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Chiesi

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	**Volume:**	
Name of Active Ingredient: glycopyrrolate	**Page:**	

Title of study:	Pharmacokinetic, randomised, open-label, single-dose, 3-way cross-over study of intravenous and inhaled glycopyrrolate with or without charcoal block ingestion in healthy volunteers
Investigator:	[redacted] MD
Study centre:	[redacted] (UK)
Publication (reference): None	

Studied period:	**Phase of development:** Phase I
27 July 2010 (date of first contact) 15 October 2010 (date of last contact)	

Objectives:

Primary:

To investigate the pharmacokinetics, the absolute bioavailability and the lung bioavailability of inhaled CHF 5259 (glycopyrrolate bromide 100 µg/actuation) pressurized metered dose inhaler (pMDI).

Secondary:

To investigate the safety of inhaled CHF 5259 pMDI.

Methodology:

The study was a single-centre, randomised, open-label, single-dose, 3-way cross-over study. Test Treatment 1 consisted of a single administration of 100 µg (4 puffs of 25 µg) CHF 5259 pMDI, Test Treatment 2 consisted of a single administration of 100 µg (4 puffs of 25 µg) CHF 5259 pMDI with a charcoal block, and Reference Treatment consisted of 100 µg of intravenous (i.v.) glycopyrrolate (Robinul®). Treatment periods were separated by a 5- to 10-day wash-out period.

Number of subjects *(planned and analysed)*:

20 healthy subjects (at least 7 males and 7 females) planned, 35 subjects screened, 20 subjects randomised, and 20 subjects completed

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	**Volume:**	
Name of Active Ingredient: glycopyrrolate	**Page:**	

Diagnosis and main criteria for inclusion:

Healthy male or female subjects aged 18 – 65 years inclusive, with normal lung function and normal ECG and vital signs at screening and Day 1 pre-dose of treatment period 1.

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

Test treatment 1 (T1):

4 inhalations of CHF 5259 using a hydrofluoroalkane (HFA) pMDI with 25 µg/actuation giving a total dose of 100 µg of glycopyrrolate

Test treatment 2 (T2):

4 inhalations of CHF 5259 using a HFA pMDI with 25 µg/actuation giving a total dose of 100 µg of glycopyrrolate with a charcoal block that was performed as follows:

- 10 min before inhalation, subjects were given orally a total volume of 50 mL (2 x 25 mL, if preferable) of activated charcoal suspension (0.1 g charcoal/mL water);
- at the end of the 10-s breath-holding period after each puff, subjects rinsed their mouth and gargled for about 10 s with 30 mL activated charcoal suspension, which was discharged. This procedure took no more than 30 s between each inhalation;
- at the end of inhalation treatment (4 inhalations), subjects were given orally another total volume of 50 mL (2 x 25 mL, if preferable) activated charcoal suspension;
- 1, 2 and 4 h after the treatment, subjects swallowed another total volume of 50 mL (2 x 25 mL, if preferable) activated charcoal suspension.

Batch number of CHF 5259 pMDI: [redacted], expiry date [redacted] (same batches for T1 and T2).

Duration of treatment:

Three single-dose treatment periods separated by a 5- to 10-day wash-out period.

Reference therapy, dose and mode of administration, batch number

Reference treatment (R):

Intravenous injection of 0.5 mL glycopyrrolate of a 200 µg/mL solution (Robinul®) giving a total dose of 100 µg

Batch number of Robinul® intravenous injection: [redacted]; expiry date [redacted].

