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Sharing Clinical Study Report Synopsis

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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 5259 pMDI, Atimos® pMDI	**Volume:**	
Name of Active Ingredient: glycopyrrolate, formoterol	**Page:**	

Title of Study: Open-label, randomized, single-dose, placebo-controlled, 4-way cross-over study to investigate the pharmacokinetic interaction of glycopyrrolate and formoterol in healthy subjects (TRIPLE 1)

Investigators: [redacted] MD

Study Centre(s): [redacted] Belgium

Publication (reference): None

Studied Period: 20 May 2011 (first patient first visit) 05 August 2011 (last patient last visit)	**Phase of development:** Phase I

Objectives:

Primary:

To evaluate the pharmacokinetic interaction between glycopyrrolate and formoterol by comparing the systemic exposure after a single dose of the free combination of CHF 5259 and Atimos® to that of the single components, with all treatments administered using a pressurised metered dose inhaler (pMDI).

Secondary:

To assess the safety and tolerability of the free combination of CHF 5259 pMDI and Atimos® pMDI in comparison to that of the single components.

Methodology *(Study Design):*

The study was a single-centre, randomised, open-label, single-dose, 4-way cross-over study. The test treatment (Treatment T) consisted of a single dose administration of 100 µg (4 puffs of 25 µg) CHF 5259 pMDI and 24 µg (2 puffs of 12 µg) Atimos® pMDI. Reference treatments consisted of a single dose administration of 100 µg (4 puffs of 25 µg) CHF 5259 pMDI (reference treatment 1, Treatment R1) and a single dose administration of 24 µg (2 puffs of 12 µg) Atimos® pMDI (reference treatment 2, Treatment R2). Placebo (Treatment P) consisted of 1 inhalation of placebo pMDI. Treatment periods were separated by a 7- to 10-day wash-out period.

Number of patients *(planned and analysed)*:

In order to obtain 40 evaluable subjects, 44 healthy subjects (at least 16 males and 16 females) were planned to be included. In total 107 subjects were screened, 44 subjects were randomised, and 42 subjects completed the study.

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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 pre-dose of Treatment Period 1.

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

Treatment T (test):

4 inhalations of CHF 5259 pMDI 25 µg/actuation and 2 inhalations of Atimos® pMDI 12 µg/actuation, resulting in a total dose of 100 µg glycopyrrolate and 24 µg formoterol

(CHF 5259 pMDI batch no. [redacted] recheck date [redacted]; Atimos® pMDI batch no. [redacted] expiry date [redacted])

Duration of treatment:

Four single-dose treatment periods separated by a 7- to 10-day wash-out period.

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

Treatment R1 (reference treatment 1):

4 inhalations of CHF 5259 pMDI 25 µg/actuation, resulting in a total dose of 100 µg glycopyrrolate (batch no. [redacted] recheck date [redacted])

Treatment R2 (reference treatment 2):

2 inhalations of Atimos® pMDI 12 µg/actuation, resulting in a total dose of 24 µg of formoterol (batch no. [redacted] expiry date [redacted])

Treatment P (placebo):

1 inhalation of placebo pMDI (batch no. [redacted] recheck date [redacted])

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Criteria for evaluation:

Pharmacokinetics:

Primary variables

- Plasma glycopyrrolate and formoterol: area under the plasma concentration curve (AUC_{0-t}) and maximum plasma concentration (C_{max})

Secondary variables

- Plasma glycopyrrolate $AUC_{0-30min}$, AUC_{0-32h}, $AUC_{0-\infty,}$ time to maximum plasma concentration (t_{max}), and terminal half-life ($t_{½}$)
- Plasma formoterol $AUC_{0-30min}$, AUC_{0-24h}, $AUC_{0-\infty,}$ t_{max}, and $t_{½}$

Exploratory variables

- Urine glycopyrrolate: cumulative urinary excretion (Ae_{0-4h}, Ae_{4-32h}, Ae_{0-32h}), fraction excreted unchanged (fe), and renal clearance (CLr)

Safety

- Adverse events (AEs) and adverse drug reactions (ADRs), including occurrence of paradoxical bronchospasm
- Serum potassium: value of and time to minimum plasma concentration and time (C_{min} and t_{min}) and AUC_{0-24h}
- Plasma glucose: C_{max}, t_{max}, and AUC_{0-24h}
- Lung function test: forced expiratory volume in 1 second (FEV_1)
- Laboratory tests: clinical chemistry, haematology and urinalysis
- Vital sign parameters: heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP).
- 12-lead ECG parameters: HR, intervals RR, PR, QRS and QT, and QT interval corrected for HR according to Bazett and Fridericia (QTcB and QTcF, respectively)

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Statistical methods:

Pharmacokinetic variables

- Plasma glycopyrrolate and formoterol AUC_{0-t}, $AUC_{0-30min}$, AUC_{0-24h} (for formoterol), AUC_{0-32h} (for glycopyrrolate), $AUC_{0-\infty}$, C_{max}, and $t_{½}$ 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 and R1 (for glycopyrrolate parameters) and treatments T and R2 (for formoterol parameters) were calculated with their 90% two-sided confidence intervals (CIs).
- Absence of interaction between glycopyrrolate and formoterol was concluded if the 90% CIs of the ratios of adjusted geometric means for glycopyrrolate and formoterol AUC_{0-t} and C_{max} were contained within the acceptance interval 80%-125%.
- For t_{max}, the Hodges-Lehmann nonparametric estimate of location shift between treatments T and R1 (for glycopyrrolate) and treatments T and R2 (for formoterol) based on untransformed data was provided with its 90% two-sided CI.
- For exploratory purposes, urine glycopyrrolate Ae_{0-4h}, Ae_{4-32h}, Ae_{0-32h}, fe, and CLr were summarised by treatment using descriptive statistics.

Safety variables

- The number and percentage of subjects experiencing AEs, ADRs, serious adverse events (SAEs), and AEs leading to study withdrawal were presented by treatment. AEs were summarised by System Organ Class (SOC) and Preferred Term using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary, including specific tables by AE intensity and drug causality.
- Serum potassium C_{min} and AUC_{0-24h}, plasma glucose C_{max} and AUC_{0-24h} 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 and P, R2 and P, and T and R2 were calculated with their 95% two-sided CIs.
- For serum potassium t_{min} and plasma glucose t_{max}, the Hodges-Lehmann nonparametric estimate of location shift between treatments T and P, R2 and P, and T and R2 based on untransformed data were provided with its 95% two-sided CI.
- For laboratory tests, a shift table of follow-up versus screening was presented.

Statistical methods, cont'd:

- Mean changes from pre-dose to each time point post-dose in FEV_1 were calculated with their 95% CIs by treatment.
- At each time point post-dose the following statistics were calculated by treatment for vital sign and ECG parameters:
  - mean absolute value with its 95% CI
  - mean change from pre-dose (pre-dose-adjusted value) with its 90% CI
  - mean difference versus placebo in change from pre-dose (pre-dose- and placebo-adjusted value) with its 90% CI
  - mean differences between treatments T and R1 and T and R2 in change from pre-dose with their 90% CIs

  Time profile plots, both individual and by treatment, were presented for pre-dose- and placebo-adjusted value.
- For both QTcB and QTcF, the number and percentage of subjects with the following at each time point post-dose and at any time point post-dose were presented by treatment:
  - QTc interval >450 ms, >480 ms and >500 ms
  - change from pre-dose in QTc interval >30 ms and >60 ms

Summary – Conclusions:

Pharmacokinetic Results:

Glycopyrrolate pharmacokinetic results

The pharmacokinetics of glycopyrrolate were studied in plasma and urine up to 32 h after administration of 2 active treatments (Treatments T and R1). Pre-dose plasma concentrations were always below the lower limit of quantification (BLOQ).

The main glycopyrrolate plasma pharmacokinetic parameters and the statistical analysis are shown in the tables below.

Pharmacokinetic Results, cont'd:

Pharmacokinetic parameter	CHF 5259 pMDI 100 µg + Atimos® pMDI 24 µg (T) N = 41	CHF 5259 pMDI 100 µg (R1) N = 41
C_{max} (pg/mL)	77.8 ± 50.3	62.6 ± 36.2
t_{max} (h)	0.08 (0.08-1.50)	0.08 (0.08-1.00)
$AUC_{0\text{-}30min}$ (pg.h/mL)	24.3 ± 13.6	23.4 ± 13.3
$AUC_{0\text{-}32h}$ (pg.h/mL)	167 ± 96.2	172 ± 101
$AUC_{0\text{-}t}$ (pg.h/mL)	155 ± 92.7	159 ± 98.2
$AUC_{0\text{-}\infty}$ (pg.h/mL)	148 ± 32.7 [a]	134 ± 34.9 [b]
$t_{1/2}$ (h)	4.56 ± 6.60 [c]	4.89 ± 7.35 [d]

N = number of subjects

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

[a] N = 10, [b] N = 13, [c] N = 24, [d] N = 25

Glycopyrrolate C_{max} was slightly higher following administration of CHF 5259 pMDI + Atimos® pMDI (Treatment T) than following administration of CHF 5259 pMDI alone (Treatment R1), with a point estimate of the ratio of geometric means T/R1 at 118% (90% CI 105;134). The extent of glycopyrrolate absorption was similar with or without the concomitant administration of Atimos® pMDI, indicated by point estimates T/R1 of 104% (90% CI 94;115) for $AUC_{0\text{-}30min}$, 99% (90% CI 88;111) for $AUC_{0\text{-}32h}$, and 99% (90% CI 87;111) for $AUC_{0\text{-}t}$. The terminal elimination half-life was also similar, indicated by the point estimate T/R1 of 111% (90% CI 99;126). The absorption rate of glycopyrrolate was not impacted by the concomitant administration of Atimos® pMDI, as indicated by the point estimate of 0.00 and p-value of 1 for t_{max}. Not enough data were available to perform the statistical analysis on $AUC_{0\infty}$.

Pharmacokinetic Results, cont'd

Statistical analysis of glycopyrrolate plasma pharmacokinetic parameters:

Pharmacokinetic parameter	CHF 5259 pMDI 100 µg + Atimos® pMDI 24 µg versus CHF 5259 pMDI 100 µg (T versus R1)	
	p-value[a]	Ratio PE (90% CI)[b]
C_{max}	0.0244	118.46 (104.88;133.80)
t_{max}	1.0000	0.00 (0.00;0.00)
$AUC_{0-30min}$	0.5343	103.88 (93.78;115.06)
AUC_{0-32h}	0.8509	98.70 (87.84;110.91)
AUC_{0-t}	0.8455	98.61 (87.44;111.21)
$AUC_{0-\infty}$	NA[c]	NA[c]
$t_{1/2}$	0.1324	111.43 (98.88;125.57)

PE = point estimate, NA = Not Assessed

[a] Probability of no difference between treatments (ANOVA, non-parametric test for t_{max})

[b] Point estimate and 90% CI of the least-squares geometric percentage ratio (ANOVA). For t_{max}, comparison was assessed between T and R1 using a Wilcoxon signed rank test; the Hodges-Lehmann nonparametric estimate of location shift between T and R1 based on untransformed data was provided with its 90% two-sided CI.

[c] Number of subjects with data available for both T and R1 = 4

The excretion of glycopyrrolate in urine was studied up to 32 h post-dose. The summary of glycopyrrolate urinary excretion parameters is reported in the table below:

Pharmacokinetic parameter	CHF 5259 pMDI 100 µg + Atimos® pMDI 24 µg (T) N = 39	CHF 5259 pMDI 100 µg (R1) N = 36
Ae_{0-32h} (µg)	5.45 ± 2.45	5.72 ± 2.34
Ae_{0-4h} (µg)	2.48 ± 1.12	2.81 ± 1.15
Ae_{4-32h} (µg)	2.96 ± 1.47	2.92 ± 1.34
fe (% dose)	5.45 ± 2.45	5.72 ± 2.34
CLr (mL/min)	639 ± 218	637 ± 246

N = number of subjects

Values are arithmetic means ± SD

Urinary glycopyrrolate excretion profile over 32 h post dose was, on average, similar following administration of CHF 5259 pMDI with or without Atimos® pMDI (Ae_{0-32h} 5.45 ± 2.45 µg and fe 5.45 ± 2.45 % after Treatment T, Ae_{0-32h} 5.72 ± 2.34 µg and fe 5.72 ± 2.34% after Treatment R1). About 50% of the amount excreted was found in the 0-4 h post dosing interval (Ae_{0-4h} 2.48 ± 1.12 µg and 2.81 ± 1.15 µg after Treatments T and R1, respectively). The mean (± SD) renal clearance of glycopyrrolate was also similar between Treatments T and R1 (CLr 639 ± 218 mL/min and 637 ± 246 mL/min, respectively).

Pharmacokinetic Results, cont'd:

Formoterol pharmacokinetic results

The pharmacokinetics of formoterol (Atimos®) were studied in plasma up to 24 h after administration of 2 active treatments (Treatments T and R2). Pre-dose plasma concentrations were always below the BLOQ.

The main formoterol pharmacokinetic parameters and the statistical analysis are shown in the tables below:

Pharmacokinetic parameter	CHF 5259 pMDI 100 µg + Atimos® pMDI 24 µg (T) N = 40	Atimos® pMDI 24 µg (R2) N = 41
C_{max} (pg/mL)	23.2 ± 11.3	25.4 ± 11.8
t_{max} (h)	0.17 (0.08-1.50)	0.08 (0.08-4.00)
$AUC_{0\text{-}30min}$ (pg.h/mL)	7.23 ± 3.24	7.61 ± 3.56
$AUC_{0\text{-}24h}$ (pg.h/mL)	74.1 ± 27.4	75.2 ± 26.8 [a]
$AUC_{0\text{-}t}$ (pg.h/mL)	64.0 ± 23.7	65.4 ± 23.4
$AUC_{0\text{-}\infty}$ (□g.h/mL)	92.1 ± 16.2 [b]	98.1 ± 24.8 [c]
$t_{1/2}$ (h)	4.65 ± 1.70 [d]	4.52 ± 1.56 [e]

N = number of subjects
Values are arithmetic means ± SD, except median (range) for t_{max}
[a] N = 40, [b] N = 14, [c] N = 17, [d] N = 32, [e] N =35

The extent of formoterol absorption and systemic exposure were similar following administration of CHF 5259 pMDI + Atimos® pMDI (Treatment T) or Atimos® pMDI alone (Treatment R2) , indicated by point estimates T/R2 of 91% (90% CI 80;102) for C_{max}, 99% (90% CI 85;115) for $AUC_{0\text{-}30min}$, 100% (90% CI 89;112) for $AUC_{0\text{-}24h}$, 97% (90% CI 86;110) for $AUC_{0\text{-}t}$, and 98% (90% CI 85;114) for $AUC_{0\text{-}\infty}$. The terminal elimination half-life was also similar, indicated by the point estimate T/R2 of 105% (90% CI 96;117). The time to peak plasma of formoterol was slightly decreased when Atimos® pMDI was administered together with CHF 5259 pMDI (Treatment T) compared to Atimos® pMDI administered alone (Treatment R2), as indicated by the point estimate T/R2 of 0.04 and p-value of 0.0096 for t_{max}. This slight increase may be explained by the fact that the administration of Atimos® pMDI was delayed when administered in combination with CHF 5259 pMDI (order of study drug administration in Treatment T was CHF 5259 pMDI, 4 inhalations and then Atimos® pMDI, 2 inhalations); however, this does not have any clinical relevance.

Pharmacokinetic Results, cont'd:

Statistical analysis of formoterol plasma pharmacokinetic parameters:

Pharmacokinetic parameter	CHF 5259 pMDI 100 µg + Atimos® pMDI 24 µg versus Atimos® pMDI 24 µg (T versus R2)	
	p-value[a]	Ratio PE (90% CI)[b]
C_{max}	0.1809	90.71 (80.39;102.34)
t_{max}	0.0096	0.04 (0.04;0.08)
$AUC_{0-30min}$	0.9158	99.05 (85.15;115.22)
AUC_{0-24h}	0.9907	99.92 (89.04;112.13)
AUC_{0-t}	0.7046	97.35 (86.46;109.62)
$AUC_{0-\infty}$	0.8387	98.44 (85.29;113.63)
$t_{1/2}$	0.3375	105.79 (95.89;116.71)

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 least-squares geometric percentage ratio (ANOVA). For t_{max}, comparison was assessed between T and R2 using a Wilcoxon signed rank test; the Hodges-Lehmann nonparametric estimate of location shift between T and R2 based on untransformed data was provided with its 90% two-sided CI.

Safety Results:

Adverse events

No deaths or other SAEs occurred during this study. One subject was prematurely discontinued from the study due to an AE ([redacted] [preferred term: [redacted]]) following Treatment R2. The AE was considered related to the study medication by the Investigator, based on the fact that the subject (female) did not develop such abnormality after inhalation of placebo. Further examinations to exclude a pre-existing heart abnormality were conducted on the subject; they included CT coronarography, echocardiography, effort test, and adenosine test. The CT coronarography and echocardiography showed normal results, while the subject also experienced [redacted] during the effort and adenosine tests, suggesting an effect due to sympathetic stimulation. In addition, the subject presented a "variant of normality" at baseline, showing variations that are present in 10-20% of young female population and that are often connected with high sensibility to sympathetic stimulation [1].

Thirteen (31.0%) subjects had at least one treatment-emergent AE (TEAE) in the treatment period following Treatment T. This incidence was similar to the incidences following reference treatments R1 and R2 (13 [30.2%] and 8 [18.6%], respectively) and following placebo administration (13 [30.2%] subjects).

Safety Results, Cont'd:

By preferred term, all TEAEs were reported in less than 5% of the subjects following any treatment, except for headache which was observed in 8 (19.0%), 5 (11.6%), 4 (9.3%), and 7 (16.3%) subjects following Treatments T, R1, R2, and P, respectively.

All TEAEs were at most moderate in intensity.

Clinical laboratory evaluation

Treatment-emergent laboratory abnormalities were observed in less than 5% of the subjects, with the exception of total bilirubin below normal range (8 [18.2%] subjects), monocytes (%) above normal range (4 [9.1%] subjects), and phosphorus below normal range (3 [6.8%] subjects). None of the laboratory-related abnormalities were reported as AE.

Potassium results

The profile of potassium serum concentration was studied up to 24 h after administration of placebo (P) and 2 active treatments (Treatments T and R2).

The parameters derived from potassium serum concentrations and the statistical analysis are shown in the table below:

Potassium parameters	CHF 5259 pMDI 100 µg +Atimos® pMDI 24 µg (T) N = 42	Atimos® pMDI 24 µg (R2) N = 43	Placebo (P) N = 43
C_{min} (mmol/L)	3.70 ± 0.232	3.71 ± 0.257	3.89 ± 0.185
t_{min} (h)	4.00 (0.00-12.00)	4.00 (0.25-12.00)	4.00 (0.00-8.00)
AUC_{0-24h} (mmol.h/L)	101 ± 4.40	102 ± 4.91 [a]	103 ± 4.69

N = number of subjects
Values are arithmetic means ± SD, except median (range) for t_{min}
[a] N = 42

CHF 5259 pMDI + Atimos® pMDI vs. placebo (T vs. P)
Potassium C_{min} and AUC_{0-24h} were slightly, though significantly lower following administration of CHF 5259 pMDI + Atimos® pMDI (T) than after placebo administration (P). The point estimates were 95% (95% CI 93;97) and 98% (95% CI 97;100), respectively, and p-values were less than 0.0001 and equal to 0.0121 for C_{min} and AUC_{0-24h}, respectively. The administration of CHF 5259 pMDI + Atimos® pMDI (T) had no impact on the rate of serum potassium decrease, as indicated by the point estimate of 0.00 (95% CI -1.00;0.13) and p-value of 0.9041 for the shift in t_{min} between T and P.

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Safety Results, Cont'd:

Atimos® pMDI vs. placebo (R2 vs. P)

Potassium C_{min} and AUC_{0-24h} were slightly, though significantly lower following administration of Atimos® pMDI (T) than after the administration of placebo (P). The point estimates were 95% (95% CI 93;97) and 98% (95% CI 97;100) and p-values were less than 0.0001 and equal to 0.0158 for C_{min} and AUC_{0-24h}, respectively. The administration of Atimos® pMDI (R2) had no impact on the rate of serum potassium decrease, as indicated by the point estimate of 0.00 (95% CI -1.00;0.75) and the p-value of 0.9322 for the shift in t_{min} between R2 and P.

CHF 5259 pMDI + Atimos® pMDI vs. Atimos® pMDI (T vs. R2)

Potassium C_{min} and AUC_{0-24h} were similar following administration of CHF 5259 pMDI + Atimos® pMDI (T) or Atimos® pMDI alone (R2), with point estimates of 100% (95% CI 98;102) and 100% (95% CI 98;101) and p-values of 0.7658 and 0.8418 for C_{min} and AUC_{0-24h}, respectively. The concomitant administration of CHF 5259 pMDI (T) and Atimos® pMDI had no impact on the rate of serum potassium decrease compared to what was observed following the administration of Atimos® pMDI alone (R2), as indicated by the point estimate of 0.00 (95% CI -0.75;0.38) and p-value of 0.8889 for the shift in t_{min} between T and P.

Statistical analysis of potassium serum parameters:

Potassium parameters	**CHF 5259 pMDI 100 µg + Atimos® pMDI 24 µg versus Placebo (T versus P)**		**Atimos® pMDI 24 µg versus Placebo (R2 versus P)**		**CHF 5259 pMDI 100 µg + Atimos® pMDI 24 µg versus Atimos® pMDI 24 µg (T versus R2)**	
	p-value[a]	**Ratio PE (95% CI)[b]**	**p-value[a]**	**Ratio PE (95% CI)[b]**	**p-value[a]**	**Ratio PE (95% CI)[b]**
C_{min}	<0.0001	94.78 (92.96;96.64)	<0.0001	95.11 (93.44;96.80)	0.7658	99.73 (97.91;101.58)
t_{min}	0.9041	0.00 (-1.00;0.13)	0.9322	0.00 (-1.00;0.75)	0.8889	0.00 (-0.75;0.38)
AUC_{0-24h}	0.0121	98.05 (96.57;99.54)	0.0158	98.25 (96.87;99.65)	0.8418	99.85 (98.40;101.33)

PE = point estimate

[a] Probability of no difference between treatments (ANOVA, non-parametric test for t_{min})

[b] Point estimate and 95% CI of the least-squares geometric percentage ratio (ANOVA). For t_{min}, comparison was assessed between T and P, R2 and P, and T and R2 using a Wilcoxon signed rank test; the Hodges-Lehmann nonparametric estimate of location based on untransformed data was provided with its 95% two-sided CI.

