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Sharing Clinical Study Report Synopsis

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2. SYNOPSIS

Name of Company: **Chiesi Farmaceutici S.p.A.** **Name of Finished Product:** CHF 1535 DPI **Name of Active Ingredient:** beclomethasone dipropionate plus formoterol fumarate	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	*(for National Authority Use only)*

Title of Study:	A Phase II, monocentre, open, randomized, 6-way cross-over clinical pharmacology study to evaluate the lung bioavailability of BDP/B17MP and formoterol and the total systemic exposure across two different dose strengths of CHF 1535 NEXThaler® DPI (fixed combination of beclomethasone dipropionate plus formoterol fumarate 100/6 µg and 200/6 µg) administered with and without activated charcoal in adult asthmatic patients
Investigator:	Professor [redacted], MD
Study Centre(s):	[redacted] (UK)
Publication (reference): none	
Studied Period: FPFV: 12/NOV/2012 LPLV: 21/JAN/2013 (Last Contact: 29/JAN/2013)	**Phase of development:** II

Objectives:

Primary objectives:

- To evaluate the lung bioavailability of B17MP, active metabolite of BDP, and formoterol as area under the plasma concentration versus time curve observed for time 0 up to 12 h (AUC_{0-t}) across two different dose strengths of CHF 1535 NEXThaler® DPI (100/6 µg, 200/6 µg) with activated charcoal.
- To evaluate the total systemic exposure to B17MP (active metabolite of BDP) and to formoterol as AUC_{0-t} across two different dose strengths of CHF 1535 NEXThaler® DPI (100/6 µg, 200/6 µg) without activated charcoal.

Secondary objectives:

- To evaluate the lung bioavailability and systemic exposure of BDP when CHF 1535 NEXThaler® DPI (100/6 µg, 200/6 µg) is administered with and without activated charcoal.
- To evaluate the systemic effects as glucose, potassium and cortisol levels in plasma when CHF 1535 NEXThaler® DPI (100/6 µg, 200/6 µg) is administered without activated charcoal.
- To evaluate the systemic effects and the general safety and tolerability profile when CHF 1535 NEXThaler® DPI (100/6 µg, 200/6 µg) is administered with and without activated charcoal.

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Methodology *(Study Design):*

According to the study plan, a total of 30 adult asthmatic patients were supposed to receive CHF 1535 NEXThaler® DPI 100/6 µg or 200/6 µg with or without activated charcoal, placebo or fluticasone 1000 µg. A 7 to 14-day wash-out period separated six single dose treatment visits at clinic. Blood samples were collected to evaluate pharmacokinetic (PK) and pharmacodynamic (PD) parameters. Evaluation of general safety and tolerability of the study drug was performed.

According to the randomisation list, in each of the six treatment periods, eligible patients were to receive:

- **Treatment A**: CHF 1535 100/6 NEXThaler® DPI (4 inhalations) at a total dose of BDP 400 µg / formoterol fumarate (FF) 24 µg (reported as 400/24 µg throughout the report)
- **Treatment B**: CHF 1535 200/6 NEXThaler® DPI (4 inhalations) at a total dose of BDP 800 µg / FF 24 µg (reported as 800/24 µg throughout the report)
- **Treatment C**: CHF 1535 NEXThaler® DPI (4 inhalations) placebo
- **Treatment D**: CHF 1535 100/6 NEXThaler® DPI (4 inhalations) at a total dose of BDP 400 µg / FF 24 µg, plus activated charcoal (reported as 400/24 µg +AC throughout the report)
- **Treatment E**: CHF 1535 200/6 NEXThaler® DPI (4 inhalations) at a total dose of BDP 800 µg / FF 24 µg, plus activated charcoal (reported as 800/24 µg + AC throughout the report)
- **Treatment F**: fluticasone propionate (Flixotide Accuhaler): single dose administration of Fluticasone Accuhaler 500 µg (2 inhalations) at a total dose of 1000 µg.

Number of patients *(planned and analysed)*:

Estimating a non-evaluable rate of approximately 30%, a total of 30 patients (5 patients per treatment sequence) were planned to be randomised in order to obtain 20 PK-evaluable patients.

Fourty-four subjects were screened. Fourteen subjects were screening failures, of whom 11 subjects were not eligible to enter the study, two subjects withdrew consent and one subject was not randomised for other reasons. Thirty asthmatic subjects were randomised to one of the six treatment sequences and received study drug, i.e., five subjects per treatment sequence. Twenty-seven (90.0%) randomised and treated subjects completed the study. Three (10.0%) subjects discontinued the study; one subject withdrew consent, one subject discontinued due to an adverse event (AE) (ventricular tachycardia) and one subject discontinued for other reasons (intake of non-permitted medication [i.e., penicillin] for the treatment of AE pharyngytis).

Diagnosis and main criteria for inclusion:

- Male and female adults (≥18 and ≤70 years old) with a body mass index (BMI) ≥18.5 and ≤32 kg/m^2.
- Diagnosis of asthma as defined by the Global Initiative for Asthma (GINA) guidelines, update 2011, for at least 6 months before the screening visit.
- Asthmatic patients already treated with low daily doses of inhaled corticosteroids (ICS) (e.g., Budesonide or equivalent ≤400 µg/day) or low dose of ICS/ long-acting β2-agonists fixed combinations.
- Patients with a pre-bronchodilator forced expiratory volume in 1 s (FEV_1) ≥70% of the predicted values.

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- Non- or ex-smokers who smoked less than 5 pack-years and stopped smoking for at least 1 year. (Pack-year: number of cigarettes smoked per day multiplied by the number of years of smoking/20).

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

CHF1535 via a NEXThaler® DPI:

- Total dose of 400 µg BDP and 24 µg formoterol (Treatment A).
- Total dose of 400 µg BDP and 24 µg formoterol with charcoal block (Treatment D).

CHF 1535: Batch no.: [redacted] recheck date: [redacted].

- Total dose of 800 µg BDP and 24 µg formoterol (Treatment B).
- Total dose of 800 µg BDP and 24 µg formoterol with charcoal block (Treatment E).

CHF 1535: Batch no.:[redacted], recheck date: [redacted].

Duration of treatment:

Six single daily dose treatments separated by a wash-out period of minimum 7 and maximum 14 days.

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

- Placebo via NEXThaler® DPI (Treatment C).
- Flixotide™ Accuhaler™ 500 µg. Total dose of 1000 µg fluticasone propionate (Treatment F).

Placebo: Batch no.: [redacted], expiry date: [redacted] Flixotide™
Accuhaler™: Batch no.: [redacted], expiry date: [redacted]

Pharmacokinetics:

CHF 1535 NEXThaler® DPI *with and without* activated charcoal:

Primary variables:

- B17MP AUC_{0-t}.
- Formoterol AUC_{0-t}.

Secondary variables:

- BDP: AUC_{0-t}, AUC_{0-12h}, $AUC_{0-\infty}$, C_{max}, t_{max} and $t_{½}$.
- B17MP: AUC_{0-12h}, $AUC_{0-\infty}$, C_{max}, t_{max} and $t_{½}$.
- Formoterol: AUC_{0-12h}, AUC_{0-24h}, $AUC_{0-\infty}$, C_{max}, t_{max} and $t_{½}$.

