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2. SYNOPSIS

Name of Company: **Chiesi Farmaceutici S.p.A.**	**Individual Study Table Referring to Part of the Dossier**	*(for National Authority Use only)*
Name of Finished Product: CHF 5993 pMDI	**Volume:**	
Name of Active Ingredient: Beclometasone dipropionate plus formoterol fumarate plus glycopyrronium bromide (triple combination)	**Page:**	

Title of Study:	Open-label, randomized, 3-way cross-over, placebo-controlled, single dose clinical pharmacology study in COPD patients after inhalation of CHF 5993 pMDI using the standard actuator with or without AeroChamber Plus® Flow-Vu VHC spacer (TRIPLE 4)
Investigator:	Prof. [redacted]
Study Centre:	[redacted] Poland
Publication (reference): Not applicable	

Studied Period: FPFV: 31 March 2014 LPLV: 23 February 2015	**Phase of Development:** I

Objectives:

Primary objective:

- To investigate the effect of the spacing device on the pharmacokinetics of the CHF 5993 pressurised Metered Dose Inhaler (pMDI) active ingredients, by comparing the systemic exposure (area under the plasma concentration-time curve from time 0 to the last quantifiable concentration [AUC_{0-t}] and maximum concentration [C_{max}]) of beclometasone 17-monopropionate (B17MP), formoterol and glycopyrronium bromide (GB) after a single dose of the fixed combination CHF 5993 pMDI administered using the standard actuator plus AeroChamber Plus® Flow-Vu antistatic VHC spacer (test) or the standard actuator alone (reference).

Secondary objectives:

- To compare the systemic exposure of beclometasone dipropionate (BDP) and the other pharmacokinetic (PK) parameters of BDP, B17MP, formoterol and GB after a single dose of the fixed combination CHF 5993 pMDI administered using the standard actuator plus AeroChamber Plus® Flow-Vu antistatic VHC spacer or the standard actuator alone.

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- To evaluate the systemic effects and the general safety and tolerability of the study treatments based on evaluation of adverse events (AEs), vital signs, electrocardiograms (ECGs) and clinical laboratory assessments including plasma and urinary cortisol and plasma potassium.

Exploratory objective:

- To explore the potential relationship between the inhalation ability of the patients and the systemic exposure of B17MP, formoterol and GB.

Methodology (Study Design):

In this open-label, randomised, 3-way crossover study, one single dose (4 inhalations) of CHF 5993 pMDI with (Test, treatment T) and without (Reference, treatment R) AeroChamber Plus spacer and placebo (treatment P) was administered in patients with moderate to severe chronic obstructive pulmonary disease (COPD). The pharmacokinetics of the active ingredients were evaluated after active treatments (T and R), while the general safety and tolerability of the drug, including cardiovascular monitoring, plasma potassium and plasma and urine cortisol, were evaluated after all treatments including placebo. Patients' participation involved a total of 4 visits and a follow-up phone call (or a visit, if deemed necessary by the Investigator).

Number of patients (planned and analysed):

In order to obtain 32 evaluable patients, approximately 36 patients were planned to be randomised.

A total of 42 patients were screened. Six patients were not randomised (i.e., screening failures), of whom 4 patients were not eligible to enter the study, 1 patient withdrew consent and 1 patient had an AE (i.e., [redacted]). Thirty-six patients were randomised to one of the 6 treatment sequences (R-T-P, R-P-T, T-P-R, T-R-P, P-R-T, P-T-R) and received study drug, i.e., 6 patients per treatment sequence. Thirty-five (97.2%) randomised and treated patients completed the study. One (2.8%) patient discontinued the study after inhalation of CHF 5993 pMDI placebo in Period 1 due to meeting exclusion criterion 14: Patient [redacted] had a clinically significant cardiovascular condition ([redacted]) which was not reported at screening, but discovered later based on the evaluation by Cardiabase of the pre-dose ECG on Period 1.

Diagnosis and main criteria for inclusion:

Male or female patients, aged between 45 and 70 years (inclusive) and a Body Mass Index (BMI) in the range of 18-35 kg/m^2 (inclusive), with diagnosis of COPD and a post-bronchodilator forced expiratory volume in 1 second (FEV_1) between 30% and 60% (i.e., $30\% \leq FEV_1 < 60\%$) of the predicted normal value and a post-bronchodilator FEV_1/forced vital capacity (FVC) ratio < 0.7 at screening, who are current or past smokers of at least 10 pack/years where one pack-year is equivalent to 20 cigarettes per day for 1 year.

Test product, dose and mode of administration, batch number:

CHF 5993 pMDI (BDP/formoterol fumarate (FF)/GB 100/6/25 µg fixed dose combination): 4 inhalations using AeroChamber Plus® Flow-Vu antistatic VHC spacer (treatment T) giving a total dose of 400 µg of BDP, 24 µg of FF and 100 µg of GB.

CHF 5993: Batch no.: [redacted], recheck date: [redacted]

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Duration of treatment:

This study consisted of three treatment periods (3 days), separated by a 7- to 10-day wash-out period. Total study duration was approximately 6 to 11 weeks, depending on the duration of the screening (7 to 35 days), wash-out (7 to 10 days) and follow-up (14 to 21 days) periods.

Reference therapy, dose and mode of administration, batch number:

CHF 5993 pMDI (BDP/FF/GB 100/6/25 µg fixed dose combination): 4 inhalations using standard actuator (treatment R) giving a total dose of 400 µg of BDP, 24 µg of FF and 100 µg of GB.

