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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	**Volume:**	
Name of Active Ingredient: Beclometasone dipropionate plus formoterol fumarate plus glycopyrronium bromide	**Page:**	

Title of Study:	Open-label, randomized, single-dose, 2-sequence, 2-period cross-over study to investigate the effect of inhibition of the organic cation transport in the kidneys by Cimetidine on the pharmacokinetics of CHF 5993 pMDI in healthy volunteers (TRIPLE 12)
Investigators:	[redacted], MD
Study Centre:	[redacted] (Belgium)
Publication (reference): Not applicable.	

Studied Period: FPFV: 14 May 2014 LPLV: 18 July 2014	**Phase of development:** I

Objectives:

Primary objective:

- To evaluate the pharmacokinetic interaction when CHF 5993 pressurised metered dose inhaler (pMDI) is administered with Cimetidine (probe inhibitor of the organic cation transport in the kidneys), by comparing the area under the plasma concentration-time curve from time 0 to the last quantifiable concentration (AUC_{0-t}) of glycopyrronium bromide (GB), after a single dose of the fixed combination CHF 5993 pMDI administered alone or at steady-state of Cimetidine.

Secondary objectives:

- To compare the systemic exposure of beclometasone dipropionate (BDP), beclometasone 17-monopropionate (B17MP), formoterol fumarate (FF), CHF 6006 (acidic metabolite arising from ester hydrolysis of GB) and the other pharmacokinetic parameters of GB after a single dose of the fixed combination CHF 5993 pMDI administered alone or at steady-state of Cimetidine.

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- To compare the urinary excretion of GB and formoterol after a single dose of the fixed combination CHF 5993 pMDI administered alone or at steady-state of Cimetidine.
- To assess the safety and tolerability of study treatments based on evaluation of vital signs, electrocardiograms (ECGs) and clinical laboratory assessments.

Methodology (Study Design):

Twenty-six subjects were planned to be randomised to receive the test treatment (T: repeated doses of oral Cimetidine for 6 days plus a single inhaled dose of CHF 5993 pMDI [BDP/FF/GB fixed dose combination] on the fourth day [Day 1]) and the reference treatment (R: single inhaled dose of CHF 5993 pMDI) according to a 2-sequence, 2-period, 2-way cross-over design.

A screening visit to assess subject eligibility was performed within minimum 3 and maximum 21 days before randomisation, a 10- to 14-day wash-out period was allowed between the two treatment periods and a follow-up phone call was performed 7 to 10 days after the last dose or after premature study drug discontinuation.

Number of patients (planned and analyzed):

Approximately 26 subjects were to be randomised in order to have 22 evaluable subjects by the end of the study. To ensure a balanced recruitment of males and females, at least 12 subjects of each gender were to be randomized in order to obtain at least 10 evaluable subjects.

A total of 43 subjects were screened. Seventeen subjects were not randomised (i.e., screening failures), of whom 11 subjects were not eligible to enter the study, 3 subjects withdrew consent and 3 subjects were reserve subjects. Twenty-six subjects were randomised to one of the 2 treatment sequences (T-R and R-T), i.e., 13 subjects per treatment sequence. One [redacted] subject [redacted] withdrew consent before receiving CHF 5993 but after having received Cimetidine for 3 days. Only 25 subjects received CHF 5993 in each treatment period (Safety population consisted of 25 subjects). All 25 (100%) randomised and treated subjects completed the study. Twenty-five subjects were analysed as part of the Safety population and 25 subjects were analysed as part of the PK population.

Diagnosis and main criteria for inclusion:

Healthy male and female subjects aged 18-65 years (inclusive), with normal lung function, normal ECG, and vital sign parameters at screening and on Day -1 of treatment period 1.

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

Cimetidine 800 mg (2 tablets of Cimetidine 400 mg) twice daily for 6 days. On the fourth day, in addition, 4 inhalations of CHF 5993 pMDI (BDP/FF/GB 100/6/25 µg per actuation) giving a total dose of 400 µg of BDP, 24 µg of FF and 100 µg of GB.

Cimetidine: Batch no.: [redacted] expiry date: [redacted]

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

Duration of treatment:

Two treatment periods, separated by a 10- to 14-day wash-out period.

