CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-592

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	21-592
Drug Substance	Formoterol fumarate
Drug Product	Foradil® Certihaler™
Strengths	10 μg
Route of Administration	Multi-dose dry powder inhaler (MDDPI) Oral Inhalation
Sponsor	Novartis Pharmaceuticals, Inc.
Type of submission	Original NDA
Date of submission	12/17/02
OCPB Division	DPE-II
Clinical Division	Pulmonary and Allergy Drug Products (HFD-570)
Reviewer	Shinja R. Kim, Ph.D.
Team Leader	Emmanuel Fadiran, Ph.D.

1. EXECUTIVE SUMMARY

Foradil® (formoterol fumarate) is a selective β_2- adrenergic receptor agonist, and its bronchodilatory activity is observed in patients with asthma after inhalation. It is characterized by a rapid onset and long duration of action. Foradil® in a single-dose dry powder inhaler (Aerolizer™) is approved for maintenance treatment of asthma and COPD.

Foradil® Certihaler™ is a new multi-dose dry powder inhaler (MDDPI) for the delivery of formoterol fumarate that can dispense sixty 10 μg metered (equivalent to 8.5 μg emitted) doses. Foradil® Certihaler is for long-term twice daily administration in the maintenance treatment of asthma and in the prevention of bronchospasm in adults and children 5 years of age and older, b(4)

Four PK studies (0601, 0602, 2303 and 0604) were included in Section 6 to support the NDA. Studies 0601 and 0602 were dose finding studies, conducted in adults and adolescents and children aged 5-12 years with persistent asthma, respectively. In these studies, doses of 5, 10, 15, and 30 μg formoterol and placebo were delivered by the MDDPI and 12 μg formoterol by Aerolizer. The excretion of unchanged formoterol in urine was used as a measure of systemic exposure to formoterol. Studies 2303 and 0604 were Phase III studies conducted in adults and adolescents and children aged 5-12 years with persistent asthma, respectively to evaluate the efficacy of formoterol 10 μg bid delivered by the MDDPI with placebo for 12 weeks. Unchanged formoterol was determined in plasma and urine in a subgroup of patients in these studies.

Comments (to the reviewing medical officer): Patients #10 (center 507) and #2 (center 518) from Study 0604 were not included in the PK analysis. C_{max} and $AUC_{0\text{-}12hr,\,ss}$ for patient #10 were 58.5 pg/mL and 314.5 pg•hr/mL, respectively (2.9 and 3.8 times higher than the respective mean values). C_{max} and $AUC_{0\text{-}12hr,\,ss}$ for patient #2 were 40.6 pg/mL and 426.6 pg•hr/mL, respectively (2 and 5.2 times higher than the respective mean values). These two patients, possibly, are poor metabolizers (deficient in CYP2D6 or CYP2C19). Therefore, please review their profiles for formoterol related adverse effects.

1.1. Recommendation: The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the Section 6, and found that NDA 21-592 is acceptable from a CPB standpoint provided that the sponsor agrees with the Agency's recommendation on the labeling.

Shinja R. Kim, Ph.D., DPE II

Emmanuel Fadiran, Ph.D., Team Leader

2. Table of Contents

3. Summary of Clinical Pharmacology and Biopharmaceutics Findings

The pharmacokinetic data was obtained from 4 studies (0601, 0602. 2303 and 0604) following formoterol fumarate administered by MDDPI. Studies 0601 and 0602 were dose finding studies with similar design (incomplete-block, crossover) but performed in different study populations (*i.e.*, Study 0601 in adults and adolescents and 0602 in children aged 5-12 years). Doses of 5, 10, 15, and 30 µg formoterol and placebo were delivered by the MDDPI and 12 µg formoterol by Aerolizer, b.i.d for 1 week. Unchanged and total (unchanged plus conjugated metabolites) formoterol excreted in urine (nmol and %dose) were determined in a subgroup of patients in both studies. The excretion of unchanged formoterol was used as a measure of systemic exposure to formoterol. The results of these studies are provided in Table 1. The result for total formoterol was similar to that of unchanged formoterol (page xx).

Table 1. Geometric mean (and 95% CI) for the amount excreted in urine ($Ae_{0\text{-}12h}$) as **unchanged** formoterol (nmol and %dose)

Study 0601

Dose (metered)	5 µg MDDPI	10 µg MDDPI	15 µg MDDPI	30 µg MDDPI	12 µg Aerolizer
N	30	25	31	23	27
nmol	1.34 (1.04-1.74)	2.34 (1.92-2.86)	3.47 (2.84-4.23)	4.32 (2.51-7.44)	1.89 (1.65-2.15)
%dose	11.29 (8.73-14.60)	9.86 (8.09-12.01)	9.72 (7.96-11.87)	6.05 (3.52-10.43)	6.61 (5.80-7.54)

Study 0602

Dose	5 µg MDDPI	10 µg MDDPI	15 µg MDDPI	30 µg MDDPI	12 µg Aerolizer
N	24	21	21	26	27
nmol	1.78 (1.47-2.16)	2.54 (1.93-3.35)	3.87 (2.08-7.21)	8.73 (6.55-11.63)	2.44 (1.93-3.08)
%dose	15.01 (12.38-18.20)	10.69 (8.11-14.08)	10.84 (5.82-20.21)	12.24 (9.19-16.30)	8.54 (6.76-10.78)

In both studies the systemic exposure to formoterol from 10 µg MDDPI was higher than from the Aerolizer by 49% in Study 0601 and 25 % in Study 0602 0602 based on percentage of formoterol

dose excreted in urine. In terms of absolute amounts of formoterol (i.e., nmol) excreted in urine (nmol data), the 10 µg MDDPI dose and the 12 µg Aerolizer dose differed by 23 % in Study 0601 and was similar in Study 0602. The 95% confidence intervals for the exposures from MDDPI 10 µg and Aerolizer 12 µg overlapped in each study suggesting that the absolute systemic exposure was not substantially different between the two doses (Table 1).

Two Phase III studies (#2303 and #0604) were conducted to evaluate the efficacy of formoterol 10 µg bid delivered by the MDDPI and placebo for 12 weeks. Design of these studies was similar; Study 02303 and #0604 were conducted in adults and adolescents and children aged 5-12 years, respectively. Unchanged formoterol in plasma and urine were measured in a subgroup of patients. The results of these studies are provided in Table 2.

Table 2. Summary of PK parameters for subjects administered 10 µg formoterol via MDDP

Study 2303

	Visit 2		Visit 5					
	Ae_{0-12} (nmol)	Ae_{0-12} (%dose)	Ae_{0-12} (nmol)	Ae_{0-12} (%dose)	C_{max} (pg/mL)	AUC_{0-12} (pmol.h/L)	CL_R (L/h)	R*
N	15	15	12	12	10	10	9	9
Mean	1.35	5.68	2.74	11.50	20.3	73.2	19.8	1.59
SD	0.99	4.14	1.28	5.38	5.2	39.1	12.0	0.72
Min	0.00	0.00	0.36	1.51	11.1	17.3	1.4	1.05
Median	1.67	7.02	2.91	12.24	20.3	69.8	18.4	1.38
Max	2.95	12.40	4.73	19.89	28.0	123.8	43.4	3.48

R* = accumulation ratio

Study 0604

	Visit 2		Visit 4					
	Ae_{0-12} (nmol)	Ae_{0-12} (%dose)	Ae_{0-12} (nmol)	Ae_{0-12} (%dose)	C_{max} (pg/mL)	AUC_{0-12} (pg.h/mL)	CLR (LIh)	R*
N	15	15	14	14	8	8	8	13
Mean	1.82	7.66	2.81	11.80	20.1	82.7	13.38	1.58
SD	0.80	3.36	2.31	9.73	8.5	40.9	19.75	1.17
Min	1.03	4.33	0.59	2.48	6.5	28.4	1.72	0.34
Median	1.68	7.06	1.97	8.28	17.5	81.4	6.21	1.32
Max	4.44	18.67	9.18	38.60	31.4	144.8	61.68	4.94

Note: Visit 4 and 5 refer to steady state

Formoterol was rapidly absorbed and peak concentrations were reached within the first 10 min (first sampling time) of dosing in adults and children 5-12 years of age. Accumulation of formoterol approximately 60% at steady state was seen in urine data. The mean plasma concentrations at 10 min, 2 hr and 8 hr post inhalation of 10 µg formoterol MDDPI ranged between 3.5 and 20.3 pg/mL and 6.6 and 20.1 pg/mL in adults and children with persistent asthma, respectively. The mean amount of unchanged formoterol excreted over 12 hours at steady state was similar in adults and children (2.74 nmol or 11.5% of dose; 2.81 nmol or 11.8%, respectively). Mean renal clearances for adults and children were 19.8 and 13.4 L/h respectively.

4. Question Based Review

4.1 General Attributes

4.1.1 What are the known pharmacokinetic characteristics of formoterol fumarate?

The following pharmacokinetic characteristics of formoterol fumarate have been summarized in previous submissions:

Absorption is both rapid and extensive. After a single, high dose (120 µg) the peak plasma concentration is observed at 5 minutes post inhalation, and reached maximum concentration of 92 pg/mL. At least 65% of an 80 µg tritiated oral dose is absorbed. Using urinary excretion as a measure of systemic bioavailability, unchanged "racemic" and the individual (R,R) and (S,S)-enantiomers increase in proportion to the dose (12-96 µg), and thus absorption following inhalation appears to be linear. In COPD patients treated for 12 weeks with formoterol Aerolizer 12 or 24 µg bid, the mean plasma concentrations of formoterol ranged between 4.0 and 8.8 pg/mL and 8.0 and 17.3 pg/mL, respectively at 10 min, 2 hr and 6 hr post inhalation.

Formoterol is metabolized primarily by direct glucuronidation at either the phenolic or aliphatic hydroxyl group and O-demethylation followed by glucuronidation at either phenolic hydroxyl group. Minor pathways involve sulfate conjugation of formoterol and deformylation followed by sulfate conjugation. The most prominent metabolite is the phenolic O-glucuronide of formoterol and the second major metabolite the 2'-O-glucuronide of O-demethyl formoterol. Multiple CYP450 isozymes catalyze O-demethylation (2D6, 2C19, 2C9 and 2A6), consequently, the potential for metabolic drug-drug interaction is low.

After a single oral dose ^{3}H-formoterol fumarate, 59-62% of the dose is recovered in the urine and 32-34% in the feces. Formoterol is eliminated primarily by metabolism. Following inhalation of 12-120 µg formoterol fumarate approximately 6-9% of the dose is recovered in the urine as unchanged formoterol with the (R,R) and (S,S)-enantiomers contributing 40% and 60%, respectively.

