CLINICAL PHARMACOLOGY REVIEW

NDA:	22-518
Brand Name:	Dulera
Generic Name:	Mometosone furoate / formoterol fumarate
Indication:	Asthma (b) (4) in adults and children 12 years of age and older
Dosage Form:	Inhalation aerosol
Strengths:	(b) (4) 100/5, 200/5 mcg
Route of Administration:	Oral Inhalation
Dosing regimen:	Two inhalations twice daily (morning and evening)
Applicant:	Schering-Plough and Novartis
OCP Division:	DCP2
Clinical Division:	DPAP (OND-570)
Submission Date:	May 21, 2009
Reviewers:	Ying Fan, Ph.D., Liang Zhao, Ph.D.
Team Leader (Acting):	Partha Roy, Ph. D.

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1 EXECUTIVE SUMMARY

The sponsor submitted this 505 b (1) application for Dulera oral inhalation aerosol. Dulera is a fixed dose combination product being developed for the (b) (4) twice-daily (b) (4) treatment of asthma, (b) (4) in adults and children 12 years of age and older that delivers by inhalation the corticosteroid Mometosone furoate (MF) and the long-acting β2 agonist (LABA) formoterol fumarate (F) via the hydrofluoroalkane (HFA)-propelled pressurized metered dose inhaler (pMDI). (b) (4) dose levels are proposed (b) (4) 100/5, and 200/5 mcg. The recommended dosages proposed by the sponsor are two inhalations each time, twice daily.

1.1 Recommendations

The Office of Clinical Pharmacology / Division of Clinical Pharmacology-2 (OCP / DCP-2) has reviewed NDA 22-518 submitted on May 21, 2009 and finds it acceptable, provided that a mutually satisfactory agreement can be reached between the sponsor and the agency regarding the language in the package insert.

1.2 Phase IV commitments

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics findings

Dulera is a metered dose inhaler combining two drug substances which have been previously approved for administration via oral inhalation for the treatment of asthma: Mometasone furoate (MF) inhalation powder (ASMANEX® TWISTHALER® 110 and 220 mcg) is approved in the US for maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older. Formoterol fumarate (F) inhalation powder (FORADIL® AEROLIZER® 12 mcg) is approved in the US for twice-daily (morning and evening) administration in the maintenance treatment of asthma and in the prevention of bronchospasm in adults and children 5 years of age and older with reversible obstructive airways disease, including patients with symptoms of nocturnal asthma.

Relative Bioavailability
The Sponsor's drug development program is comprised of 14 trials: 8 clinical pharmacology trials, 4 efficacy and safety trials, 1 long-term safety trial, and 1 dose counter trial. The clinical pharmacology trials are intended to establish a link between the new MF/F solution formulation delivered via pMDI with HFA and the monotherapy DPI formulations.

Pharmacokinetic profile of Dulera was evaluated in multiple studies. In healthy subjects, the systemic exposure as evidenced by Cmax and AUC (0-12h) of MF from the MF/F 800 µg/20 µg MDI product were approximately 40% and 25% lower than the marketed MF 800 µg DPI

product (Asmanex® Twisthaler®), respectively, after 5-day repeated twice-daily administration (Study P04275). In COPD patients, mean MF Cmax and AUC (0-12 hr) following inhalation of MF/F 400/10 µg MDI BID for 5 days were respectively 45% and 25% lower than MF 400 µg DPI (Asmanex®) BID for 5 days (Study P04689). However, the sponsor did not perform the relative bioavailability study in asthma patients. After abstracting the multiple dose MF PK data from the approved drug Asmanex® (refer to Clinical Pharmacology Review by Dr. Tien-Mien Chen dated 09-12-1999) and comparing that with the multiple-dose MF PK data from the 42-day HPA axis study in this application, this reviewer found that the mean MF Cmax and AUC(0-12hr) following MF/F 400 µg/10 µg MDI were lower than the MF 400 µg DPI (Asmanex®) (9.0% and 47.4% lower for Cmax and AUC (0-12 hr), respectively, Table 1). However, for asthma patients, this comparative assessment should be viewed with caution as it involves cross study and cross development comparisons with markedly different bioanalytical methodologies for MF measurement.