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

Four (4) consecutive inhalations of CHF 5993 pMDI (BDP/FF/GB 100/6/25 µg per actuation) 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]

Criteria for evaluation:

Pharmacokinetics:

Primary variable

- GB AUC_{0-t} (area under the plasma concentration-time curve from time 0 to the last quantifiable concentration).

Secondary variables

- Plasma GB C_{max} (maximum plasma concentration), AUC_{0-72h} (area under the plasma concentration-time curve from time 0 to 72 h), $AUC_{0-\infty}$ (area under the plasma concentration-time curve extrapolated to infinity), AUC_{0-12h} (area under the plasma concentration-time curve from time 0 to 12 h), t_{max} (time to C_{max}), CL/F (apparent systemic clearance), $t_{½}$ (terminal elimination half-life);
- Plasma CHF 6006, B17MP and formoterol AUC_{0-t}, C_{max}, AUC_{0-24h} (area under the plasma concentration-time curve from time 0 to 24 h), AUC_{0-72h} (only for CHF 6006), $AUC_{0-\infty}$, t_{max}, CL/F and $t_{½}$;
- Plasma BDP AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max} and $t_{½}$.
- Urine GB Ae_{0-4h}, Ae_{4-8h}, Ae_{8-12h}, Ae_{0-12h}, Ae_{12-24h}, Ae_{24-36h}, Ae_{36-48h}, Ae_{48-60h}, Ae_{60-72h}, Ae_{0-72h} (amount of drug excreted into the urine in the collection interval), fe (fraction of the dose excreted into urine) and CLr (renal clearance);
- Urine formoterol (free and total) Ae_{0-4h}, Ae_{4-8h}; Ae_{8-12h}, Ae_{12-24h}, Ae_{0-24h}, fe, CLr.

Safety:

- Adverse events (AEs) and adverse drug reactions (ADRs);
- Vital signs: systolic blood pressure (SBP), diastolic blood pressure (DBP);
- 12-lead ECG parameters extracted from Holter recordings: heart rate (HR), time interval between the Q and T waves corrected for HR with Fridericia formula (QTcF), PR and QRS;
- Clinical laboratory parameters.

Statistical methods:

Pharmacokinetic variables

- Plasma GB AUC_{0-t} (primary variable), C_{max}, AUC_{0-72h}, $AUC_{0-\infty}$, $t_{½}$, CL/F (secondary variables) were log-transformed and analysed using a linear model including treatment, sequence, period and subject within sequence as fixed effects. The ratios of adjusted geometric means between treatments T (CHF 5993 with Cimetidine) and R (CHF 5993 alone) were calculated with their 90% two-sided confidence intervals (CIs);

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- Plasma CHF 6006, B17MP and formoterol AUC_{0-t}, C_{max}, AUC_{0-24h}, AUC_{0-72h} (only for CHF 6006), $AUC_{0-\infty}$, CL/F and $t_{½}$ and plasma BDP AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, and $t_{½}$ were analysed as for GB parameters;
- For BDP, B17MP, formoterol, GB and CHF 6006 t_{max}, the Hodges-Lehmann non-parametric estimate of location shift between treatments T and R based on untransformed data was provided with its 90% two-sided CI;
- GB and formoterol (free and total) CLr was log-transformed and analysed using linear model including treatment, sequence, period and subject within sequence as fixed effects. The ratios of adjusted geometric means between treatments T (CHF 5993 with Cimetidine) and R (CHF 5993 alone) were calculated with their 90% two- sided CIs;
- GB Ae_{0-4h}, Ae_{4-8h}, Ae_{8-12h}, Ae_{12-24h}, Ae_{24-36h}, Ae_{36-48h}, Ae_{48-60h}, Ae_{60-72h}, Ae_{0-72h}, and formoterol (free and total) Ae_{0-4h}, Ae_{4-8h}, Ae_{8-12h}, Ae_{12-24h} and Ae_{0-24h} were analysed using descriptive statistics.
- GB and formoterol (free and total) fe was summarised by treatment using descriptive statistics.

