Clinical trial results:
A 52-week, double-blind, randomized, multinational, multicentre, 2-arm parallel-group, active-controlled clinical trial of fixed combination of beclometasone dipropionate plus formoterol fumarate plus glycopyrrolate bromide administered via pMDI (CHF 5993) versus fixed combination of beclometasone dipropionate plus formoterol fumarate administered via pMDI in patients with chronic obstructive pulmonary disease

Summary

EudraCT number	2013-001057-27
Trial protocol	GB BE HU DE IT CZ SK PL BG
Global end of trial date	14 January 2016

Results information

Result version number	v1 (current)
This version publication date	10 February 2017
First version publication date	10 February 2017

Trial information

Trial identification

Sponsor protocol code	CCD-1207-PR-0091

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01917331
WHO universal trial number (UTN)	-
Other trial identifiers	TRILOGY: TRILOGY

Notes:

Sponsors

Sponsor organisation name	Chiesi Farmaceutici S.p.A.
Sponsor organisation address	Via Palermo 26/A, Parma, Italy, 43122
Public contact	Clinical Trial Transparency, Chiesi Farmaceutici S.p.A., +39 0521 2791, ClinicalTrials_info@chiesi.com
Scientific contact	Clinical Trial Transparency, Chiesi Farmaceutici S.p.A., +39 0521 2791, ClinicalTrials_info@chiesi.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 May 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

• Demonstrate superiority of CHF 5993 pMDI over CHF 1535 pMDI in terms of lung function (change from baseline in pre-dose and 2-hour post-dose morning FEV1 at Week 26).

• Demonstrate superiority of CHF 5993 pMDI over CHF 1535 pMDI in terms of dyspnea (Transition Dyspnea Index focal score at Week 26).

CHF 5993 = Fixed combination of BDP and FF and GB
CHF 1535=Fixed combination of BDP and FF
BDP = Beclomethasone dipropionate
COPD=Chronic obstructive pulmonary disease
FF=Formoterol fumarate
GB=Glycopyrronium bromide
pMDI=Pressurised metered dose inhaler

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practices (GCP) guidelines, and national legal requirements.

At all visits, from screening onward, concomitant medications, adverse events and vital signs were recorded, COPD exacerbations were assessed and 12-lead electrocardiogram (ECG) and physical examinations were performed. Treatment compliance was evaluated on the basis of the information recorded daily by the patient on the digital platform.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 March 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 53
Country: Number of subjects enrolled	Mexico: 4
Country: Number of subjects enrolled	Romania: 105
Country: Number of subjects enrolled	Russian Federation: 320
Country: Number of subjects enrolled	Ukraine: 224
Country: Number of subjects enrolled	Poland: 113
Country: Number of subjects enrolled	Slovakia: 33

Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Bulgaria: 92
Country: Number of subjects enrolled	Czech Republic: 208
Country: Number of subjects enrolled	Germany: 63
Country: Number of subjects enrolled	Hungary: 103
Country: Number of subjects enrolled	Italy: 23
Worldwide total number of subjects	1368
EEA total number of subjects	767

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)	0
Adults (18-64 years)	739
From 65 to 84 years	627
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Overall, 1812 patients were screened according to inclusion and exclusion criteria; of these 1368 patients were randomized.

Pre-assignment

Screening details:

Pre-screening visit was at most 1 week before the screening visit when inclusion/exclusion criteria were assessed and the run-in period of 2 weeks started. During the run-in period patients stopped their current treatment and received an open-label CHF 1535 pMDI to take as 2 puffs bid for 2 weeks (BDP 400 µg/FF 24 µg daily).

Period 1

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

Blinding implementation details:

Interactive Response Technology was used to assign study medication kits in order to have an inventory control and patient dosing tracking. In addition, the IRT maintained quantities, kit numbers, drug types,batch/code number, expiration dates and it monitored inventory levels at all sites and managed the drug re-supply.

The canisters/actuators of CHF 5993 pMDI and CHF 1535 pMDI were of identical appearance.

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment A - fixed combination CHF 5993 100/6/12.5µg

Arm description:

Treatment A:
CHF 5993 pMDI: Patients followed a schedule of 2 puffs of CHF 5993 100/6/12.5 µg bid.
Therefore, the total daily dose was BDP/FF/GB 400/24/50 µg;

BDP=Beclomethasone dipropionate
GB=Glycopyrronium bromide
FF=Formoterol fumarate
CHF 5993 pMDI=Fixed combination of BDP 50µg, FF 6 µg, GB 12.5µg per metered dose

Arm type	Experimental
Investigational medicinal product name	CHF 5993 100/6/12.5 µg
Investigational medicinal product code	
Other name	BDP/FF/GB, Fixed combination of beclomethasone dipropionate, formoterol fumarate, Glycopyrronium bromide
Pharmaceutical forms	Pressurised inhalation, solution
Routes of administration	Inhalation use

Dosage and administration details:

Dose: BDP 100 µg, FF 6 µg, GB 12.5 µg per actuation, 2 puffs bid (twice daily).
Total daily dose: BDP 400 µg, FF 24 µg, GB 50 µg.

Mode of administration: pMDI using a standard actuator. If patients inhaled their usual COPD pMDI treatments with a spacer device, they were provided with the AeroChamber Plus™ to be used when taking the pMDI study treatments.

Arm title	Treatment B - fixed combination CHF 1535 100/6µg

Arm description:

Treatment B:
CHF 1535 pMDI: Patients followed a schedule of 2 puffs of CHF 1535 100/6 µg bid.

Therefore, the total daily dose was BDP/FF 400/24 µg.

BDP=Beclomethasone dipropionate
FF=Formoterol fumarate
CHF 1535 pMDI=Fixed combination of BDP 100µg, FF 6 µg,

Arm type	Active comparator
Investigational medicinal product name	CHF 1535 100/6 µg
Investigational medicinal product code	
Other name	BDP/FF, Fixed combination of beclomethasone dipropionate and formoterol fumarate
Pharmaceutical forms	Pressurised inhalation, solution
Routes of administration	Inhalation use

Dosage and administration details:

Dose: BDP 100 µg, FF 6 µg per actuation, 2 puffs bid. (twice daily).
Total daily dose: BDP 400 µg, FF 24 µg.

Mode of administration: pMDI using a standard actuator. If patients inhaled their usual COPD pMDI treatments with a spacer device, they were provided with the AeroChamber Plus™ to be used when taking the pMDI study treatments.

Number of subjects in period 1	Treatment A - fixed combination CHF 5993 100/6/12.5µg	Treatment B - fixed combination CHF 1535 100/6µg
Started	687	681
Completed	602	579
Not completed	85	102
Adverse event, serious fatal	13	15
Consent withdrawn by subject	45	54
Adverse event, non-fatal	20	17
Other	-	2
Lost to follow-up	2	5
Lack of efficacy	3	6
Protocol deviation	2	3

Baseline characteristics

Reporting groups

Reporting group title	Treatment A - fixed combination CHF 5993 100/6/12.5µg

Reporting group description:

Treatment A:
CHF 5993 pMDI: Patients followed a schedule of 2 puffs of CHF 5993 100/6/12.5 µg bid.
Therefore, the total daily dose was BDP/FF/GB 400/24/50 µg;

BDP=Beclomethasone dipropionate
GB=Glycopyrronium bromide
FF=Formoterol fumarate
CHF 5993 pMDI=Fixed combination of BDP 50µg, FF 6 µg, GB 12.5µg per metered dose

Reporting group title	Treatment B - fixed combination CHF 1535 100/6µg

Reporting group description:

Treatment B:
CHF 1535 pMDI: Patients followed a schedule of 2 puffs of CHF 1535 100/6 µg bid.
Therefore, the total daily dose was BDP/FF 400/24 µg.

BDP=Beclomethasone dipropionate
FF=Formoterol fumarate
CHF 1535 pMDI=Fixed combination of BDP 100µg, FF 6 µg,

Reporting group values	Treatment A - fixed combination CHF 5993 100/6/12.5µg	Treatment B - fixed combination CHF 1535 100/6µg	Total
Number of subjects	687	681	1368
Age categorical Units: Subjects			
Adults (18-64 years)	391	348	739
From 65-84 years	295	332	627
85 years and over	1	1	2
Age continuous Units: years			
arithmetic mean	63.3	63.8	
standard deviation	± 7.9	± 8.2	-
Gender categorical Units: Subjects			
Female	178	154	332
Male	509	527	1036
Race Units: Subjects			
Other	3	1	4
White	684	680	1364

End points

End points reporting groups

Reporting group title	Treatment A - fixed combination CHF 5993 100/6/12.5µg

Reporting group description:

Treatment A:
CHF 5993 pMDI: Patients followed a schedule of 2 puffs of CHF 5993 100/6/12.5 µg bid.
Therefore, the total daily dose was BDP/FF/GB 400/24/50 µg;

BDP=Beclomethasone dipropionate
GB=Glycopyrronium bromide
FF=Formoterol fumarate
CHF 5993 pMDI=Fixed combination of BDP 50µg, FF 6 µg, GB 12.5µg per metered dose

Reporting group title	Treatment B - fixed combination CHF 1535 100/6µg

Reporting group description:

Treatment B:
CHF 1535 pMDI: Patients followed a schedule of 2 puffs of CHF 1535 100/6 µg bid.
Therefore, the total daily dose was BDP/FF 400/24 µg.

BDP=Beclomethasone dipropionate
FF=Formoterol fumarate
CHF 1535 pMDI=Fixed combination of BDP 100µg, FF 6 µg,

Primary: 1_Change from baseline in pre-dose morning FEV1 at week 26

End point title	1_Change from baseline in pre-dose morning FEV1 at week 26

End point description:

FEV1=Forced expiratory volume in the 1st second. It is the volume of air that can be forced out in one second after taking a deep breath.

End point type	Primary

End point timeframe:

Baseline to Week 26.

