is the real number of patients analyzed.
[289] - This is the real number of patients analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Induced sputum eosinophil cont - Change from Baseline to End of treatment

End point title	Induced sputum eosinophil cont - Change from Baseline to End of treatment

End point description:

End point type	Secondary

End point timeframe:

Induced sputum eosinophil count was performed locally in a subgroup of 48 patients (at V2 and V5) at selected sites.
Data for change from Baseline to End of treatment are reported here.

End point values	Arm A - ITT population	Arm B - ITT population	Arm C - ITT population	Arm D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10[290]	10[291]	7[292]	8[293]
Units: percentage				
arithmetic mean (standard deviation)	-0.9 (± 11.47)	3 (± 15.54)	0.71 (± 8.73)	-0.63 (± 16.24)

Notes:
[290] - This is the real number of patients analyzed.
[291] - This is the real number of patients analyzed.
[292] - This is the real number of patients analyzed.
[293] - This is the real number of patients analyzed.

Statistical analyses

Statistical analysis title	Arm A vs Arm B
Comparison groups	Arm A - ITT population v Arm B - ITT population
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other[294]
P-value	= 0.576
Method	ANCOVA
Parameter estimate	Least square means difference
Point estimate	-3.15

Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.56
upper limit	8.26

Notes:

[294] - Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Statistical analysis title	Arm C vs Arm D
Comparison groups	Arm C - ITT population v Arm D - ITT population
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	other[295]
P-value	= 0.818
Method	ANCOVA
Parameter estimate	Least square means difference
Point estimate	1.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.97
upper limit	13.78

Notes:

[295] - Comparisons between treatments were done using the same ANCOVA model as for the primary analysis without testing for non-inferiority.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were assessed at Weeks −2 (run in, Visit 1), 0 (Visit 2), 4 (Visit 3), 8 (Visit 4), and 12 (Visit 5) , and at Week 14 by phone call.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	11.1

Reporting groups	
Reporting group title	Arm A - Safety analysis
Reporting group description:	
All subjects randomised to treatment with CHF 1535 NEXT DPI®, 1 inhalation bid (daily dose: BDP 200 µg/FF 12 µg) + placebo pMDI, 1 inhalation bid who took at least one dose of study medication.	
Reporting group title	Arm B - Safety analysis
Reporting group description:	
All subjects randomised to treatment with CHF 1535 pMDI, 1 inhalation bid (daily dose: BDP 200 µg/FF 12 µg) + placebo NEXT DPI®, 1 inhalation bid who took at least one dose of study medication.	
Reporting group title	Arm C - Safety analysis
Reporting group description:	
All subjects randomised to treatment with CHF 1535 NEXT DPI®, 2 inhalations bid (daily dose: BDP 400 µg/FF 24 µg) + placebo pMDI, 2 inhalations bid who took at least one dose of study medication.	
Reporting group title	Arm D - Safety analysis
Reporting group description:	
All subjects randomised to treatment with CHF 1535 pMDI, 2 inhalations bid (daily dose: BDP 400 µg/FF 24 µg) + placebo NEXT DPI®, 2 inhalations bid who took at least one dose of study medication.	

Serious adverse events	Arm A - Safety analysis	Arm B - Safety analysis	Arm C - Safety analysis
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 172 (0.58%)	1 / 173 (0.58%)	0 / 177 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Reproductive system and breast disorders			
Uterine polyp			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 172 (0.00%)	1 / 173 (0.58%)	0 / 177 (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			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	0 / 177 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Hepatitis B			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 172 (0.58%)	0 / 173 (0.00%)	0 / 177 (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

Serious adverse events	Arm D - Safety analysis		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 173 (0.58%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Reproductive system and breast disorders			
Uterine polyp			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 173 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Hepatitis B			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 173 (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: 0.1 %