CHF 5993: Batch no.: [redacted], recheck date: [redacted]

CHF 5993 placebo: 4 inhalations of CHF 5993 placebo pMDI (treatment P).

CHF 5993 placebo: Batch no.: [redacted], recheck date: [redacted]

Criteria for evaluation:

Pharmacokinetic variables:

Primary variables:

- Plasma B17MP, formoterol and GB AUC_{0-t} and C_{max}.

Secondary variables:

- Plasma B17MP, formoterol and GB $AUC_{0-30min}$ (area under the plasma concentration-time curve from time 0 to 30 min), AUC_{0-24h} (area under the plasma concentration-time curve from time 0 to 24 h) (B17MP and formoterol only), AUC_{0-48h} (area under the plasma concentration-time curve from time 0 to 48 h) (GB only), $AUC_{0-\infty}$ (area under the plasma concentration-time curve extrapolated to infinity), t_{max} (time to C_{max}) and $t_{1/2}$ (terminal elimination half-life).
- Plasma BDP AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max} and $t_{1/2}$.

Pharmacodynamic variables:

- 24-h cortisol plasma profile (C_{min} [minimum concentration], t_{min} [time to C_{min}] and AUC_{0-24h}).
- 24-h cortisol urinary excretion (Ae [amount excreted] and Ae/Ae_{creat} [amount excreted normalised for creatinine excretion]).
- 24-h potassium plasma profile (C_{min}, t_{min} and AUC_{0-24h}).

Safety:

- Adverse events and adverse drug reactions (ADRs).
- Post-dose FEV_1, to assess potential occurrence of paradoxical bronchospasm.
- Vital signs: systolic blood pressure (SBP), diastolic blood pressure (DBP).
- Holter-extracted 12-lead ECG parameters: heart rate (HR), time interval between the Q and T waves corrected for HR with Fridericia formula (QTcF), time interval between the beginning of the Q wave and the termination of the S wave (QRS) and time interval between the onset of the P wave and the beginning of the QRS complex (PR).

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- Peak HR over 2 h post-dose, HR AUC_{0-2h} (area under the observation-time curve from time 0 to 2 h), AUC_{0-4h} (area under the observation-time curve from time 0 to 4 h) and AUC_{0-12h} (area under the observation-time curve from time 0 to 12 h) normalised by time.

Statistical methods:

Pharmacokinetic variables:

- Plasma B17MP, formoterol and GB AUC_{0-t}, C_{max}, $AUC_{0-30min}$, AUC_{0-24h} (for B17MP and formoterol), AUC_{0-48h} (for GB), $AUC_{0-\infty}$ and $t_{1/2}$ and plasma BDP AUC_{0-t}, $AUC_{0-\infty}$, C_{max} and $t_{1/2}$ were log-transformed and analysed using a linear model including treatment, sequence, period and patient within sequence as fixed effects. The ratios of adjusted geometric means between the 2 active treatments (T and R) were calculated with their 90% two-sided confidence intervals (CIs).
- For t_{max}, T and R were compared using the Wilcoxon signed rank test based on untransformed data and the Hodges-Lehmann non-parametric estimate of location shift was provided with its 90% two-sided CI.
- The potential relationship between the inhalation ability of the patients and the systemic exposure of B17MP, formoterol and GB was explored. B17MP, formoterol and GB AUC_{0-t} and C_{max} were compared between:
  - CHF 5993 with spacer and CHF 5993 without spacer separately for good and poor coordinators, using the same linear model defined for the primary PK analysis. The ratios of adjusted geometric means between the 2 active treatments (T and R) were calculated with their 90% two-sided CIs;
  - good coordinators without spacer and poor coordinators with spacer, using a linear model including group (good coordinators without spacer or poor coordinators with spacer) as fixed effect. The ratio of adjusted geometric means between good and poor coordinators was calculated with its 90% two-sided CIs;
  - good coordinators with spacer and poor coordinators with spacer, using a linear model including group (good coordinators with spacer or poor coordinators with spacer) as fixed effect. The ratio of adjusted geometric means between good and poor coordinators was calculated with its 90% two-sided CIs.

Poor and good coordinators were identified based on the values of formoterol $AUC_{0-30min}$ obtained using CHF 5993 without spacer. Patients with $AUC_{0-30min}$ < median $AUC_{0-30min}$ value were classified as poor coordinators, while patients with $AUC_{0-30min} \geq$ median $AUC_{0-30min}$ value were classified as good coordinators (Singh et al. Br J Clin Pharmacol 2011).

Pharmacodynamic variables:

- Plasma cortisol C_{min} and AUC_{0-24h}, cortisol urinary excretion (Ae and Ae/Ae_{creat}) and plasma potassium C_{min} and AUC_{0-24h} were log-transformed and analysed using a linear model including treatment, sequence, period and patient within sequence as fixed effects. The ratios of adjusted geometric means between the treatments (T, R and P) were calculated with their 95% two-sided CIs.
- Plasma cortisol and potassium t_{min} was summarised by treatment using descriptive statistics.