Safety Results, Cont'd:

Glucose results

The profile of glucose plasma concentration was studied up to 24 h after administration of placebo (P) and 2 active treatments (Treatments T and R2).
The parameters derived from glucose plasma concentrations and the statistical analysis are shown in the table below:

Glucose parameters	CHF 5259 pMDI 100 µg +Atimos® pMDI 24 µg (T) N = 42	Atimos® pMDI 24 µg (R2) N = 43	Placebo (P) N = 43
C_{max} (mmol/L)	7.13 ± 1.40	7.06 ± 1.53	5.96 ±0.825
t_{max} (h)	4.00 (0.50-12.00)	4.00 (4.00-12.00)	6.00 (0.50-24.00)
AUC_{0-24h} (mmol.h/L)	126 ± 11.4	126 ± 11.8 [a]	120 ± 9.25

N = number of subjects
Values are arithmetic means ± SD, except median (range) for t_{max}
[a] N = 42

CHF 5259 pMDI + Atimos® pMDI vs. Placebo (T vs. P)
Glucose C_{max} and AUC_{0-24h} were slightly, though significantly higher following administration of CHF 5259 pMDI + Atimos® pMDI (T) than after placebo administration (P). The point estimates were 118% (95% CI 113;124) and 105% (95% CI 104;107) for C_{max} and AUC_{0-24h}, respectively, and both p-values were lower than 0.0001. The administration of CHF 5259 pMDI + Atimos® pMDI (T) slightly, though significantly anticipated the plasma glucose peak, as indicated by the point estimate of -1.75 (95% CI -4.00;0.00) and p-value of 0.0017 for the shift in t_{max} between T and P.
Atimos® pMDI vs. Placebo (R2 vs. P)
Glucose C_{max} and AUC_{0-24h} were slightly, though significantly higher following administration of Atimos® pMDI (T) than after the administration of placebo (P). The point estimates were 117% (95% CI 111;123) and 105% (95% CI 103;107) for C_{max} and AUC_{0-24h}, respectively, and p-values were both less than 0.0001. The administration of Atimos® pMDI (R2) slightly, though significantly anticipated the plasma glucose peak, as indicated by the point estimate of -1.00 (95% CI -3.00;0.00) and p-value of 0.0417 for the shift in t_{max} between R2 and P.
CHF 5259 pMDI + Atimos® pMDI vs. Atimos® pMDI (T vs. R2)
Glucose C_{max} and AUC_{0-24h} were similar following administration of CHF 5259 pMDI + Atimos® pMDI (T) or Atimos® pMDI alone (R2), with point estimates of 101% (95% CI 97;106) and 100% (95% CI 98;102) and p-values of 0.5364 and 0.9318 for C_{max} and AUC_{0-24h}, respectively. The concomitant administration of CHF 5259 pMDI (T) slightly anticipated the plasma glucose peak compared to what was observed following the administration of Atimos® pMDI alone (R2), as indicated by the point estimate of 0.00 (95% CI -1.00;0.00) and p-value of 0.0486 for the shift in t_{max} between T and P.

Safety Results, Cont'd:

Statistical analysis of glucose plasma parameters:

Glucose parameters	CHF 5259 pMDI 100 µg + Atimos® pMDI 24 µg versus Placebo (T versus P)		Atimos® pMDI 24 µg versus Placebo (R2 versus P)		CHF 5259 pMDI 100 µg + Atimos® pMDI 24 µg versus Atimos® pMDI 24 µg (T versus R2)	
	p-value[a]	Ratio PE (95% CI)[b]	p-value[a]	Ratio PE (95% CI)[b]	p-value[a]	Ratio PE (95% CI)[b]
C_{max}	<0.0001	118.29 (113.04;123.77)	<0.0001	117.21 (111.43;123.29)	0.5364	101.35 (97.04;105.84)
t_{max}	0.0017	-1.75 (-4.00;0.00)	0.0417	-1.00 (-3.00;0.00)	0.0486	0.00 (-1.00;0.00)
AUC_{0-24h}	<0.0001	105.18 (103.71;106.67)	<0.0001	105.32 (103.29;107.40)	0.9318	100.07 (98.41;101.76)