Non-serious adverse events	Arm A - Safety analysis	Arm B - Safety analysis	Arm C - Safety analysis
Total subjects affected by non-serious adverse events			
subjects affected / exposed	61 / 172 (35.47%)	65 / 173 (37.57%)	56 / 177 (31.64%)
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 172 (1.74%)	1 / 173 (0.58%)	0 / 177 (0.00%)
occurrences (all)	3	1	0
Circulatory collapse			
subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	1 / 177 (0.56%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Hyperthermia			
subjects affected / exposed	1 / 172 (0.58%)	0 / 173 (0.00%)	0 / 177 (0.00%)
occurrences (all)	1	0	0
Asthenia			
subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	1 / 177 (0.56%)
occurrences (all)	0	0	1
Chest pain			
subjects affected / exposed	2 / 172 (1.16%)	0 / 173 (0.00%)	0 / 177 (0.00%)
occurrences (all)	3	0	0
Fatigue			
subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	1 / 177 (0.56%)
occurrences (all)	0	0	1
Chest discomfort			
subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	1 / 177 (0.56%)
occurrences (all)	0	0	1
Irritability			
subjects affected / exposed	1 / 172 (0.58%)	0 / 173 (0.00%)	0 / 177 (0.00%)
occurrences (all)	1	0	0
Oedema peripheral			
subjects affected / exposed	1 / 172 (0.58%)	0 / 173 (0.00%)	0 / 177 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			

Dysmenorrhoea			
subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	1 / 177 (0.56%)
occurrences (all)	0	0	1
Prostatitis			
subjects affected / exposed	1 / 172 (0.58%)	0 / 173 (0.00%)	0 / 177 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 172 (1.16%)	2 / 173 (1.16%)	6 / 177 (3.39%)
occurrences (all)	2	2	6
Dysphonia			
subjects affected / exposed	0 / 172 (0.00%)	1 / 173 (0.58%)	0 / 177 (0.00%)
occurrences (all)	0	1	0
Throat irritation			
subjects affected / exposed	0 / 172 (0.00%)	1 / 173 (0.58%)	2 / 177 (1.13%)
occurrences (all)	0	1	2
Bronchospasm			
subjects affected / exposed	1 / 172 (0.58%)	0 / 173 (0.00%)	0 / 177 (0.00%)
occurrences (all)	1	0	0
Dyspnoea			
subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	1 / 177 (0.56%)
occurrences (all)	0	0	1
Nasal congestion			
subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	1 / 177 (0.56%)
occurrences (all)	0	0	1
Oropharyngeal pain			
subjects affected / exposed	0 / 172 (0.00%)	1 / 173 (0.58%)	0 / 177 (0.00%)
occurrences (all)	0	1	0
Rhinitis allergic			
subjects affected / exposed	1 / 172 (0.58%)	0 / 173 (0.00%)	0 / 177 (0.00%)
occurrences (all)	1	0	0
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	16 / 172 (9.30%)	20 / 173 (11.56%)	13 / 177 (7.34%)
occurrences (all)	22	20	13
Blood glucose increased			

subjects affected / exposed	3 / 172 (1.74%)	5 / 173 (2.89%)	3 / 177 (1.69%)
occurrences (all)	3	5	3
Electrocardiogram T wave abnormal			
subjects affected / exposed	3 / 172 (1.74%)	2 / 173 (1.16%)	1 / 177 (0.56%)
occurrences (all)	3	3	1
Blood cortisol decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 172 (1.16%)	1 / 173 (0.58%)	2 / 177 (1.13%)
occurrences (all)	2	1	2
Blood triglycerides increased			
subjects affected / exposed	0 / 172 (0.00%)	2 / 173 (1.16%)	3 / 177 (1.69%)
occurrences (all)	0	2	3
Gamma-glutamyl transferase increased			
subjects affected / exposed	0 / 172 (0.00%)	4 / 173 (2.31%)	1 / 177 (0.56%)
occurrences (all)	0	4	1
Blood potassium increased			
subjects affected / exposed	1 / 172 (0.58%)	3 / 173 (1.73%)	0 / 177 (0.00%)
occurrences (all)	1	3	0
Cortisol free urine decreased			
subjects affected / exposed	3 / 172 (1.74%)	0 / 173 (0.00%)	1 / 177 (0.56%)
occurrences (all)	3	0	1
Cortisol free urine increased			
subjects affected / exposed	0 / 172 (0.00%)	2 / 173 (1.16%)	0 / 177 (0.00%)
occurrences (all)	0	2	0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	1 / 177 (0.56%)
occurrences (all)	0	0	1
Creatinine urine increased			
subjects affected / exposed	1 / 172 (0.58%)	0 / 173 (0.00%)	1 / 177 (0.56%)
occurrences (all)	1	0	1
Blood cholesterol increased			
subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	1 / 177 (0.56%)
occurrences (all)	0	0	1
Electrocardiogram normal			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	1 / 177 (0.56%)
occurrences (all)	0	0	1
Electrocardiogram poor r-wave progression			
subjects affected / exposed	1 / 172 (0.58%)	0 / 173 (0.00%)	0 / 177 (0.00%)
occurrences (all)	1	0	0
Electrocardiogram Q wave abnormal			
subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	0 / 177 (0.00%)
occurrences (all)	0	0	0
Urea urine increased			
subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	1 / 177 (0.56%)
occurrences (all)	0	0	1
White blood cell count increased			
subjects affected / exposed	0 / 172 (0.00%)	1 / 173 (0.58%)	0 / 177 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	0 / 177 (0.00%)
occurrences (all)	0	0	0
Arthropod sting			
subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	0 / 177 (0.00%)
occurrences (all)	0	0	0
Concussion			
subjects affected / exposed	0 / 172 (0.00%)	1 / 173 (0.58%)	0 / 177 (0.00%)
occurrences (all)	0	1	0
Contusion			
subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	0 / 177 (0.00%)
occurrences (all)	0	0	0
Joint dislocation			
subjects affected / exposed	0 / 172 (0.00%)	1 / 173 (0.58%)	0 / 177 (0.00%)
occurrences (all)	0	1	0
Postoperative fever			
subjects affected / exposed	1 / 172 (0.58%)	0 / 173 (0.00%)	0 / 177 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			