Table 1. Dose normalized arithmetic mean (CV%) MF exposures following multiple-dose inhalations from MF/F MDIs and F Asmanex DPI

Parameters *	Healthy subject		Asthma patients		COPD patients	
	MDI (5 days) (Study P04275)	DPI (5 days) (Study P04275)	MDI (42 days) (Study P03705)	DPI (28 days) (Asmanex)**	MDI (5 days) (Study P04689)	DPI (5 days) (Study P04689)
AUC (pg hr/mL)	**1100 (35)**	**1410 (22)**	**577 (40)**	**634 (66)**	**484 (56)**	**646 (47)**
Cmax (pg/mL)	**120.5 (36)**	**191.5 (23)**	**60.0 (36)**	**114 (52)**	**49.2 (55)**	**90.2 (48)**

*The PK parameters are dose normalized to 400 mcg/10 mcg BID
** Data abstracted from original Asmanex NDA (refer to Dr. Tien-Mien. Chen's review dated 09/12/1999)
Note: AUC and Cmax data are expressed as arithmetic mean (CV%)

The systemic exposure (Cmax and AUC) of F from the MF/F MDI is similar to that from the marketed F DPI product (Foradil® Aerolizer®) after single dose administration of MF/F 100/10 µg MDI, MF/F 400/10 µg MDI and F 12 µg (10 µg emitted dose) DPI in asthma patients (Table 2 from Study P05643). The geometric mean ratios (90% CIs) for Ae(0-24hr) between MF/F 100/10 µg vs. F 12 µg and between MF/F 400/10 µg vs. F 12 µg were 106.6 (94.5-120.3) and 112.5 (99.9-126.7), respectively Relative bioavailability assessment of formoterol after multiple dose administration was not conducted.

Table 2 Plasma and Urine Pharmacokinetic Parameters for Formoterol

Protocol No. P05643 (H2201)

Treatment	Tmax (hr) Median (Range)	Cmax (pmol/mL) Mean[a] ± SD	AUC(0-2 hr) (pmol·hr/L) Mean[a] ± SD	Ae(0-24 hr) (nmol) Mean[a] ± SD
MDI MF/F 100 mcg/10 mcg (n=24)	1.00 (0.17–2.08)	23.8 ± 13.0[b]	31.6 ± 15.0[c]	1.58 ± 0.78[b]
MDI MF/F 400 mcg/10 mcg (n=24)	0.58 (0.13–2.08)[b]	23.4 ± 7.3[b]	33.9 ± 10.7	1.63 ± 0.65
F MDI 10 mcg (n=24)	1.08 (0.05–2.08)	22.3 ± 6.1	33.7 ± 11.8	1.76 ± 0.75[b]
F Aerolizer® 12 mcg (n=24)	0.58 (0.05–2.08)[b]	21.6 ± 8.5[b]	29.6 ± 11.7[b]	1.42 ± 0.54

Ae(0-24hr)=amount excreted in urine during the interval 0 hr to 24 hr. AUC(0-2 hr)=area under the plasma concentration–time curve from 0 to 2 hr postdose; Cmax=maximum observed plasma concentration
a: Arithmetic mean.
b: n=25.
c: n=23.

In order to know whether it is reasonable to abstract the MF PK data from the approved drug Asmanex®, the accumulation was calculated in healthy subjects and asthma patients (Table 3 and Table 4). The single-dose and multiple-dose PK data in asthma patients were obtained from the previous submission for Asmanex®. The accumulation indices for AUC (0-12) and Cmax in healthy subjects were similar to those in asthma patients for both MDI formulation and DPI formulation (the accumulation indices for AUC (0-12) were 3.38 for MDI and 2.22 for DPI in healthy subjects, and 3.39 for MDI and 2.45 for DPI in asthma patients; accumulations for Cmax were 3.55 for MDI and 2.08 for DPI in healthy subjects, and 3.00 for MDI and 2.17 for DPI in asthma patients). The results indicate that the cross study and cross development comparison is reasonable.

Table 3 Dose normalized arithmetic mean (CV%) MF exposures following single-dose and multiple-dose inhalations from MF/F MDIs and F Asmanex DPI in healthy subjects

Parameters*	Single-dose		Multiple-dose		Accumulation
	MDI	DPI	MDI	DPI	
AUC (0-t)	**325 (51)**	**635 (33)**	**1100 (35)**	**1410 (22)**	**3.38 (MDI) 2.22 (DPI)**
Cmax	**33.9 (49)**	**92 (36)**	**120.5 (36)**	**191.5 (23)**	**3.55 (MDI) 2.08 (DPI)**

*The PK parameters are dose normalized to 400 mcg/10 mcg BID, and 400 mcg single dose

Table 4 Dose normalized arithmetic mean (CV%) MF exposures following single-dose and multiple-dose inhalations from MF/F MDIs and F Asmanex DPI in asthma patients

Parameters*	Single-dose		Multiple-dose		Accumulation Index
	MDI	DPI	MDI	DPI**	
AUC (0-t)	**170 (94)**	**259 (125)**	**577 (40)**	**634 (66)**	**3.39 (MDI)** **2.45 (DPI)**
Cmax	**20.0 (88)**	**52.6 (112)**	**60.0 (36)**	**114 (52)**	**3.00 (MDI)** **2.17 (DPI)**

*The PK parameters are dose normalized to 400 mcg/10 mcg BID, and 400 mcg single dose
** Data abstracted from original Asmanex NDA (refer to Dr. T-M Chen.'s review dated 09/12/1999)

Drug-Drug and Formulation Interactions
Study P03658 is an open-label, single-dose, 4 treatments (MF 800 µg MDI, F 20 µg MDI, MF 800 µg MDI + F 20 µg MDI, MF/F 800/20 µg MDI) crossover study in 27 healthy subjects to explore the potential for drug-drug interaction as well as formulation effect. The results indicate there is no drug-drug interaction between MF and F and no formulation effect for the combination product. The mean AUC and Cmax for MF and F are comparable when MF and F are administered from the new fixed-dose combination MDI device (MF/F MDI) vs coadministration from single-ingredient MDI devices (MF MDI + F MDI). Systemic exposure of MF and F is also similar between coadministration of the single ingredients and the individual drugs administered alone.

Hypothalamic-pituitary-adrenal (HPA) Axis study results
In addition, the sponsor conducted a 6-week, placebo- and active-controlled study in asthma patients to evaluate the effect of MF on the HPA axis (Study P03705). It was a randomized, open-labeled, placebo- and active-controlled, parallel group, 6-week study to evaluate the effect of corticosteroids on the HPA axis. The multiple-dose PK of MF in patients with asthma was also evaluated in this study. Following multiple BID oral inhalations of MF/F 200/10 µg (n=13), mean cortisol AUC (0-24 hr) values were similar to the placebo (n=16) (<10% change from Baseline). Day 42: Day –1 AUC (0-24 hr) ratios for MF/F 400/10 mcg (n=15) and Fluticasone propionate/salmeterol 460/42 mcg (active control, n=16) BID treatments were respectively 22% lower and 34% lower compared to placebo treatment. The HPA axis study (29 days) results (refer to Dr. T-M Chen's Clinical Pharmacology Review of the original Asmanex NDA application (NDA #21067) dated 09-12-1999) for the approved MF (Asmanex®) at 440 mcg QD are as follows: plasma cortisol AUC (0-24h) (202 mcg.hr/dL) was approximately 18% lower compared to placebo (245 mcg.hr/dL). Although the study duration for the dedicated HPA axis study in the original Asmanex submission (NDA # 21-067) was not long enough, the cortisol suppression results for MF/F from the current submission are generally showing similar trend as has been noted previously with the reference drug Asmanex® and active control fluticasone propionate/salmeterol (Advair®).

The effect of inhaled mometasone furoate administered via DULERA on adrenal function was also evaluated in an open-label 1-year safety study (Study P04139) in patients with asthma ages 12 years and above. This study did not have a placebo arm. At Week 52, the mean plasma

cortisol AUC(0-24 hr) was 2.2%, 29.6%, 16.7%, and 32.2% lower from baseline for the MF/F 200/10 mcg, MF/F 400/10 mcg, Fluticasone/Salmeterol 250/50 mcg, and Fluticasone/Salmeterol 500/50 mcg treatment groups, respectively.

Conclusions

The systemic exposure of MF was found to be lower than the approved drug Asmanex® following both administration of MF/F 800/20 μg BID and Asmanex MF 800 μg BID for 5 days in healthy subjects; and administration of MF/F 400/10 μg BID and Asmanex MF 400 μg BID for 5 days in COPD patients. However, the sponsor did not provide the relative bioavailability data comparing the MF/F MDI with the Asmanex MF in asthma patients. Therefore, this reviewer borrowed the MF PK data from the original Asmanex development program (see Dr. Tien-Mien Chen's review dated 09-12-1999) and made a comparative evaluation with the MF PK data from MF/F MDI product presented under the current submission. The trend of lower MF exposure from the proposed MF/F MDI product compared to the already approved MF DPI Asmanex product, noted in healthy and COPD patients remained unchanged even in asthma patients. Since oral absolute biovailability of MF is less than 1%, almost all the systemic exposure from Dulera can be attributed to absorption through the lungs. Generally, systemic exposure of inhaled corticosteroids is associated with systemic safety only, but for inhaled corticosteroids such as mometasone with almost no oral bioavailability, systemic exposure may be indicative of local lung exposure..

Single-dose relative bioavailability evaluation of formoterol in asthma patients was available. The systemic exposure of F from the MF/F MDI products (100/10 μg and 400/10 μg strengths) was found to be comparable to that from the marketed F DPI product (Foradil® Aerolizer®) after single dose administration in asthma patients.

Because there is no PK interaction between MF and F, we can use the original labeling information (approved individual drug) for this combination product.

The sponsor also conducted a dedicated HPA axis study. For the dedicated the HPA axis study, there are some deficiencies noted: 1) the number of subjects per treatment arm (n<20) is considered less than ideal (n~35-40); 2) open label study design instead of generally expected double-blind study design. However, based on the results from the HPA axis study in this application, the cortisol suppression data from the proposed product exhibited similar trend with the reference MF Asmanex as well as the positive control (Fluticasone/Salmeterol combination).

While the proposed indication of Dulera is in patients 12 years and older, there were no PK data submitted for adolescents ages 12 to 17 years, neither from a dedicated HPA-axis study nor from the Phase 3 trials. This concern was previously communicated to the Applicant at the pre-NDA meeting on December 18, 2008, and again in the 74-day filing letter. In response, the Sponsor stated that they plan to obtain PK data in children 5 to 11 years of age in the future after which they would interpolate PK information for adolescents using population PK analysis. The sponsor's approach for collecting PK information in adolescents is considered acceptable from clinical pharmacology perspective based on following reasons: 1) The mono-therapy drugs MF (Asmanex®) and F (Foradil®) were approved by Agency and have been in the market for many years for patients older than 4 years of age (MF) and 5 years of age (F) and it has been found that

there is no drug-drug interaction between MF and F; 2) the systemic exposure of MF and F was either lower (MF) or comparable (F) to the approved monotherapy drugs (Asmanex® and Foradil®); 3) the Sponsor included sufficient number (n~300) of subjects 12 to 17 years of age in the Phase 3 safety and efficacy studies and there is no particular difference in safety profile observed compared to adults.

2 QUESTION BASED REVIEW

2.1 General Attributes/Background

2.1.1 What is the pertinent regulatory background of DULERA?

The sponsor Schering-Plough submitted a 505 (b) (1) New Drug Application (NDA 22-518) for Dulera® (mometasone furoate/formoterol fumarate) (b) (4) 100/5, and 200/5 mcg inhalation aerosol on May 21, 2009. The proposed indication is for (b) (4) twice-daily (b) (4) treatment of asthma, (b) (4), in adults and children 12 years of age and older.

DULERA is a metered dose inhaler combining two drug substances which have been previously approved for administration via oral inhalation for the treatment of asthma: Mometasone furoate inhalation powder (ASMANEX® TWISTHALER® 110 and 220 mcg) is approved in the US for maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older. Formoterol fumarate inhalation powder (FORADIL® AEROLIZER® 12 mcg) is approved in the US for twice-daily (morning and evening) administration in the maintenance treatment of asthma and in the prevention of bronchospasm in adults and children 5 years of age and older with reversible obstructive airways disease, including patients with symptoms of nocturnal asthma.

Mometasone furoate (MF) is an inhaled corticosteroid (ICS). It is a potent glucocorticosteroid which, when taken daily via oral inhalation and on a long term basis, controls asthma through its anti-inflammatory activity. Formoterol fumarate (F) is a long-acting acting beta-agonist (LABA) which provides a rapid onset of bronchodilation when administered via oral inhalation. The ICS/LABA combination of MF and F is an effective asthma controller medication with the added benefits of convenience to patients, potentially improved patient compliance and assurance that the LABA component is always co-administered with an ICS.

In the filing meeting, the Agency asked the sponsor to justify the reason for not obtaining PK samples in adolescents in the pivotal Phase III trials. In this submission, sponsor's response is as follows: At the time the pivotal Phase III trial protocols were written and initiated there was no validated highly sensitive plasma assay for mometasone furoate (MF) or a validated plasma formoterol assay capable of characterizing the PK profiles of these drugs at the doses used in these trials. Furthermore, even when these assay methods became available during the trials, the blood sample processing equipment (b) (4) and storage conditions required (eg, -20°C for MF and -70°C for formoterol) make it impractical for most investigational sites. In view of the fact that the Sponsor collected PK samples in patients 18 years and older and has a plan to collect PK samples in children aged 5 to 11 years as part of the pediatric investigational plan, the Sponsor will use a modeling approach to estimate the PK parameters and profiles of MF and formoterol in children 12 to 18 years of age.

This reviewer accepts sponsor's response regarding unavailability of validated highly sensitive plasma assay for MF or F at the time of initiation of Phase III trial coupled with difficulty in blood sample storage and processing at most clinical sites.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Dulera contains both mometasone furoate and formoterol fumarate; therefore, the mechanisms of actions for the individual components apply to Dulera. Mometasone furoate is a corticosteroid demonstrating potent anti-inflammatory activity. The precise mechanism of corticosteroid action on asthma is not known. Formoterol fumarate is a long-acting β2-agonist that binds to β2-adrenoceptors, causing relaxation of bronchial smooth muscle and inhibition of the release of pro-inflammatory mediators from mast cells. The sponsor claimed that Dulera is expected to offer potentially important benefits to asthma patients through the combination of rapid anti-inflammatory effects and good asthma control provided by mometasone furoate and with rapid and long-lasting bronchodilation provided by formoterol fumarate. The proposed indication for Dulera is for the (b) (4) treatment of asthma (b) (4) (b) (4) in patients 12 years of age and older.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

Dulera is a fixed dose combination product that delivers by inhalation the corticosteroid mometosone furoate and the long-acting β2 agonist (LABA) formoterol fumarate via the hydrofluoroalkane (HFA)-propelled pressurized metered dose inhaler (pMDI), which has (b) (4) strengths: (b) (4), 100/5 mcg, and 200/5 mcg. The recommended dosages proposed by the sponsor are summarized below.

Previous Therapy	Recommended Dose	Maximum Recommended Daily Dose
(b) (4)		
Inhaled medium dose corticosteroids	DULERA 100/5, 2 inhalations twice daily	400/20 mcg
Inhaled high dose corticosteroids	DULERA 200/5, 2 inhalations twice daily	800/20 mcg

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The Applicant's drug development program is comprised of 14 trials: 8 clinical pharmacology trials, 4 efficacy and safety trials, 1 long-term safety trial, and 1 dose counter trial. The Applicant also references 3 dose-ranging trials conducted with the MF monotherapy under a separate IND. The submission also relies on the Agency's previous findings of efficacy and safety of the approved reference monotherapy products. The clinical pharmacology trials are intended to establish a link between the new MF/F solution formulation delivered via pMDI with HFA and

the monotherapy DPI formulations. The MF MDI and F MDI comparators used in these trials were developed for the purposes of the MF/F development program and have not been approved for the treatment of asthma. A total of 2977 patients were included in the 4 pivotal efficacy and safety trials: (b) (4), P04334, P04431, and P04705, of which 1232 patients received MF/F, 620 received MF alone, 390 received F alone, 384 received placebo, and 351 received fluticasone/salmeterol active comparator (F/SC).

The table 5 below outlines the clinical pharmacology studies included in the application.