Safety variables

- The number of subjects who experienced at least one treatment-emergent adverse reaction (TEAE), drug-related TEAE, serious TEAE, serious related TEAE, TEAE leading to study drug discontinuation, and TEAE leading to death were summarised by treatment. Adverse events were summarised by System Organ Class and Preferred Term using the Medical Dictionary for Regulatory Activities (MedDRA);
- At each time point post-dose the following statistics were calculated by treatment for vital signs (SBP, DBP) and for 12-lead triplicate ECG parameters extracted from Holter recordings (HR, QTcF, PR and QRS):
  - mean absolute value with its 95% CI;
  - mean change from baseline (baseline-adjusted value) with its 90% CI (95% for vital signs);
- Mean time profile plots were presented by treatment for baseline-adjusted values;
- For QTcF, the number and percentage of subjects with a
  - QTcF interval >450 ms, >480 ms and >500 ms for male subjects; QTcF interval >470 ms, >500 ms for female subjects;
  - change from baseline in QTcF interval >30ms and >60 ms

  at each time point post-dose and any time point post-dose were presented by treatment;
- Clinical laboratory parameters were summarised using descriptive statistics; shift tables from screening to End of Study were also presented.

Summary – Conclusions:

Pharmacokinetic Results:

Glycopyrronium bromide

The pharmacokinetics of GB were studied up to 72 h after a single administration of fixed combination CHF 5993 pMDI alone (Treatment R) and at steady-state of Cimetidine (Treatment T). After inhalation of both treatments, GB was rapidly absorbed showing a peak of plasma concentrations at 5 min post-dose (first sampling time point).

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The following conclusions are based on PK parameters calculated by applying *method 2* of BLQ handling (refer to Section 9.8.2.2 "Changes after database lock" for details), setting BLQ values to LLOQ/2 (except for pre-dose BLQ that were set to 0).

Co-administration of CHF 5993 pMDI with Cimetidine resulted in a slight but significant increase in the systemic availability of GB in terms of plasma AUC_{0-t} (T/R PE and 90% CI: 116.48% [107.26; 126.50%]) and C_{max} (T/R PE and 90% CI: 125.91% [100.44; 157.83%]). Plasma exposure for GB was slightly higher in females than in males in both treatments and it was higher after co-administration of CHF 5993 pMDI with Cimetidine in both genders.

Median t_{max} was not statistically significantly different between both treatments (0.08 h for T and R treatments).

The urinary excretion of GB was almost comparable after both treatments. The excretion of GB in urine represented 5-6% of the administered dose, with about 44 and 47% of the total amount excreted within the first 12 h for Treatments T and R, respectively. The increased systemic availability of GB after co-administration of CHF 5993 pMDI with Cimetidine resulted in a slight but significantly lower CLr (T/R PE and 90% CI: 79.76% [70.83; 89.83%]) compared to CHF 5993 pMDI alone.

Glycopyrronium bromide plasma and urine PK parameters (*method 2*)

PK parameter (unit)	Treatment T (Cimetidine + CHF 5993 pMDI)	Treatment R (CHF 5993 pMDI)
Plasma	**N=25**	**N=25**
C_{max} (pg/mL)	63.3 ± 57.0	47.8 ± 40.6
AUC_{0-t} (h.pg/mL)	330 ± 138[a]	272 ± 70.6
AUC_{0-12h} (h.pg/mL)	138 ± 69.6[a]	111 ± 51.0
AUC_{0-72h} (h.pg/mL)	330 ± 138[a]	272 ± 70.6
$AUC_{0-\infty}$ (h.pg/mL)	NC	NC
t_{max} (h)	0.08 (0.08; 4.02)	0.08 (0.05; 2.00)
$t_{1/2}$ (h)	NC	NC
CL/F (mL/min)	5690 ± 1709[a]	6474 ± 1393
Urine	**N=25**	**N=25**
Ae_{0-4h} (µg)	1.51 ± 1.01[b]	1.48 ± 0.770[d]
Ae_{4-8h} (µg)	0.631 ± 0.314[b]	0.678 ± 0.330[d]
Ae_{8-12h} (µg)	0.421 ± 0.262[b]	0.360 ± 0.178[d]
Ae_{12-24h} (µg)	0.982 ± 0.600[b]	0.862 ± 0.345[d]
Ae_{24-36h} (µg)	0.717 ± 0.564[b]	0.619 ± 0.333[d]
Ae_{36-48}h (µg)	0.581 ± 0.371[b]	0.534 ± 0.285[d]
Ae_{48-60h} (µg)	0.538 ± 0.379[b]	0.457 ± 0.276[d]
Ae_{60-72h} (µg)	0.445 ± 0.324[b]	0.368 ± 0.219[d]
Ae_{0-12h} (µg)	2.56 ± 1.41[b]	2.52 ± 1.18[d]
Ae_{0-72}h (µg)	5.83 ± 3.34[b]	5.36 ± 2.34[d]
fe (%)	5.83 ± 3.34[b]	5.36 ± 2.34[d]
CLr (mL/min)	296 ± 196[c]	330 ± 127[d]