Sinus bradycardia			
subjects affected / exposed	2 / 172 (1.16%)	1 / 173 (0.58%)	1 / 177 (0.56%)
occurrences (all)	3	2	1
Tachycardia			
subjects affected / exposed	0 / 172 (0.00%)	2 / 173 (1.16%)	2 / 177 (1.13%)
occurrences (all)	0	2	2
Bradycardia			
subjects affected / exposed	1 / 172 (0.58%)	2 / 173 (1.16%)	0 / 177 (0.00%)
occurrences (all)	1	2	0
Bundle branch block			
subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	1 / 177 (0.56%)
occurrences (all)	0	0	1
Bundle branch block right			
subjects affected / exposed	1 / 172 (0.58%)	0 / 173 (0.00%)	0 / 177 (0.00%)
occurrences (all)	1	0	0
Synus arrhytmia			
subjects affected / exposed	1 / 172 (0.58%)	0 / 173 (0.00%)	1 / 177 (0.56%)
occurrences (all)	1	0	1
Angina pectoris			
subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	2 / 177 (1.13%)
occurrences (all)	0	0	2
Atrioventricular block first degree			
subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	1 / 177 (0.56%)
occurrences (all)	0	0	1
Sinus tachycardia			
subjects affected / exposed	0 / 172 (0.00%)	1 / 173 (0.58%)	1 / 177 (0.56%)
occurrences (all)	0	1	1
Bundle branch block left			
subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	1 / 177 (0.56%)
occurrences (all)	0	0	1
Myocardial ischaemia			
subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	1 / 177 (0.56%)
occurrences (all)	0	0	1
Supraventricular extrasystoles			
subjects affected / exposed	1 / 172 (0.58%)	0 / 173 (0.00%)	0 / 177 (0.00%)
occurrences (all)	1	0	0

Nervous system disorders			
Headache			
subjects affected / exposed	3 / 172 (1.74%)	4 / 173 (2.31%)	2 / 177 (1.13%)
occurrences (all)	3	6	4
Tremor			
subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	7 / 177 (3.95%)
occurrences (all)	0	0	7
Dizziness			
subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	1 / 177 (0.56%)
occurrences (all)	0	0	1
Syncope			
subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	1 / 177 (0.56%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	0 / 177 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Conjunctivitis			
subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	0 / 177 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 172 (0.58%)	0 / 173 (0.00%)	2 / 177 (1.13%)
occurrences (all)	1	0	3
Abdominal pain			
subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	0 / 177 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	1 / 172 (0.58%)	1 / 173 (0.58%)	0 / 177 (0.00%)
occurrences (all)	1	1	0
Food poisoning			
subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	2 / 177 (1.13%)
occurrences (all)	0	0	2
Aphthous stomatitis			
subjects affected / exposed	0 / 172 (0.00%)	1 / 173 (0.58%)	0 / 177 (0.00%)
occurrences (all)	0	1	0