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Safety variables

- The number and percentage of patients experiencing treatment-emergent AEs (TEAEs), ADRs, serious AEs (SAEs), severe AEs, AEs leading to study withdrawal and AEs leading to death were presented by treatment. Adverse events were also summarised by System Organ Class (SOC) and preferred term using the MedDRA (Medical Dictionary for Regulatory Activities) dictionary.
- Mean changes from pre-dose to 30 min point post-dose in FEV_1 were calculated with their 95% CIs by treatment.
- At each time point post-dose, the mean absolute values of vital signs (SBP, DBP) and 12-lead ECG parameters (HR, QTcF, PR and QRS) were calculated with their 95% CIs by treatment.
- At each time point post-dose, the change from pre-dose in vital signs (SBP, DBP) and 12-lead ECG parameters (HR, QTcF, PR and QRS) were analysed using a linear model including treatment, period and patient as fixed effects, and the pre-dose value as a covariate. The adjusted mean changes from pre-dose with each treatment and the adjusted mean differences between treatments were estimated by the model with their 90% CIs (95% CIs for vital signs).
- The number and percentage of patients with a
    - QTcF interval > 450 ms, > 480 ms and > 500 ms for males and > 470 ms and > 500 ms for females.
    - change from pre-dose in QTcF interval > 30 ms and > 60 ms

  at each time point post-dose and at any time point post-dose are presented by treatment.
- Peak HR over 2 h post-dose, HR AUC_{0-2h}, AUC_{0-4h} and AUC_{0-12h} normalised by time were analysed using a linear model including treatment, period and patient as fixed effects, and the baseline HR value as a covariate. The adjusted means with each treatment and the adjusted mean differences between treatments were estimated by the model with their 90% CIs and p-values.

Summary – Results:

Pharmacokinetic Results:

Glycopyrronium Bromide

The pharmacokinetics of GB were studied in plasma up to 48 h post-dose.

Glycopyrronium bromide AUC_{0-t} and C_{max} were higher after inhalation of CHF 5993 pMDI with spacer compared to inhalation without spacer, with point estimates (PE) (90% CI) of the ratio of 144.8% (127.4; 164.6%) and 160.4% (131.5; 195.7%), respectively. Glycopyrronium bromide $AUC_{0-30min}$ and AUC_{0-48h} were also higher after inhalation of CHF 5993 pMDI with spacer compared to inhalation without spacer. The PEs (90% CI) of the ratios were 160.0% (133.9; 191.1%) and 144.8% (127.4; 164.5%) for $AUC_{0-30min}$ and AUC_{0-48h}, respectively.

Median t_{max} was not different when comparing inhalation of CHF 5993 pMDI with spacer to inhalation of CHF 5993 pMDI without spacer as indicated by the median difference (PE of location shift) (0 hour).

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The exploratory analysis clearly suggests that the increase in lung and total exposure of GB when using the spacer was mainly observed in patients with poor coordination. Indeed, in patients with poor coordination, plasma C_{max}, $AUC_{0\text{-}30min}$ and $AUC_{0\text{-}t}$ increased by 138%, 122% and 66%, respectively, while in patients with good coordination, the increase was relevant only for plasma $AUC_{0\text{-}t}$, but to a lesser extent (27%). The exploratory analysis also suggests that, in patients with poor and with good coordination, a similar lung and total exposure of GB was achieved when using the spacer.

Glycopyrronium Bromide PK Parameters

PK Parameter (Unit)	CHF 5993 pMDI Spacer N = 34	CHF 5993 pMDI N = 35
C_{max} (pg/mL)	121 ± 69.5[a]	80.2 ± 45.5
$AUC_{0\text{-}t}$ (h.pg/mL)	475 ± 243[a]	319 ± 110
$AUC_{0\text{-}30min}$ (h.pg/mL)	41.7 ± 23.1[a]	27.4 ± 13.4
$AUC_{0\text{-}48h}$ (h.pg/mL)	475 ± 243[a]	319 ± 110
$AUC_{0\text{-}\infty}$ (h.pg/mL)	587 ± 203[b]	506 ± 62.5[b]
t_{max} (h)	0.08 (0.08; 1.00)[a]	0.08 (0.08; 2.00)
$t_{1/2}$ (h)	19.1 ± 5.76[c]	17.2 ± 3.66[d]

N = number of subjects
Values are arithmetic mean ± SD except for t_{max}: median and (min; max)
[a] n = 33; [b] n = 10; [c] n = 13; [d] n = 11

Statistical Analysis on Glycopyrronium Bromide PK Parameters

PK Parameter (Unit)	Treatment T (CHF 5993 pMDI Spacer) Versus Treatment R (CHF 5993 pMDI) Ratio PE (90% CI)[a]
$AUC_{0\text{-}t}$ (h.pg/mL)[b]	144.8 (127.4; 164.6)
C_{max} (pg/mL)[b]	160.4 (131.5; 195.7)
$AUC_{0\text{-}30min}$ (h.pg/mL)[b]	160.0 (133.9; 191.1)
$AUC_{0\text{-}48h}$ (h.pg/mL)[b]	144.8 (127.4; 164.5)
t_{max} (h)[b]	0.00 (0.00; 0.05)
$t_{1/2}$ (h)[c]	154.1 (95.5; 248.8)

PE: point estimate
[a] Point estimate and 90% CI of the ratios of adjusted geometric means (ANOVA) for C_{max}, AUCs and $t_{1/2}$. For t_{max}, the Hodges-Lehman non-parametric estimate of location shift between treatments T and R based on untransformed data is provided with its 90% CI. Only the patients providing data for both the treatments T and R were considered in the estimation of the models.
[b] n = 33 for both treatments
[c] n = 7 for both treatments

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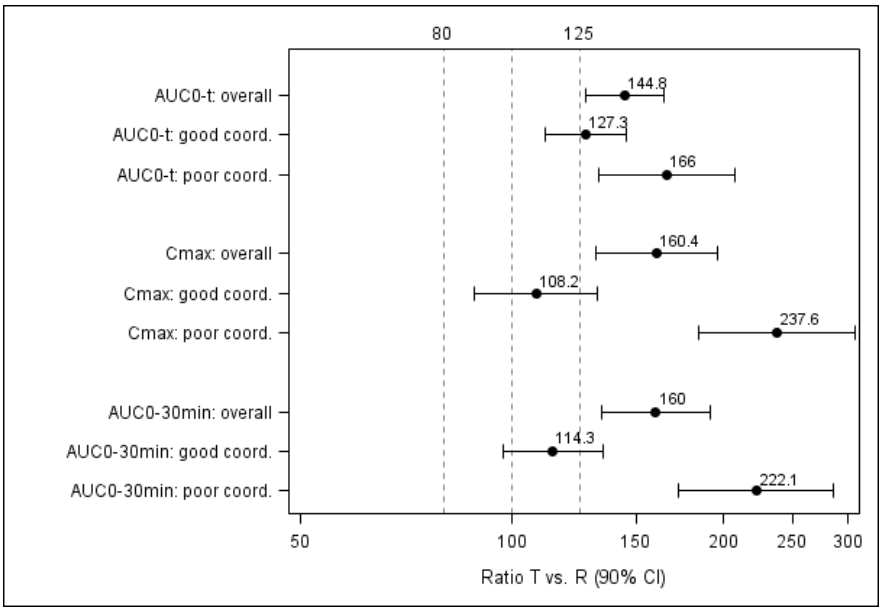
Forest Plot of the Test vs Reference Ratios for GB Parameters (Overall and Stratified by Inhalation Ability)



Formoterol

The pharmacokinetics of formoterol were studied in plasma up to 24 h post-dose.

Formoterol C_{max} and $AUC_{0\text{-}30min}$ were higher after inhalation of CHF 5993 pMDI with spacer compared to inhalation without spacer, with PEs (90% CI) of the ratios of 157.5% (132.9; 186.7%) and 153.1% (126.6; 185.1%), respectively.

Formoterol $AUC_{0\text{-}t}$ and $AUC_{0\text{-}24h}$ were lower after inhalation of CHF 5993 pMDI with spacer compared to inhalation without spacer. The PEs (90% CI) of the ratios were 76.4% (65.4; 89.2%) and 77.7% (67.0; 90.1%) for $AUC_{0\text{-}t}$ and $AUC_{0\text{-}24h}$, respectively.

Median t_{max} was not different when comparing inhalation of CHF 5993 pMDI with spacer to inhalation of CHF 5993 pMDI without spacer as indicated by the median difference (PE [90% CI] of location shift) of -0.05 hours (-0.17; 0.00).

The exploratory analysis clearly suggests that the increase in lung exposure of formoterol when using the spacer was mainly observed in patients with poor coordination. Indeed, in patients with poor coordination, plasma C_{max} and $AUC_{0\text{-}30min}$ increased by 126% and 140%, respectively, while no relevant increase in these parameters was observed in patients with good coordination. Total exposure of formoterol (plasma $AUC_{0\text{-}t}$) was decreased (by 38%) in patients with good coordination when using the spacer, while no change in this parameter was observed in patients with poor coordination.

The exploratory analysis also suggests that, in patients with poor and with good coordination, a similar lung and total exposure of formoterol was achieved when using the spacer.

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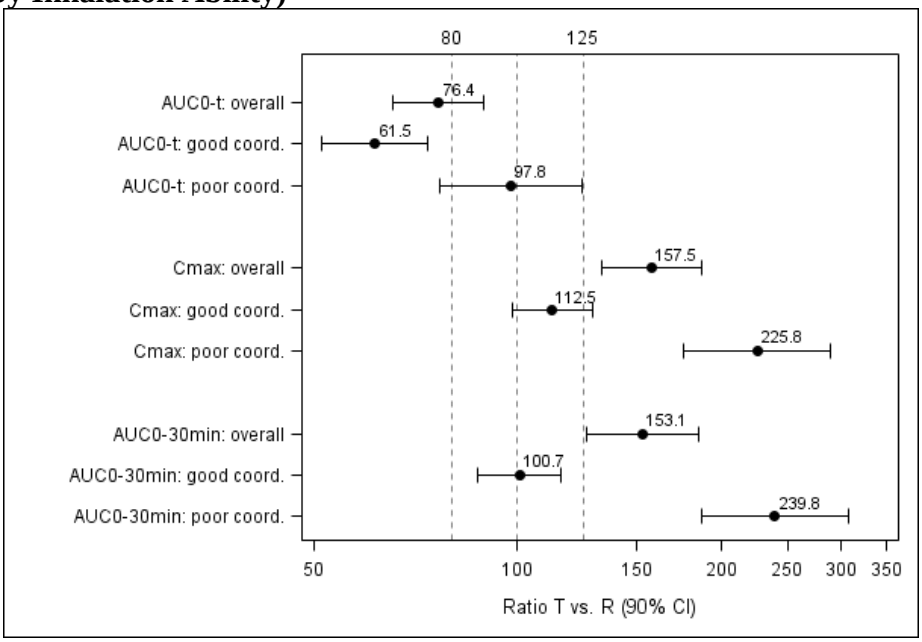
Formoterol PK Parameters		
PK Parameter (Unit)	**CHF 5993 pMDI Spacer N = 34**	**CHF 5993 pMDI N = 35**
C_{max} (pg/mL)	42.3 ± 18.1	27.1 ± 12.7[c]
AUC_{0-t} (h.pg/mL)	78.3 ± 45.5	95.2 ± 40.4[c]
$AUC_{0-30min}$ (h.pg/mL)	13.9 ± 6.11	9.48 ± 4.56[c]
AUC_{0-24h} (h.pg/mL)	90.5 ± 51.5	108 ± 41.2[c]
$AUC_{0-\infty}$ (h.pg/mL)	150 ± 67.5[a]	121 ± 39.8[d]
t_{max} (h)	0.08 (0.08; 0.25)	0.17 (0.08; 2.00)[c]
$t_{1/2}$ (h)	6.33 ± 2.97[b]	5.44 ± 2.63[e]

N = number of subjects
Values are arithmetic mean ± SD except for t_{max}: median and (min; max)
[a] n = 6; [b] n = 25; [c] n = 34; [d] n = 21; [e] n = 27

Statistical Analysis on Formoterol PK Parameters	
	Treatment T (CHF 5993 pMDI Spacer) Versus Treatment R (CHF 5993 pMDI)
PK Parameter (Unit)	**Ratio PE (90% CI)[a]**
AUC_{0-t} (h.pg/mL)[b]	76.4 (65.4; 89.2)
C_{max} (pg/mL)[b]	157.5 (132.9; 186.7)
$AUC_{0-30min}$ (h.pg/mL)[b]	153.1 (126.6; 185.1)
AUC_{0-24h} (h.pg/mL)[b]	77.7 (67.0; 90.1)
t_{max} (h)[b]	-0.05 (-0.17; 0.00)
$t_{1/2}$ (h)[c]	118.4 (100.2; 140.0)

PE: point estimate
[a] Point estimate and 90% CI of the ratios of adjusted geometric means (ANOVA) for C_{max}, AUCs and $t_{1/2}$. For t_{max}, the Hodges-Lehman non-parametric estimate of location shift between treatments T and R based on untransformed data is provided with its 90% CI. Only the patients providing data for both the treatments T and R were considered in the estimation of the models.
[b] n = 34 for both treatments
[c] n = 20 for both treatments

Forest Plot of the Test vs Reference Ratios for Formoterol Parameters (Overall and Stratified by Inhalation Ability)



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BDP

The pharmacokinetics of BDP were studied in plasma up to 24 h post-dose.

BDP AUC_{0-t} and C_{max} were higher after inhalation of CHF 5993 pMDI with spacer compared to inhalation without spacer, with PEs (90% CI) of the ratios of 304.4% (228.0; 406.5%) and 314.0% (236.3; 417.3%), respectively.

Median t_{max} was similar when comparing inhalation of CHF 5993 pMDI with spacer to inhalation of CHF 5993 pMDI without spacer as indicated by the median difference (PE of location shift) (0 hour).

BDP PK Parameters

PK Parameter (Unit)	CHF 5993 pMDI Spacer N = 34	CHF 5993 pMDI N = 35
C_{max} (pg/mL)	2778 ± 1677	1008 ± 823
AUC_{0-t} (h.pg/mL)	377 ± 235	150 ± 130
$AUC_{0-\infty}$ (h.pg/mL)	386 ± 175[a]	230 ± 128[b]
t_{max} (h)	0.08 (0.08; 0.08)	0.08 (0.08; 0.25)
$t_{1/2}$ (h)	0.216 ± 0.0844[a]	0.149 ± 0.0605[b]

N = number of subjects
Values are arithmetic mean ± SD except for t_{max}: median and (min; max)
[a] n = 21; [b] n = 17

Statistical Analysis on BDP PK Parameters

PK Parameter (Unit)	Treatment T (CHF 5993 pMDI Spacer) Versus Treatment R (CHF 5993 pMDI) Ratio PE (90% CI)[a]
AUC_{0-t} (h.pg/mL)[b]	304.4 (228.0; 406.5)
C_{max} (pg/mL)[b]	314.0 (236.3; 417.3)
t_{max} (h)[b]	0.00 (0.00; 0.00)
$t_{1/2}$ (h)[c]	117.5 (98.2; 140.5)

PE: point estimate
[a] Point estimate and 90% CI of the ratios of adjusted geometric means (ANOVA) for C_{max}, AUCs and $t_{1/2}$. For t_{max}, the Hodges-Lehman non-parametric estimate of location shift between treatments T and R based on untransformed data is provided with its 90% CI. Only the patients providing data for both the treatments T and R were considered in the estimation of the models.
[b] n = 34 for both treatments
[c] n = 9 for both treatments

B17MP

The pharmacokinetics of B17MP were studied in plasma up to 24 h post-dose.

B17MP C_{max} and $AUC_{0-30min}$ were higher after inhalation of CHF 5993 pMDI with spacer compared to inhalation without spacer, with PEs (90% CI) of the ratios of 114.8% (101.4; 130.0%) and 120.6% (102.9; 141.3%), respectively.

B17MP AUC_{0-t}, AUC_{0-24h} and $AUC_{0-\infty}$ were lower after inhalation of CHF 5993 pMDI with spacer compared to inhalation without spacer. The PEs (90% CI) of the ratios were 63.4% (58.1; 69.1%), 64.2% (58.8; 70.0%) and 63.7% (58.5; 69.5%) for AUC_{0-t}, AUC_{0-24h} and $AUC_{0-\infty}$, respectively.

Median t_{max} was shorter when comparing inhalation of CHF 5993 pMDI with spacer to inhalation of CHF 5993 pMDI without spacer as indicated by the p-value < 0.001 and the median difference (PE of location shift) -0.42 hours.