End point values	Treatment A - fixed combination CHF 5993 100/6/12.5µg	Treatment B - fixed combination CHF 1535 100/6µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	642[1]	616[2]		
Units: litre(s)				
least squares mean (confidence interval 95%)	0.082 (0.062 to 0.102)	0.001 (-0.019 to 0.021)		

Notes:

[1] - ITT population; Change from baseline available;

[2] - ITT population; Change from baseline available;

Statistical analyses

Statistical analysis title	Adjusted mean difference between treatment groups
Comparison groups	Treatment B - fixed combination CHF 1535 100/6µg v Treatment A - fixed combination CHF 5993 100/6/12.5µg

Number of subjects included in analysis	1258
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.081
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.052
upper limit	0.109

Notes:

[3] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at Screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Treatment A (CHF 5993 pMDI) - Treatment B (CHF 1535 pMDI)

Primary: 2_Change from baseline to 2-hour post-dose value of FEV1 at Week 26

End point title	2_Change from baseline to 2-hour post-dose value of FEV1 at Week 26

End point description:

Change from baseline to 2-hour post-dose value of FEV1 at Week 26.

End point type	Primary

End point timeframe:

Baseline to 2-hour post-dose at Week 26.

End point values	Treatment A - fixed combination CHF 5993 100/6/12.5µg	Treatment B - fixed combination CHF 1535 100/6µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	631[4]	609[5]		
Units: litre(s)				
least squares mean (confidence interval 95%)	0.261 (0.24 to 0.283)	0.145 (0.123 to 0.166)		

Notes:

[4] - ITT population; Change from baseline available;

[5] - ITT population; Change from baseline available;

Statistical analyses

Statistical analysis title	Adjusted mean difference between treatment groups
Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg

Number of subjects included in analysis	1240
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.117
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.086
upper limit	0.147

Notes:

[6] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, Country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at Screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Treatment A (CHF 5993 pMDI) - Treatment B (CHF 1535 pMDI)

Primary: 3_TDI focal score at Week 26

End point title	3_TDI focal score at Week 26

End point description:

TDI focal score is a symptom-based variable, used to assess breathlessness and the impact of intervention. The BDI/TDI is a clinical rating method based on a validated instrument, developed to measure the impact of dyspnoea on three domains: functional impairment, magnitude of task, and magnitude of effort.

The BDI scores range from 0 (very severe impairment) to 4 (no impairment) for each domain with the baseline focal score consisting of the sum of each domain (i.e. from 0 to 12). Change from baseline in dyspnoea severity was measured using the TDI. TDI score ranges from -3 (major deterioration) to +3 (major improvement) for each domain with the TDI focal score consisting in the sum of each domain (i.e. from -9 to +9).

BDI and TDI are based on validated questionnaires. BDI focal score is the baseline value from which TDI focal score is assessed.

BDI=Baseline Dyspnoea Index
TDI=Transition Dyspnoea Index

End point type	Primary

End point timeframe:

Baseline to Week 26.

End point values	Treatment A - fixed combination CHF 5993 100/6/12.5µg	Treatment B - fixed combination CHF 1535 100/6µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	642[7]	619[8]		
Units: score				
least squares mean (confidence interval 95%)	1.71 (1.5 to 1.92)	1.5 (1.29 to 1.71)		

Notes:

[7] - ITT population; Change from baseline available;

[8] - ITT population; Change from baseline available;

Statistical analyses

Statistical analysis title	Adjusted mean difference between treatment groups
Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1261
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.16
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.51

Notes:

[9] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at Screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Treatment A (CHF 5993 pMDI) - Treatment B (CHF 1535 pMDI)

Secondary: 4_Change from baseline in pre-dose morning FEV1 at all study visits

End point title	4_Change from baseline in pre-dose morning FEV1 at all study visits

End point description:

Change from baseline in pre-dose morning FEV1 at all study visits.

Shown are the number of subjects included in the model and the number of subjects with available results at the indicated week (Wk).

End point type	Secondary

End point timeframe:

Baseline and each study visit (Week 4, 12, 26, 40, 52).

End point values	Treatment A - fixed combination CHF 5993 100/6/12.5µg	Treatment B - fixed combination CHF 1535 100/6µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	681[10]	670[11]		
Units: litre(s)				
least squares mean (confidence interval 95%)				

Week 4	0.093 (0.076 to 0.109)	0.022 (0.005 to 0.039)		
Week 12	0.078 (0.06 to 0.096)	0.01 (-0.008 to 0.028)		
Week 26	0.082 (0.062 to 0.102)	0.001 (-0.019 to 0.021)		
Week 40	0.095 (0.073 to 0.116)	0.018 (-0.004 to 0.04)		
Week 52	0.071 (0.05 to 0.093)	0.008 (-0.014 to 0.03)		

Notes:

[10] - ITT population (analysed)
Wk 04 n=679
Wk 12 n=660
Wk 26 n=642
Wk 40 n=622
Wk 52 n=606

[11] - ITT population (analysed)
Wk 04 n=669
Wk 12 n=654
Wk 26 n=616
Wk 40 n=597
Wk 52 n=578

Statistical analyses

Statistical analysis title	Adjusted mean difference btw treat groups Wk 4

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 4.

The number of subjects in this analysis shown (1351) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects in this analysis with available data is 1348:
n (CHF 5993 pMDI)=679
n (CHF 1535 pMDI)=669

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1351
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.071
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.047
upper limit	0.094

Notes:

[12] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

CHF 5993 pMDI - CHF 1535 pMDI

Statistical analysis title	Adjusted mean difference btw treat groups Wk 12

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 12.

The number of subjects in this analysis shown (1351) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects in this analysis with available data is 1314:
n (CHF 5993 pMDI)=660
n (CHF 1535 pMDI)=654

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1351
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.068
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.042
upper limit	0.094

Notes:

[13] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

CHF 5993 pMDI - CHF 1535 pMDI

Statistical analysis title	Adjusted mean difference btw treat groups Wk 26

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 26.

The number of subjects in this analysis shown (1351) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects in this analysis with available data is 1258:
n (CHF 5993 pMDI)=642
n (CHF 1535 pMDI)=616

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1351
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.081
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.052
upper limit	0.109

Notes:

[14] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	Adjusted mean difference btw treat groups Wk 40

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 40.

The number of subjects in this analysis shown (1351) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects in this analysis with available data is 1219:
n (CHF 5993 pMDI)=622
n (CHF 1535 pMDI)=597

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1351
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.077
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.046
upper limit	0.108

Notes:

[15] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

CHF 5993 pMDI - CHF 1535 pMDI

Statistical analysis title	Adjusted mean difference btw treat groups Wk 52

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 52.

The number of subjects in this analysis shown (1351) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects in this analysis with available data is 1184:
n (CHF 5993 pMDI)=606
n (CHF 1535 pMDI)=578

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1351
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.063

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.032
upper limit	0.094

Notes:

[16] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

CHF 5993 pMDI - CHF 1535 pMDI

Secondary: 5_Change from baseline to the average over the treatment period in pre-dose morning FEV1

End point title	5_Change from baseline to the average over the treatment period in pre-dose morning FEV1

End point description:

Change from baseline to the average over the treatment period in pre-dose morning FEV1.

Shown are the number of subjects included in the model and the number of subjects with available results at the indicated week (Wk).

End point type	Secondary

End point timeframe:

Baseline to the overall treatment period (Week 4 to Week 52).

End point values	Treatment A - fixed combination CHF 5993 100/6/12.5µg	Treatment B - fixed combination CHF 1535 100/6µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	681[17]	670[18]		
Units: litre(s)				
least squares mean (confidence interval 95%)	0.084 (0.067 to 0.1)	0.012 (-0.005 to 0.029)		

Notes:

[17] - ITT population; Change from baseline available;

[18] - ITT population; Change from baseline available;

Statistical analyses

Statistical analysis title	Adjusted mean difference between treatment groups.

Statistical analysis description:

Adjusted mean difference between treatment groups.

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1351
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.072

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.048
upper limit	0.096

Notes:

[19] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at Screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

CHF 5993 pMDI - CHF 1535 pMDI

Secondary: 6_FEV1 response (change from baseline in pre-dose morning FEV1 ≥100 mL) at Week 26 and Week 52

End point title	6_FEV1 response (change from baseline in pre-dose morning FEV1 ≥100 mL) at Week 26 and Week 52

End point description:

FEV1 response is defined as a change from baseline in pre-dose morning FEV1 ≥100 mL. If the change from baseline was <100 mL, the patient was classed as a non-responder in terms of FEV1. Subjects with missing pre-dose morning FEV1 value at the relevant time points were also classified as non-responders.

Results are shown as the number of responders for the comparison of CHF 5993 pMDI vs CHF 1535 pMDI.

End point type	Secondary

End point timeframe:

Baseline to study visit at Week 26, Week 52.

End point values	Treatment A - fixed combination CHF 5993 100/6/12.5µg	Treatment B - fixed combination CHF 1535 100/6µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	687[20]	680[21]		
Units: subject				
Week 26	287	165		
Week 52	259	158		

Notes:

[20] - ITT population

[21] - ITT population

Statistical analyses

Statistical analysis title	Btw grp analysis, change in FEV1 ≥100 mL, Wk 26

Statistical analysis description:

Between group analysis (change from baseline in pre-dose morning FEV1 ≥100 mL, Week 26).

CHF 5993 pMDI / CHF 1535 pMDI

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg

Number of subjects included in analysis	1367
Analysis specification	Pre-specified
Analysis type	superiority[22]
P-value	< 0.001
Method	Logistic model
Parameter estimate	Odds ratio (OR)
Point estimate	2.299
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.817
upper limit	2.91

Notes:

[22] - Analysis is based on a logistic model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as factors and the baseline FEV1 value as a covariate.

Statistical analysis title	Btw grp analysis, change in FEV1 ≥100 mL, Wk 52

Statistical analysis description:

Between group analysis (change from baseline in pre-dose morning FEV1 ≥100 mL, Week 52).

CHF 5993 pMDI / CHF 1535 pMDI

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1367
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	< 0.001
Method	Logistic model
Parameter estimate	Odds ratio (OR)
Point estimate	2.061
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.621
upper limit	2.62

Notes:

[23] - Analysis is based on a logistic model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as factors and the baseline FEV1 value as a covariate.

Secondary: 7_Change from baseline to 2-hour post-dose value of FEV1 at all study visits

End point title	7_Change from baseline to 2-hour post-dose value of FEV1 at all study visits

End point description:

Change from baseline to 2-hour post-dose value of FEV1 at all study visits.

Shown are the number of subjects included in the model and the number of subjects with available results at the indicated week (Wk).