Pharmacodynamics

CHF 1535 NEXThaler® DPI *with and without* activated charcoal:

- Heart rate (HR) AUC_{0-12h}/12h.
- Blood pressure (BP): Supine blood pressure (SBP) AUC_{0-12h}/12h and diastolic blood pressure (DBP): AUC_{0-12h}/12h.

CHF 1535 NEXThaler® DPI *without* activated charcoal and placebo:

- Plasma glucose AUC_{0-4h} ,AUC_{0-12h}, C_{max}, t_{max}.
- Plasma potassium AUC_{0-4h} ,AUC_{0-12h}, C_{min}, t_{min}.

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CHF 1535 NEXThaler® DPI *without* activated charcoal, placebo and fluticasone propionate:

- Plasma cortisol $AUC_{0\text{-}24h}$, C_{min}, t_{min}.

Safety:

- Adverse events, serious AEs (SAEs) and adverse drug reactions (ADRs).
- Plasma cortisol, glucose, and potassium.
- HR, SBP, and DBP.
- QTcB and QTcF.

Statistical methods:

Pharmacokinetic variables:

- $AUC_{0\text{-}t}$, $AUC_{0\text{-}12h}$, $AUC_{0\text{-}24h}$ (for formoterol only), $AUC_{0\text{-}\infty}$, terminal elimination half-life ($t_{1/2}$) and C_{max} 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 treatments were calculated with their 90% confidence intervals (CIs). All variables, with the exception of $t_{1/2}$ and the formoterol ones, were dose-normalised before proceeding with the analysis.
- The two-sided 90% CIs were considered to evaluate the equivalence of the formoterol 24 µg given with the two different doses of BDP. The bioequivalence of the formoterol given with different strengths of ICS could be declared if the CIs were within the 80% - 125% range.
- The dose proportionality of B17MP was evaluated according to the indication of the EMA Guideline on the Investigation of Bioequivalence 2010: if the difference in dose-adjusted mean AUCs of the two strengths was no more than 25%, the dose proportionality was confirmed.
- Plasma B17MP, formoterol and BDP t_{max} were summarised by treatment group using descriptive statistics and non-parametrical analysis was applied.
- Plasma concentration/time curves, individual and based on mean values by treatment, were presented in linear/linear and log/linear scale.

Pharmacodynamic variables

- Heart rate, SBP and DBP $AUC_{0\text{-}12h}$/12h, measured during the administration of CHF 1535 with and without activated charcoal and placebo, were analysed by using an analysis of variance model (treatment, sequence, period and patient within sequence as fixed effects) with 95% CIs for the treatment ratios.
- Plasma glucose and potassium $AUC_{0\text{-}4h}$, $AUC_{0\text{-}12h}$, C_{max} (for glucose) or C_{min} (for potassium), measured during administration of CHF 1535 without activated charcoal and placebo, were log-transformed and analysed using a linear model including treatment, sequence, period and patient within sequence as fixed effects and 95% CIs for the treatment ratios. T_{min} (for potassium) or t_{max} (for glucose) were analysed via a non-parametrical analysis (Wilcoxon signed rank test adapted to cross-over design).
- Cortisol $AUC_{0\text{-}24h}$, C_{min}, measured during administration of CHF 1535 without activated charcoal, placebo and fluticasone propionate, were log-transformed and analysed using a linear model including treatment, sequence, period and patient within sequence as fixed effects and 95% CIs for the treatment ratios. T_{min} was analysed via a non-parametrical analysis (Wilcoxon signed rank test adapted to cross-over design).

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Statistical methods, Cont'd:

Safety variables

- The number and percentage of patients experiencing AEs, ADRs, SAEs and AEs leading to study withdrawal were presented for each treatment. Adverse events were summarised for each treatment by System Organ Class and Preferred Term using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.
- The number and percentage of patients with laboratory values (plasma potassium, plasma glucose plasma cortisol) outside the normal ranges.
- At each time point post-dose the following statistics were calculated by treatment for BP parameters (SBP, DBP) and for Holter parameters (HR, QTcB, QTcF):
  - mean absolute value with its 95% CI;
  - mean pre-dose-adjusted value with its 90% CI (95% CI for BP);
  - mean difference vs. placebo in pre-dose-adjusted value (pre-dose and placebo-adjusted value) with its 90% CI (95% CI for BP).
- Time profile plots were presented for mean pre-dose and placebo-adjusted values by treatment. For HR, QTcB and QTcF time profile plots superimposed on the formoterol plasma concentration/time curves were also presented.
- For QTcF and QTcB, the number and percentage of patients with a QTc interval >450 ms, >480 ms and >500 ms were calculated.
- The change from pre-dose in QTc interval >30 ms and >60 ms at each time point post-dose and at any time point post-dose was presented by treatment.

These analyses were performed both in safety and PK/PD population.

Summary – Conclusions:

Pharmacokinetic Results:

BDP pharmacokinetic results

The pharmacokinetics of BDP was studied in plasma up to 12 h after administration of the treatment. The main BDP plasma PK parameters and the statistical analysis are shown in the tables below.

	CHF 1535 DPI			
PK parameter	**400/24 µg (A) N=29**	**800/24 µg (B) N=26**	**400/24 µg + AC (D) N=27**	**800/24 µg + AC (E) N=29**
C_{max} (pg/mL)	2698 ± 819	3816 ± 1666	2372 ± 693	3402 ± 1155
t_{max} (h)	0.08 (0.07-0.17)	0.08 (0.08-0.25)	0.10 (0.08-0.15)	0.10 (0.08-0.17)
AUC_{0-12h} (pg.h/mL)	695 ± 165	1261 ± 449	704 ± 205 [a]	1356 ± 423 [b]
AUC_{0-t} (pg.h/mL)	673 ± 169	1237 ± 447	686 ± 208 [a]	1338 ± 419 [b]
$AUC_{0-\infty}$ (pg.h/mL)	696 ± 169	1262 ± 447	707 ± 209 [a]	1361 ± 421 [b]
$t_{1/2}$ (h)	0.403 ± 0.207	0.495 ± 0.195	0.459 ± 0.156 [a]	0.545 ± 0.204 [b]

N = number of subjects with data in the PK/PD population
Values are arithmetic means ± SD, except median (range) for t_{max}
[a] N = 26, [b] N = 28

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CHF1535 800/24 µg vs. 400/24 µg (B vs. A), CHF 1535 800/24 µg + AC vs. 400/24 µg + AC (E vs. D)

BDP C_{max} increased less than dose-proportionally throughout the CHF 1535 dose range 400/24 µg to 800/24 µg (without or with charcoal block), as indicated by the 90% CIs of the point estimates for dose-normalised C_{max} (60.56 – 75.86% for B vs. A and 63.11 – 78.74% for E vs. D). AUCs increased proportionally with the dose (without or with charcoal), as indicated by the 90% CIs of the point estimates for dose-normalised AUC_{0-t} (83.16 – 98.46% for B vs. A and 89.09 - 105.61% for E vs. D), AUC_{0-12h} (81.92 – 96.82% for B vs. A and 87.95 – 104.08% for E vs. D) and $AUC_{0-\infty}$ (82.40 – 97.35% for B vs. A and 87.93 – 104.01% for E vs. D).