N: number of subjects
Values are arithmetic mean (± SD), except for t_{max}: median (min; max)
NC: not calculated
[a] N=24; [b] N=23; [c] N=22; [d] N=21

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Statistical analysis on glycopyrronium bromide plasma and urine PK parameters (*method 2*)

PK parameter (unit)	Treatment T (Cimetidine + CHF 5993 pMDI) versus Treatment R (CHF 5993 pMDI)	
	p-value[a]	**Ratio PE (90% CI)[b]**
C_{max} (pg/mL)[c]	0.0940	125.91 (100.44; 157.83)
AUC_{0-t} (h.pg/mL)[d]	0.0044	116.48 (107.26; 126.50)
AUC_{0-12h} (h.pg/mL)[d]	0.0092	121.22 (107.97; 136.09)
AUC_{0-72h} (h.pg/mL)[d]	0.0043	116.49 (107.27; 126.51)
t_{max} (h)[c]	0.3765	0.00 (0.00; 0.42)
$t_{1/2}$ (h)	NC	NC
CL/F (mL/min)[d]	0.0043	85.84 (79.05; 93.22)
CLr (mL/min)[e]	0.0043	79.76 (70.83; 89.83)

PE: point estimate
[a] Probability of no difference between treatments (ANOVA, non-parametric test for t_{max})
[b] Point estimate and 90% CI of the ratios of adjusted geometric LS means (ANOVA) for C_{max}, AUCs, $t_{1/2}$, CL/F and CLr. For t_{max}, 90% CI calculated by the method of Hodges-Lehmann.
[c] N=25 for both treatments
[d] N=24 for both treatments
[e] N=18 for both treatments
NC: not calculated ($t_{1/2}$ could not be estimated for all subjects in both treatments)

CHF 6006

The pharmacokinetics of CHF 6006 (metabolite of GB) were studied up to 72 h after a single administration of fixed combination CHF 5993 pMDI alone (Treatment R) and at steady-state of Cimetidine (Treatment T). The average plasma CHF 6006 profiles showed a peak at 6 h post-dose following both treatments.

Co-administration of CHF 5993 pMDI with Cimetidine resulted in a significant increase of the systemic availability of CHF 6006 in terms of AUCs and C_{max} (T/R PE and 90% CI: 170.35% [122.24; 237.39%] for AUC_{0-t}, 165.91% [119.46; 230.42%] for AUC_{0-72h} and 158.39% [127.28; 197.11%] for C_{max}).

CHF 6006 plasma PK parameters

PK parameter (unit)	Treatment T (Cimetidine + CHF 5993 pMDI)	Treatment R (CHF 5993 pMDI)
Plasma	**N=25**	**N=25**
C_{max} (pg/mL)	99.7 ± 48.4	68.5 ± 39.9[c]
AUC_{0-t} (h.pg/mL)	880 ± 590	641 ± 463[c]
AUC_{0-72h} (h.pg/mL)	1027 ± 598	761 ± 493[c]
$AUC_{0-\infty}$ (h.pg/mL)	734 ± 237[a]	1287 ± 571[d]
t_{max} (h)	6.00 (4.00; 8.02)	6.00 (4.00; 8.00)[e]
$t_{1/2}$ (h)	18.2 ± 21.4[b]	14.0 ± 18.7[f]

N = number of subjects
Values are arithmetic mean (± SD) except for t_{max}: median and (min; max)
[a] N=6; [b] N=10; [c] N=24; [d] N=3; [e] N=23; [f] N=5