Diarrhoea			
subjects affected / exposed	1 / 172 (0.58%)	0 / 173 (0.00%)	0 / 177 (0.00%)
occurrences (all)	1	0	0
Dry mouth			
subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	0 / 177 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	0 / 172 (0.00%)	1 / 173 (0.58%)	0 / 177 (0.00%)
occurrences (all)	0	1	0
Enteritis			
subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	1 / 177 (0.56%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	1 / 177 (0.56%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	0 / 177 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 172 (0.58%)	0 / 173 (0.00%)	0 / 177 (0.00%)
occurrences (all)	1	0	0
Hepatitis toxic			
subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	1 / 177 (0.56%)
occurrences (all)	0	0	1
Liver disorder			
subjects affected / exposed	1 / 172 (0.58%)	0 / 173 (0.00%)	0 / 177 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 172 (0.00%)	1 / 173 (0.58%)	0 / 177 (0.00%)
occurrences (all)	0	1	0
Eczema			
subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	0 / 177 (0.00%)
occurrences (all)	0	0	0
Rash			

subjects affected / exposed	1 / 172 (0.58%)	0 / 173 (0.00%)	0 / 177 (0.00%)
occurrences (all)	1	0	0
Urticaria			
subjects affected / exposed	1 / 172 (0.58%)	0 / 173 (0.00%)	0 / 177 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 172 (0.58%)	1 / 173 (0.58%)	0 / 177 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 172 (2.91%)	3 / 173 (1.73%)	7 / 177 (3.95%)
occurrences (all)	5	3	7
Respiratory tract infection			
subjects affected / exposed	2 / 172 (1.16%)	1 / 173 (0.58%)	3 / 177 (1.69%)
occurrences (all)	2	1	3
Rhinitis			
subjects affected / exposed	0 / 172 (0.00%)	5 / 173 (2.89%)	1 / 177 (0.56%)
occurrences (all)	0	6	1
Respiratory tract infection viral			
subjects affected / exposed	2 / 172 (1.16%)	1 / 173 (0.58%)	0 / 177 (0.00%)
occurrences (all)	2	1	0
Bronchitis			
subjects affected / exposed	1 / 172 (0.58%)	2 / 173 (1.16%)	0 / 177 (0.00%)
occurrences (all)	1	2	0
Acute sinusitis			
subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	2 / 177 (1.13%)
occurrences (all)	0	0	2
Pharyngitis			
subjects affected / exposed	2 / 172 (1.16%)	0 / 173 (0.00%)	0 / 177 (0.00%)
occurrences (all)	3	0	0
Tracheobronchitis			
subjects affected / exposed	0 / 172 (0.00%)	2 / 173 (1.16%)	0 / 177 (0.00%)
occurrences (all)	0	3	0
Acute tonsillitis			

subjects affected / exposed	0 / 172 (0.00%)	1 / 173 (0.58%)	0 / 177 (0.00%)
occurrences (all)	0	1	0
Bronchitis bacterial			
subjects affected / exposed	1 / 172 (0.58%)	0 / 173 (0.00%)	1 / 177 (0.56%)
occurrences (all)	1	0	1
Gastroenteristis			
subjects affected / exposed	1 / 172 (0.58%)	1 / 173 (0.58%)	0 / 177 (0.00%)
occurrences (all)	1	1	0
Cystitis			
subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	0 / 177 (0.00%)
occurrences (all)	0	0	0
Ear infection			
subjects affected / exposed	0 / 172 (0.00%)	1 / 173 (0.58%)	0 / 177 (0.00%)
occurrences (all)	0	1	0
Infected cyst			
subjects affected / exposed	1 / 172 (0.58%)	0 / 173 (0.00%)	0 / 177 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	0 / 172 (0.00%)	1 / 173 (0.58%)	0 / 177 (0.00%)
occurrences (all)	0	1	0
Oral herpes			
subjects affected / exposed	1 / 172 (0.58%)	0 / 173 (0.00%)	0 / 177 (0.00%)
occurrences (all)	1	0	0
Pharyngotonsillitis			
subjects affected / exposed	1 / 172 (0.58%)	0 / 173 (0.00%)	0 / 177 (0.00%)
occurrences (all)	1	0	0
Rhinotracheitis			
subjects affected / exposed	1 / 172 (0.58%)	0 / 173 (0.00%)	0 / 177 (0.00%)
occurrences (all)	1	0	0
Tooth infection			
subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	0 / 177 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	1 / 172 (0.58%)	0 / 173 (0.00%)	0 / 177 (0.00%)
occurrences (all)	1	0	0
Viral rhinitis			