PE = point estimate

[a] Probability of no difference between treatments (ANOVA, non-parametric test for t_{min})

[b] Point estimate and 95% CI of the least-squares geometric percentage ratio (ANOVA). For t_{min}, comparison was assessed between T and P, R2 and P, and T and R2 using a Wilcoxon signed rank test; the Hodges-Lehmann nonparametric estimate of location based on untransformed data was provided with its 95% two-sided CI.

ECG and vital signs

Apart from one subject whose ECG showed [redacted] reported as AE (leading to withdrawal from the study), no ECG-related or vital sign-related AEs were reported.

Following all treatments, HR increased from pre-dose to a maximum at 4 hours after inhalation, coincidently with the planned lunch. Considering mean placebo-adjusted HR values however, comparable increases from pre-dose were seen following inhalation of treatments that included formoterol (Treatments T and R2; 6.0 and 6.5 bpm, respectively at 25 min following inhalation), whereas no increase was observed during Treatment R1 (maximum mean pre-dose placebo-adjusted HR change: 2.1 bpm). Similarly, mean QTcF values following Treatments T and R2 went up from 402.4 and 402.0 ms, respectively, at pre-dose to maxima of 416.3 and 416.0 ms, respectively, at 15 min post-dose, and remained at similar values until 4h post-dose, whereas QTcF values following Treatment R1 did not change in time. The effect of formoterol plasma concentration on HR and QTc increases could not be ruled out judging from time correlation plots between glycopyrrolate or formoterol peak plasma concentrations and increases in QTc and HR. No enhancement of this effect by the addition of glycopyrrolate could however be seen. The observed variations following inhalation of glycopyrrolate were more likely related to the circadian rhythm and meal intake.

Safety Results, Cont'd:

None of the subjects had a treatment-emergent QTc value >480 ms or QTc changes from pre-dose >60 ms. Treatment-emergent QTcF values >450 ms at any post-dose time point were seen in one (2.3%) subject, following Treatment R2. None of the abnormalities in ECG were considered to be clinically significant.

Lung function tests

No relevant differences in FEV_1 were observed between active treatments. No lung function-related AEs were reported.

Conclusion:

No impact of formoterol on glycopyrrolate overall systemic exposure was found since the 90% CI of the ratio of geometric means of glycopyrrolate AUCs between the test treatment (CHF 5259 pMDI + Atimos® pMDI) and the reference treatment (CHF 5259 pMDI) were within the acceptance interval 80-125%. Absence of impact of formoterol on glycopyrrolate absorption cannot be concluded since the 90% CI for glycopyrrolate C_{max} were outside the acceptance interval (105%-134%). However, the increased peak level of glycopyrrrolate after administration of the free combination of CHF 5259 pMDI + Atimos® pMDI compared to CHF 5259 pMDI alone, was devoid of any effect in terms of tolerability since no differences in serum potassium profile, plasma glucose profile, or ECG values were observed between the two treatments.

No impact of glycopyrrolate on the pharmacokinetics of formoterol was found since the 90% CI of the ratio of geometric means of formoterol C_{max} and AUCs between the test treatment and Atimos® pMDI were within the acceptance interval 80-125%. Consistently, overall no impact of glycopyrrolate was found on the evolution of serum potassium and plasma glucose levels following formoterol administration.

The administered treatments were safe and well tolerated. No differences in safety and tolerability profile were observed for the free combination of CHF 5259 pMDI + Atimos® pMDI in comparison to that of the single components.

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References

1. Chuan Chou T. and Knilans T. K. Electrocardiography in Clinical Practice Fourth Edition, W.B. Saunders Company