The terminal elimination half-life ($t_{1/2}$) was longer after inhalation of CHF 1535 800/24 µg than after inhalation of CHF 1535 400/24 µg (with or without charcoal block), as indicated by the 90% CIs of the point estimates for $t_{1/2}$ for the comparison B vs. A (121.02 – 156.33%) and the comparison E vs. D (107.65 - 139.33%).

The rate of absorption (t_{max}) was similar after inhalation of CHF 1535 800/24 µg and 400/24 µg, without or with charcoal block, as indicated by the 90% CIs of the point estimates for t_{max} (0.00 – 0.00 for B vs. A and -0.01 – 0.02 for E vs. D).

CHF 1535 400/24 µg + AC vs. 400/24 µg (D vs. A), CHF 1535 800/24 µg + AC vs. 800/24 µg (E vs. B)

BDP C_{max} and AUCs were similar following administration of CHF 1535 with (D or E) or without charcoal block (A or B, respectively). This is indicated by the 90% CIs of the point estimates for dose-normalised C_{max} (80.67 – 100.65% for D vs. A and 83.73 – 104.89% for E vs. B), AUC_{0-t} (94.46 – 111.71% for B vs. A and 101.04 – 120.01% for E vs. D), AUC_{0-12h} (93.64 - 110.56% for D vs. A and 100.39 – 119.03% for E vs. B) and $AUC_{0-\infty}$ (94.24 – 111.21% for D vs. A and 100.40 – 118.99% for E vs. B).

The terminal elimination half-life ($t_{1/2}$) was slightly longer following administration of CHF 1535 with (D or E) than without charcoal block (A or B, respectively), as indicated by the 90% CIs of the point estimates for $t_{1/2}$ for the comparison D vs. A (109.70 – 141.47%) and the comparison E vs. B (97.35 – 126.37%).

The rate of absorption (t_{max}) was similar following administration of CHF 1535 at the dose level 800/24 µg with or without charcoal block, as indicated by the 90% CI of the point estimates for t_{max} (0.00 – 0.02 for E vs. B). At the dose level 400/24 µg, t_{max} was slightly higher with the charcoal block than without the charcoal block, as indicated by the 90% CI of the point estimates for t_{max} (0.01 – 0.03 for D vs. A).

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PK parameters	CHF 1535 DPI 800/24 µg versus 400/24 µg (B versus A) Ratio PE (90% CI) [a]	CHF 1535 DPI 800/24 µg + AC versus 400/24 µg + AC (E versus D) Ratio PE (90% CI) [a]
C_{max}	67.78 (60.56; 75.86)	70.49 (63.11; 78.74)
t_{max}	0.00 (0.00;0.00)	0.01 (-0.01;0.02)
AUC_{0-t}	90.49 (83.16;98.46)	97.00 (89.09;105.61)
AUC_{0-12h}	89.06 (81.92;96.82)	95.68 (87.95; 104.08)
$AUC_{0-\infty}$	89.57 (82.40;97.35)	95.63 (87.93;104.01)
$t_{1/2}$	137.55 (121.02; 156.33)	122.47 (107.65;139.33)

PK parameters	CHF 1535 DPI 400/24 µg + AC versus 400/24 µg (D versus A) Ratio PE (90% CI) [a]	CHF 1535 DPI 800/24 µg + AC versus 800/24 µg (E versus B) Ratio PE (90% CI) [a]
C_{max}	90.11 (80.67;100.65)	93.72 (83.73;104.89)
t_{max}	0.02 (0.01;0.03)	0.02 (0.00;0.02)
AUC_{0-t}	102.73 (94.46;111.71)	110.11 (101.04;120.01)
AUC_{0-12h}	101.75 (93.64;110.56)	109.31 (100.39; 119.03)
$AUC_{0-\infty}$	102.37 (94.24;111.21)	109.30 (100.40;118.99)
$t_{1/2}$	124.57 (109.70; 141.47)	110.92 (97.35;126.37)

PE = point estimate

[a] Point estimate and 90% CI of the ratios of adjusted geometric means of log-transformed parameters from the linear model. C_{max}, AUC_{0-t}, AUC_{0-12h} and $AUC_{0-\infty}$ were dose-normalised before log-transformation. For t_{max}, comparisons were assessed using a Wilcoxon signed rank test; the Hodges-Lehmann non-parametric estimate of location shifts based on untransformed data was provided with its 90% two-sided CI.

B17MP pharmacokinetic results

The pharmacokinetics of B17MP was studied in plasma up to 12 h after administration of the treatment. The main B17MP plasma PK parameters and the statistical analysis are shown in the tables below.

PK parameters	CHF 1535 DPI 400/24 µg (A) N=29	CHF 1535 DPI 800/24 µg (B) N=26	CHF 1535 DPI 400/24 µg + AC (D) N=27	CHF 1535 DPI 800/24 µg + AC (E) N=29
C_{max} (pg/mL)	656 ± 138	1081 ± 271	635 ± 155	1097 ± 277
t_{max} (h)	0.50 (0.08-1.00)	0.50 (0.15-2.00)	0.50 (0.17-0.77)	0.50 (0.15-1.00)
AUC_{0-12h} (pg.h/mL)	2810 ± 603	4841 ± 1168	2306 ± 571	4081 ± 930
AUC_{0-t} (pg.h/mL)	2812 ± 603	4842 ± 1167	2303 ± 573	4081 ± 929
$AUC_{0-\infty}$ (pg.h/mL)	3086 ± 709	5350 ± 1385	2541 ± 678	4484 ± 1042
$t_{1/2}$ (h)	3.36 ± 0.527	3.42 ± 0.557	3.49 ± 0.609	3.52 ± 0.639

N = number of subjects with data in the PK/PD population

Values are arithmetic means ± SD, except median (range) for t_{max}

CHF 1535 800/24 µg vs. 400/24 µg (B vs. A), CHF 1535 800/24 µg + AC vs. 400/24 µg + AC (E vs. D)

B17MP C_{max} and AUCs increased proportionally with the dose throughout the CHF 1535 dose range 400/24 µg to 800/24 µg (without or with charcoal block), as indicated by the 90% CIs of the point estimates for dose-normalised C_{max} (76.12 – 86.08% for B vs. A and 82.40 – 92.98% for E vs. D), AUC_{0-t} (80.61 – 90.21% for B vs. A and 85.03 – 94.97% for E vs. D), AUC_{0-12h} (80.66 - 90.26% for B vs. A and 84.91 – 94.83% for E vs. D) and $AUC_{0-\infty}$ (81.09 – 90.83% for B vs. A and 84.66 – 94.63% for E vs. D).

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The terminal elimination half-life ($t_{1/2}$) of B17MP was equivalent at both dose levels (without or with charcoal block), as indicated by the 90% CIs of the point estimates for $t_{1/2}$ for the comparison B vs. A (97.05 – 106.07%) and the comparison E vs. D (95.63 – 104.36%).