subjects affected / exposed	0 / 172 (0.00%)	1 / 173 (0.58%)	0 / 177 (0.00%)
occurrences (all)	0	1	0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 172 (0.58%)	0 / 173 (0.00%)	0 / 177 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Hyperglycemia			
subjects affected / exposed	1 / 172 (0.58%)	1 / 173 (0.58%)	2 / 177 (1.13%)
occurrences (all)	1	1	2
Hypertriglyceridaemia			
subjects affected / exposed	2 / 172 (1.16%)	0 / 173 (0.00%)	2 / 177 (1.13%)
occurrences (all)	2	0	2
Diabetes mellitus			
subjects affected / exposed	1 / 172 (0.58%)	1 / 173 (0.58%)	0 / 177 (0.00%)
occurrences (all)	1	1	0
Glucose tolerance impaired			
subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	1 / 177 (0.56%)
occurrences (all)	0	0	1
Hypercholesterolaemia			
subjects affected / exposed	0 / 172 (0.00%)	1 / 173 (0.58%)	0 / 177 (0.00%)
occurrences (all)	0	1	0
Hyperkalaemia			
subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	1 / 177 (0.56%)
occurrences (all)	0	0	1
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 172 (0.00%)	0 / 173 (0.00%)	1 / 177 (0.56%)
occurrences (all)	0	0	1

Non-serious adverse events	Arm D - Safety analysis		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	62 / 173 (35.84%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Circulatory collapse			

subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Hyperthermia			
subjects affected / exposed	3 / 173 (1.73%)		
occurrences (all)	3		
Asthenia			
subjects affected / exposed	1 / 173 (0.58%)		
occurrences (all)	1		
Chest pain			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	1 / 173 (0.58%)		
occurrences (all)	1		
Chest discomfort			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Irritability			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Oedema peripheral			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Prostatitis			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	3 / 173 (1.73%)		
occurrences (all)	3		

Dysphonia			
subjects affected / exposed	3 / 173 (1.73%)		
occurrences (all)	3		
Throat irritation			
subjects affected / exposed	1 / 173 (0.58%)		
occurrences (all)	2		
Bronchospasm			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Dyspnoea			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Nasal congestion			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Rhinitis allergic			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	12 / 173 (6.94%)		
occurrences (all)	14		
Blood glucose increased			
subjects affected / exposed	4 / 173 (2.31%)		
occurrences (all)	4		
Electrocardiogram T wave abnormal			
subjects affected / exposed	5 / 173 (2.89%)		
occurrences (all)	5		
Blood cortisol decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 173 (1.16%)		
occurrences (all)	2		
Blood triglycerides increased			

subjects affected / exposed	2 / 173 (1.16%)			
occurrences (all)	2			
Gamma-glutamyl transferase increased				
subjects affected / exposed	1 / 173 (0.58%)			
occurrences (all)	1			
Blood potassium increased				
subjects affected / exposed	1 / 173 (0.58%)			
occurrences (all)	1			
Cortisol free urine decreased				
subjects affected / exposed	1 / 173 (0.58%)			
occurrences (all)	1			
Cortisol free urine increased				
subjects affected / exposed	1 / 173 (0.58%)			
occurrences (all)	1			
Alanine aminotransferase increased				
subjects affected / exposed	1 / 173 (0.58%)			
occurrences (all)	1			
Creatinine urine increased				
subjects affected / exposed	0 / 173 (0.00%)			
occurrences (all)	0			
Blood cholesterol increased				
subjects affected / exposed	0 / 173 (0.00%)			
occurrences (all)	0			
Electrocardiogram normal				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 173 (0.00%)			
occurrences (all)	0			
Electrocardiogram poor r-wave progression				
subjects affected / exposed	0 / 173 (0.00%)			
occurrences (all)	0			
Electrocardiogram Q wave abnormal				
subjects affected / exposed	1 / 173 (0.58%)			
occurrences (all)	1			
Urea urine increased				

subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
White blood cell count increased			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 173 (0.58%)		
occurrences (all)	1		
Arthropod sting			
subjects affected / exposed	1 / 173 (0.58%)		
occurrences (all)	1		
Concussion			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Contusion			
subjects affected / exposed	1 / 173 (0.58%)		
occurrences (all)	1		
Joint dislocation			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Postoperative fever			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	9 / 173 (5.20%)		
occurrences (all)	10		
Tachycardia			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Bradycardia			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Bundle branch block			

subjects affected / exposed	2 / 173 (1.16%)		
occurrences (all)	2		
Bundle branch block right			
subjects affected / exposed	2 / 173 (1.16%)		
occurrences (all)	2		
Synus arrhytmia			
subjects affected / exposed	1 / 173 (0.58%)		
occurrences (all)	1		
Angina pectoris			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Atrioventricular block first degree			
subjects affected / exposed	1 / 173 (0.58%)		
occurrences (all)	1		
Sinus tachycardia			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Bundle branch block left			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Myocardial ischaemia			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Supraventricular extrasystoles			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 173 (2.31%)		
occurrences (all)	4		
Tremor			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	2 / 173 (1.16%)		
occurrences (all)	2		

Syncope			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 173 (0.58%)		
occurrences (all)	1		
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 173 (0.58%)		
occurrences (all)	1		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	2 / 173 (1.16%)		
occurrences (all)	2		
Abdominal pain upper			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Food poisoning			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Aphthous stomatitis			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Dry mouth			
subjects affected / exposed	1 / 173 (0.58%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Enteritis			

subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Toothache			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	1 / 173 (0.58%)		
occurrences (all)	1		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Hepatitis toxic			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Liver disorder			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Eczema			
subjects affected / exposed	1 / 173 (0.58%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Urticaria			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 173 (0.58%)		
occurrences (all)	1		
Infections and infestations			

Nasopharyngitis				
subjects affected / exposed	5 / 173 (2.89%)			
occurrences (all)	6			
Respiratory tract infection				
subjects affected / exposed	1 / 173 (0.58%)			
occurrences (all)	1			
Rhinitis				
subjects affected / exposed	0 / 173 (0.00%)			
occurrences (all)	0			
Respiratory tract infection viral				
subjects affected / exposed	2 / 173 (1.16%)			
occurrences (all)	2			
Bronchitis				
subjects affected / exposed	1 / 173 (0.58%)			
occurrences (all)	1			
Acute sinusitis				
subjects affected / exposed	1 / 173 (0.58%)			
occurrences (all)	1			
Pharyngitis				
subjects affected / exposed	1 / 173 (0.58%)			
occurrences (all)	1			
Tracheobronchitis				
subjects affected / exposed	1 / 173 (0.58%)			
occurrences (all)	1			
Acute tonsillitis				
subjects affected / exposed	1 / 173 (0.58%)			
occurrences (all)	1			
Bronchitis bacterial				
subjects affected / exposed	0 / 173 (0.00%)			
occurrences (all)	0			
Gastroenteristis				
subjects affected / exposed	0 / 173 (0.00%)			
occurrences (all)	0			
Cystitis				
subjects affected / exposed	1 / 173 (0.58%)			
occurrences (all)	1			

Ear infection			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Infected cyst			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Oral herpes			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Pharyngotonsillitis			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Rhinotracheitis			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Tooth infection			
subjects affected / exposed	1 / 173 (0.58%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Viral rhinitis			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Hyperglycemia			
subjects affected / exposed	1 / 173 (0.58%)		
occurrences (all)	1		
Hypertriglyceridaemia			

subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Diabetes mellitus			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Glucose tolerance impaired			
subjects affected / exposed	1 / 173 (0.58%)		
occurrences (all)	1		
Hypercholesterolaemia			
subjects affected / exposed	1 / 173 (0.58%)		
occurrences (all)	2		
Hyperkalaemia			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 173 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 July 2008	To substitute the CRO in charge of monitoring, the central laboratory being used for this trial and other minor changes surrounding the Interactive Voice Response System.
16 January 2009	The aim of this amendment is to clarify several aspects in the conduct of the CCD-0705-PR-0027 Next DPI 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: