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2. SYNOPSIS

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

Title of Study:	Open-label, non-randomized, parallel-group study to investigate the pharmacokinetics, safety and tolerability of a single dose of CHF 5993 pMDI in subjects with mild, moderate and severe renal impairment in comparison with matched healthy control subjects (Triple 10)
Investigators:	Prof. [redacted]
Study Centre(s):	[redacted] Poland
Publication (reference): Not applicable	

Studied Period: FPFV: 23 January 2014 LPLV: 14 April 2015	**Phase of Development:** I

Objectives:

Primary objective:

- To characterise the pharmacokinetics (PK) of the glycopyrronium bromide (GB), component of CHF 5993 pressurised metered dose inhaler (pMDI) in subjects with mild, moderate and severe renal impairment (RI) in comparison with demographically matching healthy volunteers, by comparing the systemic exposure to GB (AUC_{0-t} [area under the plasma concentration-time curve from time 0 up to the last quantifiable concentration]), after a single dose of the fixed combination CHF 5993 pMDI (beclometasone dipropionate [BDP]/formoterol fumarate [FF]/GB 400/24/100 µg).

Secondary objectives:

- To compare the systemic exposure of BDP, beclometasone 17-monopropionate (B17MP), formoterol and the other PK parameters of GB after a single dose of the fixed combination CHF 5993 pMDI between subjects with RI and matching healthy volunteers.

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- To assess the safety and tolerability of the study treatment in subjects with mild, moderate and severe RI in comparison to matching healthy volunteers based on evaluation of adverse events (AEs), vital signs, electrocardiograms (ECGs) and clinical laboratory assessments.

Methodology (Study Design):

The clinical study had an open-label, non-randomised, parallel-group design, where one single dose (4 inhalations) of CHF 5993 pMDI was administered to evaluate the PK, safety and tolerability of the drug in subjects with mild, moderate and severe RI in comparison to healthy subjects. Approximately 24 subjects with RI were to be enrolled together with an adequate number of healthy subjects matching the renal impaired-subjects for gender, Body Mass Index (BMI) and age. Their participation involved a total of 2 visits and a follow-up phone call (or a visit, if deemed necessary by the Investigator). The end of the study was defined as the last visit of the last subject in the study (follow-up contact/visit included).

One single administration of CHF 5993 pMDI was given by inhalation to all subjects, consisting of 4 inhalations of CHF 5993 pMDI (BDP/FF/GB 100/6/25 µg per actuation) giving a total dose of 400 µg of BDP, 24 µg of FF and 100 µg of GB.

Number of patients *(planned and analysed)*:

Eight subjects in each RI group were to be enrolled, as well as an adequate number of healthy subjects to find a match for each renal impaired subject in terms of age (± 5 years), gender and BMI (± 10%).

The following subject groups were included in the study:

- healthy subjects (estimated glomerular filtration rate [eGFR] ≥ 80 mL/min/1.73 m^2);
- mild RI (50 ≤ eGFR < 80 mL/min/1.73 m^2);
- moderate RI (30 ≤ eGFR < 50 mL/min/1.73 m^2);
- severe RI (eGFR < 30 mL/min/1.73 m^2).

A total of 72 subjects were screened, i.e., 34 renal impaired patients and 38 healthy volunteers. Healthy volunteer screening failures (21 subjects) were not recorded in the clinical database. Nine renal impaired patients were not enrolled (i.e., screening failures), of whom 8 subjects were not eligible to enter the study and 1 subject withdrew consent.

Forty-two subjects were enrolled in one of the 4 subject groups: 17 healthy subjects, 9 mild renal impaired subjects, 7 moderate renal impaired subjects and 9 severe renal impaired subjects. For each subject in a RI group, a corresponding matched healthy subject was enrolled. A healthy subject could be matched to one or more renal impaired subjects. The matching groups for each RI group consisted of 9 (mild RI), 7 (moderate RI) and 8 (severe RI) healthy subjects. Note that one healthy subject not matched to any of the renal impaired patients was only included in the sensitivity analysis and in the analyses where the group of healthy volunteers was considered as a whole. All 42 enrolled and treated subjects completed the study.

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Diagnosis and main criteria for inclusion:

All subjects: Male and female subjects, aged 40 to 65 years (inclusive), weighing at least 50 kg with a BMI of 18 to 35 kg/m^2 (inclusive).

Healthy subjects only: Subjects with a serum creatinine within the normal range (0.5-1.0 mg/dL for women and 0.7-1.2 mg/dL for men) and eGFR ≥ 80 mL/min/1.73 m^2 who were matched to at least one renal impaired subject with respect to age (± 5 years), gender and BMI (± 10%).

Renal impaired subjects only: Subjects with stable renal disease (i.e., eGFR < 80 mL/min/1.73 m^2) (mild, moderate or severe) without evidence of any significant progression and/or deterioration of the renal disease (i.e., no significant change for 12 weeks). Fluctuations in potassium and creatinine levels within ± 20% in the last 12 weeks were accepted.

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

CHF 5993 pMDI (BDP/FF/GB 100/6/25 µg per actuation): 4 inhalations of CHF 5993 pMDI giving a total dose of 400 µg of BDP, 24 µg of FF and 100 µg of GB.

CHF 5993 100/6/25 µg: Batch no.: [redacted], recheck date: [redacted]

Duration of treatment:

One single administration of CHF 5993 pMDI (4 inhalations). The subjects' participation involved a total of 2 visits (i.e., a screening visit lasting approximately 0.5 days and a treatment visit lasting approximately 4 days) and a follow-up phone call (or visit), spread over approximately 2.5 to 5 weeks, depending on the duration of the screening and follow-up period.

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

Not applicable.

Criteria for evaluation:

Pharmacokinetic variables:

Primary variables:

- Plasma GB AUC_{0-t}.

Secondary variables:

- Plasma GB AUC_{0-72h} (area under the plasma concentration-time curve from time 0 up to the 72 h time point), $AUC_{0-\infty}$ (area under the plasma concentration-time curve extrapolated to infinity), AUC_{0-12h} (area under the plasma concentration-time curve from time 0 up to the 12 h time point), C_{max} (maximum plasma concentration), t_{max} (time to C_{max}), $t_{1/2}$ (terminal elimination half-life) and CL/F (apparent systemic clearance).
- Plasma B17MP and formoterol AUC_{0-t}, C_{max}, t_{max}, AUC_{0-24h} (area under the plasma concentration-time curve from time 0 up to the 24 h time point), $AUC_{0-\infty}$, $t_{1/2}$ and formoterol CL/F.
- Plasma BDP AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, and $t_{1/2}$.

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- Urine GB $Ae_{0\text{-}4h}$, $Ae_{4\text{-}8h}$, $Ae_{8\text{-}12h}$, $Ae_{12\text{-}24h}$, $Ae_{24\text{-}36h}$, $Ae_{36\text{-}48h}$, $Ae_{48\text{-}60h}$, $Ae_{60\text{-}72h}$, $Ae_{0\text{-}72h}$ (amount excreted into the urine in the collection interval x-y h), fe (fraction of the dose excreted into urine) and CLr (renal clearance).
- Urine formoterol (free and total) $Ae_{0\text{-}4h}$, $Ae_{4\text{-}8h}$, $Ae_{8\text{-}12h}$, $Ae_{12\text{-}24h}$, $Ae_{0\text{-}24h}$, fe and CLr (CLr for total formoterol only).

Safety:

- Adverse events and adverse drug reactions (ADRs).
- Vital signs: systolic blood pressure (SBP), diastolic blood pressure (DBP).
- 12-lead ECG parameters: heart rate (HR), time interval between the Q and T waves corrected for HR according to Fridericia (QTcF), time interval between the beginning of the Q wave and termination of the S wave (QRS), and time interval between the onset of the P wave and the beginning of the QRS complex (PR).
- ECG-derived parameters: Peak HR within the first 4 h, HR $AUC_{0\text{-}4h}$ (area under the observation-time curve for HR from time 0 to 4 h), and HR $AUC_{0\text{-}12h}$ (area under the observation-time curve for HR from time 0 to 12 h).
- Laboratory safety parameters.

Statistical methods:

Pharmacokinetic variables

- All GB, formoterol, B17MP and BDP plasma PK parameters (excepts for t_{max}) and GB and total formoterol CLr were compared between renal impaired and matching healthy subjects using an analysis of covariance model (ANCOVA) on the log-transformed data, with subject group as factor and BMI, age and gender as covariates. The analysis was conducted comparing each group of renal impaired subjects with the corresponding group of matching healthy subjects. The adjusted means ratio between each group of renal impaired subjects and the corresponding healthy subjects was calculated together with its 90% confidence interval (CI).
- For GB, B17MP, formoterol and BDP t_{max}, the Hodges-Lehmann non-parametric estimate of location shift between renal impaired and healthy subjects based on untransformed data was provided with its 90% two-sided CI.
- GB $Ae_{0\text{-}4h}$, $Ae_{4\text{-}8h}$, $Ae_{8\text{-}12h}$, $Ae_{12\text{-}24h}$, $Ae_{24\text{-}36h}$, $Ae_{36\text{-}48h}$, $Ae_{48\text{-}60h}$, $Ae_{60\text{-}72h}$, $Ae_{0\text{-}72h}$ and fe, and formoterol (free and total) $Ae_{0\text{-}4h}$, $Ae_{4\text{-}8h}$, $Ae_{8\text{-}12h}$, $Ae_{12\text{-}24h}$, $Ae_{0\text{-}24h}$ and fe were analysed using descriptive statistics.
- The analysis for the PK variables for plasma GB was repeated using an ANCOVA model that accounted for the potential correlation between matched pairs of subjects. The analysis was performed on the log-transformed data, with subject group as a factor, BMI, age and gender as covariates and a random effect for each matched pair. Subjects that were matched share a random effect while each healthy subjects that was not matched to a renal impaired patient was included in the analysis with a random effect of its own.

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- Correlation between CLr of GB and formoterol and degree of RI in terms of eGFR was analysed with a linear regression model. The correlation analysis was done also for CL/F, AUC_{0-t} and C_{max} of formoterol and GB and for AUC_{0-t} and C_{max} of B17MP. Point estimates of the model parameters together with their CIs were presented.

Safety variables

- The number and percentage of subjects who experienced at least one treatment-emergent adverse event (TEAE) was summarised by subject group (i.e., renal impaired subjects and healthy subjects).
- For ECG parameters (HR, PR, QRS, QTcF), the average of the triplicates at each time point pre-dose and post-dose was considered for the statistical analysis. The following statistics were calculated by subject group at each time point post-dose:
    - mean absolute value with its 95% CI;
    - mean change from baseline with its 90% CI.
- For QTcF, the number and percentage of subjects with a
    - QTcF interval > 450 ms, > 480 ms and > 500 ms for male subjects and > 470 ms and > 500 ms (for female subjects);
    - change from baseline in QTcF interval > 30 ms and > 60 ms;

  at each time point post-dose and any time point post-dose were presented by subject group.
- In addition, mean time profile plots of ECG parameter changes from baseline were presented for each renal impaired group with their matching healthy subjects.
- Superimposed profiles of HR and QTcF changes from baseline with GB and formoterol concentrations over time were presented.
- Peak HR within the first 4 h, HR AUC_{0-4h} and HR AUC_{0-12h} were summarised by subject group using descriptive statistics and the 95% CI of the mean.
- For vital signs (SBP, DBP), the mean absolute value and the mean change from baseline with their 95% CI were calculated by subject group at each time point post-dose.
- Laboratory safety parameters were summarised using descriptive statistics. In addition, shift tables from screening to Day 4 were presented.

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Summary – Results:

Pharmacokinetic Results:

Glycopyrronium bromide

The systemic exposure (AUCs) to GB was similar between subjects with mild and moderate RI and matched healthy subjects (apart from AUC_{0-12h} of subjects with moderate RI which was 30% higher), while it was increased (AUC_{0-12h}: 3.2-fold, AUC_{0-72h}: 2.6-fold, AUC_{0-t}: 2.5-fold) in subjects with severe RI.

C_{max} was 35% lower in subjects with mild RI and similar in subjects with moderate RI, as compared to healthy subjects, while it was 1.9-fold higher in subjects with severe RI. The time to peak concentration (t_{max}) was similar between subjects with mild and moderate RI and the matched healthy subjects, while it was delayed by 55 min in subjects with severe RI.

The total body clearance (CL/F) was similar in subjects with mild and moderate RI, as compared to the matched healthy subjects, while it was 61% decreased in subjects with severe RI.

Compared to the matched healthy subjects, renal clearance (CLr) was decreased by 51%, 54% and 87% in subjects with mild, moderate and severe RI, respectively.

There seems to be a tendency to a strong linear relationship between eGFR and CLr, and to a moderate linear relationship between eGFR and CL/F, AUC_{0-t} and AUC_{0-12h}, with a positive slope for CLr and CL/F and a negative slope for AUC.

Glycopyrronium Bromide PK Parameters

PK parameter	Mild renal impairment			Moderate renal impairment			Severe renal impairment		
	Renal impaired	Healthy	Ratio (90%CI)[a]	Renal impaired	Healthy	Ratio (90%CI)[a]	Renal impaired	Healthy	Ratio (90%CI)[a]
AUC_{0-t} (h.pg/mL)	255.7	291.1	87.9 (73.8; 104.6)	317.3	279.3	113.6 (83.2; 155.1)	589.4	233.8	252.1 (160.0; 397.1)
AUC_{0-72h} (h.pg/mL)	255.7	291.1	87.9 (73.8; 104.6)	317.3	279.3	113.6 (83.2; 155.1)	595.0	232.3	256.1 (163.9; 400.1)
AUC_{0-12h} (h.pg/mL)	99.0	112.5	88.0 (65.8; 117.8)	145.3	111.8	130.0 (82.0; 205.9)	256.8	79.2	324.4 (202.6; 519.4)
C_{max} (pg/mL)	27.2	41.9	64.9 (40.2; 104.7)	39.4	40.9	96.4 (49.6; 187.5)	44.1	23.7	186.5 (119.7; 290.5)
CL/F (mL/min)	6517.2	5725.5	113.8 (95.6; 135.5)	5253.2	5966.9	88.0 (64.5; 120.2)	2801.0	7173.5	39.0 (25.0; 61.0)
t_{max} (h)	0.21	0.08	0.09 (0.00; 0.92)	0.08	0.08	0.00 (-0.09; 0.17)	1.00	0.13	0.92 (0.17; 1.50)
CLr (mL/min)	183.0	374.3	48.9 (38.3; 62.4)	171.9	376.8	45.6 (37.1; 56.2)	49.8	385.9	12.9 (9.1; 18.2)

Values are adjusted means except for t_{max}: median.

[a] The adjusted mean ratio of RI vs. matched healthy volunteers with its 90% CI, based on ANCOVA model with subject group (renal impaired vs. healthy) as factor and BMI, age and gender as covariates. For t_{max}, the Hodges-Lehmann non-parametric estimate of location shift between renal impaired and healthy based on untransformed data, is provided with its 90% CI.

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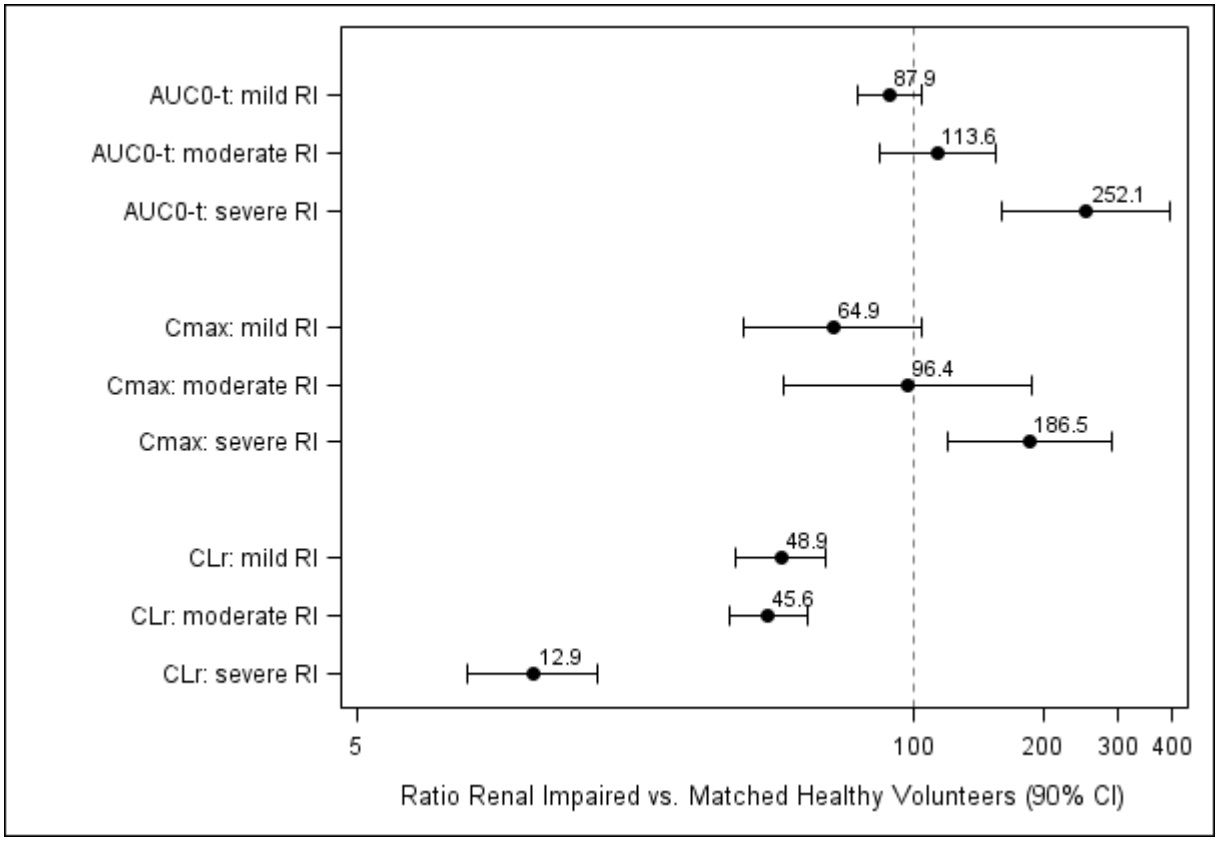
Forest Plot of the Renal Impaired Subjects vs Matching Healthy Volunteers Ratios for GB PK Parameters (PK Population)



Formoterol

The analysis for the PK variables of formoterol were run both including and excluding Patients [redacted] and [redacted] (severe renal impaired) and the matched healthy subjects since, after database lock, in the bioanalytical reports, quantifiable pre-dose samples at concentrations higher than 10% of C_{max} were discovered for these two patients. Pre-dose samples >10% C_{max} indicates sample contamination and thus meets condition for the exclusion of the profiles pre-defined in the PK Data Review Report. Since the evidence for the exclusion of the profiles was discovered only after DB lock, both analyses are reported.

The systemic exposure (AUCs) to formoterol was decreased (AUC_{0-24h}: 24%, AUC_{0-t}: 26%) in subjects with mild RI and similar in subjects with moderate RI, as compared to healthy subjects, while it was increased (AUC_{0-24h}: 2.9-fold, AUC_{0-t}: 3.1-fold) in subjects with severe renal impairment. After exclusion of Patients [redacted] and [redacted] and their matched healthy volunteers, AUCs were similar in subjects with severe RI, compared to healthy subjects.

C_{max} was 52% and 41% lower in subjects with mild and moderate RI, respectively, compared to healthy subjects, while it was similar for subjects with severe RI. After exclusion of Patients [redacted] and [redacted] and their matched healthy volunteers, C_{max} was 45% lower in subjects with severe RI, compared to healthy subjects. The time to peak concentration (t_{max}) was delayed by 15 min and 110 min between subjects with mild and moderate RI, respectively, compared to healthy subjects, while it was similar for subjects with severe RI.

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The total body clearance (CL/F) was increased by 31% in subjects with mild RI and similar in subjects with moderate RI, while it was decreased by 66% in subjects with severe RI, compared to healthy subjects. After exclusion of Patients [redacted] and [redacted] and their matched healthy volunteers, CL/F was similar between subjects with severe RI and healthy volunteers.

Terminal half-life was similar between subjects with mild, moderate and severe RI, and healthy subjects.

Compared to the matched healthy subjects, renal clearance increased by 56% for subjects with mild RI, and was similar for subjects with moderate RI, while it was decreased by 49% for subjects with severe RI.

No linear relationship was observed between eGFR and CLr, CL/F, AUC_{0-t} and C_{max}.

Formoterol PK Parameters

PK parameter	Mild renal impairment			Moderate renal impairment			Severe renal impairment [1]		
	Renal impaired	Healthy	Ratio (90%CI)[a]	Renal impaired	Healthy	Ratio (90%CI)[a]	Renal impaired	Healthy	Ratio (90%CI)[a]
AUC_{0-t} (h.pg/mL)	54.2	73.0	74.3 (51.3; 107.5)	78.6	70.4	111.6 (65.9; 188.8)	82.6	70.7	116.9 (73.8; 185.0)
AUC_{0-24h} (h.pg/mL)	62.0	81.2	76.3 (51.4; 113.3)	91.8	80.5	114.0 (68.0; 191.2)	94.8	81.8	115.9 (74.7; 179.9)
C_{max} (pg/mL)	14.9	31.2	47.7 (34.3; 66.2)	18.2	30.9	59.1 (36.8; 94.8)	17.6	32.2	54.6 (38.7; 77.0)
CL/F (mL/min)	6456.8	4927.2	131.0 (88.3; 194.5)	4358.1	4969.7	87.7 (52.3; 147.0)	4217.6	4888.6	86.3 (55.6; 133.9)
t_{max} (h)	0.38	0.08	0.25 (0.09; 0.92)	2.00	0.08	1.83 (0.00; 1.92)	0.21	0.08	0.13 (0.00; 1.92)
$t_{1/2}$ (h)	4.4	3.9	113.9 (79.8; 162.6)	4.9	3.6	136.0 (58.0; 319.0)	5.0	4.6	107.2 (54.4; 211.2)
CLr (mL/min)	981.7	629.9	155.8 (86.2; 281.6)	632.1	628.6	100.6 (47.1; 214.8)	343.2	674.9	50.9 (20.2; 128.3)

Values are adjusted means except for t_{max}: median.

[a] The adjusted mean ratio of RI vs. matched healthy volunteers with its 90% CI, based on ANCOVA model with subject group (renal impaired vs. healthy) as factor and BMI, age and gender as covariates. For t_{max}, the Hodges-Lehmann non-parametric estimate of location shift between renal impaired and healthy based on untransformed data, is provided with its 90% CI.

[1]: Patients [redacted] and [redacted] (contaminated samples) and the matched healthy volunteers were excluded.

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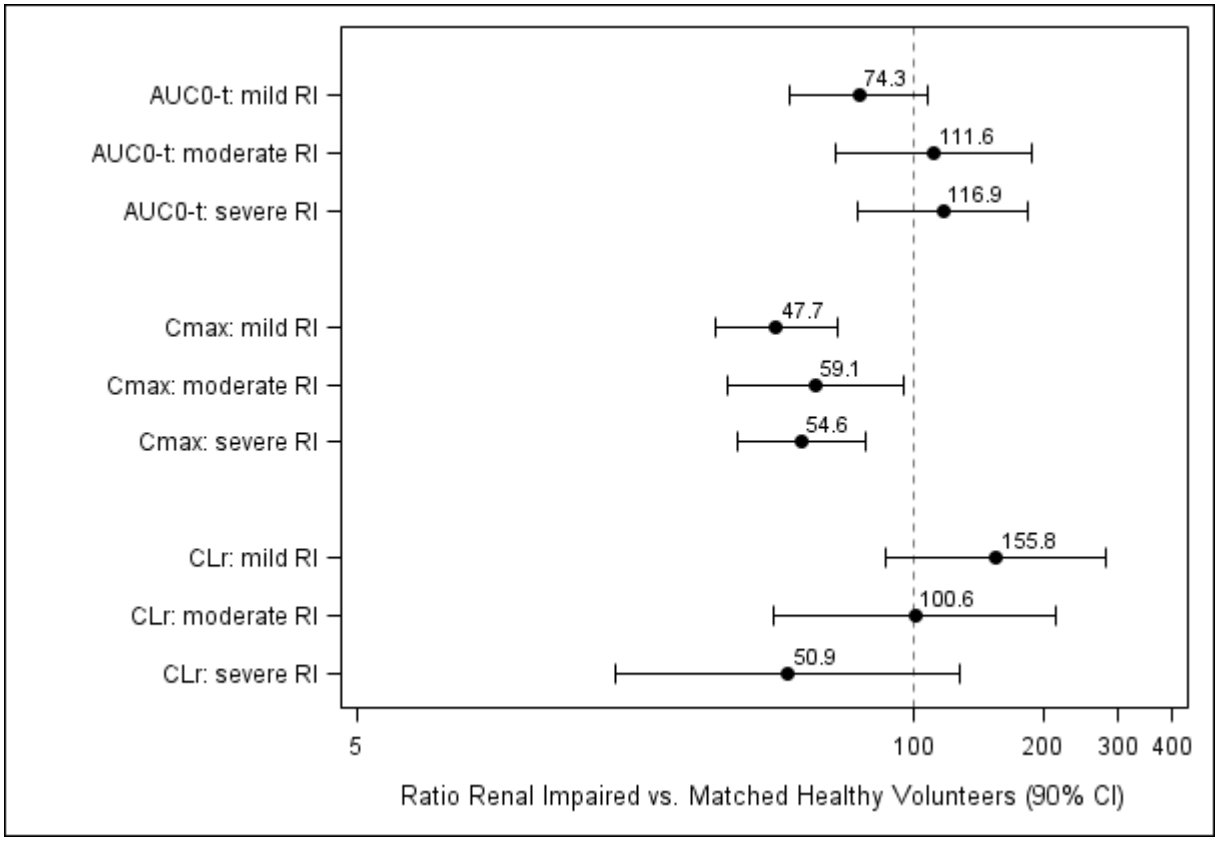
Forest Plot of the Renal Impaired Subjects* vs Matching Healthy Volunteers Ratios for Formoterol PK Parameters (PK Population)



* Severe Patients [redacted] and [redacted] (contaminated samples) and the matched healthy volunteers were excluded.