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	**Volume:**	
Name of Active Ingredient: glycopyrrolate	**Page:**	

Criteria for evaluation:
Pharmacokinetics:

- Plasma PK variables:
  - AUC_{0-24h}, AUC_{0-t}, $AUC_{0-\infty}$, and $t_{1/2}$ (all treatments)
  - $AUC_{0-30min}$, C_{max}, t_{max}, F, CL/F, and V_z/F (only for T1 and T2)
  - CL, V_z (only for R)
- Urine PK variables:
  - Ae_{0-4h}, Ae_{4-8h}, Ae_{8-24h}, Ae_{0-24h}, fe, and CLr

Safety:

- Adverse events (AEs) and adverse drug reactions (ADRs), including occurrence of paradoxical bronchospasm, and laboratory safety, vital signs, ECG, and lung function parameters

Statistical methods:

AUC_{0-t}, $AUC_{0-\infty}$, and $t_{1/2}$ were log-transformed and submitted to a mixed model with treatment, period, and sequence as fixed effects and subject nested within sequence as random effect. The ratios of adjusted geometric means between T1 and R, T2 and R, and T1 and T2 were calculated with their 90% 2-sided confidence intervals (CIs).

$AUC_{0-30min}$ and C_{max} were log-transformed and submitted to a mixed model with treatment, period and sequence as fixed effects and subject nested within sequence as random effect. Only data from treatment periods with T1 and T2 were used in the estimation of the model. The ratio of adjusted geometric means between T1 and T2 were calculated with its 90% 2-sided CI.

For t_{max}, the Hodges-Lehmann nonparametric estimate of location shift between T1 and T2 based on untransformed data was provided with its 90% two-sided CI. Absolute bioavailability (T1 and T2), CL/F (T1 and T2), CL (R), V_z/F (T1 and T2), and V_z (R) were summarized using descriptive statistics.

Plasma concentration/time curves, individual and based on mean values by treatment, were presented in linear/linear and log/linear scale.

Ae_{0-4h}, Ae_{4-8h}, Ae_{8-24h}, Ae_{0-24h}, fe, and CLr were summarized using descriptive statistics.

Bar charts showing the amount of drug excreted in urine at the different time intervals, individual and based on mean values by treatment were presented.

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	**Volume:**	
Name of Active Ingredient: glycopyrrolate	**Page:**	

Statistical methods, Cont'd:

Safety parameters were summarized by treatment.

The number and percentage of subjects experiencing AEs, ADRs, serious adverse events (SAEs) and AEs leading to study withdrawal were presented. The occurrence of paradoxical bronchospasm was of special interest. AEs were also summarized by System Organ Class and Preferred Term using the Medical Dictionary for Regulatory Activities, including specific tables by AE intensity and drug causality.

Mean changes from pre-dose to each post-dose time point in lung function parameters (FEV_1, FVC, FEV_1/FVC) were calculated with their 95% confidence intervals (CIs).

At each post-dose time point the following statistics were calculated for vital signs (heart rate [HR], systolic blood pressure [SBP], diastolic blood pressure [DBP]) and for 12-lead ECG parameters (ventricular HR, PR-, QRS-, and QT-intervals, and correction of the QT-interval for heart rate by Fridericia's [QTcF] and Bazett's [QTcB] method): mean absolute value with its 95% CI and mean change from pre-dose with its 90% CI.

Time profile plots, both individual and by treatment, were presented for baseline-adjusted vital signs (HR, SBP, DBP) and 12-lead ECG parameters (ventricular HR, PR, QRS, QT, QTcB, QTcF).

The number and percentage of subjects who had a QTcB and QTcF interval >450 ms, >480 ms and >500 ms and the change from pre-dose in QTcB and QTcF interval >30 ms and >60 ms were calculated at each time point post-dose and at any time point post-dose.

Mean changes from pre-dose to post-dose in quantitative laboratory parameters (clinical chemistry, haematology and urinalysis) were calculated with their 95% CIs by treatment. Shift tables from pre-dose to post-dose, with regard to normal range, was presented for all relevant laboratory parameters.

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	**Volume:**	
Name of Active Ingredient: glycopyrrolate	**Page:**	

Summary – Conclusions

Pharmacokinetic results

The pharmacokinetics of glycopyrrolate was studied in plasma and urine up to 24 h after administration of the 2 active pMDI treatments (Treatments T1, T2) as well as an intravenous administration (Treatment R). Pre-dose plasma concentrations were always below the lower limit of quantification (BLOQ).

Pharmacokinetic parameter	**CHF 5259 pMDI 100 µg (T1) N = 20**	**CHF 5259 pMDI 100 µg + charcoal block (T2) N = 20**	**Robinul® i.v. injection100 µg, (R) N = 20**
Plasma			
C_{max} (pg/mL) *(for T1 and T2)*	130 ± 79.9	135 ± 92.3	-
t_{max} (h) *(for T1 and T2)*	0.08 (0.08-0.25)	0.08 (0.08-0.25)	-
$AUC_{0\text{-}30min}$ (pg.h/mL) *(for T1 and T2)*	44.0 ± 23.9	43.1 ± 26.0	-
$AUC_{0\text{-}24h}$ (pg.h/mL)	315 ± 96.3 [a]	266 ± 134 [b]	2598 ± 512
$AUC_{0\text{-}t}$ (pg.h/mL)	321± 100	274 ± 127	2584 ± 524
$AUC_{0\text{-}\infty}$ (pg.h/mL)	NC [c]	NC [d]	2665 ± 561 [a]
$t_{1/2}$ (h)	14.5 ± 15.6 [f]	9.26 ± 8.19 [e]	5.92 ± 2.70 [a]
F *(for T1 and T2)*	0.128 ± 0.0481 [a]	0.105 ± 0.0487 [b]	-
CL/F (mL/min) *(for T1 and T2)*	5967 ± 2716 [a]	8667 ± 7763 [b]	-
CL (mL/min)	764 [#]	910 [#]	667 ±138
V_z/F (L) *(for T1 and T2)*	6420 ± 5963 [f]	8972 ± 9212 [e]	-
V_z (L) *(for R)*	-	-	323 ± 129 [a]
Urine			
$Ae_{0\text{-}24h}$ (µg)	5.95 ± 2.47	4.93 ± 3.12 [g]	40.1 ± 24.9 [h]
$Ae_{0\text{-}4h}$ (µg)	3.09 ± 1.88	2.55 ± 1.92 [h]	35.7 ± 23.4
$Ae_{4\text{-}8h}$ (µg)	1.06 ± 0.494	0.785 ± 0.483 [h]	2.09 ± 0.927 [h]
$Ae_{8\text{-}24h}$ (µg)	1.81 ± 0.881	1.78 ± 1.04	2.59 ± 1.70
fe (% dose)	5.95 ± 2.47	4.93 ± 3.12 [g]	40.1 ± 24.9 [h]
CLr (mL/min)	315 ± 124 [a]	299 ± 96.7 [a]	263 ± 139 [h]

N = number of subjects
NC = Not Calculated
Values are arithmetic means ± SD, except median (range) for t_{max}
[a] N = 15, [b] N = 16, [c] N = 2, [d] N = 0, [e] N = 3, [f] N = 7, [g] N = 18, [h] N = 19
[#] Values for CL in treatments T1 and T2 are calculated as (arithmetic mean CL/F)* arithmetic mean F

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	**Volume:**	
Name of Active Ingredient: glycopyrrolate	**Page:**	

Pharmacokinetic results, cont'd

After inhalation of both test treatments, glycopyrrolate was rapidly absorbed showing a peak concentration at 5 min post-dose. Glycopyrrolate C_{max} and $AUC_{0\text{-}30min}$ were, on average, similar following administration of CHF 5259 pMDI with or without charcoal block with point estimates of 102% and 107%, respectively. Accordingly, the 90% CI of the ratio of geometric means T1/T2 were 85 – 123% and 92-124% for C_{max} and $AUC_{0\text{-}30min}$, respectively, indicating that the rate of lung absorption of glycopyrrolate was comparable with the two treatment procedures. The overall systemic exposure was slightly decreased using the charcoal block (T2) as indicated by the point estimates (T1/T2) of 124% (90% CI 104-149) for $AUC_{0\text{-}t}$ and 123 (90% CI 99-153) for $AUC_{0\text{-}24h}$. The small magnitude of these differences suggests limited gastrointestinal absorption of glycopyrrolate. Not enough data were available to perform the statistical analysis on $AUC_{0\text{-}\infty}$ and $t_{1/2}$.

Statistical analysis of plasma pharmacokinetic parameters

Pharmacokinetic parameter	CHF 5259 pMDI 100 µg versus CHF 5259 pMDI 100 µg + charcoal block (T1 versus T2)		CHF 5259 pMDI 100 µg versus Robinul® i.v. injection 100 µg (T1 versus R)		CHF 5259 pMDI 100 µg + charcoal block versus Robinul® i.v. injection 100 µg (T2 versus R)	
	p-value[a]	Ratio PE (90% CI)[b]	p-value[a]	Ratio PE (90% CI)[b]	p-value[a]	Ratio PE (90% CI)[b]
C_{max}	0.8371	102.20 (85.24;122.53)	-	-	-	-
t_{max}	0.7813	0.00 (0.00;0.00)	-	-	-	-
$AUC_{0\text{-}30min}$	0.4335	107.00 (92.39;123.92)	-	-	-	-
$AUC_{0\text{-}24h}$	0.1212	123.06 (98.68;153.46)	<0.0001	11.35 (9.15;14.06)	<0.0001	9.22 (7.50;11.33)
$AUC_{0\text{-}t}$	0.0503	124.47 (103.71;149.39)	<0.0001	11.93 (9.94;14.32)	<0.0001	9.58 (7.99;11.50)
$AUC_{0\text{-}\infty}$	NA[c,d]	NA[c,d]	NA[c]	NA[c]	NA[d]	NA[d]
$t_{1/2}$	NA[e]	NA[e]	0.7302	116.88 (53.21; 256.73)	NA[e]	NA[e]

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 T1 and T2 using a Wilcoxon signed rank test; the Hodges-Lehmann nonparametric estimate of location shift between T1 and T2 based on untransformed data was provided with its 90% two-sided CI.

[c] N for T1 = 2, [d] N for T2 = 0, [e] N for T2 = 3

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	**Volume:**	
Name of Active Ingredient: glycopyrrolate	**Page:**	

Pharmacokinetic results, cont'd

The systemic exposure measured by AUC_{0-24h} and AUC_{0-t} was significantly lower after inhalation of CHF 5259 pMDI compared to the i.v. administration of Robinul® by an estimated 89% (PE 11.35) and 88% (PE 11.93), respectively, and with a p-value <0.0001 for both parameters. No significant difference was found for $t_{1/2}$.

The systemic exposure measured by AUC_{0-24h} and AUC_{0-t} was significantly lower after inhalation of CHF 5259 pMDI using the charcoal block technique compared to the i.v. administration of Robinul®, by an estimated 91% (PE 9.22) and 90% (PE 9.58), respectively, and with a p-value <0.0001 for both parameters. Not enough data were available to perform the statistical analysis on $AUC_{0-\infty}$ and $t_{1/2}$.

The mean absolute bioavailability (measured by F for the Treatment T1) was 12.8%; the lung bioavailability (measured by F for the Treatment T2) was 10.5%.

The excretion of glycopyrrolate in urine was studied up to 24 h post-dose. The summary of glycopyrrolate urinary excretion pharmacokinetic parameters is reported in the table below.

Pharmacokinetic parameter	CHF 5259 pMDI 100 µg (Treatment T1) N = 20	CHF 5259 pMDI 100 µg + charcoal block (Treatment T2) N = 20	Robinul® i.v. injection 100 µg (Treatment R) N = 20
Ae_{0-24h} (µg)	5.95 ± 2.47	4.93 ± 3.12 [a]	40.1 ± 24.9 [b]
Ae_{0-4h} (µg)	3.09 ± 1.88	2.55 ± 1.92 [b]	35.7 ± 23.4
Ae_{4-8h} (µg)	1.06 ± 0.494	0.785 ± 0.483 [b]	2.09 ± 0.927 [b]
Ae_{8-24h} (µg)	1.81 ± 0.881	1.78 ± 1.04	2.59 ± 1.70
fe (% dose)	5.95 ± 2.47	4.93 ± 3.12 [a]	40.1 ± 24.9 [b]
CLr (mL/min)	315 ± 124 [c]	299 ± 96.7 [c]	263 ± 139 [b]