End point type	Secondary

End point timeframe:

Baseline to 2-hour post-dose at each study visit (Week 0, 4, 12, 26, 40, 52).

End point values	Treatment A - fixed combination CHF 5993 100/6/12.5µg	Treatment B - fixed combination CHF 1535 100/6µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	686[24]	679[25]		
Units: litre(s)				
least squares mean (confidence interval 95%)				
Week 0	0.215 (0.203 to 0.228)	0.138 (0.126 to 0.15)		
Week 4	0.268 (0.25 to 0.286)	0.153 (0.135 to 0.171)		
Week 12	0.261 (0.241 to 0.281)	0.146 (0.125 to 0.166)		
Week 26	0.261 (0.24 to 0.283)	0.145 (0.123 to 0.166)		
Week 40	0.253 (0.23 to 0.275)	0.15 (0.127 to 0.174)		
Week 52	0.249 (0.226 to 0.273)	0.146 (0.122 to 0.17)		

Notes:

[24] - ITT population (analysed)
W 0 n=683
W 4 n=675
W 12 n=657
W 26 n=631
W 40 n=615
W 52 n=598

[25] - ITT population (analysed)
W 0 n=674
W 4 n=660
W 12 n=648
W 26 n=609
W 40 n=590
W 52 n=575

Statistical analyses

Statistical analysis title	Adjusted mean difference btw treat groups Wk 0

Statistical analysis description:

Adjusted mean differences between treatments in 2-hour post-dose FEV1 at Week 0.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1365) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1357:
n (CHF 5993 p65) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg

Number of subjects included in analysis	1365
Analysis specification	Pre-specified
Analysis type	superiority[26]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.077
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.06
upper limit	0.095

Notes:

[26] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at Screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	Adjusted mean difference btw treat groups Wk 4

Statistical analysis description:

Adjusted mean differences between treatments in 2-hour post-dose FEV1 at Week 4.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1365) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1335:
n (CHF 5993 pMDI)=675
n (CHF 1535 pMDI)=660

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1365
Analysis specification	Pre-specified
Analysis type	superiority[27]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.116
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.09
upper limit	0.141

Notes:

[27] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at Screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	Adjusted mean difference btw treat groups Wk 12

Statistical analysis description:

Adjusted mean differences between treatments in 2-hour post-dose FEV1 at Week 12.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1365) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1305:

n (CHF 5993 pMDI)=657
n (CHF 1535 pMDI)=648

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1365
Analysis specification	Pre-specified
Analysis type	superiority[28]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.116
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.087
upper limit	0.144

Notes:

[28] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at Screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	Adjusted mean difference btw treat groups Wk 26

Statistical analysis description:

Adjusted mean differences between treatments in 2-hour post-dose FEV1 at Week 26.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1365) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1240:
n (CHF 5993 pMDI)=631
n (CHF 1535 pMDI)=609

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1365
Analysis specification	Pre-specified
Analysis type	superiority[29]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.117
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.086
upper limit	0.147

Notes:

[29] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at Screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	Adjusted mean difference btw treat groups Wk 40

Statistical analysis description:

Adjusted mean differences between treatments in 2-hour post-dose FEV1 at Week 40.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1365) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1205:
n (CHF 5993 pMDI)=615
n (CHF 1535 pMDI)=590

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1365
Analysis specification	Pre-specified
Analysis type	superiority[30]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.102
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	0.135

Notes:

[30] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at Screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	Adjusted mean difference btw treat groups Wk 52

Statistical analysis description:

Adjusted mean differences between treatments in 2-hour post-dose FEV1 at Week 52.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1365) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1173:
n (CHF 5993 pMDI)=598
n (CHF 1535 pMDI)=575

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1365
Analysis specification	Pre-specified
Analysis type	superiority[31]
P-value	< 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.103
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.069
upper limit	0.137

Notes:

[31] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at Screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Secondary: 8_Change from pre-dose to 2-hour post-dose value of FEV1 at all study

visits

End point title	8_Change from pre-dose to 2-hour post-dose value of FEV1 at all study visits

End point description:

Change from pre-dose to 2-hour post-dose value of FEV1 at all study visits.

The number of patients shown represents the ITT population; change from baseline for available patients at the specified week (Wk) for the comparison of CHF 5993 pMDI vs CHF 1535 pMDI.

Shown are the number of subjects included in the ITT population and the number of subjects with available results at the indicated week (Wk).

End point type	Secondary

End point timeframe:

Pre-dose to 2-hour post-dose at each study visit (Week 4, 12, 26, 40, 52).

End point values	Treatment A - fixed combination CHF 5993 100/6/12.5µg	Treatment B - fixed combination CHF 1535 100/6µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	687[32]	680[33]		
Units: litre(s)				
least squares mean (confidence interval 95%)				
Week 4	0.177 (0.165 to 0.189)	0.13 (0.118 to 0.143)		
Week 12	0.183 (0.171 to 0.194)	0.138 (0.126 to 0.149)		
Week 26	0.18 (0.169 to 0.192)	0.149 (0.138 to 0.161)		
Week 40	0.159 (0.147 to 0.171)	0.138 (0.125 to 0.15)		
Week 52	0.18 (0.167 to 0.193)	0.146 (0.133 to 0.159)		

Notes:

[32] - ITT population
Wk 04 n=674
Wk 12 n=658
Wk 26 n=632
Wk 40 n=616
Wk 52 n=599

[33] - ITT population
Wk 04 n=661
Wk 12 n=648
Wk 26 n=610
Wk 40 n=591
Wk 52 n=575

Statistical analyses

Statistical analysis title	Adjusted mean difference btw treat groups Wk 4

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 4.

The number of subjects in this analysis shown (1367) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1355.
n (CHF 5993 pMDI)=674
n (CHF 1535 pMDI)=661

CHF 5993 pMDI vs CHF 1535 pMDI

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1367
Analysis specification	Pre-specified
Analysis type	superiority[34]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.046
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.029
upper limit	0.064

Notes:

[34] - Analysis is based on an ANCOVA model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at Screening as fixed effects, and the pre-dose value at the visit as a covariate.

Statistical analysis title	Adjusted mean difference btw treat groups Wk 12

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 12.

The number of subjects in this analysis shown (1367) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1306.
n (CHF 5993 pMDI)=658
n (CHF 1535 pMDI)=648
CHF 5993 pMDI vs CHF 1535 pMDI

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1367
Analysis specification	Pre-specified
Analysis type	superiority[35]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.045
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.029
upper limit	0.062

Notes:

[35] - Analysis is based on an ANCOVA model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at Screening as fixed effects, and the pre-dose value at the visit as a covariate.

Statistical analysis title	Adjusted mean difference btw treat groups Wk 26

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 26.

The number of subjects in this analysis shown (1367) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1242.
n (CHF 5993 pMDI)=632
n (CHF 1535 pMDI)=610
CHF 5993 pMDI vs CHF 1535 pMDI

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1367
Analysis specification	Pre-specified
Analysis type	superiority[36]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.031
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.015
upper limit	0.047

Notes:

[36] - Analysis is based on an ANCOVA model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at Screening as fixed effects, and the pre-dose value at the visit as a covariate.

Statistical analysis title	Adjusted mean difference btw treat groups Wk 40

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 40.

The number of subjects in this analysis shown (1367) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1207.
n (CHF 5993 pMDI)=616
n (CHF 1535 pMDI)=591
CHF 5993 pMDI vs CHF 1535 pMDI

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1367
Analysis specification	Pre-specified
Analysis type	superiority[37]
P-value	= 0.013
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.022
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.005
upper limit	0.039

Notes:

[37] - Analysis is based on an ANCOVA model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at Screening as fixed effects, and the pre-dose value at the visit as a covariate.

Statistical analysis title	Adjusted mean difference btw treat groups Wk 52

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 52.

The number of subjects in this analysis shown (1367) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1174.
n (CHF 5993 pMDI)=599
n (CHF 1535 pMDI)=575
CHF 5993 pMDI vs CHF 1535 pMDI

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1367
Analysis specification	Pre-specified
Analysis type	superiority[38]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.034
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.016
upper limit	0.052

Notes:

[38] - Analysis is based on an ANCOVA model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at Screening as fixed effects, and the pre-dose value at the visit as a covariate.

Secondary: 9_TDI focal score at all study visits

End point title	9_TDI focal score at all study visits

End point description:

TDI focal score is a symptom-based variable, used to assess breathlessness and the impact of intervention. The BDI/TDI is a clinical rating method based on a validated instrument, developed to measure the impact of dyspnoea on three domains: functional impairment, magnitude of task, and magnitude of effort.

The BDI scores range from 0 (very severe impairment) to 4 (no impairment) for each domain with the baseline focal score consisting of the sum of each domain (i.e. from 0 to 12). Change from baseline in dyspnoea severity was measured using the TDI. TDI score ranges from -3 (major deterioration) to +3 (major improvement) for each domain with the TDI focal score consisting in the sum of each domain (i.e. from -9 to +9).

BDI and TDI are based on validated questionnaires. BDI focal score is the baseline value from which TDI focal score is assessed.

BDI=Baseline Dyspnoea Index
TDI=Transition Dyspnoea Index

End point type	Secondary

End point timeframe:

Baseline and each study visit (Week 4, 12, 26, 40, 52).