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Statistical analysis on CHF 6006 plasma PK parameters		
PK parameter (unit)	**Treatment T (Cimetidine + CHF 5993 pMDI) versus Treatment R (CHF 5993 pMDI)**	
	p-value[a]	**Ratio PE (90% CI)[b]**
C_{max} (pg/mL)[c]	0.0015	158.39 (127.28; 197.11)
AUC_{0-t} (h.pg/mL)[c]	0.0115	170.35 (122.24; 237.39)
AUC_{0-72h} (h.pg/mL)[c]	0.0147	165.91 (119.46; 230.42)
t_{max} (h)[d]	0.0164	-1.00 (-1.91; 0.00)

PE = point estimate
[a] Probability of no difference between treatments (ANOVA, non-parametric test for t_{max})
[b] Point estimate and 90% CI of the ratios of adjusted geometric LS means (ANOVA) for C_{max}, AUCs, $t_{1/2}$ and CL/F. For t_{max}, 90% CI calculated by the method of Hodges-Lehmann.
[c] N=24 for both treatments
[d] N=23 for both treatments

Formoterol

The pharmacokinetics of formoterol were studied up to 24 h after a single administration of fixed combination CHF 5993 pMDI alone (Treatment R) and at steady-state of Cimetidine (Treatment T). After inhalation of both treatments, formoterol was rapidly absorbed showing a peak of plasma concentrations at 5 min post-dose (first sampling time point).

Co-administration of CHF 5993 pMDI with Cimetidine resulted in a slight but statistically significant increase of total exposure (AUCs) of formoterol (T/R PE and 90% CI: 121.25% [109.08; 134.78%] for AUC_{0-t} and 123.80% [111.39; 137.60%] for AUC_{0-24h}) while C_{max} was similar after both treatments (T/R PE and 90% CI: 107.27% [92.28; 124.68%]).

The urinary excretion of free and total formoterol was similar after the two treatments. The excretion of unchanged formoterol in urine represented approximately 4 to 5% (free formoterol) and 13% (total formoterol) of the administered dose in both treatments, with about 50% (free formoterol) to 60% (total formoterol) of the total amount excreted within the first 4 h. The increased systemic availability of formoterol after co-administration of CHF 5993 pMDI with Cimetidine resulted in a slightly but significantly lower CLr (T/R PE and 90% PE: 74.55% [65.00; 85.49%]) compared to CHF 5993 pMDI alone.

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Formoterol plasma and urinary PK parameters		
PK parameter (unit)	**Treatment T (Cimetidine + CHF 5993 pMDI)**	**Treatment R (CHF 5993 pMDI)**
Plasma	**N=25**	**N=25**
C_{max} (pg/mL)	27.2 ± 14.4[a]	24.2 ± 13.1
AUC_{0-t} (h.pg/mL)	74.3 ± 32.7[a]	60.3 ± 27.5
AUC_{0-24h} (h.pg/mL)	86.1 ± 39.2[a]	68.7 ± 33.2
$AUC_{0-\infty}$ (h.pg/mL)	91.7 ± 34.1[b]	102 ± 23.0 [c]
t_{max} (h)	0.08 (0.08; 2.00)[a]	0.08 (0.05; 2.00)
$t_{1/2}$ (h)	4.48 ± 1.42[a]	3.92 ± 0.950[d]
CL/F (mL/min)	5948 ±3306[a]	7397 ± 3781
Urine (free formoterol)	**N=25**	**N=25**
Ae_{0-4h} (µg)	0.519 ± 0.196	0.624 ± 0.244
Ae_{4-8h} (µg)	0.229 ± 0.0948	0.250 ± 0.115[e]
Ae_{8-12h} (µg)	0.129 ± 0.0457	0.124 ± 0.0543
Ae_{12-24h} (µg)	0.187 ± 0.0761	0.190 ± 0.0662
Ae_{0-24h} (µg)	1.06 ± 0.378	1.27 ± 0.447[e]
fe (%)	4.43 ± 1.58	5.29 ± 1.86[e]
CLr (mL/min)	231 ± 78.5[a]	313 ± 98.2 [e]
Urine (total formoterol)	**N=25**	**N=25**
Ae_{0-4h} (µg)	1.71 ± 0.721	1.79 ± 0.945
Ae_{4-8h} (µg)	0.709 ± 0.394	0.643 ± 0.253[e]
Ae_{8-12h} (µg)	0.275 ± 0.133	0.243 ± 0.108
Ae_{12-24h} (µg)	0.395 ± 0.173	0.360 ± 0.142
Ae_{0-24h} (µg)	3.09 ± 1.25	3.03 ± 1.12[e]
fe (%)	12.9 ± 5.22	12.6 ± 4.67[e]