The rate of absorption (t_{max}) was similar after inhalation of CHF 1535 800/24 µg and 400/24 µg, without or with charcoal block, as indicated by the 90% CIs of the point estimates for t_{max} (0.00 – 0.25 for B vs. A and 0.00 – 0.13 for E vs. D).

CHF 1535 400/24 µg + AC vs. 400/24 µg (D vs. A), CHF 1535 800/24 µg + AC vs. 800/24 µg (E vs. B)

B17MP C_{max} and AUCs were equivalent for CHF 1535 800/24 µg following administration with or without charcoal block. This is indicated by the 90% CIs of the point estimates for dose-normalised C_{max} (97.82 – 110.63%), AUC_{0-t} (81.07 – 90.73%, AUC_{0-12h} (81.06 – 90.70%) and $AUC_{0-\infty}$ (80.66 – 90.35%) for E vs. B.

B17MP C_{max} was equivalent for CHF 1535 400/24 µg following administration with or without charcoal block, while AUCs were slightly lower after administration with charcoal block. This is indicated by the 90% CIs of the point estimates for dose-normalised C_{max} (90.56 – 102.20%), AUC_{0-t} (77.00 – 86.01%), AUC_{0-12h} (77.16 - 86.16%) and $AUC_{0-\infty}$ (77.42 – 86.54%) for D vs. A.

The terminal elimination half-life ($t_{1/2}$) of B17MP was equivalent following administration of CHF 1535 with (D or E) or without charcoal block (A or B, respectively), as indicated by the 90% CIs of the point estimates for $t_{1/2}$ for the comparison D vs. A (99.04 – 108.07%) and the comparison E vs. B (97.44 – 106.49%).

The rate of absorption (t_{max}) of B17MP was similar following administration of CHF 1535 with (D or E) or without charcoal block (A or B, respectively), as indicated by the 90% CIs of the point estimates for t_{max} (-0.08 – 0.13 for D vs. A and -0.08 – 0.00 for E vs. B).

PK parameters	**CHF 1535 DPI 800/24 µg versus 400/24 µg (B versus A)**	**CHF 1535 DPI 800/24 µg + AC versus 400/24 µg + AC (E versus D)**
	Ratio PE (90% CI) [a]	**Ratio PE (90% CI) [a]**
C_{max}	80.95 (76.12; 86.08)	87.53 (82.40;92.98)
t_{max}	0.00 (0.00;0.25)	0.00 (0.00;0.13)
AUC_{0-t}	85.28 (80.61;90.21)	89.86 (85.03;94.97)
AUC_{0-12h}	85.33 (80.66;90.26)	89.73 (84.91;94.83)
$AUC_{0-\infty}$	85.82 (81.09;90.83)	89.51 (84.66;94.63)
$t_{1/2}$	101.46 (97.05;106.07)	99.90 (95.63;104.36)

PK parameters	**CHF 1535 DPI 400/24 µg + AC versus 400/24 µg (D versus A)**	**CHF 1535 DPI 800/24 µg + AC versus 800/24 µg (E versus B)**
	Ratio PE (90% CI) [a]	**Ratio PE (90% CI) [a]**
C_{max}	96.20 (90.56;102.20)	104.03 (97.82;110.63)
t_{max}	0.00 (-0.08;0.13)	0.00 (-0.08;0.00)
AUC_{0-t}	81.38 (77.00;86.01)	85.76 (81.07;90.73)
AUC_{0-12h}	81.53 (77.16;86.16)	85.75 (81.06;90.70)
$AUC_{0-\infty}$	81.85 (77.42;86.54)	85.37 (80.66;90.35)
$t_{1/2}$	103.45 (99.04;108.07)	101.86 (97.44;106.49)

PE = point estimate

[a] Point estimate and 90% CI of the ratios of adjusted geometric means of log-transformed parameters from the linear model. C_{max}, AUC_{0-t}, AUC_{0-12h} and $AUC_{0-\infty}$ were dose-normalised before log-transformation. For t_{max}, comparisons were assessed using a Wilcoxon signed rank test; the Hodges-Lehmann non-parametric estimate of location shifts based on untransformed data was provided with its 90% two-sided CI.

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Formoterol pharmacokinetic results

The pharmacokinetics of formoterol was studied in plasma up to 12 h (with charcoal block) or 24 h (without charcoal block) after administration of the treatment. The main formoterol plasma PK parameters and the statistical analysis are shown in the tables below:

PK parameters	CHF 1535 DPI			
	400/24 µg (A) N=29	800/24 µg (B) N=26	400/24 µg + AC (D) N=27	800/24 µg + AC (E) N=29
C_{max} (pg/mL)	55.8 ± 15.2	44.6 ± 12.0	57.6 ± 19.8	45.7 ± 14.6
t_{max} (h)	0.10 (0.08-0.25)	0.09 (0.08-0.18)	0.13 (0.08-0.17)	0.12 (0.08-0.18)
AUC_{0-12h} (pg.h/mL)	113 ± 25.7	99.0 ± 29.7	89.7 ± 28.7	72.3 ± 25.5
AUC_{0-24h} (pg.h/mL)	129 ± 33.5	113 ± 42.2	NA	NA
AUC_{0-t} (pg.h/mL)	122 ± 33.8	106 ± 41.5	88.2 ± 29.9	69.7 ± 26.4
$AUC_{0-\infty}$ (pg.h/mL)	148 ± 24.7 [a]	139 ± 45.3 [c]	127 ± 25.5 [e]	97.0 ± 16.2 [e]
$t_{1/2}$ (h)	6.34 ± 1.81 [b]	6.31 ± 2.76 [d]	5.53 ± 1.62	5.73 ± 2.22 [b]

N = number of subjects with data in the PK/PD population
NA = not applicable
Values are arithmetic means ± SD, except median (range) for t_{max}
[a] N = 18, [b] N = 28, [c] N = 14, [d] N = 25, [e] N = 10

CHF 1535 800/24 µg vs. 400/24 µg (B vs. A), CHF 1535 800/24 µg + AC vs. 400/24 µg + AC (E vs. D)

Formoterol C_{max} and AUCs were lower after inhalation of CHF 1535 800/24 µg than after inhalation of CHF 1535 400/24 µg (without or with charcoal block), as indicated by the 90% CIs of the point estimates for C_{max} (72.63 - 87.18% for B vs. A and 73.29 – 87.69% for E vs. D), AUC_{0-t} (75.22 – 92.40% for B vs. A and 70.72 – 86.55% for E vs. D), AUC_{0-12h} (78.35 - 94.37% for B vs. A and 73.13 – 87.80% for E vs. D), and AUC_{0-24h} (77.04 – 93.39% for B vs. A).

The terminal elimination half-life ($t_{1/2}$) was similar at both dose levels (with or without charcoal block), as indicated by the 90% CIs of the point estimates for $t_{1/2}$ for the comparison B vs. A (84.99 – 114.74%) and the comparison E vs. D (83.68 – 111.97%).

The rate of absorption (t_{max}) of formoterol was similar after inhalation of CHF 1535 800/24 µg and 400/24 µg, without or with charcoal block, as indicated by the 90% CIs of the point estimates for t_{max} (0.00 - 0.00 for B vs. A and -0.03 – 0.01 for E vs. D).

CHF 1535 400/24 µg + AC vs. 400/24 µg (D vs. A), CHF 1535 800/24 µg + AC vs. 800/24 µg (E vs. B)

Formoterol C_{max} was similar following administration of CHF 1535 with (D or E) or without charcoal block (A or B, respectively), as indicated by the 90% CIs of the point estimates for C_{max} (92.35 – 110.50% for D vs. A and 92.89 – 111.51% for E vs. B). Formoterol AUC_{0-12h} was lowered by the charcoal block, as indicated by the 90% CIs of the point estimate for this parameter (68.60 – 82.36% for D vs. A and 63.82 – 76.88% for E vs. B).

The rate of absorption (t_{max}) was similar following administration of CHF 1535 with (D or E) or without charcoal block (A or B, respectively), as indicated by the 90% CIs of the point estimates for t_{max} (-0.01 – 0.03 for D vs. A and 0.00 – 0.02 for E vs. B).

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PK parameters	CHF 1535 DPI 800/24 µg versus 400/24 µg (B versus A)	CHF 1535 DPI 800/24 µg + AC versus 400/24 µg + AC (E versus D)
	Ratio PE (90% CI) [a]	Ratio PE (90% CI) [a]
C_{max}	79.57 (72.63; 87.18)	80.17 (73.29;87.69)
t_{max}	0.00 (0.00;0.00)	-0.01 (-0.03;0.01)
AUC_{0-t}	83.37 (75.22;92.40)	78.23 (70.72;86.55)
AUC_{0-12h}	85.99 (78.35;94.37)	80.13 (73.13;87.80)
AUC_{0-24h}	84.82 (77.04;93.39)	NA
$AUC_{0-\infty}$	92.55 (85.58;100.09)	81.13 (72.13;91.25)
$t_{1/2}$	98.75 (84.99;114.74)	96.80 (83.68;111.97)

PK parameters	CHF 1535 DPI 400/24 µg + AC versus 400/24 µg (D versus A)	CHF 1535 DPI 800/24 µg + AC versus 800/24 µg (E versus B)
	Ratio PE (90% CI) [a]	Ratio PE (90% CI) [a]
C_{max}	101.02 (92.35;110.50)	101.77 (92.89;111.51)
t_{max}	0.01 (-0.01;0.03)	0.02 (0.00;0.02)
AUC_{0-12h}	75.17 (68.60;82.36)	70.05 (63.82;76.88)

PE = point estimate
NA = not applicable
[a] Point estimate and 90% CI of the ratios of adjusted geometric means of log-transformed parameters from the linear model. For t_{max}, comparisons were assessed using a Wilcoxon signed rank test; the Hodges-Lehmann non-parametric estimate of location shifts based on untransformed data was provided with its 90% two-sided CI.

Pharmacodynamic Results:

Potassium pharmacodynamic results

The pharmacodynamics of potassium was studied in plasma up to 12 h after administration of the treatment. The main potassium plasma PD parameters and the statistical analysis are shown in the tables below.

PD parameters	CHF 1535 DPI 400/24 µg (A) N=29	CHF 1535 DPI 800/24 µg (B) N=26	Placebo (C) N=27
C_{min} (mEq/L)	3.80 ± 0.280	3.83 ± 0.239	3.82 ± 0.287
t_{min} (h)	2.00 (0.00-12.03)	1.01 (0.00-12.02)	0.75 (0.00-12.05)
AUC_{0-4h} (mEq.h/L)	16.2 ± 1.21	16.0 ± 0.796 [a]	16.6 ± 0.964 [b]
AUC_{0-12h} (mEq.h/L)	48.8 ± 2.77	48.7 ± 2.54 [a]	49.6 ± 2.76 [b]

N = number of subjects with data in the PK/PD population
Values are arithmetic means ± SD, except median (range) for t_{min}
[a] N = 23, [b] N = 26

CHF 1535 800/24 µg vs. 400/24 µg (B vs. A)

Potassium C_{min}, AUC_{0-4h} and AUC_{0-12h} were not statistically different after inhalation of CHF 1535 400/24 µg and 800/24 µg, as indicated by the 95% CIs of the point estimates for C_{min} (98.16 – 103.44% for B vs. A), AUC_{0-4h} (98.27 – 102.51% for B vs. A) and AUC_{0-12h} (98.60 - 102.85% for B vs. A).

The time to C_{min} (t_{min}) was also similar after inhalation of CHF 1535 400/24 µg and 800/24 µg, with a 95% CI of the point estimates for t_{min} of -1.00 – 0.52 for B vs. A.

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CHF 1535 400/24 µg vs. placebo (A vs. C), CHF 1535 800/24 µg vs. placebo (B vs. C)

Potassium C_{min} and AUC_{0-12h} were not statistically different after inhalation of CHF 1535 400/24 µg and 800/24 µg by comparison to the placebo treatment, as indicated by the 95% CIs of the point estimates for C_{min} (97.43 – 102.67% for A vs. C and 98.14 – 103.49% for B vs. C), and AUC_{0-12h} (96.87 – 100.83% for A vs. C and 97.39 - 101.70% for B vs. C), while AUC_{0-4h} was lower for the active treatment versus placebo as indicated by the 95% CIs of the point estimates for AUC_{0-4h} (95.50 – 99.40% for A vs. C and 95.70 – 99.93% for B vs. C).

The time to C_{min} (t_{min}) was also similar after inhalation of CHF 1535 400/24 µg and 800/24 µg by comparison to the placebo treatment, as indicated by the 95% CIs of the point estimates for t_{min} (-2.00 – 0.75 for A vs. C and -3.23 – 0.89 for B vs. C).

PD parameters	**CHF 1535 DPI 800/24 µg versus 400/24 µg (B versus A)**	
	Ratio PE (95% CI) [a]	**p-value**
C_{min}	100.77 (98.16; 103.44)	0.5602
t_{min}	0.00 (-1.00;0.52)	0.9227
AUC_{0-4h}	100.37 (98.27;102.51)	0.7259
AUC_{0-12h}	100.70 (98.60;102.85)	0.5067

PD parameters	**CHF 1535 DPI 400/24 µg versus Placebo (A versus C)**		**CHF 1535 DPI 800/24 µg versus Placebo (B versus C)**	
	Ratio PE (95% CI) [a]	**p-value**	**Ratio PE (95% CI) [a]**	**p-value**
C_{min}	100.01 (97.43;102.67)	0.9919	100.78 (98.14;103.49)	0.5582
t_{min}	0.00 (-2.00;0.75)	0.7789	-0.50 (-3.23;0.89)	0.8873
AUC_{0-4h}	97.43 (95.50;99.40)	0.0120	97.79 (95.70;99.93)	0.0433
AUC_{0-12h}	98.83 (96.87;100.83)	0.2410	99.52 (97.39;101.70)	0.6575

PE = point estimate

[a] Point estimate and 95% CI of the ratios of adjusted geometric means of log-transformed parameters from the linear model. For t_{min}, comparisons were assessed using a Wilcoxon signed rank test; the Hodges-Lehmann non-parametric estimate of location shifts based on untransformed data was provided with its 95% two-sided CI.

Glucose pharmacodynamics results

The pharmacodynamics of glucose was studied in plasma up to 12 h after administration of the treatment. The main glucose plasma PD parameters and the statistical analysis are shown in the tables below.

PD parameters	**CHF 1535 DPI**		**Placebo (C) N=27**
	400/24 µg (A) N=29	**800/24 µg (B) N=27**	
C_{max} (mg/dL)	116 ± 14.0	118 ± 13.8	113 ± 11.8
t_{max} (h)	8.02 (0.27-12.23)	8.02 (0.00-12.18)	12.00 (0.00-12.15)
AUC_{0-4h} (mg.h/dL)	378 ± 27.3	383 ± 34.7 [a]	364 ± 21.2 [a]
AUC_{0-12h} (mg.h/dL)	1209 ± 107	1231 ± 98.9 [a]	1164 ± 83.7 [a]

N = number of subjects with data in the PK/PD population

Values are arithmetic means ± SD, except median (range) for t_{min}

[a] N = 26

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CHF 1535 800/24 µg vs. 400/24 µg (B vs. A)

Glucose C_{max}, AUC_{0-4h} and AUC_{0-12h} were not statistically different after inhalation of CHF 1535 400/24 µg and 800/24 µg, as indicated by the 95% CIs of the point estimates for C_{max} (97.02 – 106.78% for B vs. A), AUC_{0-4h} (98.92 – 103.67% for B vs. A) and AUC_{0-12h} (99.35 - 105.25% for B vs. A).

The time to C_{max} (t_{max}) was also similar after inhalation of CHF 1535 400/24 µg and 800/24 µg, with a 95% CI of the point estimates for t_{max} of -2.63 – 2.00 for B vs. A.

CHF 1535 400/24 µg vs. placebo (A vs. C), CHF 1535 800/24 µg vs. placebo (B vs. C)

Glucose C_{max} was not statistically different after inhalation of CHF 1535 400/24 µg by comparison to the placebo treatment, as indicated by the 95% CIs of the point estimates for C_{max} (98.65 – 108.74% for A vs. C) while C_{max} after inhalation of CHF 1535 800/24 µg and AUC_{0-4h} and AUC_{0-12h} after inhalation of both CHF 1535 400/24 µg and 800/24 µg were higher compared to the placebo treatment, as indicated by the 95% CIs of the point estimates for C_{max} (100.42 – 110.67% for B vs. C), AUC_{0-4h} (101.50 – 106.40% for A vs. C and 102.71 – 107.83% for B vs. C) and AUC_{0-12h} (101.87 - 107.94% for A vs. C and 104.07 – 110.47% for B vs. C).

The time to C_{max} (t_{max}) was also similar after inhalation of CHF 1535 400/24 µg and 800/24 µg by comparison with the placebo treatment, as indicated by the 95% CIs of the point estimates for t_{max} (-3.97 – 0.03 for A vs. C and -4.00 – 0.02 for B vs. C).

PD parameters	**CHF 1535 DPI 800/24 µg versus 400/24 µg (B versus A)**	
	Ratio PE (95% CI) [a]	**p-value**
C_{max}	101.78 (97.02;106.78)	0.4627
t_{max}	-0.02 (-2.63;2.00)	0.6787
AUC_{0-4h}	101.27 (98.92;103.67)	0.2858
AUC_{0-12h}	102.25 (99.35;105.25)	0.1267

PD parameters	**CHF 1535 DPI 400/24 µg versus Placebo (A versus C)**		**CHF 1535 DPI 800/24 µg versus Placebo (B versus C)**	
	Ratio PE (95% CI) [a]	**p-value**	**Ratio PE (95% CI) [a]**	**p-value**
C_{max}	103.57 (98.65;108.74)	0.1535	105.42 (100.42;110.67)	0.0340
t_{max}	0.00 (-3.97;0.03)	0.6479	-0.03 (-4.00;0.02)	0.0902
AUC_{0-4h}	103.92 (101.50;106.40)	0.0020	105.24 (102.71;107.83)	0.0001
AUC_{0-12h}	104.86 (101.87;107.94)	0.0019	107.22 (104.07;110.47)	<0.0001

PE = point estimate

[a] Point estimate and 95% CI of the ratios of adjusted geometric means of log-transformed parameters from the linear model. For t_{max}, comparisons were assessed using a Wilcoxon signed rank test; the Hodges-Lehmann non-parametric estimate of location shifts based on untransformed data was provided with its 95% two-sided CI.

Cortisol pharmacodynamics results

The pharmacodynamics of cortisol was studied in plasma up to 24 h after administration of the treatment. The main cortisol plasma PD parameters and the statistical analysis are shown in the tables below.

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PD parameters	CHF 1535 DPI		Placebo (C)	Fluticasone propionate (F)
	400/24 µg (A) N=29	800/24 µg (B) N=27	N=28	N=28
C_{min} (ng/mL)	12.6 ± 8.66	12.7 ± 12.1	13.7 ± 8.23	11.4 ± 7.38
t_{min} (h)	16.03 (2.00-20.05)	16.03 (4.00-20.00)	16.05 (11.98-20.08)	16.02 (8.02-20.00)
AUC_{0-24h} (ng.h/mL)	1132 ± 473	1054 ± 526	1370 ± 445 [a]	1101 ± 268

N = number of subjects with data in the PK/PD population
Values are arithmetic means ± SD, except median (range) for t_{min}
[a] N = 27

CHF 1535 800/24 µg vs. 400/24 µg (B vs. A)

Cortisol C_{min} and AUC_{0-24h} were not statistically different after inhalation of CHF 1535 400/24 µg and 800/24 µg, as indicated by the 95% CIs of the point estimates for C_{min} (74.76 - 121.92% for B vs. A), and AUC_{0-24h} (83.91 – 103.15% for B vs. A).

The time to C_{min} (t_{min}) was also similar after inhalation of CHF 1535 400/24 µg and 800/24 µg, with a 95% CI of the point estimates for t_{min} of -2.08 – 1.92 for B vs. A.

CHF 1535 400/24 µg vs. placebo (A vs. C), CHF 1535 800/24 µg vs. placebo (B vs. C), fluticasone propionate vs. placebo (F vs. C)

Cortisol AUC_{0-24h} was lower in the active treatments (CHF 1535 400/24 µg and 800/24 µg, fluticasone propionate) compared to the placebo treatment. This is indicated by the 95% CIs of the point estimates for AUC_{0-24h} (74.44 – 91.72% for A vs. C, 69.24 – 85.35% for B vs. C and 74.89 – 92.32% for F vs. C). C_{min} was not statistically different compared to placebo, as indicated by the 95% CIs of the point estimates for C_{min} (70.14 – 114.37% for A vs. C, 66.96 - 109.20% for B vs. C and 66.91 – 109.12% for F vs. C).

The time to C_{min} (t_{min}) was similar after inhalation of CHF 1535 400/24 µg and placebo. After inhalation of CHF 1535 800/24 µg and fluticasone propionate, t_{min} was slightly lower than in the placebo group. This is indicated by the 95% CIs of the point estimates for t_{min} (-4.00 – 0.93 for A vs. C, -2.99 – -0.04 for B vs. C and -2.03 – -0.02 for F vs. C).

CHF 1535 400/24 µg vs. fluticasone propionate (A vs. F), CHF 1535 800/24 µg vs. fluticasone propionate (B vs. F)

Cortisol C_{min} was not statistically different after inhalation of CHF 1535 400/24 µg or CHF 1535 800/24 µg than after inhalation of fluticasone propionate treatment as indicated by the 95% CIs of the point estimates for C_{min} (82.08 - 133.86% for A vs. F and 78.45 – 127.66% for B vs. F). Cortisol AUC_{0-24h} was similar after inhalation of CHF 1535 and fluticasone propionate, as indicated by the 95% CIs of the point estimates for AUC_{0-24h} (89.62 – 110.18% for A vs. F and 83.42 – 102.46% for B vs. F).

The time to C_{min} (t_{min}) was similar in the three treatments, as indicated by the 95% CIs of the point estimates for t_{min} (-2.96 – 2.02 for A vs. F and -1.98 – 1.05 for B vs. F).

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PD parameters	CHF 1535 DPI 800/24 µg versus 400/24 µg (B versus A)		Fluticasone propionate versus Placebo (F versus C)	
	Ratio PE (95% CI) [a]	p-value	Ratio PE (95% CI) [a]	p-value
C_{min}	95.47 (74.76;121.92)	0.7067	85.45 (66.91;109.12)	0.2039
t_{min}	-0.95 (-2.08;1.92)	0.6393	-1.04 (-2.03;-0.02)	0.0214
AUC_{0-24h}	93.03 (83.91;103.15)	0.1675	83.15 (74.89;92.32)	0.0008

PD parameters	CHF 1535 DPI 400/24 µg versus Placebo (A versus C)		CHF 1535 DPI 800/24 µg versus Placebo (B versus C)	
	Ratio PE (95% CI) [a]	p-value	Ratio PE (95% CI) [a]	p-value
C_{min}	89.57 (70.14;114.37)	0.3720	85.51 (66.96;109.20)	0.2061
t_{min}	-0.98 (-4.00;0.93)	0.2433	-1.94 (-2.99;-0.04)	0.0038
AUC_{0-24h}	82.63 (74.44;91.72)	0.0005	76.87 (69.24;85.35)	<0.0001

PD parameters	CHF 1535 DPI 400/24 µg versus Fluticasone propionate (A versus F)		CHF 1535 DPI 800/24 µg versus Fluticasone propionate (B versus F)	
	Ratio PE (95% CI) [a]	p-value	Ratio PE (95% CI) [a]	p-value
C_{min}	104.82 (82.08;133.86)	0.7022	100.08 (78.45;127.66)	0.9951
t_{min}	0.03 (-2.96;2.02)	0.5644	0.01 (-1.98;1.05)	0.9420
AUC_{0-24h}	99.37 (89.62;110.18)	0.9038	92.45 (83.42;102.46)	0.1323

PE = point estimate

[a] Point estimate and 95% CI of the ratios of adjusted geometric means of log-transformed parameters from the linear model. For t_{min}, comparisons were assessed using a Wilcoxon signed rank test; the Hodges-Lehmann non-parametric estimate of location shifts based on untransformed data was provided with its 95% two-sided CI.

Cardiovascular assessments results

The cardiovascular parameters were assessed up to 12 h after administration of the treatment. The results of the cardiovascular assessments and the statistical analysis are shown in the tables below.

AUC_{0-12h}/12h	CHF 1535 DPI				Placebo (C) N=28
	400/24 µg (A) N=29	800/24 µg (B) N=27	400/24 µg + AC (D) N=27	800/24 µg +AC (E) N=29	
Heart rate (bpm)	68.4 ± 11.3	68.3 ± 11.2	67.1 ± 10.6 [a]	67.6 ± 12.0 [a]	64.2 ± 10.9 [b]
Systolic BP (mmHg)	119 ± 12.1	119 ± 11.0	121 ± 10.5	121 ± 12.0	118 ± 11.2
Diastolic BP (mmHg)	70.6 ± 9.74	70.4 ± 9.07	72.2 ± 7.33	71.7 ± 9.84	70.4 ± 6.33

N = number of subjects with data in the PK/PD population

Values are arithmetic means ± SD, except median (range) for t_{min}

[a] N = 26, [b] N = 27

Heart rate, SBP and DBP AUC_{0-12h}/12h were not statistically different after inhalation of CHF 1535 400/24 µg and 800/24 µg. Heart rate was higher in the CHF 1535 treatments (CHF 1535 400/24 µg and 800/24 µg, without or with charcoal block) compared to the placebo treatment, as indicated by the 95% CIs of the point estimates for HR AUC_{0-12h}/12h (104.77 - 110.26% for A vs. C, 104.86 - 110.34% for B vs. C, 103.40 - 108.89% for D vs. C and 104.90 - 110.57% for E vs. C).

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Both SBP and DBP were higher following administration of CHF 1535 400/24 µg with activated charcoal, when compared to the administration of CHF 1535 400/24 µg without activated charcoal or compared to placebo. This is indicated by the 95% CIs of the point estimates for SBP AUC_{0-12h}/12h (100.49 - 104.13% for D vs. A and 100.84 - 104.48% for D vs. C) and for DBP AUC_{0-12h}/12h (101.11 - 107.31% for D vs. A and 100.01 - 106.12% for D vs. C). In addition, SBP was higher following administration of CHF 1535 800/24 µg with activated charcoal compared to the placebo treatment, as indicated by the 95% CIs of the point estimate for SBP AUC_{0-12h}/12h (100.96 - 104.61% for E vs. C). Diastolic BP was similar after inhalation of CHF 1535 800/24 µg with activated charcoal compared to the placebo treatment as indicated by the 95% CIs of the point estimates for DBP AUC_{0-12h}/12h (93.38 - 104.41% for E vs. C).

Parameters	**CHF 1535 DPI 800/24 µg versus 400/24 µg (B versus A)**		**CHF 1535 DPI 800/24 µg + AC versus 400/24 µg + AC (E versus D)**	
	Ratio PE (95% CI) [a]	**p-value**	**Ratio PE (95% CI) [a]**	**p-value**
Heart rate	100.08 (97.58;102.64)	0.9514	101.50 (98.88;104.19)	0.2612
Systolic BP	100.71 (98.93;102.52)	0.4325	100.12 (98.35;101.92)	0.8944
Diastolic BP	101.25 (98.28;104.31)	0.4104	98.38 (95.50;101.35)	0.2795

Parameters	**CHF 1535 DPI 400/24 µg + AC versus 400/24 µg (D versus A)**		**CHF 1535 DPI 800/24 µg + AC versus 800/24 µg (E versus B)**	
	Ratio PE (95% CI) [a]	**p-value**	**Ratio PE (95% CI) [a]**	**p-value**
Heart rate	98.72 (96.22;101.29)	0.3222	100.12 (97.55;102.76)	0.9248
Systolic BP	102.29 (100.49;104.13)	0.0130	101.69 (99.90;103.52)	0.0639
Diastolic BP	104.16 (101.11;107.31)	0.0077	101.22 (98.25;104.27)	0.4219