End point values	Treatment A - fixed combination CHF 5993 100/6/12.5µg	Treatment B - fixed combination CHF 1535 100/6µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	687[39]	680[40]		
Units: score				
least squares mean (confidence interval 95%)				
Week 4	1.54 (1.35 to 1.72)	1.12 (0.94 to 1.31)		
Week 12	1.77 (1.58 to 1.97)	1.39 (1.19 to 1.58)		
Week 26	1.71 (1.5 to 1.92)	1.5 (1.29 to 1.71)		
Week 40	1.8 (1.58 to 2.01)	1.65 (1.43 to 1.86)		
Week 52	2.03 (1.81 to 2.25)	1.81 (1.59 to 2.04)		

Notes:

[39] - ITT population (analysed)
Wk 04 n=680
Wk 12 n=661
Wk 26 n=642
Wk 40 n=622
Wk 52 n=608
[40] - ITT population (analysed)
Wk 04 n=672
Wk 12 n=651
Wk 26 n=619
Wk 40 n=596
Wk 52 n=579

Statistical analyses

Statistical analysis title	Adjusted mean difference btw treat groups Wk 4

Statistical analysis description:

Adjusted mean differences between treatments for TDI focal score at Week 4.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1367) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1352:
n (CHF 5993 pMDI)=680
n (CHF 1535 pMDI)=672

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1367
Analysis specification	Pre-specified
Analysis type	superiority[41]
P-value	= 0.002
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	0.68

Notes:

[41] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at Screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	Adjusted mean difference btw treat groups Wk 12

Statistical analysis description:

Adjusted mean differences between treatments for TDI focal score at Week 12.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1367) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1312:
n (CHF 5993 pMDI)=661
n (CHF 1535 pMDI)=651

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1367
Analysis specification	Pre-specified
Analysis type	superiority[42]
P-value	= 0.007
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.11
upper limit	0.66

Notes:

[42] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at Screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	Adjusted mean difference btw treat groups Wk 26

Statistical analysis description:

Adjusted mean differences between treatments for TDI focal score at Week 26.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1367) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1261:
n (CHF 5993 pMDI)=642
n (CHF 1535 pMDI)=619

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1367
Analysis specification	Pre-specified
Analysis type	superiority[43]
P-value	= 0.16
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.21

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.51

Notes:

[43] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at Screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	Adjusted mean difference btw treat groups Wk 40

Statistical analysis description:

Adjusted mean differences between treatments for TDI focal score at Week 40.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1367) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1218:
n (CHF 5993 pMDI)=622
n (CHF 1535 pMDI)=596

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1367
Analysis specification	Pre-specified
Analysis type	superiority[44]
P-value	= 0.343
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16
upper limit	0.45

Notes:

[44] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at Screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	Adjusted mean difference btw treat groups Wk 52

Statistical analysis description:

Adjusted mean differences between treatments for TDI focal score at Week 52.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1367) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1187:
n (CHF 5993 pMDI)=608
n (CHF 1535 pMDI)=579

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg

Number of subjects included in analysis	1367
Analysis specification	Pre-specified
Analysis type	superiority[45]
P-value	= 0.186
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.53

Notes:

[45] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at Screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Secondary: 10_TDI response (focal score ≥1) at Week 26 and Week 52

End point title	10_TDI response (focal score ≥1) at Week 26 and Week 52

End point description:

TDI response is defined as a TDI focal score ≥1. If the TDI focal score was <1, the patient was classified as a non-responder in terms of TDI. Patients with missing TDI focal score at the relevant time points were also classed as non-responders.

Results are shown as the number of responders for the comparison of CHF 5993 pMDI vs CHF 1535 pMDI.

TDI=Transition Dyspnoea Index

End point type	Secondary

End point timeframe:

Week 26, Week 52.

End point values	Treatment A - fixed combination CHF 5993 100/6/12.5µg	Treatment B - fixed combination CHF 1535 100/6µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	687[46]	680[47]		
Units: subjects				
Week 26	394	352		
Week 52	370	354		

Notes:

[46] - ITT population

[47] - ITT population

Statistical analyses

Statistical analysis title	Between group analysis (TDI score ≥1, Week 26)

Statistical analysis description:

Between treatment group analysis for subjects with a TDI focal score ≥1 at Week 26.

CHF 5993 pMDI vs CHF 1535 pMDI

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1367
Analysis specification	Pre-specified
Analysis type	superiority[48]
P-value	= 0.027
Method	Logistic model
Parameter estimate	Odds ratio (OR)
Point estimate	1.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.029
upper limit	1.594

Notes:

[48] - Analysis is based on a logistic model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at Screening as factors and the baseline TDI focal score value as a covariate.

Statistical analysis title	Between group analysis (TDI score ≥1, Week 52)

Statistical analysis description:

Between treatment group analysis for subjects with a TDI focal score ≥1 at Week 52.

CHF 5993 pMDI vs CHF 1535 pMDI

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1367
Analysis specification	Pre-specified
Analysis type	superiority[49]
P-value	= 0.43
Method	Logistic model
Parameter estimate	Odds ratio (OR)
Point estimate	1.093
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.877
upper limit	1.362

Notes:

[49] - Analysis is based on a logistic model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at Screening as factors and the baseline TDI focal score value as a covariate.

Secondary: 11_Change from baseline in Saint George’s respiratory questionnaire (SGRQ) at all study visits: Total Score

End point title	11_Change from baseline in Saint George’s respiratory questionnaire (SGRQ) at all study visits: Total Score

End point description:

SGRQ Total Score.

SGRQ is a questionnaire developed to measure health in chronic airflow limitation.
SGRQ questionnaire was completed by the patient at all study visits (Week 0 baseline, 4, 12, 26, 40, 52).
In this study, the Total Score for SGRQ was calculated, whereby lower scores correspond to better health. Moreover, 3 component scores of SGRQ were calculated: Symptoms, Activity, and Impacts on

daily life.

Change from baseline in SGRQ Total Score was calculated and presented for this end point.

Shown are the number of subjects included in the model and the number of subjects with available results at the indicated week (Wk).

SGRQ=Saint George's respiratory questionnaire

End point type	Secondary

End point timeframe:

Baseline and each study visit (Week 4, 12, 26, 40, 52).

End point values	Treatment A - fixed combination CHF 5993 100/6/12.5µg	Treatment B - fixed combination CHF 1535 100/6µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	658[50]	644[51]		
Units: score				
least squares mean (confidence interval 95%)				
Week 4	-3.66 (-4.41 to -2.91)	-2.19 (-2.96 to -1.43)		
Week 12	-4.7 (-5.58 to -3.81)	-2.66 (-3.55 to -1.77)		
Week 26	-4.76 (-5.69 to -3.83)	-3.43 (-4.38 to -2.47)		
Week 40	-5.48 (-6.49 to -4.47)	-4.08 (-5.11 to -3.05)		
Week 52	-5.12 (-6.18 to -4.06)	-3.43 (-4.51 to -2.35)		

Notes:

[50] - ITT population (analysed)
Wk 04 n=628
Wk 12 n=601
Wk 26 n=594
Wk 40 n=572
Wk 52 n=559

[51] - ITT population (analysed)
Wk 04 n=607
Wk 12 n=597
Wk 26 n=558
Wk 40 n=545
Wk 52 n=532

Statistical analyses

Statistical analysis title	Adjusted mean difference btw treat groups Wk 4

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 4.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1302) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1235:
n (CHF 5993 pMDI)=628
n (CHF 1535 pMDI)=607

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v

	Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1302
Analysis specification	Pre-specified
Analysis type	superiority[52]
P-value	= 0.007
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-1.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.54
upper limit	-0.39

Notes:

[52] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	Adjusted mean difference btw treat groups Wk 12

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 12.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1302) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1198:
n (CHF 5993 pMDI)=601
n (CHF 1535 pMDI)=597

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1302
Analysis specification	Pre-specified
Analysis type	superiority[53]
P-value	= 0.002
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-2.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	-0.78

Notes:

[53] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	Adjusted mean difference btw treat groups Wk 26

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 26.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1302) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1152:
n (CHF 5993 pMDI)=594
n (CHF 1535 pMDI)=558

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1302
Analysis specification	Pre-specified
Analysis type	superiority[54]
P-value	= 0.051
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-1.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.66
upper limit	0.01

Notes:

[54] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	Adjusted mean difference btw treat groups Wk 40

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 40.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1302) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1117:
n (CHF 5993 pMDI)=572
n (CHF 1535 pMDI)=545

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1302
Analysis specification	Pre-specified
Analysis type	superiority[55]
P-value	= 0.057
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.85
upper limit	0.04

Notes:

[55] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	Adjusted mean difference btw treat groups Wk 52

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 52.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1302) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1091:
n (CHF 5993 pMDI)=559
n (CHF 1535 pMDI)=532

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1302
Analysis specification	Pre-specified
Analysis type	superiority[56]
P-value	= 0.029
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-1.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	-0.17

Notes:

[56] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Secondary: 12_Change from baseline in Saint George's respiratory questionnaire (SGRQ) at all study visits: Symptoms Score

End point title	12_Change from baseline in Saint George's respiratory questionnaire (SGRQ) at all study visits: Symptoms Score

End point description:

SGRQ Symptoms Score.

SGRQ is a questionnaire developed to measure health in chronic airflow limitation.
SGRQ questionnaire was completed by the patient at all study visits (Week 0 baseline, 4, 12, 26, 40, 52).
In this study, the Total Score for SGRQ was calculated, whereby lower scores correspond to better health. Moreover, 3 component scores of SGRQ were calculated: Symptoms, Activity, and Impacts on daily life.

Change from baseline in SGRQ Symptoms Score was calculated and presented for this end point.

Shown are the number of subjects included in the model and the number of subjects with available results at the indicated week (Wk).

SGRQ=Saint George's respiratory questionnaire

End point type	Secondary

End point timeframe:

Baseline and each study visit (Week 4, 12, 26, 40, 52).