N = number of subjects
Values are arithmetic mean (± SD) except for t_{max}: median and (min; max)
[a] N=24; [b] N=13;[c] N= 11; [d] N=21; [e] N=18

Statistical analysis on formoterol plasma and urine PK parameters		
PK parameter (unit)	**Treatment T (Cimetidine + CHF 5993 pMDI) versus Treatment R (CHF 5993 pMDI)**	
	p-value[a]	**Ratio PE (90% CI)[b]**
C_{max} (pg/mL)[c]	0.4319	107.27 (92.28; 124.68)
AUC_{0-t} (h.pg/mL)[c]	0.0049	121.25 (109.08; 134.78)
AUC_{0-24h} (h.pg/mL)[c]	0.0022	123.80 (111.39; 137.60)
$AUC_{0-\infty}$ (h.pg/mL)[d]	0.4845	105.78 (90.53; 123.60)
t_{max} (h)[c]	0.7881	0.00 (-0.01; 0.06)
$t_{1/2}$ (h)[e]	0.0144	115.45 (105.28; 126.61)
CL/F (mL/min)[c]	0.0022	80.77 (72.67; 89.78)
CLr (mL/min)[f]	0.0019	74.55 (65.00; 85.49)

PE = point estimate
[a] Probability of no difference between treatments (ANOVA, non-parametric test for t_{max})
[b] Point estimate and 90% CI of the ratios of adjusted geometric LS means (ANOVA) for C_{max}, AUCs, $t_{1/2}$ and CL/F. For t_{max}, 90% CI calculated by the method of Hodges-Lehmann.
[c] N=24 for both treatments
[d] N=6 for both treatments
[e] N=21 for both treatments
[f] N=17 for both treatments

BDP

The pharmacokinetics of BDP and B17MP were studied in plasma up to 24 h after a single administration of fixed combination CHF 5993 pMDI alone (Treatment R) and at steady-state of Cimetidine (Treatment T).

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Plasma BDP concentration reached a maximum 5 min post-dose in both treatments.

No statistically significant difference was found for BDP AUC_{0-t} and C_{max} (T/R PE and 90% CI: 91.53% [74.37; 112.65%] for C_{max} and 95.01% [77.15; 117.00%] for AUC_{0-t}], indication similar systemic availability after both treatments.

BDP plasma PK parameters

PK parameter (unit)	Treatment T (Cimetidine + CHF 5993 pMDI)	Treatment R (CHF 5993 pMDI)
overall	**N=25**	**N=25**
C_{max} (pg/mL)	1020 ± 576	1095 ± 699
AUC_{0-t} (h.pg/mL)	142 ± 93.3	143 ± 91.0
$AUC_{0-\infty}$ (h.pg/mL)	208 ± 97.3[a]	195 ± 92.2[b]
t_{max} (h)	0.08 (0.08; 0.08)	0.08 (0.05; 0.12)
$t_{1/2}$ (h)	0.124 ± 0.0436[a]	0.119 ± 0.0471[b]

N = number of subjects
Values are arithmetic mean (± SD) except for t_{max}: median and (min; max)
[a] N=11; [b] N=15

Statistical analysis on BDP plasma PK parameters

PK parameter (unit)	Treatment T (Cimetidine + CHF 5993 pMDI) versus Treatment R (CHF 5993 pMDI)	
	p-value[a]	**Ratio PE (90% CI)[b]**
C_{max} (pg/mL)[c]	0.4726	91.53 (74.37; 112.65)
AUC_{0-t} (h.pg/mL)[c]	0.6773	95.01 (77.15; 117.00)
$AUC_{0-\infty}$ (h.pg/mL)[d]	0.4410	110.74 (87.08; 140.83)
t_{max} (h)[c]	0.1850	0.00 (0.00; 0.00)
$t_{1/2}$ (h)[d]	0.7489	106.12 (75.20; 149.77)

PE = point estimate
[a] Probability of no difference between treatments (ANOVA, non-parametric test for t_{max})
[b] Point estimate and 90% CI of the ratios of adjusted geometric LS means (ANOVA) for C_{max}, AUCs, $t_{1/2}$.
For t_{max}, 90% CI calculated by the method of Hodges-Lehmann.
[c] N=25 for both treatments
[d] N=8 for both treatments

B17MP

The average plasma B17MP profiles showed a peak at 0.5 h post-dose after both treatments.