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The exploratory analysis clearly suggests that the increase in lung exposure of B17MP when using the spacer was mainly observed in patients with poor coordination. Indeed, in patients with poor coordination, plasma C_{max} and $AUC_{0\text{-}30min}$ increased by 44% and 66%, respectively, while no increase in these parameters was observed in patients with good coordination. Total exposure of B17MP (plasma $AUC_{0\text{-}t}$) was decreased when using the spacer in both the patients with good coordination (decrease of 42%) and poor coordination (decrease of 30%). The exploratory analysis also suggests that, in patients with poor and with good coordination, a similar lung and total exposure of B17MP was achieved when using the spacer.

B17MP PK parameters

PK Parameter (Unit)	CHF 5993 pMDI Spacer N = 34	CHF 5993 pMDI N = 35
C_{max} (pg/mL)	1195 ± 556	1033 ± 442
$AUC_{0\text{-}t}$ (h.pg/mL)	2640 ± 1101	4055 ± 1432
$AUC_{0\text{-}30min}$ (h.pg/mL)	437 ± 165	386 ± 193
$AUC_{0\text{-}24h}$ (h.pg/mL)	2842 ± 1117	4312 ± 1473
$AUC_{0\text{-}\infty}$ (h.pg/mL)	2857 ± 1160[a]	4349 ± 1498
t_{max} (h)	0.16 (0.08; 0.50)	0.50 (0.08; 2.00)
$t_{1/2}$ (h)	4.07 ± 1.35	4.25 ± 1.58

N = number of subjects
Values are arithmetic mean ± SD except for t_{max}: median and (min; max)
[a] n = 33

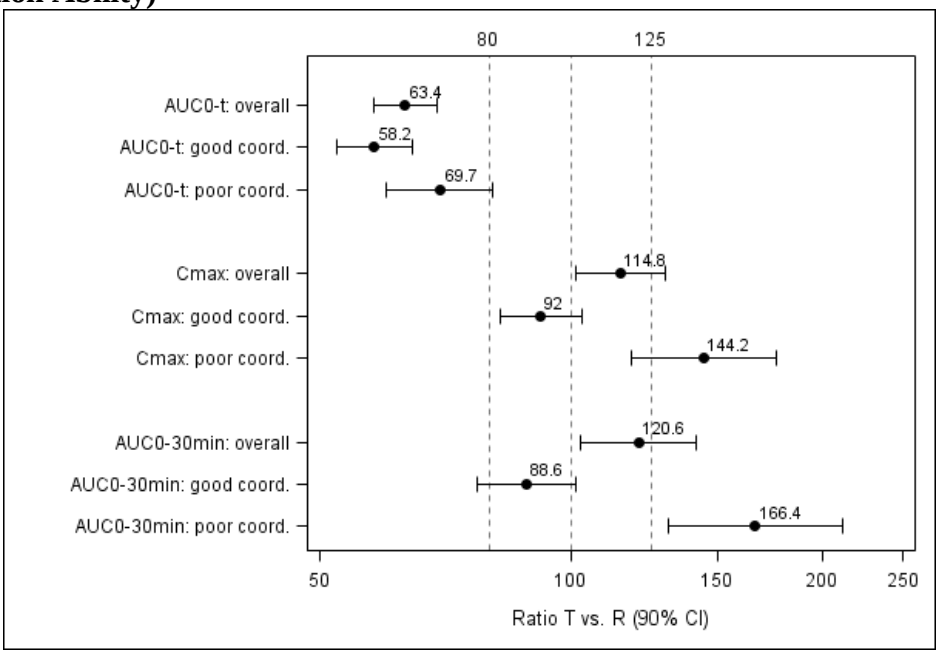
Statistical Analysis on B17MP PK Parameters

PK Parameter (Unit)	Treatment T (CHF 5993 pMDI Spacer) Versus Treatment R (CHF 5993 pMDI) Ratio PE (90% CI)[a]
$AUC_{0\text{-}t}$ (h.pg/mL)[b]	63.4 (58.1; 69.1)
C_{max} (pg/mL)[b]	114.8 (101.4; 130.0)
$AUC_{0\text{-}30min}$ (h.pg/mL)[b]	120.6 (102.9; 141.3)
$AUC_{0\text{-}24h}$ (h.pg/mL)[b]	64.2 (58.8; 70.0)
$AUC_{0\text{-}\infty}$ (h.pg/mL)[c]	63.7 (58.5; 69.5)
t_{max} (h)[b]	-0.42 (-0.51; -0.25)
$t_{1/2}$ (h)[b]	95.6 (90.2; 101.3)

PE: point estimate
[a] Point estimate and 90% CI of the ratios of adjusted geometric means (ANOVA) for C_{max}, AUCs and $t_{1/2}$. For t_{max}, the Hodges-Lehman non-parametric estimate of location shift between treatments T and R based on untransformed data is provided with its 90% CI. Only the patients providing data for both the treatments T and R were considered in the estimation of the models.
[b] n = 34 for both treatments
[c] n = 33 for both treatments

SYNOPSIS

Forest Plot of the Test vs Reference Ratios for B17MP Parameters (Overall and Stratified by Inhalation Ability)



Pharmacodynamic Results:

Average plasma potassium profiles were similar following inhalation of CHF 5993 pMDI with or without spacer with a slight decrease up to 4 h. When compared to the placebo treatment, a very slight decrease in plasma potassium C_{min} and AUC_{0-24h} was observed with both active treatments (decrease of 2% and 1% with CHF 5993 pMDI with spacer, and of 4% and 3% with CHF 5993 pMDI without spacer, respectively).