End point values	Treatment A - fixed combination CHF 5993 100/6/12.5µg	Treatment B - fixed combination CHF 1535 100/6µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	674[57]	664[58]		
Units: score				
least squares mean (confidence interval 95%)				
Week 4	-5.02 (-6.1 to -3.95)	-3.83 (-4.92 to -2.75)		
Week 12	-5.09 (-6.29 to -3.89)	-4.56 (-5.77 to -3.34)		
Week 26	-6.8 (-8.06 to -5.53)	-5.17 (-6.46 to -3.88)		
Week 40	-8.35 (-9.73 to -6.96)	-7.12 (-8.53 to -5.71)		
Week 52	-8.22 (-9.67 to -6.77)	-7.26 (-8.74 to -5.78)		

Notes:

[57] - ITT population (analysed)
Wk 04 n=652
Wk 12 n=636
Wk 26 n=620
Wk 40 n=601
Wk 52 n=584
[58] - ITT population (analysed)
Wk 04 n=637
Wk 12 n=629
Wk 26 n=589
Wk 40 n=576
Wk 52 n=558

Statistical analyses

Statistical analysis title	Adjusted mean difference btw treat groups Wk 4

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 4.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1338) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1289:
n (CHF 5993 pMDI)=652
n (CHF 1535 pMDI)=637

Comparison groups	Treatment B - fixed combination CHF 1535 100/6µg v Treatment A - fixed combination CHF 5993 100/6/12.5µg
Number of subjects included in analysis	1338
Analysis specification	Pre-specified
Analysis type	superiority[59]
P-value	= 0.126
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.72
upper limit	0.34

Notes:

[59] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	Adjusted mean difference btw treat groups Wk 12

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 12.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1338) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1265:
n (CHF 5993 pMDI)=636
n (CHF 1535 pMDI)=629

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1338
Analysis specification	Pre-specified
Analysis type	superiority[60]
P-value	= 0.54
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.24
upper limit	1.17

Notes:

[60] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	Adjusted mean difference btw treat groups Wk 26

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 26.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1338) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1209:
n (CHF 5993 pMDI)=620
n (CHF 1535 pMDI)=589

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1338
Analysis specification	Pre-specified
Analysis type	superiority[61]
P-value	= 0.077
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-1.63

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.44
upper limit	0.17

Notes:

[61] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	Adjusted mean difference btw treat groups Wk 40

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 40.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1338) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1177:
n (CHF 5993 pMDI)=601
n (CHF 1535 pMDI)=576

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1338
Analysis specification	Pre-specified
Analysis type	superiority[62]
P-value	= 0.224
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.21
upper limit	0.75

Notes:

[62] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	Adjusted mean difference btw treat groups Wk 52

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 52.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1338) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1142:
n (CHF 5993 pMDI)=584
n (CHF 1535 pMDI)=558

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg

Number of subjects included in analysis	1338
Analysis specification	Pre-specified
Analysis type	superiority[63]
P-value	= 0.364
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.03
upper limit	1.11

Notes:

[63] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Secondary: 13_Change from baseline in Saint George's respiratory questionnaire (SGRQ) at all study visits: Impacts Score

End point title	13_Change from baseline in Saint George's respiratory questionnaire (SGRQ) at all study visits: Impacts Score

End point description:

SGRQ Impacts Score.

SGRQ is a questionnaire developed to measure health in chronic airflow limitation.
SGRQ questionnaire was completed by the patients at all study visits (Week 0 baseline, 4, 12, 26, 40, 52).
In this study, the Total Score for SGRQ was calculated, whereby lower scores correspond to better health. Moreover, 3 component scores of SGRQ were calculated: Symptoms, Activity, and Impacts on daily life.

Change from baseline in SGRQ Impacts Score was calculated and presented for this end point.

Shown are the number of subjects included in the model and the number of subjects with available results at the indicated week (Wk).

SGRQ=Saint George's respiratory questionnaire

End point type	Secondary

End point timeframe:

Baseline and each study visit (Week 4, 12, 26, 40, 52).

End point values	Treatment A - fixed combination CHF 5993 100/6/12.5µg	Treatment B - fixed combination CHF 1535 100/6µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	678[64]	668[65]		
Units: score				
least squares mean (confidence interval 95%)				
Week 4	-3.44 (-4.34 to -2.54)	-2.29 (-3.2 to -1.38)		
Week 12	-4.65 (-5.69 to -3.62)	-2.72 (-3.76 to -1.68)		

Week 26	-4.88 (-5.96 to -3.8)	-3.5 (-4.6 to -2.39)		
Week 40	-5.33 (-6.45 to -4.2)	-3.75 (-4.89 to -2.6)		
Week 52	-4.68 (-5.85 to -3.51)	-2.59 (-3.79 to -1.4)		

Notes:

[64] - ITT population (analysed)
Wk 04 n=668
Wk 12 n=641
Wk 26 n=627
Wk 40 n=608
Wk 52 n=590

[65] - ITT population (analysed)
Wk 04 n=654
Wk 12 n=636
Wk 26 n=594
Wk 40 n=576
Wk 52 n=559

Statistical analyses

Statistical analysis title	Adjusted mean difference btw treat groups Wk 4

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 4.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1346) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1322:
n (CHF 5993 pMDI)=668
n (CHF 1535 pMDI)=654

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1346
Analysis specification	Pre-specified
Analysis type	superiority[66]
P-value	= 0.077
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.43
upper limit	0.13

Notes:

[66] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	Adjusted mean difference btw treat groups Wk 12

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 12.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1346) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1277:
n (CHF 5993 pMDI)=641
n (CHF 1535 pMDI)=636

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1346
Analysis specification	Pre-specified
Analysis type	superiority[67]
P-value	= 0.01
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-1.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	-0.46

Notes:

[67] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	Adjusted mean difference btw treat groups Wk 26

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 26.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1346) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1221:
n (CHF 5993 pMDI)=627
n (CHF 1535 pMDI)=594

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1346
Analysis specification	Pre-specified
Analysis type	superiority[68]
P-value	= 0.079
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-1.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.93
upper limit	0.16

Notes:

[68] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	Adjusted mean difference btw treat groups Wk 40

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 40.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1346) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1284:
n (CHF 5993 pMDI)=608
n (CHF 1535 pMDI)=576

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1346
Analysis specification	Pre-specified
Analysis type	superiority[69]
P-value	= 0.054
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-1.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.19
upper limit	0.03

Notes:

[69] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	Adjusted mean difference btw treat groups Wk 52

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 52.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1346) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1149:
n (CHF 5993 pMDI)=590
n (CHF 1535 pMDI)=559

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1346
Analysis specification	Pre-specified
Analysis type	superiority[70]
P-value	= 0.015
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-2.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.76
upper limit	-0.41

Notes:

[70] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Secondary: 14_Change from baseline in Saint George's respiratory questionnaire (SGRQ) at all study visits: Activity Score

End point title	14_Change from baseline in Saint George's respiratory questionnaire (SGRQ) at all study visits: Activity Score

End point description:

SGRQ Activity Score.

SGRQ is a questionnaire developed to measure health in chronic airflow limitation.
SGRQ questionnaire was completed by the patients at all study visits (Week 0 baseline, 4, 12, 26, 40, 52).
In this study, the Total Score for SGRQ was calculated, whereby lower scores correspond to better health. Moreover, 3 component scores of SGRQ were calculated: Symptoms, Activity, and Impacts on daily life.

Change from baseline in SGRQ Activity Score was calculated and presented for this end point.

Shown are the number of subjects included in the model and the number of subjects with available results at the indicated week (Wk).

SGRQ=Saint George's respiratory questionnaire

End point type	Secondary

End point timeframe:

Baseline and each study visit (Week 4, 12, 26, 40, 52).

End point values	Treatment A - fixed combination CHF 5993 100/6/12.5µg	Treatment B - fixed combination CHF 1535 100/6µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	672[71]	661[72]		
Units: score				
least squares mean (confidence interval 95%)				
Week 4	-2.69 (-3.65 to -1.73)	-1.21 (-2.18 to -0.24)		
Week 12	-3.93 (-5.03 to -2.83)	-1.35 (-2.46 to -0.24)		
Week 26	-3.88 (-5.01 to -2.75)	-2.17 (-3.33 to -1.02)		
Week 40	-4.35 (-5.54 to -3.15)	-2.74 (-3.96 to -1.51)		
Week 52	-4.26 (-5.49 to -3.02)	-2.95 (-4.21 to -1.68)		

Notes:

[71] - ITT population (analysed)
Wk 04 n=659
Wk 12 n=626
Wk 26 n=616
Wk 40 n=596
Wk 52 n=583
[72] - ITT population (analysed)

Wk 4 n=639
Wk 12 n=621
Wk 26 n=585
Wk 40 n=562
Wk 52 n=554

Statistical analyses

Statistical analysis title	Adjusted mean difference btw treat groups Wk 4

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 4.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1333) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1298:
n (CHF 5993 pMDI)=659
n (CHF 1535 pMDI)=639

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1333
Analysis specification	Pre-specified
Analysis type	superiority[73]
P-value	= 0.034
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-1.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.84
upper limit	-0.11

Notes:

[73] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	Adjusted mean difference btw treat groups Wk 12

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 12.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1333) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1247:
n (CHF 5993 pMDI)=626
n (CHF 1535 pMDI)=621

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg

Number of subjects included in analysis	1333
Analysis specification	Pre-specified
Analysis type	superiority[74]
P-value	= 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-2.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.14
upper limit	-1.01

Notes:

[74] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	Adjusted mean difference btw treat groups Wk 26

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 26.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1333) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1201:
n (CHF 5993 pMDI)=616
n (CHF 1535 pMDI)=585

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1333
Analysis specification	Pre-specified
Analysis type	superiority[75]
P-value	= 0.039
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-1.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.33
upper limit	-0.09

Notes:

[75] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	Adjusted mean difference btw treat groups Wk 40

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 40.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1333) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1158:

n (CHF 5993 pMDI)=596
n (CHF 1535 pMDI)=562

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1333
Analysis specification	Pre-specified
Analysis type	superiority[76]
P-value	= 0.065
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-1.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.32
upper limit	-0.1

Notes:

[76] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Statistical analysis title	Adjusted mean difference btw treat groups Wk 52

Statistical analysis description:

Adjusted mean difference between treatment groups at Week 52.
CHF 5993 pMDI vs CHF 1535 pMDI

The number of subjects in this analysis shown (1333) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1158:
n (CHF 5993 pMDI)=596
n (CHF 1535 pMDI)=562

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1333
Analysis specification	Pre-specified
Analysis type	superiority[77]
P-value	= 0.145
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.08
upper limit	0.45

Notes:

[77] - Analysis is based on a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

Secondary: 15_SGRQ response (change from baseline in Total score ≤-4) at Week 26 and Week 52

End point title	15_SGRQ response (change from baseline in Total score ≤-4) at Week 26 and Week 52

End point description:

SGRQ response is defined as a change from baseline in SGRQ total score ≤ -4. If the change from baseline was > -4, the patient was classed as a non-responder in terms of SGRQ. Patients with missing change from baseline at the relevant time points were also classified as non-responders.

Results are shown as the number of responders for the comparison of CHF 5993 pMDI vs CHF 1535 pMDI.

SGRQ=Saint George's respiratory questionnaire

End point type	Secondary

End point timeframe:

Baseline to Week 26, Week 52.