Parameters	**CHF 1535 DPI 400/24 µg versus Placebo (A versus C)**		**CHF 1535 DPI 800/24 µg versus Placebo (B versus C)**	
	Ratio PE (95% CI) [a]	**p-value**	**Ratio PE (95% CI) [a]**	**p-value**
Heart rate	107.48 (104.77;110.26)	<0.0001	107.56 (104.86;110.34)	<0.0001
Systolic BP	100.35 (98.58;102.15)	0.7011	101.06 (99.28;102.87)	0.2435
Diastolic BP	98.90 (96.00;101.88)	0.4613	100.13 (97.19;103.15)	0.9309

Parameters	**CHF 1535 DPI 400/24 µg + AC versus Placebo (D versus C)**		**CHF 1535 DPI 800/24 µg + AC versus Placebo (E versus C)**	
	Ratio PE (95% CI) [a]	**p-value**	**Ratio PE (95% CI) [a]**	**p-value**
Heart rate	106.11 (103.40;108.89)	<0.0001	107.70 (104.90;110.57)	<0.0001
Systolic BP	102.65 (100.84;104.48)	0.0043	102.77 (100.96;104.61)	0.0030
Diastolic BP	103.02 (100.01;106.12)	0.0496	101.35 (98.38;104.41)	0.3738

PE = point estimate
BP = blood pressure
[a] Point estimate and 95% CI of the ratios of adjusted geometric means of log-transformed parameters from the linear model.

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Safety Results:

Treatment-Emergent Adverse Events	Placebo N=28	CHF 1535 400/24 µg N=29	CHF 1535 800/24 µg N=27	CHF 1535 400/24 µg + AC N=27	CHF 1535 800/24 µg + AC N=29	Fluticasone propionate N=28
Most frequently reported AEs (in ≥2 subjects during any treatment)						
Headache	2 (7.1)	4 (13.8)	3 (11.1)	5 (18.5)	3 (10.3)	2 (7.1)
Gastroenteritis	0	0	0	0	2 (6.9)	0
Nasopharyngitis	2 (7.1)	0	0	0	0	0
Nausea	0	0	0	2 (7.4)	0	0
n (%) with at least one TEAE	6 (21.4)	7 (24.1)	8 (29.6)	9 (33.3)	7 (24.1)	8 (28.6)
n (%) of deaths	0	0	0	0	0	0
n (%) with at least one serious TEAE	0	0	0	0	0	0
n (%) with at least one TEAE leading to withdrawal	0	1 (3.4)	0	0	1 (3.4)	0
n (%) with at least one severe TEAE	0	1 (3.4)	0	0	0	0
n (%) with at least one TEAE considered to be treatment-related by the Investigator	0	0	0	0	0	0

No deaths or other SAEs occurred during the study. Treatment-emergent AEs leading to discontinuation of study drugs were reported for two subjects, i.e., ventricular tachycardia that started 8.5 h after inhalation of CHF 1535 400/24 µg and pharyngitis after inhalation of CHF1535 800/24 µg. Both events were considered not related to the study drug by the Investigator. For the latter subject, the reason for study discontinuation was reported as the intake of a non-permitted medication (penicillin) for the treatment of the AE.

Treatment-emergent AEs were observed in 7 (24.1%), 8 (29.6%), 9 (33.3%), 7 (24.1%), 8 (28.6%), and 6 (21.4%) subjects after inhalation of CHF 1535 400/24 µg, CHF 1535 800/24 µg, CHF 1535 400/24 µg + AC, CHF 1535 800/24 µg +AC, fluticasone propionate and placebo, respectively.

No TEAEs were considered to be treatment-related by the Investigator.

By preferred term, all TEAEs were reported in at most two subjects per treatment, except for headache in 4 (13.8%), 3 (11.1%), 5 (18.5%), 3 (10.3%), 2 (7.1%) and 2 (7.1%) subjects after inhalation of CHF 1535 400/24 µg, CHF 1535 800/24 µg, CHF 400/24 µg + AC, CHF 1535 800/24 µg + AC fluticasone propionate, and placebo, respectively. All TEAEs were mild or moderate in intensity except for one severe TEAE (i.e., ventricular tachycardia after administration of CHF 1535 400/24 µg).

Similar mean changes over time in supine DBP and SBP were observed after inhalation of CHF 1535 (any dose) and placebo.

Mean changes over time from baseline in HR, QTcB, and QTcF values were similar following inhalation of any CHF 1535 dose but larger after inhalation of CHF 1535 (any dose) than after inhalation of placebo.

No treatment-emergent QTcB or QTcF values of >480 ms were reported. None of the subjects had an increase of >60 ms versus reference in QTcB or QTcF.

None of the vital signs or ECG abnormalities were considered to be clinically relevant and were reported as AE except for ventricular tachycardia (verbatim: non-sustained ventricular tachycardia) in one subject after inhalation of CHF 1535 400/24 µg.

SYNOPSIS

Conclusion:

The lung bioavailability of BDP and the total systemic exposure to BDP in terms of AUC_{0-t} increased proportionally with the dose throughout the CHF 1535 dose range 400/24 µg and 800/24 µg; C_{max} increased less than dose proportionally.

The lung bioavailability of B17MP (active metabolite of BDP) and the total systemic exposure to B17MP increased proportionally with the dose throughout the CHF 1535 dose range 400/24 µg and 800/24 µg, when administered with and without activated charcoal.

For formoterol, the bioequivalence in terms of lung bioavailability and total systemic exposure cannot be concluded. The 90% CIs of the point estimates comparing the dose 800/24 µg of BDP to the dose 400/24 µg for AUC_{0-t} (with as well as without activated charcoal) are laying below the acceptance range of 80.00 – 125.00%.

The two dose levels of CHF 1535 (400/24 µg and 800/24 µg), administered with and without activated charcoal were not different in terms of impact on plasmatic levels of potassium, glucose and cortisol and on mean cardiovascular parameters (HR, SBP and DBP). The two dose levels CHF 1535 (400/24 µg and 800/24 µg) both induced at the same extent a significant decrease in plasmatic cortisol availability (measured as AUC_{0-24h}) compared to the placebo group, a decrease in plasma potassium (measured as AUC_{0-4h}) and an increase in plasma glucose (measured as AUC_{0-4h} and AUC_{0-12h}). Fluticasone propionate was chosen as the active comparator available on the market to evaluate the effects on plasma cortisol levels. CHF1535 (at both dose levels) showed a comparable decrease in plasma cortisol (AUC_{0-24h} and C_{min}) as fluticasone propionate, confirming a similar effect on the hypothalamic-pituitary-adrenal axis, even at the highest dose of the combination. The two dose levels CHF 1535 (400/24 µg and 800/24 µg) with and without activated charcoal induced a similar increase in cardiovascular parameters (increase in HR, SBP and DBP) measured as AUC_{0-12h}/12h, compared to placebo.

Single doses of CHF 1535 via a NEXThaler® DPI up to 800 µg of BDP + 24 µg FF were generally safe and well tolerated in the exposed subjects.

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