BDP

The systemic exposure (AUC_{0-t}) to BDP was decreased by 43%, 69% and 45% in subjects with mild, moderate and severe RI, respectively, compared to healthy subjects.

C_{max} was decreased by 31%, 68%, 49% in subjects with mild, moderate and severe RI, respectively, compared to healthy subjects.

BDP PK Parameters

PK parameter	Mild renal impairment			Moderate renal impairment			Severe renal impairment		
	Renal impaired	Healthy	Ratio (90%CI)[a]	Renal impaired	Healthy	Ratio (90%CI)[a]	Renal impaired	Healthy	Ratio (90%CI)[a]
AUC_{0-t} (h.pg/mL)	66.3	116.9	56.7 (35.9; 89.6)	29.0	95.1	30.5 (15.3; 60.6)	57.8	105.3	54.8 (29.6; 101.6)
C_{max} (pg/mL)	541.0	786.4	68.8 (45.2; 104.7)	227.3	712.5	31.9 (14.6; 69.7)	396.7	781.9	50.7 (28.0; 91.9)

Values are adjusted means.

[a] The adjusted mean ratio of RI vs. matched healthy volunteers with its 90% CI, based on ANCOVA model with subject group (renal impaired vs. healthy) as factor and BMI, age and gender as covariates.

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B17MP

The systemic exposure (AUCs) was decreased in subjects with mild (AUC_{0-t}: 31%, AUC_{0-24h}: 29%, $AUC_{0-\infty}$: 22%) and moderate (AUC_{0-t}: 31%, AUC_{0-24h}: 26%, $AUC_{0-\infty}$: 22%) RI, compared to healthy subjects, while it was similar for subjects with severe RI.

C_{max} was decreased in subjects with mild, moderate and severe RI by 46%, 39% and 26%, respectively, compared to healthy subjects. The time to peak concentration (t_{max}) was similar for subjects with mild RI, compared to healthy subjects, while it was delayed by 50 min and 45 min for subjects with moderate and severe RI, respectively.

Terminal half-life was similar between subjects with mild, moderate and severe RI, and healthy subjects.

No linear relationship is observed between eGFR and AUC_{0-t} or C_{max}.

B17MP PK Parameters

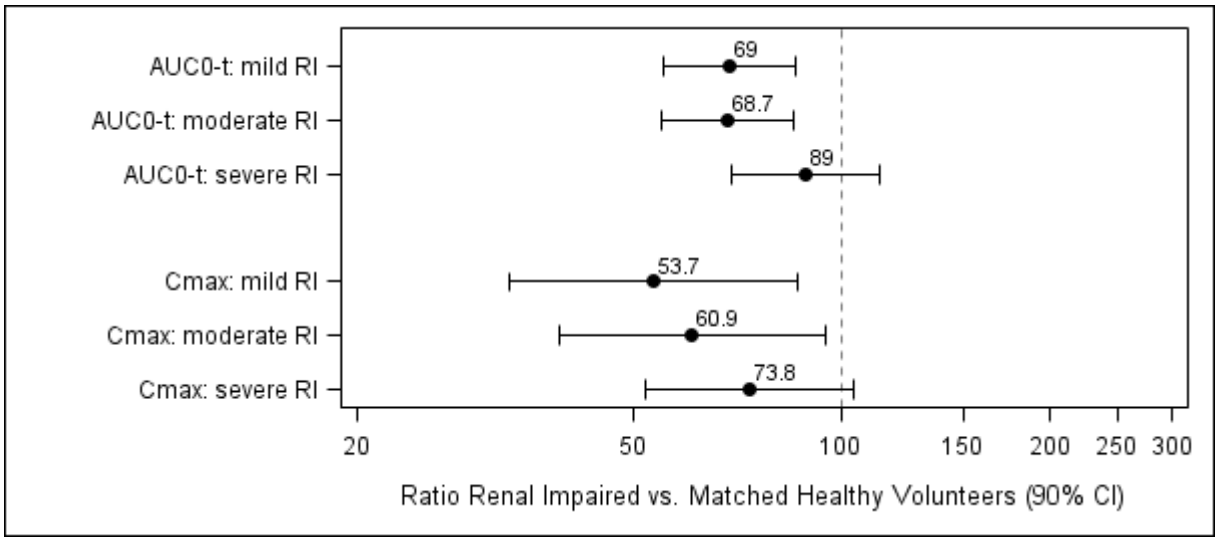
PK parameter	Mild renal impairment			Moderate renal impairment			Severe renal impairment		
	Renal impaired	Healthy	Ratio (90%CI)[a]	Renal impaired	Healthy	Ratio (90%CI)[a]	Renal impaired	Healthy	Ratio (90%CI)[a]
AUC_{0-t} (h.pg/mL)	2403.6	3483.2	69.0 (55.3; 86.1)	2355.6	3428.9	68.7 (55.1; 85.6)	2534.4	2848.4	89.0 (69.7; 113.5)
AUC_{0-24h} (h.pg/mL)	2666.9	3760.3	70.9 (58.1; 86.6)	2618.2	3531.7	74.1 (60.9; 90.2)	2750.6	3014.9	91.2 (73.6; 113.1)
$AUC_{0-\infty}$ (h.pg/mL)	2914.8	3727.2	78.2 (61.2; 99.9)	2786.0	3589.1	77.6 (62.8; 96.0)	2882.4	2932.5	98.3 (76.7; 126.0)
C_{max} (pg/mL)	451.6	841.0	53.7 (33.2; 86.8)	420.5	690.4	60.9 (39.1; 94.9)	472.0	639.9	73.8 (52.1; 104.3)
t_{max} (h)	0.25	0.17	0.17 (0.00; 0.75)	1.00	0.17	0.83 (0.09; 1.83)	1.00	0.25	0.75 (0.25; 0.83)
$t_{1/2}$ (h)	4.5	4.3	104.3 (88.9; 122.4)	4.3	4.7	91.3 (75.4; 110.4)	4.9	4.2	115.7 (97.1; 137.9)