End point values	Treatment A - fixed combination CHF 5993 100/6/12.5µg	Treatment B - fixed combination CHF 1535 100/6µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	687[78]	680[79]		
Units: subject				
Week 26	321	246		
Week 52	297	244		

Notes:

[78] - ITT population

[79] - ITT population

Statistical analyses

Statistical analysis title	Btw grp analysis, change in SGRQ score ≤-4, Wk 26

Statistical analysis description:

SGRQ response = Subjects with a change from baseline in Total Score ≤-4, at week 26.
Between group analysis (change from baseline in SGRQ Total score ≤-4, Week 26).

CHF 5993 pMDI / CHF 1535 pMDI

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1367
Analysis specification	Pre-specified
Analysis type	superiority[80]
P-value	< 0.001
Method	Logistic model
Parameter estimate	Odds ratio (OR)
Point estimate	1.521
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.211
upper limit	1.911

Notes:

[80] - Analysis is based on a logistic model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as factors and the baseline SGRQ total score value as a covariate.

Statistical analysis title	Btw grp analysis, change in SGRQ score ≤-4, Wk 52

Statistical analysis description:

SGRQ response = Subjects with a change from baseline in Total Score ≤-4, at week 52.
Between group analysis (change from baseline in SGRQ Total score ≤-4, Week 52).

CHF 5993 pMDI / CHF 1535 pMDI

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1367
Analysis specification	Pre-specified
Analysis type	superiority[81]
P-value	= 0.014
Method	Logistic model
Parameter estimate	Odds ratio (OR)
Point estimate	1.327
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.06
upper limit	1.661

Notes:

[81] - Analysis is based on a logistic model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as factors and the baseline SGRQ total score value as a covariate.

Secondary: 16_Change from baseline for percentage of days without intake of rescue medication

End point title	16_Change from baseline for percentage of days without intake of rescue medication

End point description:

Days without intake of rescue medication.

Change from baseline to each inter-visit period and for the entire treatment period (Week 1-52) in the percentage of days without intake of rescue medication.

Shown are the number of subjects included in the model and the number of subjects with available results at the indicated week (Wk).

End point type	Secondary

End point timeframe:

Baseline to Week 4, 12, 26, 40, 52.

End point values	Treatment A - fixed combination CHF 5993 100/6/12.5µg	Treatment B - fixed combination CHF 1535 100/6µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	653[82]	645[83]		
Units: days				
least squares mean (confidence interval 95%)				
Week 1-4	6.67 (4.89 to 8.44)	2.46 (0.67 to 4.25)		
Week 5-12	6.23 (4.19 to 8.27)	3.18 (1.12 to 5.24)		

Week 13-26	5.49 (3.3 to 7.67)	2.4 (0.19 to 4.6)		
Week 27-40	4.39 (2.07 to 6.72)	2.79 (0.43 to 5.15)		
Week 41-52	3.82 (1.45 to 6.19)	1.24 (-1.17 to 3.65)		
Week 1-52	5.01 (3.05 to 6.98)	2.36 (0.37 to 4.35)		

Notes:

[82] - ITT population
W 1-4 n=645
W 5-12 n=642
W 13-26 n=627
W 27-40 n=601
W 41-52 n=578
W 1-52 n=650

[83] - ITT population
W 1-4 n=637
W 5-12 n=629
W 13-26 n=610
W 27-40 n=572
W 41-52 n=552
W 1-52 n=640

Statistical analyses

Statistical analysis title	Adjusted mean difference btw treat groups W 1-4

Statistical analysis description:

Adjusted mean difference between treatment groups during Week 1-4.
CHF 5993 pMDI - CHF 1535 pMDI

The number of subjects in this analysis shown (1298) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1282:
n (CHF 5993 pMDI)=645
n (CHF 1535 pMDI)=637

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1298
Analysis specification	Pre-specified
Analysis type	superiority[84]
P-value	= 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	4.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.69
upper limit	6.73

Notes:

[84] - Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates.

Statistical analysis title	Adjusted mean difference btw treat groups W 5-12

Statistical analysis description:

Adjusted mean difference between treatment groups during Week 5-12.
CHF 5993 pMDI - CHF 1535 pMDI

The number of subjects in this analysis shown (1298) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1271:
n (CHF 5993 pMDI)=642
n (CHF 1535 pMDI)=629

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1298
Analysis specification	Pre-specified
Analysis type	superiority[85]
P-value	= 0.039
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	3.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	5.95

Notes:

[85] - Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates.

Statistical analysis title	Adjusted mean difference btw treat groups W 13-26

Statistical analysis description:

Adjusted mean difference between treatment groups during Week 13-26.
CHF 5993 pMDI - CHF 1535 pMDI

The number of subjects in this analysis shown (1298) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1237:
n (CHF 5993 pMDI)=627
n (CHF 1535 pMDI)=610

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1298
Analysis specification	Pre-specified
Analysis type	superiority[86]
P-value	= 0.051
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	3.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	6.2

Notes:

[86] - Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates.

Statistical analysis title	Adjusted mean difference btw treat groups W 27-40

Statistical analysis description:

Adjusted mean difference between treatment groups during Week 27-40.
CHF 5993 pMDI - CHF 1535 pMDI

The number of subjects in this analysis shown (1298) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1173:
n (CHF 5993 pMDI)=601
n (CHF 1535 pMDI)=572

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1298
Analysis specification	Pre-specified
Analysis type	superiority[87]
P-value	= 0.342
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.71
upper limit	4.91

Notes:

[87] - Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates.

Statistical analysis title	Adjusted mean difference btw treat groups W 41-52

Statistical analysis description:

Adjusted mean difference between treatment groups during Week 41-52.
CHF 5993 pMDI - CHF 1535 pMDI

The number of subjects in this analysis shown (1298) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1130:
n (CHF 5993 pMDI)=578
n (CHF 1535 pMDI)=552

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1298
Analysis specification	Pre-specified
Analysis type	superiority[88]
P-value	= 0.134
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	2.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	5.97

Notes:

[88] - Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates.

Statistical analysis title	Adjusted mean difference btw treat groups W 1-52

Statistical analysis description:

Adjusted mean difference between treatment groups during Week 1-52.
CHF 5993 pMDI - CHF 1535 pMDI

The number of subjects in this analysis shown (1298) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1290:
n (CHF 5993 pMDI)=650
n (CHF 1535 pMDI)=640

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1298
Analysis specification	Pre-specified
Analysis type	superiority[89]
P-value	= 0.063
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	2.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	5.45

Notes:

[89] - Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates.

Secondary: 17_Change from baseline for the average use of rescue medication

End point title	17_Change from baseline for the average use of rescue medication

End point description:

Average use of rescue medication.

Change from baseline to each inter-visit period and for the entire treatment period (Week 1-52) in the average use of rescue medication (number of puffs/day).

Shown are the number of subjects included in the model and the number of subjects with available results at the indicated week (Wk).

End point type	Secondary

End point timeframe:

Baseline to Week 4, 12, 26, 40, 52.

End point values	Treatment A - fixed combination CHF 5993 100/6/12.5µg	Treatment B - fixed combination CHF 1535 100/6µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	653[90]	645[91]		
Units: puffs/day				
least squares mean (confidence interval 95%)				
Week 1-4	-0.29 (-0.38 to -0.2)	-0.07 (-0.17 to 0.02)		
Week 5-12	-0.25 (-0.36 to -0.14)	-0.06 (-0.17 to 0.05)		
Week 13-26	-0.21 (-0.32 to -0.09)	-0.02 (-0.14 to 0.1)		
Week 27-40	-0.09 (-0.22 to 0.04)	0.02 (-0.11 to 0.15)		
Week 41-52	-0.04 (-0.17 to 0.09)	0.07 (-0.07 to 0.21)		
Week 1-52	-0.15 (-0.26 to -0.04)	0 (-0.11 to 0.12)		

Notes:

[90] - ITT population
W 1-4 n=645
W 5-12 n=642
W 13-26 n=627
W 27-40 n=601
W 41-52 n=578
W 1-52 n=650

[91] - ITT population
W 1-4 n=637
W 5-12 n=629
W 13-26 n=610
W 27-40 n=572
W 41-52 n=552
W 1-52 n=640

Statistical analyses

Statistical analysis title	Adjusted mean difference btw treat groups W 1-4

Statistical analysis description:

Adjusted mean difference between treatment groups during Week 1-4.
CHF 5993 pMDI - CHF 1535 pMDI

The number of subjects in this analysis shown (1298) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1282:
n (CHF 5993 pMDI)=645
n (CHF 1535 pMDI)=637

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1298
Analysis specification	Pre-specified
Analysis type	superiority[92]
P-value	= 0.001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.21

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.34
upper limit	-0.08

Notes:

[92] - Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates.

Statistical analysis title	Adjusted mean difference btw treat groups W 5-12

Statistical analysis description:

Adjusted mean difference between treatment groups during Week 5-12.
CHF 5993 pMDI - CHF 1535 pMDI

The number of subjects in this analysis shown (1298) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1271:
n (CHF 5993 pMDI)=642
n (CHF 1535 pMDI)=629

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1298
Analysis specification	Pre-specified
Analysis type	superiority[93]
P-value	= 0.016
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	-0.04

Notes:

[93] - Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates.

Statistical analysis title	Adjusted mean difference btw treat groups W 13-26

Statistical analysis description:

Adjusted mean difference between treatment groups during Week 13-26.
CHF 5993 pMDI - CHF 1535 pMDI

The number of subjects in this analysis shown (1298) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1237:
n (CHF 5993 pMDI)=627
n (CHF 1535 pMDI)=610

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg

Number of subjects included in analysis	1298
Analysis specification	Pre-specified
Analysis type	superiority[94]
P-value	= 0.029
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	-0.02

Notes:

[94] - Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates.

Statistical analysis title	Adjusted mean difference btw treat groups W 27-40

Statistical analysis description:

Adjusted mean difference between treatment groups during Week 27-40.
CHF 5993 pMDI - CHF 1535 pMDI

The number of subjects in this analysis shown (1298) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1173:
n (CHF 5993 pMDI)=601
n (CHF 1535 pMDI)=572

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1298
Analysis specification	Pre-specified
Analysis type	superiority[95]
P-value	= 0.225
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	0.07

Notes:

[95] - Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates.