Plasma formoterol kinetics and urinary excretion data indicate a biphasic elimination with a terminal half-life of racemic formoterol measured at 10 h. The terminal elimination half-lives of the (R,R) and (S,S)-enantiomers measured by urinary excretion are 13.9 h and 12.3 h, respectively.

4.2 Clinical Pharmacology

4.2.1. What is the bioavailability of formoterol from the MDDPI compared to the Aerolizer in adults and children? Is there any difference in bioavailability of formoterol between adults and children?

The bioavailability of formoterol from the MDDPI as compared with the Aerolizer was investigated in Studies 0601 and 0602 by measuring the urinary excretion of the drug.

Study 0601 was a dose finding study in adults and adolescents asthma patients (age ranged 20-73 years). Subjects were treated on a b.i.d. basis for 7 days per treatments: placebo, Aerolizer 12 µg, formoterol MDDPI 5, 10, 15 and 30 µg. Urine was collected over 12 h after the last dose of

each treatment period. Tables 1 and 2 summarize the urine excretion data for unchanged and total formoterol, respectively.

Table 1. Geometric mean (and 95% CI) of unchanged formoterol (as nmol and %dose) excreted in urine ($Ae_{0\text{-}12h}$) – Study 0601

Dose (metered)	5 µg MDDPI	10 µg MDDPI	15 µg MDDPI	30 µg MDDPI	12 µg Aerolizer
N	30	25	31	23	27
nmol	1.34 (1.04-1.74)	2.34 (1.92-2.86)	3.47 (2.84-4.23)	4.32 (2.51-7.44)	1.89 (1.65-2.15)
%dose	11.29 (8.73-14.60)	9.86 (8.09-12.01)	9.72 (7.96-11.87)	6.05 (3.52-10.43)	6.61 (5.80-7.54)

Table 2. Geometric mean (and 95% CI) of total formoterol (as nmol and %dose) excreted in urine ($Ae_{0\text{-}12h}$) – Study 0601

Dose	5 µg MDDPI	10 µg MDDPI	15 µg MDDPI	30 µg MDDPI	12 µg Aerolizer
N	30	25	31	23	27
nmol	2.08 (1.62-2.67)	3.45 (2.89-4.13)	5.29 (4.31-6.51)	6.28 (3.99-9.88)	3.33 (2.81-3.94)
%dose	17.48 (13.62-22.44)	14.51 (12.14-17.35)	14.84 (12.07-18.24)	8.80 (5.59-13.86)	11.66 (9.84-13.82)

The design of Study 0602 was similar to that of Study 0601, except that study 0602 was performed in children aged 5 to 12 years old. Urine excretion data from this study are summarized in Tables 3 and 4.

Table 3. Geometric mean (and 95% CI) of unchanged formoterol (as nmol and %dose) excreted in urine ($Ae_{0\text{-}12h}$) – Study 0602

Dose	5 µg MDDPI	10 µg MDDPI	15 µg MDDPI	30 µg MDDPI	12 µg Aerolizer
N	24	21	21	26	27
nmol	1.78 (1.47-2.16)	2.54 (1.93-3.35)	3.87 (2.08-7.21)	8.73 (6.55-11.63)	2.44 (1.93-3.08)
%dose	15.01 (12.38-18.20)	10.69 (8.11-14.08)	10.84 (5.82-20.21)	12.24 (9.19-16.30)	8.54 (6.76-10.78)

Table 4. Geometric mean (and 95% CI) of total formoterol (as nmol and %dose) excreted in urine ($Ae_{0\text{-}12h}$) – Study 0602

Dose	5 µg MDDPI	10 µg MDDPI	15 µg MDDPI	30 µg MDDPI	12 µg Aerolizer
N	24	21	21	26	27
nmol	2.45 (2.03-2.95)	3.43 (2.64-4.46)	5.22 (3.08-8.84)	11.60 (8.47-15.87)	3.44 (2.61-4.51)
%dose	20.58 (17.10-24.77)	14.43 (11.11-18.75)	14.64 (8.65-24.78)	16.25 (11.88-22.25)	12.04 (9.16-15.82)

In both studies the systemic exposure to formoterol from 10 µg MDDPI, compared to 12 µg from the Aerolizer, was higher for the MDDPI than the Aelolizer by 49% in Study 0601 and 25 % in Study 0602 based on percentage of formoterol dose excreted in urine. However, in terms of absolute amounts of formoterol excreted in urine (nmol data), the 10 µg MDDPI dose and the 12 µg Aerolizer dose differed by 23 % in Study 0601 and were similar in Study 0602. The 95% confidence intervals for the exposures from MDDPI 10 µg and Aerolizer 12 µg overlapped in each study suggesting that the absolute systemic exposure was not substantially different between the two doses.

There were no substantial difference in the urinary excretion between adults and children ages 5-12 years for the 10 µg MDDPI dose where the 95% confidence intervals of the geometric mean urinary excretion of both unchanged and total formoterol almost completely overlapped between the two populations (Figures 1 and 2). However, the amount excreted in urine in children was approximately twice as high (*i.e.*, higher exposure) as the adults following 30 µg MDDPI dose. Inter-subject variability, except for 5 µg MDDPI dose, was generally higher among children than adults. Variability for the Aerolizer tended to be lower than that for the MDDPI doses (*e.g.*, 12 µg Aerolizer *vs.* 10 µg MDDPI) in study with adults, while variability seemed to be similar for both devices in study with children.

Figure 1. Geometric means and 95% confidence intervals for the urinary excretion of unchanged formoterol ($Ae_{0\text{-}12h}$, %dose)

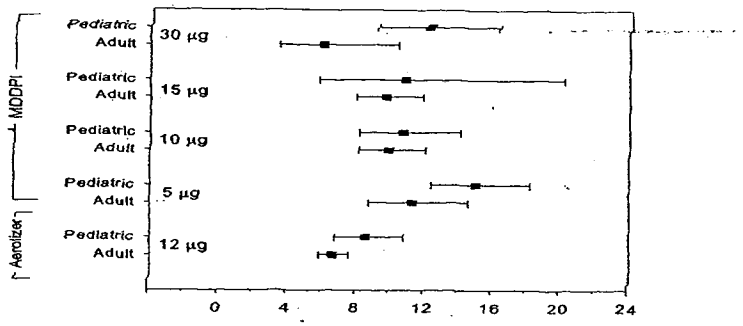
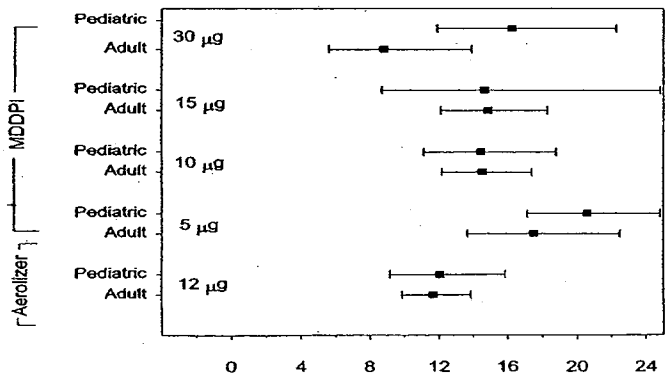


Figure 2. Geometric means and 95% confidence intervals for the urinary excretion of total formoterol ($Ae_{0\text{-}12h}$, %dose)



In conclusion, (1) the systemic exposure to formoterol as assessed by urinary excretion (%does excreted) following 10 µg MDDPI dose was higher, *i.e.*, 49% in adults and 25 % in children,

compared to 12 µg Aeolizer, based on percentage dose of formoterol excreted in urine. However, in terms of absolute amounts of formoterol excreted in urine (nmol data), the 10 µg MDDPI dose and the 12 µg Aerolizer dose differed by 23 % in adults and were similar in children. (2) There were no substantial difference in the urinary excretion between adults and children 5-12 years of age, except 30 µg MDDPI dose. (3) Inter-subject variability was generally higher among children compared to adults.

4.2.2 Based on PK parameters, what is the degree of linearity or non-linearity in the dose-exposure relationship?

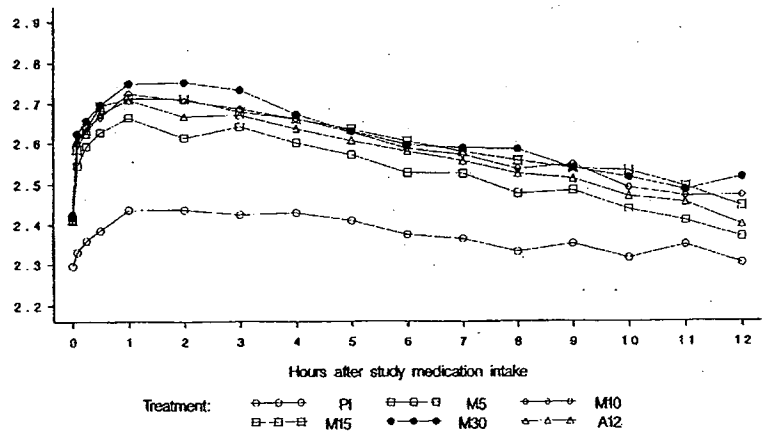
In adults study, the amount of unchanged formoterol excreted into urine as a percentage of dose ranged approximately 6-11%, while that in children ranged 11-15% across the dose range 5 to 30 µg. The dose proportionality of formoterol utilizing the MDDPI device was investigated by this reviewer using power model (linear regression). Power model for adults: Amount excreted in urine for unchanged = $e^{-0.32} * (dose)^{0.68}$; Amount excreted in urine for total $e^{-0.11} * (dose)^{0.65}$. Power model for children: Amount excreted in urine for unchanged = $e^{-0.42} * (dose)^{0.89}$; Amount excreted in urine for total $e^{-0.28} * (dose)^{0.87}$. Therefore, dose proportionality in the dose range of 5 to 30 µg was appears to be established based on the model. It was reported (PI) that PK following inhalation of 12 to 96 mcg of formoterol fumarate in 10 healthy males was linear.

4.2.3 What are the characteristics of the exposure-response/dose-response relationships for efficacy? Does the dose-finding study provide for the optimal dose to be used for Phase 3 study (studies)?

FEV_1 (forced expiratory volume in one second) relative to baseline was measured as the primary efficacy (bronchodilatory response) assessment parameter.