Values are adjusted means except for t_{max}: median.

[a] The adjusted mean ratio of RI vs. matched healthy volunteers with its 90% CI, based on ANCOVA model with subject group (renal impaired vs. healthy) as factor and BMI, age and gender as covariates. For t_{max}, the Hodges-Lehmann non-parametric estimate of location shift between renal impaired and healthy based on untransformed data, is provided with its 90% CI.

SYNOPSIS

Forest Plot of the Renal Impaired Subjects vs Matching Healthy Volunteers Ratios for B17MP PK Parameters (PK Population)



Safety Results:

No TEAEs occurred during the study.

No clinically relevant trends or changes from baseline in laboratory, vital sign or ECG parameters were observed.

In males, a QTcF interval of > 450 ms was observed in 1 moderate renal impaired subject. In females, a QTcF interval of > 470 ms was observed in 1 moderate renal impaired subject. None of the subjects had an increase from baseline in QTcF of more than 30 ms.

Conclusion:

The degree of RI had an impact on GB systemic exposure which tended to increase with decreasing renal function. This effect was mainly observed in subjects with severe RI. An effect of RI on total systemic clearance was observed only in severe RI subjects, while renal clearance was decreased in each group of subjects with RI as compared to healthy subjects, showing a strong correlation between renal clearance and the degree of RI. Taken together these results suggest that non-renal clearance plays a role in GB elimination and is able to counterbalance the reduced renal elimination of GB in patients with mild and moderate RI.

The degree of RI had no impact on formoterol systemic exposure being AUCs similar or even lower in each group of subjects with different degree of RI as compared to healthy subjects, while C_{max} was reduced by approximately 50% in all groups of renal impaired subjects as compared to healthy subjects. The total systemic clearance of formoterol was slightly increased in subjects with mild RI and was similar in subjects with moderate and severe RI, as compared to healthy subjects. Renal clearance of total formoterol was, respectively, increased, unchanged and decreased in subjects with mild, moderate and severe RI, as compared to healthy subjects. However, no linear relationship between the degree of RI and the renal clearance of total formoterol was detected.

BDP systemic exposure, in terms of both AUCs and C_{max}, was lower in renal impaired patients as compared to healthy subjects.

SYNOPSIS

In agreement with the parent compound data, B17MP systemic exposure was lower in renal impaired subjects as compared to healthy subjects; however, the differences between RI and healthy subjects tended to decrease when the degree of RI increased.

The assessment of AEs, laboratory parameters, vital signs, and ECG did not reveal any safety issue in this study. Despite a higher exposure of GB, especially when CHF 5993 pMDI was administered in subjects with severe RI, the study treatment showed good and similar safety profiles in all groups with varying degrees of RI and in the matched healthy subjects.

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