Statistical analysis title	Adjusted mean difference btw treat groups W 41-52

Statistical analysis description:

Adjusted mean difference between treatment groups during Week 41-52.
CHF 5993 pMDI - CHF 1535 pMDI

The number of subjects in this analysis shown (1298) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1130:

n (CHF 5993 pMDI)=578
n (CHF 1535 pMDI)=552

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1298
Analysis specification	Pre-specified
Analysis type	superiority[96]
P-value	= 0.262
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.08

Notes:

[96] - Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates.

Statistical analysis title	Adjusted mean difference btw treat groups W 1-52

Statistical analysis description:

Adjusted mean difference between treatment groups during Week 1-52.
CHF 5993 pMDI - CHF 1535 pMDI

The number of subjects in this analysis shown (1298) is due to an innate error within the EudraCT database. The correct number of participating subjects is shown below.

The total number of subjects with available data in this analysis is 1290:
n (CHF 5993 pMDI)=650
n (CHF 1535 pMDI)=640

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1298
Analysis specification	Pre-specified
Analysis type	superiority[97]
P-value	= 0.062
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	0.01

Notes:

[97] - Analysis is based on a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates.

Secondary: 18_Moderate and severe COPD exacerbation rate over 52 weeks of treatment

End point title	18_Moderate and severe COPD exacerbation rate over 52 weeks of treatment

End point description:

Rate of moderate or severe COPD exacerbation.

Evaluate the rate of moderate or severe COPD exacerbation over 52 weeks of treatment.
Data are presented as Adjusted Exacerbation Rate per Patient per Year (95% CI).

Shown are the number of subjects included in the model and the number of subjects with available results.

COPD=Chronic obstructive pulmonary disease

End point type	Secondary

End point timeframe:

Baseline to Week 52 (entire treatment period).

End point values	Treatment A - fixed combination CHF 5993 100/6/12.5µg	Treatment B - fixed combination CHF 1535 100/6µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	687[98]	680[99]		
Units: exacerbation/patient/year				
number (confidence interval 95%)	0.41 (0.358 to 0.469)	0.53 (0.468 to 0.6)		

Notes:

[98] - ITT population

[99] - ITT population

Statistical analyses

Statistical analysis title	Adjusted rate ratio for mod and sev exacerbations

Statistical analysis description:

Adjusted rate ratio for moderate and severe exacerbations.
CHF 5993 pMDI / CHF 1535 pMDI

Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1367
Analysis specification	Pre-specified
Analysis type	superiority[100]
P-value	= 0.005
Method	Negative binomial model
Parameter estimate	Adjusted Rate Ratio
Point estimate	0.773
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.647
upper limit	0.924

Notes:

[100] - Analysis is based on a negative binomial model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at Screening as fixed effects, and log-time on study as an offset.

Secondary: 19_Time to first moderate or severe COPD exacerbation

End point title	19_Time to first moderate or severe COPD exacerbation

End point description:

Time to first moderate or severe COPD exacerbation.

Shown are the number of subjects included in the model and the number of subjects with available results.

COPD=Chronic obstructive pulmonary disease

End point type	Secondary

End point timeframe:

Baseline to Week 52 (entire treatment period).

End point values	Treatment A - fixed combination CHF 5993 100/6/12.5µg	Treatment B - fixed combination CHF 1535 100/6µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	678[101]	680[102]		
Units: Subjects, at least 1 mod or sev exacerbt	214	240		

Notes:

[101] - ITT population

[102] - ITT population

Statistical analyses

Statistical analysis title	Time to first moderate or severe COPD exacerbation
Comparison groups	Treatment A - fixed combination CHF 5993 100/6/12.5µg v Treatment B - fixed combination CHF 1535 100/6µg
Number of subjects included in analysis	1358
Analysis specification	Pre-specified
Analysis type	superiority[103]
P-value	= 0.02
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.803
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.668
upper limit	0.967

Notes:

[103] - Analysis is based on a Cox proportional hazards model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at Screening as factors.

CHF 5993 pMDI / CHF 1535 pMDI

Secondary: 20_Vital signs: Systolic blood pressure

End point title	20_Vital signs: Systolic blood pressure

End point description:

Systolic Blood Pressure.

Results represent changes from baseline (Week 0, pre-dose), on Week 26 and Week 52 (pre-dose and 10-minute post-dose).

Shown are the number of subjects included in the safety population and the number of subjects with available results.

End point type	Secondary

End point timeframe:

Baseline to Week 4, 12, 26, 40, 52 (data shown are for Week 26 and Week 52).

End point values	Treatment A - fixed combination CHF 5993 100/6/12.5µg	Treatment B - fixed combination CHF 1535 100/6µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	687[104]	680[105]		
Units: mmHg				
arithmetic mean (confidence interval 95%)				
Week 0, 10 min post-dose	-0.8 (-1.4 to -0.3)	-0.7 (-1.2 to -0.1)		
Week 26, pre-dose	0.3 (-0.6 to 1.2)	-0.5 (-1.4 to 0.4)		
Week 26, 10 min post-dose	-1 (-1.9 to -0.1)	-1.9 (-2.8 to -1.1)		
Week 52, pre-dose	-0.2 (-1.2 to 0.7)	-1.3 (-2.3 to -0.2)		
Week 52, 10 min post-dose	-1.2 (-2.2 to -0.3)	-2 (-3 to -1)		

Notes:

[104] - Safety pop
W 0 post n=683
W 26 pre n=643
W 26 post n=633
W 52 pre n=608
W 52 post n=603

[105] - Safety pop
W 0 post n=679
W 26 pre n=619
W 26 post n=612
W 52 pre n=579
W 52 post n=576

Statistical analyses

No statistical analyses for this end point

Secondary: 21_Vital signs: Diastolic blood pressure

End point title	21_Vital signs: Diastolic blood pressure

End point description:

Diastolic Blood Pressure.

Results represent changes from baseline (Week 0, pre-dose), on Week 26 and Week 52 (pre-dose and 10-minute post-dose).

Shown are the number of subjects included in the safety population and the number of subjects with available results.

End point type	Secondary

End point timeframe:

Baseline to Week 4, 12, 26, 40, 52 (data shown are for Week 26 and Week 52).

End point values	Treatment A - fixed combination CHF 5993 100/6/12.5µg	Treatment B - fixed combination CHF 1535 100/6µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	687[106]	680[107]		
Units: mmHg				
arithmetic mean (confidence interval 95%)				
Week 0, 10 min post-dose	-0.5 (-0.9 to 0)	-0.3 (-0.7 to 0.1)		
Week 26, pre-dose	-0.3 (-1 to 0.4)	0.4 (-0.2 to 1)		
Week 26, 10 min post-dose	-1 (-1.6 to -0.3)	-0.5 (-1.2 to 0.1)		
Week 52, pre-dose	-0.5 (-1.2 to 0.2)	-0.1 (-0.7 to 0.6)		
Week 52, 10 min post-dose	-1.4 (-2.1 to -0.7)	-0.6 (-1.2 to 0.1)		

Notes:

[106] - Safety pop
W 0 post n=683
W 26 pre n=643
W 26 post n=633
W 52 pre n=608
W 52 post n=603

[107] - Safety pop
W 0 post n=679
W 26 pre n=619
W 26 post n=612
W 52 pre n=579
W 52 post n=576

Statistical analyses

No statistical analyses for this end point

Secondary: 22_Vital signs: Body mass index

End point title	22_Vital signs: Body mass index

End point description:

Body Mass Index.

Results represent changes from baseline (Week 0), on Week 26 and Week 52.

Shown are the number of subjects included in the safety population and the number of subjects with available results.

End point type	Secondary

End point timeframe:

Baseline to Week 4, 12, 26, 40, 52 (data shown are for Week 26 and Week 52).

End point values	Treatment A - fixed combination CHF 5993 100/6/12.5µg	Treatment B - fixed combination CHF 1535 100/6µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	687[108]	680[109]		
Units: kg/m2				
arithmetic mean (confidence interval 95%)				
Week 26	0.17 (0.09 to 0.25)	-0.02 (-0.09 to 0.06)		
Week 52	0.12 (0 to 0.23)	-0.05 (-0.15 to 0.05)		

Notes:

[108] - Safety population
Wk 26 n=643
Wk 52 n=608
[109] - Safety population
Wk 26 n=620
Wk 52 n=579

Statistical analyses

No statistical analyses for this end point

Secondary: 23_Electrocardiogram parameters: Heart rate

End point title	23_Electrocardiogram parameters: Heart rate

End point description:

Heart Rate.

Results represent changes from baseline (Week 0, pre-dose), on Week 26 and Week 52 (pre-dose and 10-minute post-dose).

Shown are the number of subjects included in the safety population and the number of subjects with available results.

End point type	Secondary

End point timeframe:

Baseline to Week 4, 12, 26, 40, 52 (data shown are for Week 26 and Week 52).

End point values	Treatment A - fixed combination CHF 5993 100/6/12.5µg	Treatment B - fixed combination CHF 1535 100/6µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	687[110]	680[111]		
Units: bpm				
arithmetic mean (standard deviation)				
Week 0, 10 min post-dose	-2.68 (± 5.71)	-3.03 (± 5.43)		

Week 26, pre-dose	-0.28 (± 10.56)	-0.24 (± 11.52)		
Week 26, 10 min post-dose	-2.01 (± 10.92)	-1.99 (± 11.42)		
Week 52, pre-dose	0.56 (± 11.05)	0.56 (± 11.22)		
Week 52, 10 min post-dose	-0.71 (± 10.93)	-0.66 (± 11.63)		

Notes:

[110] - Safety pop
W 0 post n=658
W 26 pre n=618
W 26 post n=611
W 52 pre n=588
W 52 post n=583

[111] - Safety pop
W 0 post n=656
W 26 pre n=597
W 26 post n=592
W 52 pre n=557
W 52 post n=554

Statistical analyses

No statistical analyses for this end point

Secondary: 24_Electrocardiogram parameters: QTcF interval

End point title	24_Electrocardiogram parameters: QTcF interval

End point description:

QTcF (Fridericia's Corrected QT Interval).

Results represent changes from baseline (Week 0, pre-dose), on Week 26 and Week 52 (pre-dose and 10-minute post-dose).

Shown are the number of subjects included in the safety population and the number of subjects with available results.

End point type	Secondary

End point timeframe:

Baseline to Week 4, 12, 26, 40, 52 (data shown are for Week 26 and Week 52).