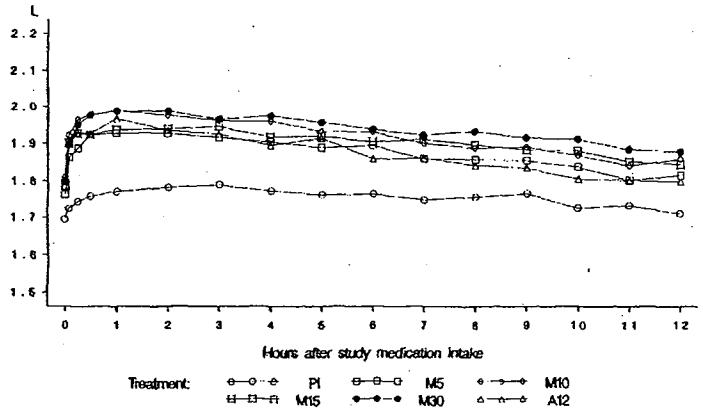
In Study 0601 (adults), Statistically significant increases of 12-hr AUC of FEV_1 after 1 week of treatment, compared with placebo, were observed for all 4 formoterol MDDPI doses and the 12 µg Aerolizer® dose (Figure 5). There were no significant differences in AUC of FEV_1 between any of the 4 MDDPI doses compared with the Aerolizer® dose, but statistically significant difference was observed between the 10, 15 and 30 µg MDDPI doses compare to the 5 µg MDDPI dose.

Figure 5 12-hour profile of least-squares means of FEV_1 after 1 week treatment in Study 0601



In Study 0602 (children), all four MDDPI doses and the Aerolizer dose demonstrated statistically and clinically significant increases in FEV_1 AUC over 12 hours compared to placebo. There were no significant differences among the formoterol doses (Figure 6).

Figure 6. 12-hour profile of least-squares means of FEV_1 after 1 week treatment in Study 0602



The amount of dose excreted (i.e., based on nmol) as unchanged (and total) formoterol in the 12-hour dosing interval following 12 µg Aerolizer™ was in between that following 5 and 10 µg formoterol by MDDPI in adults, while that was similar to after 10 µg MDDPI in children.

Overall, efficacy and PK data appears to support the choice of 10 µg formoterol MDDPI for further development in Phase 3 studies.

4.2.4. Does formoterol MDDPI has the potential to prolong QT? Was there any dose-dependent increase in QT? How does the QT profile of test product compare to that of the reference product?

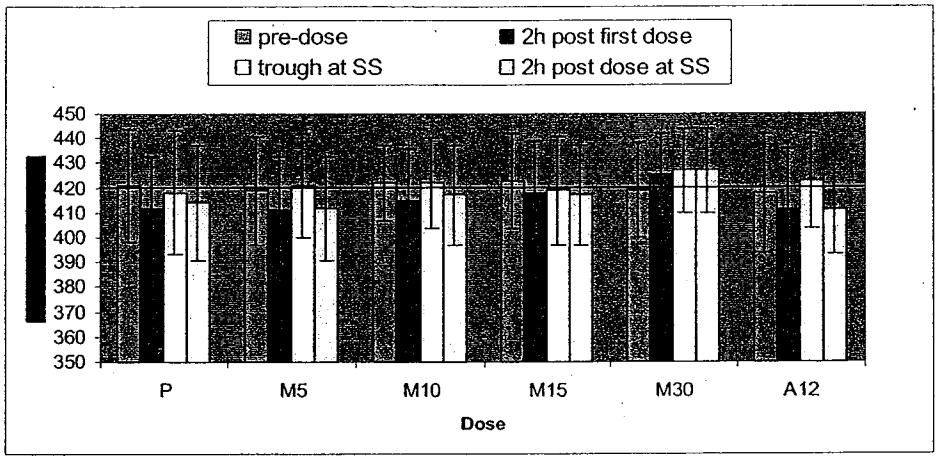
ECG was obtained pre-dose and 2-hrs post dose after the first dose and 1 week of treatment in two dose-finding studies. The mean (± SD) of QTc (msc), corrected by Bazett's formula, after each treatment are presented in Figure 7.

In Study 0601 (adults), statistically significant increases in QTc interval relative to placebo were observed at 2 hr following the first dose of 15 and 30 µg (the least squares mean estimates (LSM) of differences from placebo was 12 and 7 ms following 30 and 15 µg via MDDPI) and 1 week after of treatment of 30 µg formoterol via MDDPI (9 ms). Four patients (6%) had a QTc interval >460 msc at any time of the study, however, these patients had QTc values either >460 ms before the treatment, lower than 460 ms or no change after one week of treatment.

This reviewer analyzed QT data using Fridericia (QTcF) as well as Bazett's correction method (the sponsor used Bazett's method only). The mean differences of QTcF from placebo was <5 ms following all treatments (*i.e.*, doses used in this study did not affect the QTc by Fridericia's method), while QTc changes were similar to the sponsor's results (*i.e.*, described above and Figure 7). Since formoterol (β2-agonist; common adverse effects includes tachycardia) affects heart rate, QT correction using Fridericia's method is the most appropriate method of correction.

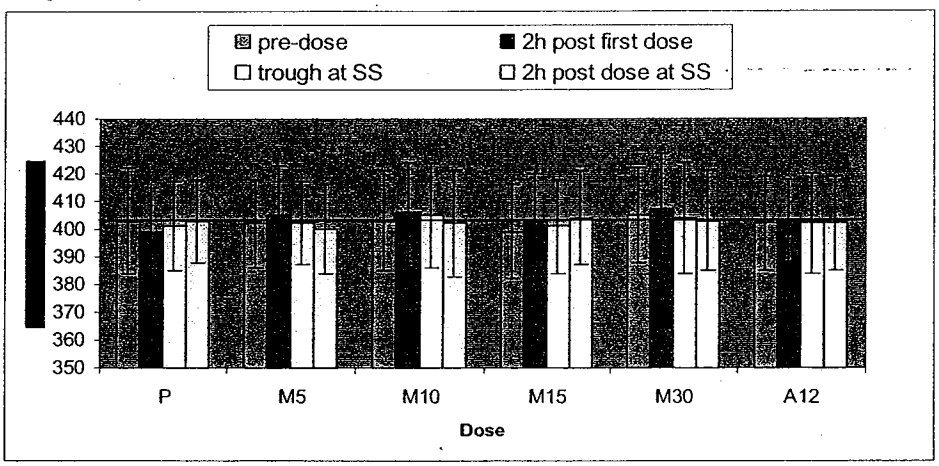
Figure 7. Mean (± SD) of QTc (msc) by Treatment

Study 0601 (adults)



M5, 10, 15, 30 = 5, 10, 15, 30 µg formoterol administered bid from the MDDPI, A12 = 12 µg formoterol administered bid from the Aerolizer®, P = Placebo

Study 0602 (Children)



In Study 0602 (children), all 4 MDDPI doses of formoterol produced statistically significant increases in QTc within 2 hrs after the first inhalation compared to placebo (LSM of differences from placebo was 7-10 ms) but this differences were not found after a 1 week of treatment. The increase in QTc observed 2 hrs post first inhalation following 12 µg Aerolizer compared with placebo was not statistically significant. There were no significant difference on QTc measured 2 hrs post first inhalation among the 4 MDDPI, nor between any of the 4 MDDPI doses and Aerolizer® dose. There was no patient with QTc values >460 msc.

QT correction by Fridericia equation produced slightly different values compared to that by Bazett's equation. In conclusion, change in QTc following the proposed therapeutic dose, 10 µg MDDPI, was not significant.

4.2.4 What are the PK parameter values after the multiple dose of 10 µg formoterol MDDPI in asthmatic adults and children 5-12 years of age population?

Pharmacokinetic data was collected in sub-set of populations from two Phase 3 studies, in which 10 µg bid formoterol was delivered by the MDDPI for 12 weeks in adults and adolescents (Study 2303) and in children 5-12 years of age (Study 0604).

In Study 2303, PK samples were taken from 51 subjects from 4 selected centers, of which 16 subjects received formoterol 10 µg bid. Plasma samples for unchanged formoterol were measured in pre-dose samples following 4 and 8 weeks of treatment. After 12 weeks of treatment, pre-dose and 10 min, 30 min, 1, 2, 4, 8, and 12 hr post-dose (plasma) samples were collected. Urine samples were collected pre-dose and during the interval of 0-12 hours following the first dose and following 12 weeks of treatment. The mean plasma concentration-time profile is presented in Figure 3 and the summary of PK parameters after 10 µg formoterol is given in Table 5.

Figure 3. Mean (and SD) plasma concentration-time profile for formoterol via MDDPI at steady state

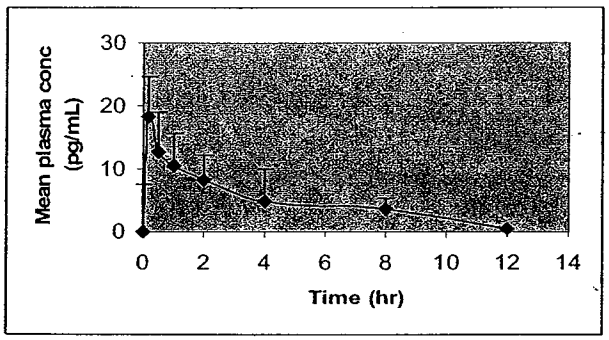


Table 5. Summary of PK parameters for subjects administered 10 µg formoterol via MDDP

	Visit 2		Visit 5					
	Ae_{0-12} (nmol)	Ae_{0-12} (%dose)	Ae_{0-12} (nmol)	Ae_{0-12} (%dose)	C_{max} (pg/mL)	AUC_{0-12} (pmol.h/L)	CL_R (L/h)	R*
N	15	15	12	12	10	10	9	9
Mean	1.35	5.68	2.74	11.50	20.3	73.2	19.8	1.59
SD	0.99	4.14	1.28	5.38	5.2	39.1	12.0	0.72
Min	0.00	0.00	0.36	1.51	11.1	17.3	1.4	1.05
Median	1.67	7.02	2.91	12.24	20.3	69.8	18.4	1.38
Max	2.95	12.40	4.73	19.89	28.0	123.8	43.4	3.48

R* = accumulation ratio

Formoterol was rapidly absorbed and peak concentrations were reached within the first 10 min of dosing. The accumulation ratio was assessed by the ratio of formoterol excreted at steady-state to formoterol excreted after the first dose. Accumulation of approximately 60% at steady state was seen in urine, which is comparable to previously reported value to Aerolizer (63 to 73%). The (arithmetic) mean of the amount of unchanged formoterol excreted at steady state (2.74 nmol or 11.5% of dose) was similar to that seen in Study 0601 (2.61 nmol or 11% of dose). Mean renal

clearance was 19.8 L/h which is similar to that seen previously following treatment of healthy volunteers with a single high dose (120 µg) of formoterol via the Aerolizer (18 L/h).