N = number of subjects
Values are arithmetic means ± SD, except median (range) for t_{max}
[a] N = 18, [b] N = 19, [c] N = 15

Urinary glycopyrrolate excretion profile was, on average, similar following inhalation of CHF 5259 pMDI with or without charcoal block. The mean fraction of the glycopyrrolate dose excreted unchanged (fe) was 5.95 % after T1 and 4.93 % after T2. After both test treatments about 50% of the amount excreted was found in the 0-4 h post dosing interval. Similar renal clearance was observed after inhalation of CHF 5259 pMDI with or without charcoal block (CLr 315 ± 124 mL/min and 299 ± 96.7 mL/min after T1 and T2, respectively). After i.v. administration, a glycopyrrolate excretion about 10-fold higher compared to both inhaled test treatments was observed (fe 40.1 %), with about 89% of the amount excreted in the 0-4 h post dosing interval. The mean renal clearance after i.v. administration was of the same order than after the test treatments (CLr 263 ± 139 mL/min).

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	**Volume:**	
Name of Active Ingredient: glycopyrrolate	**Page:**	

Safety results

No deaths, other SAEs, or events of paradoxical bronchospasm occurred during this study. None of the subjects discontinued study medication due to an AE.

Fourteen (70.0%) subjects had at least one TEAE during the study. At least one TEAE was reported in 8 (40.0%) subjects following Treatment R, 5 (25.0%) subjects following Treatment T2, and in 4 (20.0%) subjects following Treatment T1.

Most TEAEs were mild or moderate in severity during the study. One (5.0%) subject had a severe TEAE, i.e., headache following Treatment R.

One (5.0%) subject had a treatment-related TEAE during the study, i.e., dry mouth following Treatment R.

All TEAEs by preferred term were reported in only 1 subject in the whole study, except for headache (6 [30.0%] subjects), oropharyngeal pain (2 [10.0%] subjects), and nasopharyngitis (2 [10.0%] subjects). Headache was reported in 2 (10.0%) subjects following Treatment T1 and in 3 (15.0%) subjects each after Treatment T2 and Treatment R. Both events of oropharyngeal pain were reported following Treatment R and both events of nasopharyngitis after Treatment T1.

Among subjects with a normal laboratory value at baseline, the most frequently observed treatment-emergent laboratory abnormality was haematocrit value below normal in 3 (15.0%) subjects following Treatment T2. Haematocrit value below normal was observed in 1 (5.0%) subject following Treatment T1 and in none of the subjects following Treatment R. None of the laboratory-related abnormalities were reported as AE.

No clinically relevant trends or changes in mean or median ECG and vital signs values were observed. No ECG- or vital signs-related AEs were reported.

Mean HR change from baseline over time was similar after all treatments, with lowest values around 2 h post-dose, followed by an increase around 4 h post-dose. Mean QTcB and QTcF changes from baseline over time were similar after all treatments, with peaks around 2 h post-dose. For all parameters, values at 24 h post-dose were similar to the pre-dose values. No time correlation between peak plasma concentrations and changes in HR or QTc was seen. The observed variations were more likely related to the circadian rhythm and meal intake.

None of the subjects had a treatment-emergent QTcB or QTcF value >500 ms.

One (5.0%) subject had a treatment-emergent QTcF value >450 ms during the study (465 ms corresponding to an increase from baseline of 53 ms). None of the subjects had increases in QTcF versus baseline >60 ms. None of the ECG abnormalities were considered to be clinically relevant.

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	**Volume:**	
Name of Active Ingredient: glycopyrrolate	**Page:**	

Safety results, cont'd

As a post-hoc analysis, mean $AUC_{0\text{-}24h}/24$ for HR, QTcB, and QTcF was calculated, showing similar results after all treatments, despite the different magnitude of systemic exposure after intravenous administration in comparison with the inhalation treatments.