End point values	Treatment A - fixed combination CHF 5993 100/6/12.5µg	Treatment B - fixed combination CHF 1535 100/6µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	687[112]	680[113]		
Units: msec				
arithmetic mean (standard deviation)				
Week 0, 10 min post-dose	-0.55 (± 10.68)	-0.27 (± 11.11)		
Week 26, pre-dose	0.38 (± 14.08)	0.76 (± 15.76)		
Week 26, 10 min post-dose	-0.09 (± 14.41)	-0.38 (± 15.97)		
Week 52, pre-dose	-0.08 (± 14.43)	-0.96 (± 16.31)		
Week 52, 10 min post-dose	0.07 (± 14.26)	-1.1 (± 16.36)		

Notes:

[112] - Safety pop
W 0 post n=657
W 26 pre n=618
W 26 post n=611
W 52 pre n=589
W 52 post n=583

[113] - Safety pop
W 0 post n=656
W 26 pre n=597
W 26 post n=592
W 52 pre n=557
W 52 post n=554

Statistical analyses

No statistical analyses for this end point

Secondary: 25_Electrocardiogram parameters: PR interval

End point title	25_Electrocardiogram parameters: PR interval

End point description:

PR Interval.

Results represent changes from baseline (Week 0, pre-dose), on Week 26 and Week 52 (pre-dose and 10-minute post-dose).

Shown are the number of subjects included in the safety population and the number of subjects with available results.

End point type	Secondary

End point timeframe:

Baseline to Week 4, 12, 26, 40, 52 (data shown are for Week 26 and Week 52).

End point values	Treatment A - fixed combination CHF 5993 100/6/12.5µg	Treatment B - fixed combination CHF 1535 100/6µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	687[114]	680[115]		
Units: msec				
arithmetic mean (standard deviation)				
Week 0, 10 min post-dose	-0.65 (± 8.1)	-0.67 (± 7.74)		
Week 26, pre-dose	-1.14 (± 12.82)	-0.23 (± 11.18)		
Week 26, 10 min post-dose	-1.17 (± 12.49)	-0.98 (± 11.08)		
Week 52, pre-dose	-0.35 (± 12.68)	-1.52 (± 12.89)		
Week 52, 10 min post-dose	-1.28 (± 13.31)	-2.08 (± 12.22)		

Notes:

[114] - Safety pop
W 0 post n=658
W 26 pre n=618
W 26 post n=611
W 52 pre n=589
W 52 post n=583

[115] - Safety pop
W 0 post n=656
W 26 pre n=597
W 26 post n=592
W 52 pre n=557
W 52 post n=554

Statistical analyses

No statistical analyses for this end point

Secondary: 26_Electrocardiogram parameters: QRS interval

End point title	26_Electrocardiogram parameters: QRS interval

End point description:

QRS interval.

Results represent changes from baseline (Week 0, pre-dose), on Week 26 and Week 52 (pre-dose and 10-minute post-dose).

Shown are the number of subjects included in the safety population and the number of subjects with available results.

End point type	Secondary

End point timeframe:

Baseline to Week 4, 12, 26, 40, 52 (data shown are for Week 26 and Week 52).

End point values	Treatment A - fixed combination CHF 5993 100/6/12.5µg	Treatment B - fixed combination CHF 1535 100/6µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	687[116]	680[117]		
Units: msec				
arithmetic mean (standard deviation)				
Week 0, 10 min post-dose	0.1 (± 4.72)	0.38 (± 4.57)		
Week 26, pre-dose	-0.71 (± 6.91)	-0.17 (± 6.46)		
Week 26, 10 min post-dose	-0.19 (± 6.74)	-0.39 (± 6.71)		
Week 52, pre-dose	-0.58 (± 7.76)	-0.33 (± 7.69)		
Week 52, 10 min post-dose	-0.24 (± 7.48)	-0.06 (± 7.67)		

Notes:

[116] - Safety pop
W 0 post n=658
W 26 pre n=618
W 26 post n=611
W 52 pre n=589
W 52 post n=583

[117] - Safety pop
W 0 post n=656
W 26 pre n=597
W 26 post n=592
W 52 pre n=557
W 52 post n=554

Statistical analyses

No statistical analyses for this end point

Secondary: 27_Holter electrocardiogram parameter: 24-h Average heart rate

End point title	27_Holter electrocardiogram parameter: 24-h Average heart rate

End point description:

Holter electrocardiogram parameter: 24-h Average heart rate values.

Results represent change from baseline (Week 0, pre-dose), to Week 26 and Week 52.

Shown are the number of subjects included in the safety population and the number of subjects with available results.

End point type	Secondary

End point timeframe:

Baseline, Week 26, Week 52.

End point values	Treatment A - fixed combination CHF 5993 100/6/12.5µg	Treatment B - fixed combination CHF 1535 100/6µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67[118]	71[119]		
Units: bmp				
arithmetic mean (standard deviation)				
Week 26	0.3 (± 7.27)	-0.68 (± 10.77)		
Week 52	0.45 (± 6.87)	-0.3 (± 9.09)		

Notes:

[118] - Holter subset population
Wk 26 n=60
Wk 52 n=58
[119] - Holter subset population
Wk 26 n=62
Wk 52 n=56

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from the time of patient informed consent signature to study completion or discontinuation.

Adverse event reporting additional description:

Data represent treatment-emergent adverse events (i.e. events that occurred after the first randomised study drug intake).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Treatment A - fixed combination CHF 5993 100/6 /12.5µg
Reporting group description: -	
Reporting group title	Treatment B - fixed combination CHF 1535 100/6µg

Reporting group description: -

Serious adverse events	Treatment A - fixed combination CHF 5993 100/6 /12.5µg	Treatment B - fixed combination CHF 1535 100/6µg	
Total subjects affected by serious adverse events			
subjects affected / exposed	106 / 687 (15.43%)	123 / 680 (18.09%)	
number of deaths (all causes)	15	16	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	0 / 687 (0.00%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			

subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal tract adenoma			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal cancer stage III			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	0 / 687 (0.00%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung cancer metastatic			
subjects affected / exposed	1 / 687 (0.15%)	2 / 680 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung neoplasm			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	3 / 687 (0.44%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm of conjunctiva			
subjects affected / exposed	0 / 687 (0.00%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic gastric cancer			

subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pancreatic carcinoma metastatic			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer metastatic			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 687 (0.00%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic thrombosis			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral artery aneurysm			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leriche syndrome			
subjects affected / exposed	0 / 687 (0.00%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stenosis			

subjects affected / exposed	0 / 687 (0.00%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	1 / 687 (0.15%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Device malfunction			
subjects affected / exposed	0 / 687 (0.00%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 687 (0.00%)	2 / 680 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			

subjects affected / exposed	1 / 687 (0.15%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	66 / 687 (9.61%)	75 / 680 (11.03%)	
occurrences causally related to treatment / all	0 / 87	0 / 86	
deaths causally related to treatment / all	0 / 2	0 / 4	
Chronic respiratory failure			
subjects affected / exposed	0 / 687 (0.00%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung cyst			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 687 (0.00%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 687 (0.29%)	2 / 680 (0.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Respiratory failure			
subjects affected / exposed	1 / 687 (0.15%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Vocal cord leukoplakia			

subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Alcohol abuse			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 687 (0.00%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 687 (0.00%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hip fracture			
subjects affected / exposed	0 / 687 (0.00%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 687 (0.00%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Multiple fractures			
subjects affected / exposed	0 / 687 (0.00%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple injuries			
subjects affected / exposed	0 / 687 (0.00%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax traumatic			
subjects affected / exposed	0 / 687 (0.00%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Poisoning			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural fistula			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	0 / 687 (0.00%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 687 (0.00%)	3 / 680 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 687 (0.15%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 687 (0.00%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	3 / 687 (0.44%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 687 (0.15%)	2 / 680 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Cardiac failure			
subjects affected / exposed	4 / 687 (0.58%)	3 / 680 (0.44%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 2	
Cardiac failure acute			
subjects affected / exposed	0 / 687 (0.00%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			

subjects affected / exposed	0 / 687 (0.00%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	2 / 687 (0.29%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cor pulmonale			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 687 (0.15%)	3 / 680 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Myocardial ischaemia			
subjects affected / exposed	0 / 687 (0.00%)	4 / 680 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sick sinus syndrome			
subjects affected / exposed	0 / 687 (0.00%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachyarrhythmia			
subjects affected / exposed	0 / 687 (0.00%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles			

subjects affected / exposed	0 / 687 (0.00%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	0 / 687 (0.00%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular disorder			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 687 (0.00%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 687 (0.00%)	2 / 680 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			

subjects affected / exposed	0 / 687 (0.00%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebrobasilar insufficiency			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Haemorrhagic disorder			
subjects affected / exposed	0 / 687 (0.00%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Idiopathic thrombocytopenic purpura			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness neurosensory			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 687 (0.00%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			

subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	0 / 687 (0.00%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food poisoning			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer perforation			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 687 (0.00%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic erosive gastritis			
subjects affected / exposed	0 / 687 (0.00%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernial eventration			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			

subjects affected / exposed	1 / 687 (0.15%)	2 / 680 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	2 / 687 (0.29%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	2 / 687 (0.29%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 687 (0.00%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary colic			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decubitus ulcer			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	0 / 687 (0.00%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Urinary retention			
subjects affected / exposed	0 / 687 (0.00%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 687 (0.00%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis			
subjects affected / exposed	0 / 687 (0.00%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	0 / 687 (0.00%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis C			
subjects affected / exposed	0 / 687 (0.00%)	1 / 680 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			

subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	14 / 687 (2.04%)	6 / 680 (0.88%)	
occurrences causally related to treatment / all	0 / 16	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Abnormal loss of weight			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cachexia			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	1 / 687 (0.15%)	0 / 680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Treatment A - fixed combination CHF 5993 100/6 /12.5µg	Treatment B - fixed combination CHF 1535 100/6µg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	330 / 687 (48.03%)	341 / 680 (50.15%)	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			

subjects affected / exposed	159 / 687 (23.14%)	184 / 680 (27.06%)	
occurrences (all)	212	274	
Nasopharyngitis			
subjects affected / exposed	39 / 687 (5.68%)	38 / 680 (5.59%)	
occurrences (all)	50	45	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

None.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27598678