The average plasma cortisol profiles following inhalation of CHF 5993 pMDI with or without spacer showed a decrease in plasma cortisol concentration when compared to the placebo treatment; this difference lasted until approximately 12-16 h after treatment inhalation. Plasma cortisol C_{min} and AUC_{0-24h} were both decreased by 18% compared to placebo when CHF 5993 pMDI was inhaled with spacer. After inhalation without spacer, the decrease in C_{min} and AUC_{0-24h} compared to placebo treatment was of 33% and 20%, respectively.

When evaluated over 24 h after inhalation (AUC_{0-24h}), plasma cortisol profiles were similar after inhalation of CHF 5993 pMDI with or without spacer. However, the minimum plasma cortisol concentration reached (C_{min}) was significantly higher (22%) for inhalation with spacer.

The urinary excretion of cortisol (Ae and Ae/Ae_{creat}) was similar following inhalation of CHF 5993 pMDI with or without spacer but a slight decrease of about 20% was observed after inhalation of both treatments compared to placebo.

SYNOPSIS

Safety Results:

Treatment-Emergent Adverse Events (TEAEs)	CHF 5993 pMDI Spacer N = 35		CHF 5993 pMDI N = 35		Placebo N = 36		All treatments N = 36	
	n (%)	E	n (%)	E	n (%)	E	n (%)	E
At least one TEAE	1 (2.9)	2	3 (8.6)	3	0	0	3 (8.3)	5
Treatment-related TEAE	1 (2.9)	1	2 (5.7)	2	0	0	2 (5.6)	3
Serious TEAE	0	0	0	0	0	0	0	0
Serious treatment-related TEAE	0	0	0	0	0	0	0	0
Severe TEAE	0	0	0	0	0	0	0	0
TEAE for which the study drug was permanently discontinued	0	0	0	0	0	0	0	0
TEAE with a fatal outcome	0	0	0	0	0	0	0	0
TEAEs by Preferred Term								
Tachycardia	1 (2.9)	1	1 (2.9)	1	0	0	1 (2.8)	2
Headache	1 (2.9)	1	1 (2.9)	1	0	0	2 (5.6)	2
Dyspnoea	0	0	1 (2.9)	1	0	0	1 (2.8)	1

N = number of patients in the Safety population; n = number of patients with event; E = number of events

No deaths, other SAEs or TEAEs leading to discontinuation of the study drug occurred during the study.

Overall, among the 35 patients exposed to CHF 5993, 3 (8.6%) experienced at least one TEAE. Treatment-emergent AEs were observed in 1 (2.9%) and 3 (8.6%) patients after inhalation of CHF 5993 pMDI with and without spacer, respectively, and in none of the patients after inhalation of placebo.

By preferred term, all TEAEs were reported in at most one patient, except for headache in 1 (2.9%) and 1 (2.9%) patient after inhalation of CHF 5993 pMDI with and without spacer, respectively.

All TEAEs were moderate in intensity.

Treatment-emergent AEs were considered to be treatment-related by the Investigator in 2 (5.6%) of the 36 patients: tachycardia in 1 (2.9%) patient after inhalation of CHF 5993 pMDI both with and without spacer (same patient) and headache in 1 (2.9%) patient after inhalation of CHF 5993 pMDI without spacer.

There were no statistically significant differences at any time point for DBP and at most time points for SBP when comparing test (CHF 5993 pMDI with spacer) with reference (CHF 5993 pMDI without spacer) and test with placebo.

There were no statistically significant differences for HR when comparing test vs reference. When comparing test with placebo, statistically significant differences in HR were found at several time points, with a maximum adjusted mean difference of 5.5 bpm (90% CI: 2.0; 9.0) at 4 h post-dose.

When comparing adjusted mean differences in QTcF after inhalation of test with reference and test with placebo, there were no statistical significantly differences between the two treatments at any time point, except at the 24 h post-dose time for test vs reference (adjusted mean difference of -4.1 ms, 90% CI: -7.2; -1.0) and the 15 min post-dose time point for test vs placebo (4.0 ms, 90% CI: 1.2; 6.8).

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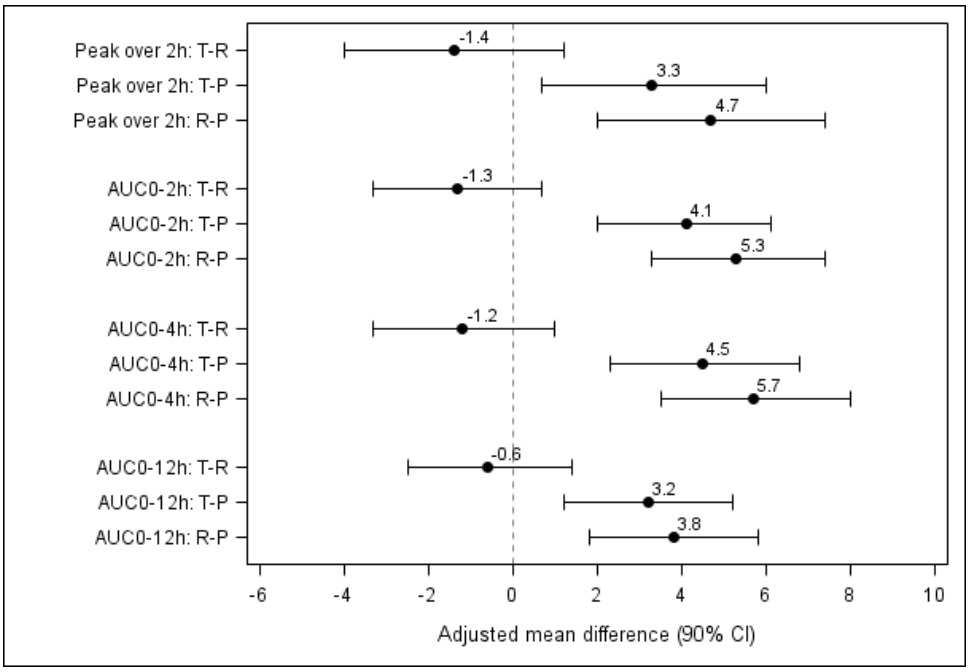
There was no significant difference in peak HR over 2 h post-dose, HR AUC_{0-2h}, HR AUC_{0-4h} and HR AUC_{0-12h} for test (CHF 5993 pMDI with spacer) vs reference (CHF 5993 pMDI without spacer). All these parameters were statistically significantly higher after active treatments (CHF 5993 pMDI with and without spacer) compared with placebo, with the largest adjusted mean differences observed on HR AUC_{0-4h}: 4.5 bpm for CHF 5993 pMDI with spacer and 5.7 bpm for CHF 5993 pMDI without spacer.