No statistically significant difference was found between treatments in terms of B17MP C_{max} (T/R PE and 90% CI: 106.59% [93.93; 120.97%]) and AUCs (T/R PE and 90% CI: 107.85% [99.17; 117.28%] for AUC_{0-t}, 107.26% [98.89; 116.34%] for AUC_{0-24h} and 107.64% [99.36; 116.62%] for $AUC_{0-\infty}$).

Mean $t_{1/2}$ was not significantly different between treatments.

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B17MP plasma PK parameters		
PK parameter (unit)	**Treatment T (Cimetidine + CHF 5993 pMDI)**	**Treatment R (CHF 5993 pMDI)**
Overall	**N=25**	**N=25**
C_{max} (pg/mL)	666 ± 275[a]	614 ± 263
AUC_{0-t} (h.pg/mL)	3181 ± 1131[a]	2869 ± 953
AUC_{0-24h} (h.pg/mL)	3470 ± 1091[a]	3163 ± 961
$AUC_{0-\infty}$ (h.pg/mL)	3537 ± 1105[b]	3177 ± 976
t_{max} (h)	0.51 (0.08; 2.00)[a]	0.50 (0.08; 2.00)
$t_{1/2}$ (h)	4.07 ± 1.02	3.94 ± 0.815

N = number of subjects
Values are arithmetic mean (± SD) except for t_{max}: median and (min; max)
[a] N=24; [b] N=23

Statistical analysis on B17MP plasma PK parameters		
PK parameter (unit)	**Treatment T (Cimetidine + CHF 5993 pMDI) versus Treatment R (CHF 5993 pMDI)**	
	p-value[a]	**Ratio PE (90% CI)[b]**
C_{max} (pg/mL)[c]	0.3955	106.59 (93.93; 120.97)
AUC_{0-t} (h.pg/mL)[c]	0.1362	107.85 (99.17; 117.28)
AUC_{0-24h} (h.pg/mL)[c]	0.1527	107.26 (98.89; 116.34)
$AUC_{0-\infty}$ (h.pg/mL)[d]	0.1286	107.64 (99.36; 116.62)
t_{max} (h)[c]	0.4786	0.02 (-0.24; 0.27)
$t_{1/2}$ (h)[e]	0.5142	102.32 (96.42; 108.59)

PE = point estimate
[a] Probability of no difference between treatments (ANOVA, non-parametric test for t_{max})
[b] Point estimate and 90% CI of the ratios of adjusted geometric LS means (ANOVA) for C_{max}, AUCs, $t_{1/2}$ and CL/F. For t_{max}, 90% CI calculated by the method of Hodges-Lehmann.
[c] N=24 for both treatments
[d] N=23 for both treatments
[e] N=25 for both treatments

Cimetidine

The Cimetidine plasma through concentrations indicated that PK steady-state was already reached on the day of CHF 5993 pMDI administration.

Safety Results:

Treatment-Emergent Adverse Events (TEAEs)	**Cimetidine + CHF 5993 pMDI N=25**		**CHF 5993 pMDI N=25**		**All treatments N=25**	
	n (%)	**E**	**n (%)**	**E**	**n (%)**	**E**
At least one TEAE	8 (32.0)	20	7 (28.0)	9	12 (48.0)	29
Treatment-related TEAE	2 (8.0)	2	1 (4.0)	1	3 (12.0)	3
Serious TEAE	0		0		0	
Serious treatment-related TEAE	0		0		0	
TEAE for which the study drug was permanently discontinued	0		0		0	
TEAE with a fatal outcome	0		0		0	
Most frequently reported TEAEs (in ≥2 subjects during any treatment)						
Headache	4 (16.0)	4	3 (12.0)	3	6 (24.0)	7
Dizziness	4 (16.0)	4	0		4 (16.0)	4
Abdominal pain	3 (12.0)	3	0		3 (12.0)	3
Abdominal discomfort	0		2 (8.0)	2	2 (8.0)	2
Vomiting	0		2 (8.0)	2	2 (8.0)	2

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

SYNOPSIS

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

Treatment-emergent AEs were observed in 8 (32.0%) and 7 (28.0%) subjects after inhalation of CHF 5993 with and without concomitant Cimetidine intake, respectively.