In Study 0604, PK samples were obtained from 38 subjects from 3 selected centers, of which 19 subjects received formoterol 10 µg bid. PK sampling scheme was identical to Study 2303, except that the plasma samples were taken after 8 weeks of treatment, instead of 12 weeks of treatment. The mean plasma concentration-time profile is presented in Figure 4 and the summary of PK parameters after 10 µg formoterol is given in Table 6. Accumulation of approximately 60% at steady state was seen in urine, which is comparable to previously reported value for the Aerolizer (18-84%). The (arithmetic) mean of the amount of unchanged formoterol excreted at steady state (2.81 nmol or 11.8% of dose) was similar to that seen in Study 0602 (2.97 nmol or 12.5% of dose). Mean renal clearance was 13.4 L/h which is lower than that of the adults.

Figure 4. Mean (and SD) plasma concentration-time profile for formoterol (10 µg bid) via MDDPI at steady state

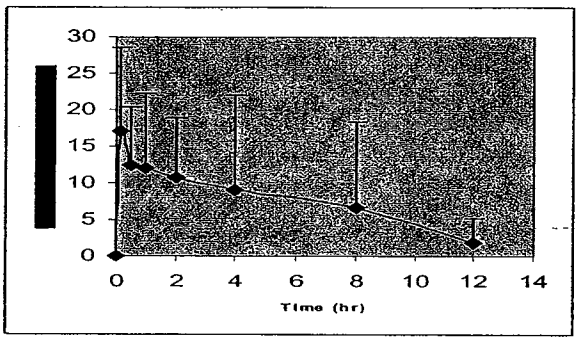


Table 6. Summary of PK parameters for subjects administered 10 µg formoterol via the MDDPI

	Visit 2		Visit 4					
	Ae_{0-12} (nmol)	Ae_{0-12} (%dose)	Ae_{0-12} (nmol)	Ae_{0-12} (%dose)	C_{max} (pg/mL)	AUC_{0-12} (pg.h/mL)	CL_R (L/h)	R*
N	15	15	14	14	8	8	8	13
Mean	1.82	7.66	2.81	11.80	20.1	82.7	13.38	1.58
SD	0.80	3.36	2.31	9.73	8.5	40.9	19.75	1.17
Min	1.03	4.33	0.59	2.48	6.5	28.4	1.72	0.34
Median	1.68	7.06	1.97	8.28	17.5	81.4	6.21	1.32
Max	4.44	18.67	9.18	38.60	31.4	144.8	61.68	4.94

In conclusion, formoterol was rapidly absorbed and peak concentrations were reached within the first 10 min (first sampling time) of dosing in adults and children 5-12 years of age. The urinary excretion of unchanged formoterol increased by approximately 60% following inhalation of 10 µg bid, via MDDPI after 12 weeks (adults) or 8 weeks (children). The mean amount of unchanged formoterol excreted over 12 hours at steady state was similar in adults and children (2.74 nmol or 11.5% of dose; 2.81 nmol or 11.8%, respectively).

4.3 Biopharmaceutics

4.3.1 Has the proposed commercial formulation and device been adequately linked to the clinical trial formulation and device?

b(4)

The formulation consists of a white, free-flowing powder [redacted] formoterol fumarate as the drug substance with lactose monohydrate and magnesium stearate as excipients. The powder [redacted] is contained in a multi-dose dry powder inhaler (MDDPI) delivering 60 doses (actuations) for oral inhalation. Composition of the to-be marketed formulation is shown in Table 7.

Table 7. Foradil 8.5 µg emitted dose (corresponding to 10 µg metered dose) MDDPI

Ingredient	Theoretical amount (mg) per emitted dose	Theoretical amount (mg) per metered dose	Function	Reference to standards
Formoterol fumarate dihydrate	0.0085	0.010	Drug substance	Novartis TM
Lactose monohydrate [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Magnesium stearate	[redacted]	[redacted]	[redacted]	[redacted]
Total weight (approx.)	[redacted]	[redacted]		

TM: Testing Monograph

* Includes Ph. Eur. and USP/NF specifications plus additional testing

b(4)

MDDPIs providing metered dose of 5 or 15 µg per actuation were used in Phase II studies (i.e., Studies 0601 and 0602) and the final (i.e., to-be marketed) formulation providing metered dose of 10 µg per actuation was used in Phase III studies (Studies 02303 and 0604). There is an approximately [redacted] decrease in inactive ingredients (lactose monohydrate and magnesium stearate) in final product compared to that with formulation used in Phase II studies. This difference is considered insignificant (confirmed with G. Poochikian, Ph. D), and the PK data from Phase II and III studies were similar. In addition, stability was done using the final formulation.

b(4)

The device, MDDPI, was used in all clinical trials. The MDDPIs provides a metered dose of 10 µg, which corresponds to an emitted dose of 8.5 µg.

4.3.2 What bioanalytical methods are used to assess concentrations of active moieties?

Unchanged formoterol was determined liquid-liquid extraction procedure and analysis of the extract by LC-MS MS. Total formoterol was determined by a liquid-liquid extraction procedure after enzymatic hydrolysis and analysis of the extract by LC-MS MS. Limit of quantifications (LOQ) for unchanged and total formoterol in urine were 0.035 and 0.14 nmol/L, respectively. LOQ for unchanged formoterol in plasma was 9.52 pmol/L. Overall, the specificity, sensitivity, linearity, accuracy, precision, recovery, and stability of formoterol were satisfactory.

5. **Labeling Recommendations:** Underlined words are addition and the crossed out words are for deletion, as follows:

b(4)

[redacted]

20 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Protocol 601 (CFOR258 0601)

Study type: Tolerability & multiple rising dose

Title: A randomized, double-blinded, placebo controlled, multiple dose (1 week) finding, multicenter, crossover study in adults and adolescents with persistent asthma comparing 4 doses (5, 10, 15 and 30 µg) of formoterol bid administered from the multiple-dose dry powder inhaler (MDDPI) to one dose (12 µg) of formoterol administered from the Aerolizer™ bid.

Investigators: [redacted] *et al.* (multicenter) b(4)

Objectives: The primary objective was to evaluate the optimal effective dose of formoterol powder delivered from the MDDPI in adults and adolescents with persistent asthma. The secondary objectives were to: (1) compare the MDDPI doses with the Aerolizer™ 12 µg bid, (2) assess dose proportionality of MDDPI doses at steady state, (3) compare the amount of unchanged and total formoterol excreted in the 12-hour dosing interval.

Methodology: Adults with persistent asthma that required treatment with inhaled bronchodilators and anti-inflammatory agents were enrolled (n = 60, 20-73 age range) and randomized to receive 4 of 6 possible treatments (5, 10, 15, 30 µg MDDPI, 12 µg Aerolizer™ and placebo). Each patient took 1 puff bid (at 12 hour intervals) from each of the 3 devices. A single-blind, 1 week run-in period on placebo was followed by 4 double-blind, 1 week treatment periods on active medication or placebo (delivered via MDDPI or Aerolizer™) with a 1week washout period in between.

Formulation: Study medication was provided in two MDDPI devices with 60 puffs each containing either 5 or 15 µg formoterol or placebo. A single-dose breath-actuated dry powder inhaler device (Aerolizer™) was used to apply bid formoterol powder capsules, containing 12 µg Foradil® or placebo, as reference therapy

Medication	Batch No.	Formulation control No.
5 µg formoterol fumarate for MDDPI	1A 66501-0-0001	3757176.00.001
15 µg formoterol fumarate for MDDPI	1A 66502-0-0001	3757184.00.001
Placebo for MDDPI	1A 66503-0-0001	3757192.00.001
12 µg formoterol fumarate for Aerolizer™	B970097	3746732.00.003
Placebo powder capsules for Aerolizer™	U050 1197	3751443.00.001

Criteria for evaluation:

PK: Unchanged and total formoterol (unchanged plus conjugated) measured in 12-hour cumulative urine samples from selected patients (centers 1, 11, 12 and 14) at the end of each of the 4 treatment periods and the total urinary excretion within 12 hours of inhalation ($Ae_{0\text{-}12h}$).

Efficacy: Primary: Standardized Area Under the Curve (AUC) of FEV_1 over 12 hours, measured at the end of each week of treatment. Secondary: FEV_1 was also measured at 3, 5, 15, 30 minutes, 1 hour and hourly up to 3 or 12 hours after initiation of each treatment in order to explore the time to onset of action. Further secondary criteria were daily symptom scores and intake of rescue bronchodilator.

Safety: Adverse events, ECGs and vital signs. ECG was obtained pre-dose and 2-hrs post dose at each visit, and QTc (by Bazett's formula) as analyzed variable.

PK Sampling: Urine was collected at pre-dose Visit 2, 12-h fraction after the last dose of each of the four treatment periods at Visit 3, 5, 7 and 9.

Analytical Methodology:
Assay Method: LC/MS/MS
Assay Sensitivity: LOQ for unchanged and total formoterol was 0.035 and 0.14 nmol/L, respectively.
Accuracy and Precision: Precision and accuracy of QC samples at four concentration levels, 0.05 to 25 nmol/L for unchanged formoterol ranged [redacted] respectively. For total formoterol, precision accuracy of QC samples at four concentration levels, 0.25 to 50 nmol/L ranged [redacted] %, respectively. b(4)

Statistical methods:

PK: The amount of unchanged or total formoterol recovered in each urine fraction was calculated by multiplying the concentration of unchanged formoterol or total formoterol (nmol/L) by the respective volume of the urine fraction (L). The percent (%) of the administered dose recovered in the urine either as unchanged or total formoterol was calculated by dividing the recovered amount (nmoles) by the administered dose (nmoles).

The lower and upper 95 % CL (confidence limit of geometric mean) and the geometric mean were computed from the log-transformed data then back-transformed to the original scale. All data were analyzed as ITT (intent to treat), "as treated" and per protocol using the SAS Version 6.12 employing mainly proc UNIVARIATE and TABULATE. "Intent to treat" was governed by the randomization code and "As treated" was governed by the switches of treatment period noted by the investigators, which included:

Centre	Patient	Period	Allocated Treatment	Actual Treatment	Comment
#1	#11	1	5 µg MDDPI	30 µg MDDPI	Period 1 and 2 switched
#1	#11	2	30 µg MDDPI	5 µg MDDPI	As above
#12	#2	2	12 µg Aerolizer	15 µg MDDPI	Medication belonged to Patient #5, Centre #12, Period 2
#12	#5	2	15 µg MDDPI	12 µg Aerolizer	Medication belonged to Patient #2, Centre #12, Period 2.

The "as treated" group, where subjects were switched, accords with the ITT population defined in the main clinical study report. "Per protocol" was governed by exclusion of outliers including non-compliant patients.

Conclusion regarding dose proportionality was only drawn if the three different approaches showed consistent outcomes (however, no formal statistical analysis was performed for the dose proportionality).

Efficacy: Efficacy data were analyzed for three populations, the intent-to-treat (ITT) population (all patients randomized with data from at least 2 treatment periods) and the per-protocol (PP) population (patients without major protocol deviations).
Safety: Descriptive statistics were used for all safety variables.

Results:

PK: Thirty-three patients (20 male and 13 female), with the mean age of 47.58 (± 18.17) years, participated in the PK assessment. The table below displays the actual number of patients per ITT, "as treated" and "per protocol" for each treatment.

Method	Placebo	5 µg MDDPI	10 µg MDDPI	15 µg MDDPI	30 µg MDDPI	12 µg Aerolizer
ITT	23	30	25	31	23	27
As treated	23	30	25	31	23	27
Per protocol	22	28	25	30	20	26

Tables 1-2 summarize the mean values for the amount excreted as unchanged and total formoterol.

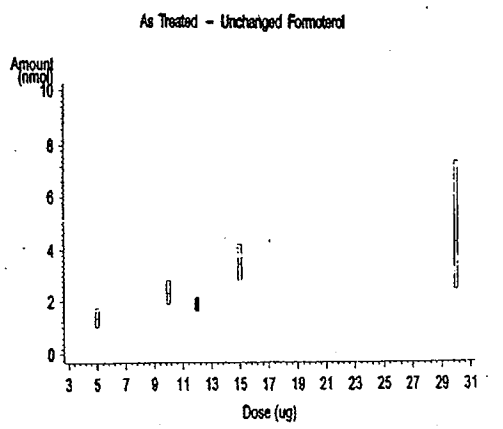
Table 1. Geometric mean (and 95% CI) for the amount excreted in urine ($Ae_{0\text{-}12h}$) as unchanged formoterol (nmol and %dose)

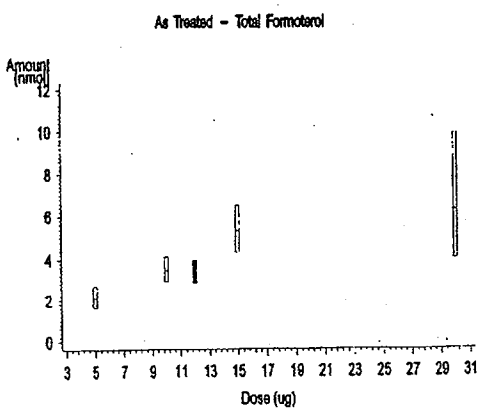
Dose (metered)	5 µg MDDPI	10 µg MDDPI	15 µg MDDPI	30 µg MDDPI	12 µg Aerolizer
N	30	25	31	23	27
nmol	1.34 (1.04-1.74)	2.34 (1.92-2.86)	3.47 (2.84-4.23)	4.32 (2.51-7.44)	1.89 (1.65-2.15)
%dose	11.29 (8.73-14.60)	9.86 (8.09-12.01)	9.72 (7.96-11.87)	6.05 (3.52-10.43)	6.61 (5.80-7.54)

Table 2. Geometric mean (and 95% CI) for the amount excreted in urine ($Ae_{0\text{-}12h}$) as total formoterol (nmol and %dose)

Dose	5 µg MDDPI	10 µg MDDPI	15 µg MDDPI	30 µg MDDPI	12 µg Aerolizer
N	30	25	31	23	27
nmol	2.08 (1.62-2.67)	3.45 (2.89-4.13)	5.29 (4.31-6.51)	6.28 (3.99-9.88)	3.33 (2.81-3.94)
%dose	17.48 (13.62-22.44)	14.51 (12.14-17.35)	14.84 (12.07-18.24)	8.80 (5.59-13.86)	11.66 (9.84-13.82)

Figures below show amount ("as treated" only) and the urinary percent dose recoveries for unchanged formoterol and total formoterol excreted in 12-h for each dose treatment, respectively.





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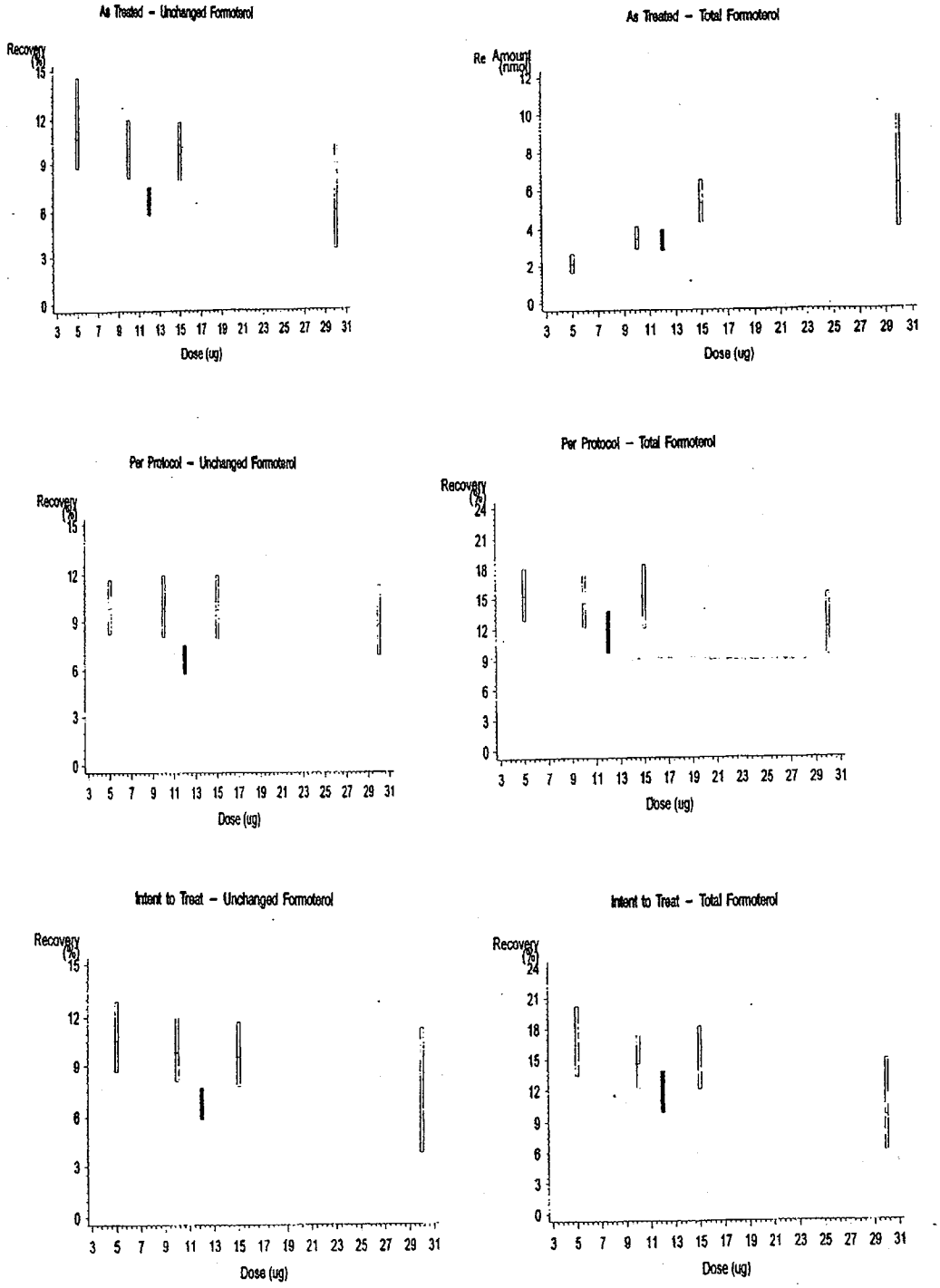

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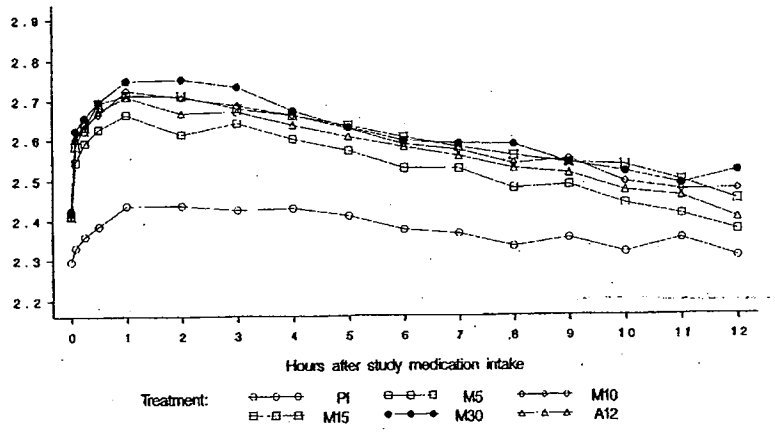
= MDDPI doses ■ = Aerolizer

The systemic exposure to formoterol from 10 µg MDDPI was higher from the MDDPI than 12 µg from the Aelolizcr. The difference was 49%. In terms of absolute amounts of formoterol excreted in urine (nmol data), the 10 µg MDDPI dose was 23% higher compared to that from the 12 µg Aerolizer dose. The 95% confidence intervals for MDDPI 10 µg and Aerolizer 12 µg

overlapped suggesting that the absolute systemic exposure was not substantially different between the two doses. From the Aerolizer device, approximately 7 % and 12.6 % of the dose was recovered as unchanged formoterol and total formoterol, respectively (Tables 1 and 2). In terms of absolute values (nmoles), the results of the current study indicate that the 12 µg Aerolizer lay between the 5 and 10 µg MDDPI dose. b(4)

The dose proportionality of formoterol utilizing the MDDPI device was not investigated in this submission. The amount of unchanged formoterol excreted into urine as a percentage of dose ranged approximately 6-11% across the dose range 5 to 30 µg. The 95% confidence intervals of the geometric means for all MDDPI doses overlapped, suggesting dose proportionality for the range of 5 to 30 µg.

Efficacy: 12-hour profile of least-squares means of FEV_1 after 1 week treatment is shown in the figure below:



Statistically significant increases of 12-hr AUC of FEV_1 after 1 week of treatment, compared with placebo, were observed for all 4 formoterol MDDPI doses and the 12 µg Aerolizer dose. The standardized FEV_1 AUC of different MDDPI doses showed no relevant dose-response from 10-30 µg, however, these doses showed statistically significant increases in FEV_1 AUC compared with the 5 µg dose. There were no significant differences between any of the 4 MDDPI doses when compared among each other with the exception of the comparison between the highest (30 µg) and lowest (5 µg) dose in adults and adolescents.