Forest Plot of the Adjusted Mean Differences in HR-Derived Parameters (Test vs Reference, Test vs Placebo and Reference vs Placebo)



No post-dose QTcF values of > 480 ms (males) or > 470 ms (females) were reported. None of the patients had an increase of > 60 ms from baseline in QTcF. In one male patient, a QTcF value > 450 ms with a concomitant increase in QcTF from baseline of > 30 ms, was reported after inhalation of placebo. An increase in QTcF from baseline of > 30 ms was reported in one female patient after inhalation of placebo.

In the analysis of selected abnormalities from ECG, 1 (2.9%) patient was reported with complete [redacted] at baseline and after inhalation of all three treatments. Sinus tachycardia (HR > 130 bpm) was reported in 1 (2.9%) patient after inhalation of CHF 5993 with spacer, in 2 (5.7%) patients after inhalation of CHF 5993 without spacer and in none of the patients after inhalation of placebo.

None of the abnormalities in laboratory parameters, vital signs, or ECG were considered to be clinically relevant and were reported as AE, except for two episodes of tachycardia reported by the same patient after inhalation of CHF 5993 pMDI both with and without spacer.

There was no decrease in FEV_1 from baseline (i.e., pre-dose) to 30 min post-dose after inhalation of CHF 5993 pMDI with and without spacer and placebo.

In conclusion, administration of CHF 5993 with or without spacer showed a good and similar safety profile independently of the observed systemic exposure in the three treatment periods.

SYNOPSIS

Conclusion:

Inhalation of CHF 5993 pMDI with spacer resulted in:

- an increase of the lung exposure (60% for C_{max} and $AUC_{0-30min}$) and total exposure (45% for AUC_{0-t}) of GB, reflecting the higher lung deposition due to the spacer, and the limited contribution of GB oral absorption to the total exposure.
- an increase of the lung exposure (C_{max} and $AUC_{0-30min}$) of formoterol (both overall of around 55%) and B17MP (both overall of around 20%), reflecting the higher lung deposition, and in a decrease in their total exposure (AUC_{0-t}), of 24% and 37%, respectively. Formoterol and B17MP oral absorption, which is not negligible, is prevented by the use of the spacer and is able to counterbalance the increased lung absorption.

The exploratory analysis clearly suggests that the increase of total exposure of GB when using the spacer was mainly observed in patients with poor coordination. In patients with both good or poor coordination, formoterol and B17MP total exposure was reduced by the use of the spacer.

Moreover, the exploratory analysis also suggests that, in patients with poor and with good coordination, a similar lung and total exposure of GB, formoterol and B17MP was achieved when using the spacer.

When compared to the placebo treatment, the average plasma potassium profiles of the treatment CHF 5993 pMDI with or without spacer showed no clinically relevant differences.

As expected, considering the BDP administered dose (400 µg), the average plasma cortisol profiles following inhalation of CHF 5993 pMDI with or without spacer showed a decrease in plasma cortisol concentration when compared to the placebo treatment. This is also evidenced by the decrease in plasma cortisol C_{min} and AUC_{0-24h} observed with CHF 5993 pMDI with or without spacer compared to placebo. A significant difference between active treatments for C_{min} was observed, with a lower suppression after CHF 5993 pMDI with spacer, reflecting the reduced systemic exposure of B17MP with this treatment. The differences between treatments in plasma cortisol concentrations lasted until approximately 12-16 h after treatment inhalation.

Similar HR and QTcF profiles were observed when comparing the inhalation of CHF 5993 pMDI with or without spacer, indicating that the increased lung and total exposure of GB (C_{max}, $AUC_{0-30min}$, AUC_{0-t}) and the increased lung exposure of formoterol (C_{max}, $AUC_{0-30min}$) due to the spacer, had no impact on cardiovascular parameters.

The assessment of AEs, vital signs, and lung function did not reveal any safety issue in this study. The study treatments showed good and similar safety profiles of CHF 5993 pMDI with and without the use of a spacer device and in comparison with placebo.

Of note, the effect of the spacer on B17MP and formoterol PK observed in this study is in line with the data of AeroChamber Plus® spacer approved for use with Foster® pMDI (Singh et al. Br J Clin Pharmacol 2011). The magnitude of the GB PK changes and the safety results provided in the present study, further confirmed by the historical safety data of the product, support the safe use of the spacer with CHF 5993 pMDI. No issues are expected in terms of efficacy since the lung deposition is increased for all CHF 5993 pMDI components using the spacer.

Date of report: 6 October 2015