By preferred term, all TEAEs were reported in at most two subjects per treatment, except for headache in 4 (16.0%) and 3 (12.0%) subjects after inhalation of CHF 5993 with and without concomitant Cimetidine intake, respectively, dizziness in 4 (16.0%) subjects after inhalation of CHF 5993 with concomitant Cimetidine intake and in no subjects after inhalation of CHF 5993 without concomitant Cimetidine intake, and abdominal pain in 3 (12.0%) subjects after inhalation of CHF 5993 with concomitant Cimetidine intake and in no subjects after inhalation of CHF 5993 without concomitant Cimetidine intake.

All TEAEs were mild or moderate in intensity.

Treatment-emergent AEs were considered to be treatment-related by the Investigator in 3 (12.0%) subjects: headache in 2 (8.0%) subjects after inhalation of CHF 5993 with concomitant Cimetidine intake and tremor in 1 (4.0%) subject after inhalation of CHF 5993 without concomitant Cimetidine intake.

No QTcF values of >450 ms (for males) or >470 ms (for females) were observed. No increases in QTcF of >60 ms were observed. An increase in QTcF of >30 ms was observed in 1 (4.0%) subject after inhalation of CHF 5993 with concomitant Cimetidine intake at 10 min, 15 min, 30 min and 2 h post-dose.

None of the abnormalities in laboratory parameters, vital signs, ECG or physical examination were considered to be clinically relevant and were reported as AE, except for palpitations in one subject after inhalation of CHF 5993 with concomitant Cimetidine intake.

In conclusion, administration of CHF 5993 with or without concomitant Cimetidine intake showed a good and similar safety profile independently of the observed systemic exposure in the two periods.

Conclusion:

Co-administration of CHF 5993 pMDI with Cimetidine resulted in a slight but significant increase of the total GB exposure (AUC_{0-t}) by 16% and of the maximum concentration (C_{max}) by 26% compared with the administration of CHF 5993 pMDI alone. As expected, time to peak (t_{max}) of GB was not influenced by Cimetidine. The increased systemic exposure of GB resulted in a slight but statistically significant decrease of GB CLr by 20% after co-administration of CHF 5993 pMDI with Cimetidine. CHF 6006 systemic exposure was significantly increased by 58% in terms of C_{max} and by 70% in terms of AUC_{0-t} after co-administration of CHF 5993 pMDI with Cimetidine compared to CHF 5993 pMDI alone, suggesting involvement of OCT2/MATE1 in CHF 6006 disposition.

The total formoterol exposure (AUC_{0-t}) showed a limited but significant 21% increase after co-administration of CHF 5993 pMDI with Cimetidine, while C_{max} as well as t_{max} were not influenced by Cimetidine. Formoterol CLr was slightly but significantly decreased by 25% after co-administration of CHF 5993 pMDI with Cimetidine, reflecting the increased systemic exposure.

SYNOPSIS

Co-administration of Cimetidine with the fixed combination CHF 5993 pMDI had no impact on the disposition of BDP and of its main metabolite B17MP which were similar after inhalation of both treatments.

The Cimetidine plasma through concentrations indicated that PK steady-state was already reached on the day of CHF 5993 pMDI inhalation.

No clinically relevant abnormalities were reported in this study. Despite a higher exposure of GB, CHF 6006 and formoterol when CHF 5993 pMDI was co-administered with Cimetidine, the study treatments showed good and similar safety profiles. Moreover, based on the magnitude of the PK changes observed in this study and on the safety data provided in the present study, further confirmed by the historical safety data of the product, no relevant drug interaction is expected when CHF 5993 pMDI is co-administered with inhibitors of the organic cation transport.

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