QTc: Summary statistics of the ECG parameter QTc are provided in Table 3.

Statistically significant increases of QTc were seen 2hrs after the first dose for the dose 30 µg MDDPI (M30) compared with placebo, 5 µg MDDPI (M5), 10 µg MDDPI (M10), and 12 µg Aerolizer (A12) and also for 15 µg MDDPI (M15) compared with placebo (Table 3, upper panel). After one week of treatment, there were no treatment differences at predose, but 2-h post dose again M30 increased QTc statistically significantly compared with placebo, M5, and A12. Significant increases compared with A12 were also found for M15 and M10 at the 2 hour post dose (Table 3, lower panel).

All patients with a QTc-interval >460 ms at any time of the study were analyzed in detail. In four (6%) patients this criterion was fulfilled at least once: One patient had a value of 480 ms already before treatment, and the different treatments did either not change the interval, or led to its shortening. His highest value (500 ms) was found after one week of washout between M5 and

placebo. The remaining three patients showed small changes of the QTc interval independently of the different treatments they received, including placebo.

Table 3. Estimates of treatment contrasts with associated 95% confidence intervals for 2 hour post dose QTc

After first inhalation

Treatment contrast						Estimated		
	LSM (SE)	N		LSM (SE)	N	difference (ms) [a]	95% CI (ms)	p-value
M30	423 (2.3)	40	Placebo	411 (2.3)	41	12	6 – 19	0.0003
M15	418 (2.2)	46	Placebo	411 (2.3)	41	7	0 – 13	0.0378
M10	417 (2.2)	43	Placebo	411 (2.3)	41	6	-1 – 12	0.0796
M5	412 (2.2)	44	Placebo	411 (2.3)	41	1	-5 – 7	0.7922
M30	423 (2.3)	40	M5	412 (2.2)	44	11	5 – 18	0.0005
M15	418 (2.2)	46	M5	412 (2.2)	44	6	-0 – 12	0.0648
M10	417 (2.2)	43	M5	412 (2.2)	44	5	-1 – 11	0.1270
M30	423 (2.3)	40	M10	417 (2.2)	43	6	0 – 13	0.0475
M15	418 (2.2)	46	M10	417 (2.2)	43	1	-5 – 7	0.7514
M30	423 (2.3)	40	M15	418 (2.2)	46	5	-1 – 12	0.0907
M30	423 (2.3)	40	A12	413 (2.1)	47	10	4 – 16	0.0020
M15	418 (2.2)	46	A12	413 (2.1)	47	4	-2 – 10	0.1464
M10	417 (2.2)	43	A12	413 (2.1)	47	3	-3 – 10	0.2653
M5	412 (2.2)	44	A12	413 (2.1)	47	-1	-7 – 5	0.6567
A12	413 (2.1)	47	Placebo	411 (2.3)	41	2	-4 – 8	0.4852

After 1 week of treatment

Treatment contrast						Estimated		
	LSM (SE)	N		LSM (SE)	N	difference (ms) [a]	95% CI (ms)	p-value
M30	424 (2.5)	38	Placebo	415 (2.5)	39	9	1 – 16	0.0190
M15	419 (2.3)	46	Placebo	415 (2.5)	39	4	-3 – 10	0.3046
M10	418 (2.3)	43	Placebo	415 (2.5)	39	2	-4 – 9	0.4878
M5	413 (2.3)	44	Placebo	415 (2.5)	39	-2	-9 – 5	0.5730
M30	424 (2.5)	38	M5	413 (2.3)	44	11	4 – 17	0.0023
M15	419 (2.3)	46	M5	413 (2.3)	44	5	-1 – 12	0.1005
M10	418 (2.3)	43	M5	413 (2.3)	44	4	-2 – 11	0.1899
M30	424 (2.5)	38	M10	418 (2.3)	43	6	-1 – 13	0.0762
M15	419 (2.3)	46	M10	418 (2.3)	43	1	-5 – 8	0.7404
M30	424 (2.5)	38	M15	419 (2.3)	46	5	-2 – 12	0.1454
M30	424 (2.5)	38	A12	411 (2.2)	47	13	6 – 20	0.0003
M15	419 (2.3)	46	A12	411 (2.2)	47	8	1 – 14	0.0185
M10	418 (2.3)	43	A12	411 (2.2)	47	7	0 – 13	0.0466
M5	413 (2.3)	44	A12	411 (2.2)	47	2	-4 – 9	0.5016
A12	411 (2.2)	47	Placebo	415 (2.5)	39	-4	-11 – 3	0.2219

[a] Least squares mean (LSM) based on the analysis of covariance model:
QT_c = patient + period + treatment + treatment baseline QT_c + error
SE = standard error of the mean; N = number of patients; CI = confidence interval
M5, M10, M15, M30 = 5, 10, 15, 30 µg formoterol administered bid from the MDDPI,
A12 = 12 µg formoterol administered bid from the Aerolizer™

In conclusion, dose-dependent changes in QTc were observed following administration of 5 to 30 µg formoterol by MDDPI. Statistically significant increases in QTc interval relative to placebo

were observed at 2 hr following the first dose of 15 and 30 μg and 1 week after of treatment of 30 μg formoterol via MDDPI.

Conclusions:

- The percent dose excreted as unchanged and total formoterol in the 12-hour dosing interval was higher (49%) when delivered via the MDDPI compared with the 12 μg Aerolizer™, suggesting higher delivery of formoterol to the lungs when delivered via the MDDPI compared with the Aerolizer™.
- 12 μg Aerolizer lay between the 5 and 10 μg MDDPI dose based on absolute values (nmoles).
- The 95% confidence intervals of the geometric means for all MDDPI doses overlap, suggesting dose proportionality for the range of 5 to 30 μg (Tables and figures).
- Statistically significant increases of 12-hr AUC of FEV_1, compared with placebo, were observed for all 4 formoterol MDDPI doses and the 12 μg Aerolizer dose. There were no significant differences between any of the 4 MDDPI doses when compared among each other with the exception of the comparison between the highest (30 μg) and lowest (5 μg) dose in adults and adolescents.
- Dose-dependent changes in QTc were observed following administration of 5 to 30 μg formoterol by MDDPI. Statistically significant increases in QTc interval relative to placebo were observed at 2 hr following the first dose of 15 and 30 μg and 1 week after of treatment of 30 μg formoterol via MDDPI.

Protocol No. 602 (CFOR2580602)

Study type: Tolerability & multiple rising doses PK

Title: A randomized, double-blind, placebo controlled, multiple dose (1 week) finding, multicenter, cross over study in children aged 5 to 12 with persistent asthma comparing 4 doses (5, 10, 15 and 30 µg) of formoterol b.i.d, administered from MDDPI to one dose (12 µg) of formoterol administered from the Aerolizer b.i.d.

b(4)

Investigators: [redacted] *et al.* (multicenter)

Objectives:

- Establish an optimal effective dose over the placebo of formoterol powder delivered from the MDDPI
- Compare the doses delivered from the MDDPI with the Aerolizer 12 µg b.i.d.
- Assess the dose proportionality of the urinary, excretion of unchanged and total formoterol at steady state after inhalation of 4 doses (5, 10, 15 and 30 µg) of formoterol when delivered via the MDDPI.
- Compare the amount of unchanged and total formoterol excreted in the 12 h dosing interval when delivered via the MDDPI and via the Aerolizer.

Methodology: This was a multicenter, randomized, double-blind, placebo controlled, multiple dose finding, incomplete block, crossover over study with PK evaluations. Study was made in children aged 5 to 12 years inclusive who have persistent asthma. Each patient received 4 out of 6 treatments delivered from MDDPI or Aerolizer™ or placebo. In selected centers, urine was collected from a total of 37 patients.

Formulation: Study medication was provided in two MDDPI devices with 60 puffs each containing either 5 or 15 µg formoterol or placebo. A single-dose breath-actuated dry powder inhaler device (Aerolizer™) was used to apply bid formoterol powder capsules, containing 12 µg Foradil® or placebo, as reference therapy

Medication	Batch No.	Formulation control No.
5 µg formoterol fumarate for MDDPI	1A 66501-0-0001	3757176.00.001
15 µg formoterol fumarate for MDDPI	1A 66502-0-0001	3757184.00.001
Placebo for MDDPI	1A 66503-0-0001	3757192.00.001
12 µg formoterol fumarate for Aerolizer™	B970097	3746732.00.003
Placebo powder capsules for Aerolizer™	U050 1197	3751443.00.001

Duration of treatment: The total duration was 8 weeks consisting of 4 single-blind wash-out periods of 1 week on placebo and 4 double-blind treatment periods of 1 week on active medication or placebo.

Criteria for evaluation:

PK: Unchanged and total formoterol (unchanged plus conjugated) measured in 12-hour cumulative urine samples from selected patients at the end of each of the 4 treatment periods and the total urinary excretion within 12 hours of inhalation ($Ae_{0\text{-}12h}$).

Efficacy: The primary efficacy variable was the standardized Area Under the Curve (AUC) of FEV_1 over 12 hours, measured at the end of each week of treatment. Secondary variables were FEV_1 measured at 3, 5, 15, 30 minutes, 1 hour and hourly up to 3 or 12 hours after initiation of

each treatment in order to explore the time to onset of action, daily asthma symptom scores, and the use of rescue medication.

Safety: Adverse events, ECGs, and vital signs.

PK Sampling schedule: Urine was collected at pre-dose at visit 2 and over a 12-h prerio after the drug administration at visits 3, 5, 7 and 9.

Analytical Methodology:
Assay Method: LC/MS/MS for unchanged and total (unchanged plus conjugated) formoterol
Assay Sensitivity: LOQ for unchanged and total formoterol was 0.035 and 0.14 nmol/L, respectively.
Accuracy and Precision: Precision and accuracy of QC samples at 5 concentration levels, 0.05 to 70 nmol/L for unchanged formoterol ranged [redacted] respectively. For total formoterol, precision accuracy of QC samples at 5 concentration levels, 0.25 to 100 nmol/L ranged [redacted], respectively. b(4)

Statistical methods:

PK: All data were analyzed as ITT (intent to treat), "as treated" and "per protocol" using the SAS Version 6.12 employing mainly proc UNIVARIATE and TABULATE. "Intent to treat" was governed by the randomization code and "As treated" was governed by the switches of treatment period noted by the investigators, which included:

Centre	Patient	Period	Allocated Treatment	Actual Treatment
#12	#1	2	5 µg MDDPI	Placebo
#12	#1	3	Placebo	5 µg MDDPI

"Per protocol" was governed by exclusion of outliers including non-compliant patients. The following data were excluded.

Centre	Patient	Period	Allocated Treatment	Reason
#12	#1	2	5 µg MDDPI	Non-compliant
#12	#1	3	Placebo	Non-compliant
#3	#3	4	30 µg MDDPI	Recovery of total formoterol > 100% of dose
#3	#6	2	15 µg MDDPI	Concentrations of unchanged and total formoterol below LOQ

Conclusion regarding dose proportionality was drawn if the three different approaches showed consistent outcomes (though, no formal statistical analysis was performed for the dose).

Efficacy: Efficacy data were analyzed for three populations, the intent-to-treat (ITT) population (all patients randomized with data from at least 2 treatment periods) and the per-protocol (PP) population (patients without major protocol deviations). Descriptive statistics were used for all safety variables.

Results: Thirty-seven patients (19 male and 18 female) participated in the PK assessment with mean height of 139.11(± 9.85) cm and the mean age of 9.32 (± 1.7) years. The table below displays the actual number of patients per ITT, "as treated" and "per protocol" for each treatment.

Method	5 µg MDDPI	10 µg MDDPI	15 µg MDDPI	30 µg MDDPI	12 µg Aerolizer
ITT	24	21	21	26	27
"As treated"	24	21	21	26	27
Per protocol	23	21	20	25	27

Tables 1-2 summarize the mean values for the amount excreted as unchanged and total formoterol.

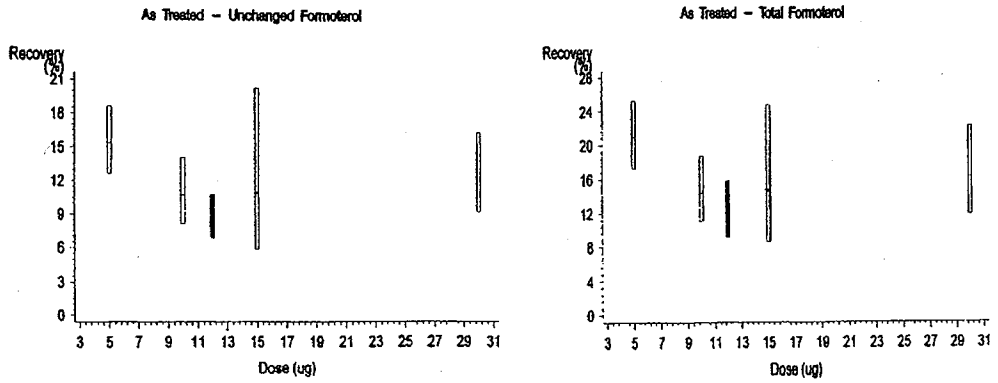
Table 1. Geometric mean (and 95% CI) for the amount excreted in urine ($Ae_{0\text{-}12h}$) as unchanged formoterol (nmol and %dose)

Dose	5 µg MDDPI	10 µg MDDPI	15 µg MDDPI	30 µg MDDPI	12 µg Aerolizer
N	24	21	21	26	27
nmol	1.78 (1.47-2.16)	2.54 (1.93-3.35)	3.87 (2.08-7.21)	8.73 (6.55-11.63)	2.44 (1.93-3.08)
%dose	15.01 (12.38-18.20)	10.69 (8.11-14.08)	10.84 (5.82-20.21)	12.24 (9.19-16.30)	8.54 (6.76-10.78)

Table 2. Geometric mean (and 95% CI) for the amount excreted in urine ($Ae_{0\text{-}12h}$) as total formoterol (nmol and %dose)

Dose	5 µg MDDPI	10 µg MDDPI	15 µg MDDPI	30 µg MDDPI	12 µg Aerolizer
N	24	21	21	26	27
nmol	2.45 (2.03-2.95)	3.43 (2.64-4.46)	5.22 (3.08-8.84)	11.60 (8.47-15.87)	3.44 (2.61-4.51)
%dose	20.58 (17.10-24.77)	14.43 (11.11-18.75)	14.64 (8.65-24.78)	16.25 (11.88-22.25)	12.04 (9.16-15.82)

Figures below show the urinary percent dose recoveries for unchanged formoterol and total formoterol excreted in 12-h for each dose treatment, respectively.



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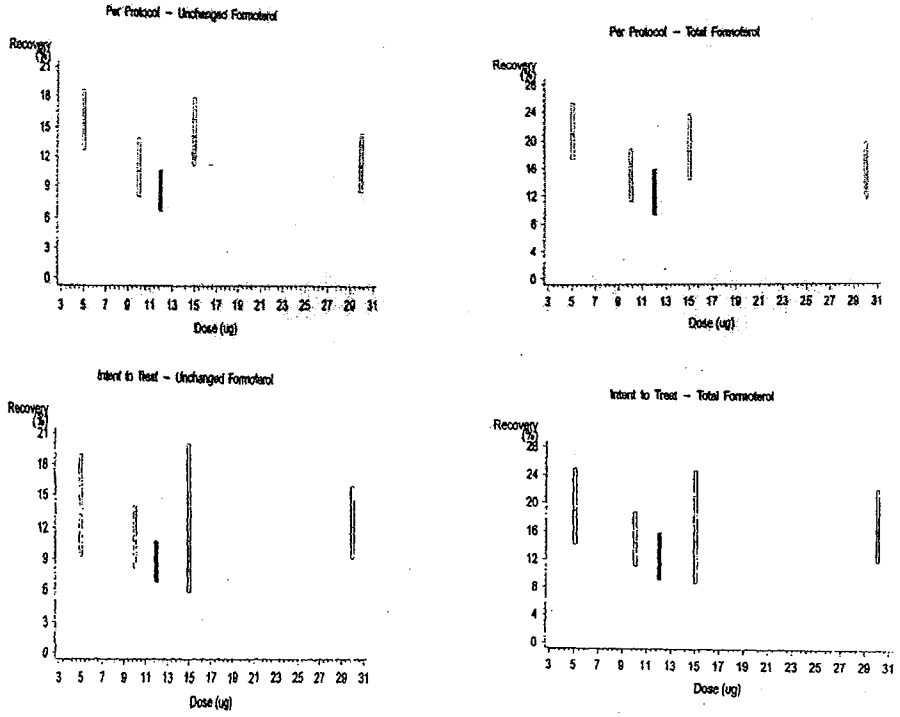

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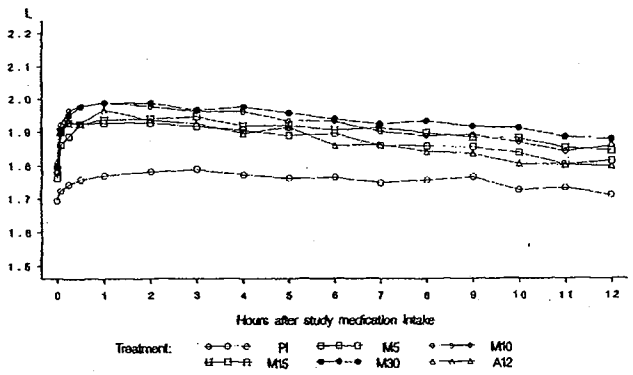
Comparison of MDDPI device with the Aerolizer: Using the urinary excretion of unchanged formoterol as a measure for the systemic exposure to the drug, it can be concluded that, for every µg of the nominal dose of formoterol fumarate, systemic exposure to unchanged formoterol was 25 % (for ITT, "as treated" and "per protocol") higher for the 10 µg MDDPI than the Aerolizer. The geometric means of the absolute excretion values (nmol) of unchanged formoterol for the 10 µg MDDPI dose and the 12 µg Aerolizer dose were 2.54 mnol and 2.44 nmol, respectively, for ITT, "as treated" and "per protocol" analysis (Table 3-2). Therefore, the absolute systemic exposure to unchanged formoterol from the 10 µg MDDPI dose was similar to that from the 12 µg Aerolizer dose.

Intersubject variation (%CV): Intersubject variation ranged 47 – 85% for unchanged formoterol and 40-110% for total formoterol with MDDPI and Aerolizer. The highest variation was shown after 30 µg dose.

Efficacy: 12-hour profile of least-squares means of FEV_1 after 1 week treatment is shown in the Figure 1.

All four MDDPI doses and the Aerolizer dose demonstrated statistically and clinically significant increases in FEV_1 AUC over 12 hours compared to placebo; however, there were no significant differences among the formoterol doses.

Figure 1. 12-hour profile of least-squares means of FEV_1 after 1 week treatment



QTc: All 4 MDDPI doses of formoterol produced a statistically significant ($p = 0.05$) increase in QTc within 2 hrs after the first inhalation, but no differences at steady state, compared to placebo. The increase in QTc observed 2 hrs post first inhalation of A12 compared with placebo was not statistically significant. There were no significant difference on QTc measured 2 hrs post first inhalation among the 4 MDDPI, nor between any of the 4 MDDPI doses and Aerolizer® dose. There was no patient with QTc values >460 msc.

Summary:

- The percent dose excreted as unchanged and total formoterol in the 12-hr dosing interval was generally higher when delivered via the MDDPI compared with the 12 μg Aerolizer, suggesting greater delivery of formoterol to the lungs when administered via the MDDPI compared with the Aerolizer.
- Absolute amounts of formoterol excreted in urine (nmol data) were similar following 10 μg MDDPI and the 12 μg Aerolizer dose.
- The 95% confidence intervals for MDDPI 10 μg and Aerolizer 12 μg overlapped suggesting that the absolute systemic exposure was not substantially different between the two doses.
- All four MDDPI doses and the Aerolizer dose demonstrated statistically and clinically significant increases in FEV_1 AUC over 12 hours compared to placebo; however, there were no significant differences among the formoterol doses.
- All 4 MDDPI doses of formoterol produced a statistically significant ($p = 0.05$) increase in QTc within 2 hrs after the first inhalation, but no differences at steady state, compared to placebo. The increase in QTc observed 2 hrs post first inhalation of A12 compared with placebo was not statistically significant.

Protocol 604 (CFOR258F0604)

Study type: Multiple-dose PK

Title: A 12-week randomized, multicenter, double-blind, placebo controlled, parallel group study in children (aged 5-12, inclusive) with persistent asthma evaluating the safety, efficacy, and pharmacokinetics of Foradil® (formoterol fumarate) 10 µg b.i.d, delivered by the multi-dose dry powder inhaler (MDDPI) versus placebo.

Objective: To evaluate the pharmacokinetics of dry powder formoterol fumarate (Foradil®) delivered via the MDDPI device after multiple dosing to children with persistent asthma in a subgroup of patients.

Study design: Foradil was administered twice daily (b.i.d) via the MDDPI compared with placebo in male and female children aged 5-12 years with persistent asthma. There were two periods in this trial. The first period (Visits 1) of the study was a 2-week single-blinded placebo run-in period and the second period (Visits 2-5) was a double-blinded treatment period lasting 12 weeks (figure below).

Period	I	II
	Single-Blind	Double-Blind
	Placebo - Run-in	Treatment
		Randomized ↓
Visit	1	2 3 4 5
Trial Week	-2	0 4 8 12
Trial drug	Placebo b.i.d.	Foradil 10µg b.i.d. or Placebo b.i.d.

Subjects: Thirty-eight patients enrolled (19 subjects per group), and 31 patients completed the trial.
Investigational drug: Foradil (batch # X089 0101 ___ ; placebo (batch # X276 0900. ___ b(4)

Sampling schedule:
Blood samples: Visit 2 (pre-dose); Visit 3 and 5 (trough samples prior to administration of the morning dose); Visit 4 (pre-dose, 10 and 30 min, 1,2, 4, 8 and 12 h after dosing).
Urine samples: Pre-dose on Visit 2 and for the interval 0-12 h on Visits 2 and 4 after the dose.

Analytical Methodology:
Assay Method: LC/MS/MS
Assay Sensitivity: LOQ was 9.52 pmol/L and 0.0357 nmol/L for plasma and urine (using 1 mL each), respectively.
Accuracy and Precision: Precision and accuracy of quality control samples at three concentration levels, 25, 100 and 300 pmol/L were _____ b(4) %, respectively for plasma. For urine, precision accuracy of QC samples at three concentration levels, 0.1, 2 and 25 nmol/L were 7.3, 7.3, and _____ respectively.

PK evaluation: AUC_{0-12}, R (accumulation factor), Ae_{0-12}, CL_R (Ae_{0-12}/ AUC_{0-12}).

Statistical methods: Descriptive statistics.

Results:

Pharmacokinetics: The mean plasma concentration-time profile for Visit 4 is presented in Figure 1. A summary of PK parameters after 10 µg Foradil is given in Table 1.

Figure 1. Mean (and SD) plasma concentration-time profile for 10 µg Foradil by MDDPI at steady state (right panel = pg/ml; left = pmol/L)

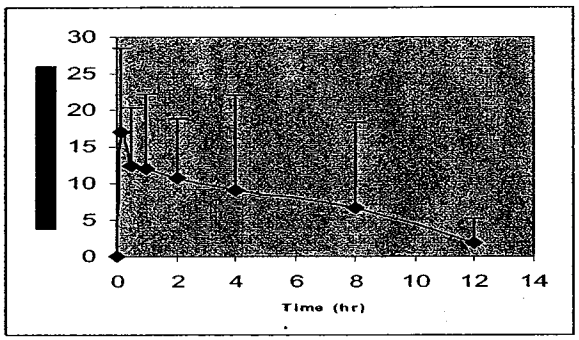


Table 1. Summary of PK parameters for subjects administered 10 µg Foradil via the MDDPI

	Visit 2				Visit 4			
	Ae_{0-12} (nmol)	Ae_{0-12} (%dose)	Ae_{0-12} (nmol)	Ae_{0-12} (%dose)	C_{max} (pg/mL)	AUC_{0-12} (pmol.h/L)	CLR (L/h)	R*
N	15	15	14	14	8	8	8	13
Mean	1.82	7.66	2.81	11.80	20.1	82.7	13.38	1.58
SD	0.80	3.36	2.31	9.73	8.5	40.9	19.75	1.17
Min	1.03	4.33	0.59	2.48	6.5	28.4	1.72	0.34
Median	1.68	7.06	1.97	8.28	17.5	81.4	6.21	1.32
Max	4.44	18.67	9.18	38.60	31.4	144.8	61.68	4.94

R = accumulation ratio

Note: The data from the patient #2 and 10 (centers 518 and 507, respectively) was not included for PK analysis due to unusually high plasma concentrations (per the sponsor). C_{max} from these patients were 58.5 and 50 pg/mL, respectively.

Summary:

- Rapid absorption with t_{max} at 10 minutes (1st sampling time) post-dose.
- C_{max} at 10 min, 2 hr and 8 hr post inhalation of 10 µg formoterol MDDPI ranged between 6.6 and 20.1 pg/mL.
- The amount of formoterol excreted unchanged in urine was on average 1.6-fold higher at steady-state (Visit 4) compared to day one of dosing (Visit 2).
- Inter-subject variation was high for all PK parameters (e.g., C_{max}, 67%, AUC_{0-12}, 49%; CL_R, 148%, Ae 81% on Visit 4).
- Quantifiable amounts of unchanged formoterol were found in the pre-dose plasma samples of several subjects on visits 3, 4 and 5 with similar concentration values, which suggests that steady state had been reached.

Comment: Patient #10 & #2, who had C_{max} concentrations of 58.5 and 51 pg/mL, respectively, are possibly poor metabolizers (deficient in CYP2D6 or CYP2C19).

Protocol 2303 (CFOR258F 2303)

Study type: Multiple-dose PK

Title: A 12-week randomized, multicenter, double-blind, placebo controlled, parallel group study evaluating the safety, efficacy, and pharmacokinetics of Foradil® (formoterol fumarate) 10 µg b.i.d, delivered by MDDPI versus placebo versus albuterol pMDI qid in patients with persistent asthma.

Objective: To evaluate the pharmacokinetics of dry powder formoterol fumarate (Foradil®) delivered via the MDDPI device after multiple dosing in subgroup of patients with persistent asthma.

Study design: Foradil was administered twice daily (b.i.d) via the MDDPI compared with placebo and albuterol pMDI qid in male and female subjects with persistent asthma. There were two periods in this trial. The first period (Visits 1) of the study was a 2-week single-blinded placebo run-in period and the second period (Visits 2-5) was a double-blinded treatment period lasting 12 weeks (figure below).

Period	I	II			
	Single-Blind Placebo - Run-in	Double-Blind, Double-Dummy Treatment			
		Randomized ↓			
Visit	1	2	3	4	5
Trial Week	-2	0	4	8	12
Trial drug	Placebo	Formoterol 10µg b.i.d. or Albuterol 180µg q.i.d. or Placebo			

Subjects: 51 patients enrolled, 16 subjects were randomized to treatment. 15 subjects provided evaluable PK dat.

Sampling schedule:
Blood samples: Visit 2 (pre-dose); Visit 3 and 5 (trough samples prior to administration of the morning dose); Visit 4 (pre-dose, 10 and 30 min, 1,2, 4, 8 and 12 h after dosing).
Urine samples: Pre-dose on Visit 2 and for the interval 0-12 h on Visits 2 and 5 after the dose.

Analytical Methodology:
Assay Method: LC/MS/MS
Assay Sensitivity: LOQ was 9.52 pmol/L and 0.0357 nmol/L for plasma and urine (using 1 mL each), respectively.
Accuracy and Precision: Precision and accuracy of quality control samples at three concentration levels, 25, 100 and 300 pmol/L were [redacted], respectively for plasma. For urine, precision accuracy of QC samples at three concentration levels, 0.1, 2 and 25 nmol/L were 51.4, [redacted] respectively. b(4)

PK evaluation: AUC_{0-12}, R (accumulation factor), Ae_{0-12}, CL_R (Ae_{0-12}/ AUC_{0-12}).
Statistical methods: Descriptive statistics.

Results

Pharmacokinetics: The mean plasma concentration-time profile for Visit 4 is presented in Figure 1. A summary of PK parameters after 10 µg Foradil is given in Table 1. The mean values of C_{max} was 17.1 pg/mL with T_{max} at 10 min, first sampling time point.

Figure 1. Mean (and SD) plasma concentration-time profile for 10 µg Foradil by MDDPI at steady state (right panel = pg/ml, left panel = pmol/L)

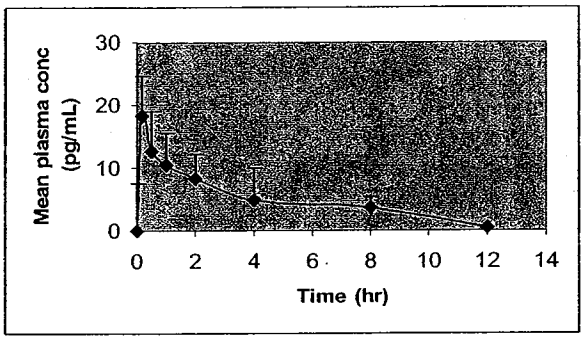


Table 1. Summary of PK parameters for subjects administered 10 µg Foradil via the MDDPI

	Visit 2				Visit 5			
	Ae_{0-12} (nmol)	Ae_{0-12} (%dose)	Ae_{0-12} (nmol)	Ae_{0-12} (%dose)	C_{max} (pg/mL)	AUC_{0-12} (pg.h/mL)	CLR (L/h)	R*
N	15	15	12	12	10	10	9	9
Mean	1.35	5.68	2.74	11.50	20.3	73.2	19.8	1.59
SD	0.99	4.14	1.28	5.38	5.2	39.1	12.0	0.72
Min	0.00	0.00	0.36	1.51	11.1	17.3	1.4	1.05
Median	1.67	7.02	2.91	12.24	20.3	69.8	18.4	1.38
Max	2.95	12.40	4.73	19.89	28.0	123.8	43.4	3.48

R = accumulation ratio

Summary:

- Maximal plasma concentrations were attained at 10 minutes (1st sampling time) post-dose, indicating that drug absorption following inhalation is rapid.
- The mean concentrations at 10 min, 2 hr and 8 hr post inhalation of 10 µg formoterol MDDPI ranged between 3.5 and 20.3 pg/mL.
- The amount of formoterol excreted unchanged in urine was on average 1.6-fold higher at steady-state (Visit 4) compared to day one of dosing (Visit 2).
- Quantifiable amounts of unchanged formoterol were found in the pre-dose plasma samples of several subjects on visits 3, 4 and 5 with similar concentration values, which suggests that steady state had been reached.
- Inter-subject variation was high for all PK parameters (e.g., C_{max}, 41%, AUC_{0-12}, 55%; CL_R, 61%, Ae 48% on Visit 5).

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/s/

Shinja Kim
9/24/03 05:35:39 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
9/24/03 05:44:45 PM
BIOPHARMACEUTICS
I concur