The largest increase from baseline in FEV_1 and FVC was observed 1 h post-dose. At 24 h post-dose values were comparable to those at baseline. No relevant differences were observed between treatments. No lung function-related AEs were reported.

Lung function parameter, mean (95% CI)	**CHF 5259 pMDI (T1) N = 20**	**CHF 5259 pMDI + charcoal block (T2) N = 20**	**Robinul® i.v. injection (R) N = 20**
FEV_1 actual values (L)			
Pre-dose	4.19 (3.72, 4.66)	4.20 (3.76, 4.6286)	4.16 (3.74, 4.57)
1 h post-dose	4.30 (3.84, 4.77)	4.33 (3.86, 4.7953)	4.29 (3.84, 4.74)
4 h post-dose	4.29 (3.84, 4.74)	4.38 (3.92, 4.8332)	4.26 (3.80, 4.72)
24 h post-dose	4.27 (3.82, 4.71)	4.29 (3.83, 4.7477)	4.14 (3.69, 4.59)
FVC actual values (L)			
Pre-dose	5.12 (4.52, 5.72)	5.11 (4.53, 5.68)	5.09 (4.55, 5.62)
1 h post-dose	5.05 (4.46, 5.65)	5.06 (4.47, 5.64)	5.04 (4.47, 5.61)
4 h post-dose	5.03 (4.43, 5.63)	5.07 (4.49, 5.64)	5.03 (4.44, 5.61)
24 h post-dose	5.05 (4.46, 5.63)	5.05 (4.46, 5.65)	5.01 (4.42, 5.60)
FEV_1/FVC ratio			
Pre-dose	0.82 (0.80, 0.85)	0.83 (0.80, 0.85)	0.82 (0.80, 0.84)
1 h post-dose	0.86 (0.83, 0.88)	0.86 (0.84, 0.88)	0.86 (0.83, 0.88)
4 h post-dose	0.86 (0.83, 0.89)	0.87 (0.85, 0.89)	0.85 (0.83, 0.88)
24 h post-dose	0.85 (0.83, 0.88)	0.86 (0.83, 0.88)	0.83 (0.81, 0.86)

N = total number of subjects; n = number of subjects with that observation

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	**Volume:**	
Name of Active Ingredient: glycopyrrolate	**Page:**	

Conclusion

On the basis of the plasma pharmacokinetic analysis of CHF 5259 pMDI, it can be observed that peak concentration and exposure over 30 min ($AUC_{0\text{-}30h}$) were similar in Treatments T1 and T2, showing that the lung bioavailability of glycopyrrolate was not influenced by the charcoal block. The prevention of gastrointestinal absorption due to charcoal block resulted in slightly decreased overall systemic exposure after inhalation of T2, suggesting very limited absorption by gastrointestinal route of the swallowed portion of inhaled glycopyrrolate. Consistently, a small difference was observed between the absolute bioavailability of inhaled CHF 5259 pMDI and the lung bioavailability estimated after inhalation of CHF 5259 pMDI using charcoal block, which amounted to 12.8 and 10.5%, respectively.

The apparent total body clearance was slightly higher when gastrointestinal absorption was prevented by charcoal blockade.

No reliable conclusions can be drawn on $AUC_{0\text{-}\infty}$, $t_{1/2}$, and the volume of distribution because of the small number of data available for these parameters in the Treatments T1 and T2.

Urinary glycopyrrolate excretion profile over 24 h post-dose was similar following inhalation of CHF 5259 pMDI with or without charcoal block (fe 5.95 % and 4.93 % after T1 and T2 respectively), while it was about 10-fold higher after i.v. administration. Similar renal clearance was found after glycopyrrolate i.v. administration and after CHF 5259 pMDI inhalation (range: 263-315 mL/min).

The administered treatments were safe and well-tolerated.

Date of report

2 April 2012 [redacted]