Table 5. Summary of clinical pharmacology studies

Study No.	Title	Population	Duration of Treatment	Numbers Enrolled/ Completed
P04275	SCH 418131: A study to evaluate the relative bioavailability of MF after administration from an MF DPI vs MF/F MDI formulation device in healthy subjects	healthy subjects	multiple dose (4.5 days)	12/12
P05644 (H2104)	A randomized, single dose, 3 period crossover study to evaluate the dosage-form proportionality of MF, dose proportionality of formoterol, and pharmacokinetics of MF and formoterol from 3 combination MDI formulations	healthy subjects	single dose	24/24
P03658	Evaluation of the potential for a pharmacokinetic interaction between MF and formoterol after single dose in healthy subjects	healthy subjects	single dose	27/24
P05642 (H2101)	A randomized, open-label, 3 period crossover study to assess the cumulative dose response to F alone and in combination with MF in subjects with mild to moderate persistent asthma	subjects with asthma	single dose	19/18
P05643 (H2201)	A randomized, single-dose, double-blind, placebo controlled crossover study to characterize the single-dose pharmacodynamics of formoterol administered alone and in combination with MF via MDI	subjects with asthma	single dose	25/25
P03705	Evaluation of the extrapulmonary effects of MF from a combination MDI formulation versus fluticasone propionate from a fluticasone propionate/salmeterol (FP/S) combination comparator on HPA-axis function	subjects with asthma	multiple dose (42 days)	66/60
P06144 (I2201)	A randomized, multicenter, double-blind, double-dummy, placebo controlled, crossover dose-ranging study to evaluate the safety and efficacy of single doses of F (6, 12 and 24 mcg [emitted 5, 10, and 20 mcg]) via an HFA MDI versus placebo and versus F (12 and 24 mcg [emitted 10 and 20 mcg]) dry powder delivered via the Aerolizer™ in subjects with persistent asthma	subjects with asthma	single dose	26/26
P04689	Evaluation of the relative bioavailability/systemic exposure of Inhaled MF from an MF/F MDI vs MF DPI formulation device in subjects with COPD	subjects with COPD	multiple dose (4.5 days)	14/14

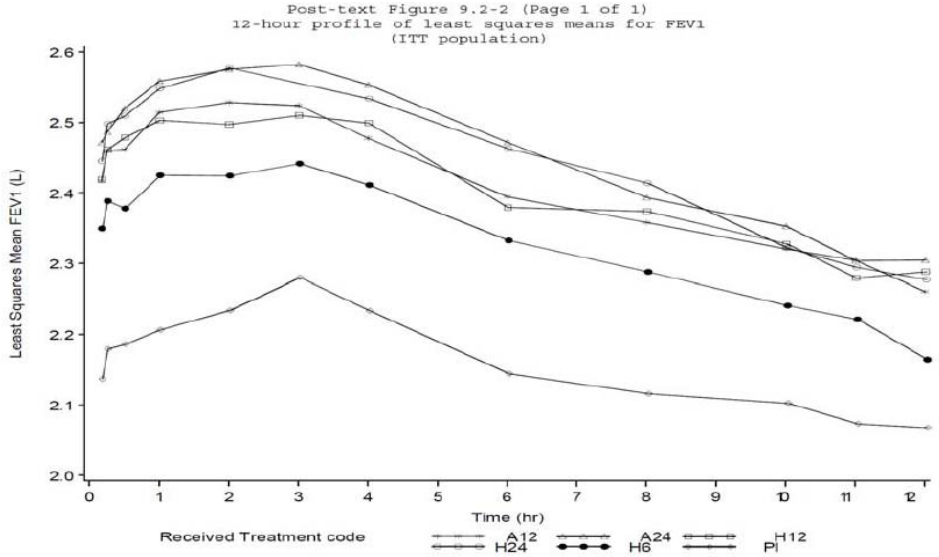
COPD=chronic obstructive pulmonary disease; DPI=dry-powder inhaler; F=formoterol fumarate; HFA=hydrofluoroalkane (propellant); HPA=hypothalamic–pituitary–adrenal; MF=mometasone furoate; MF/F=mometasone furoate/formoterol fumarate.

2.2.2 What is the basis for selecting the product doses?

Formoterol

Selection of the formoterol dose was based on the earlier formoterol DPI development program, which established 12 mcg DPI BID as safe and effective. The formoterol MDI formulation used in the dose-ranging studies was an HFA 134a product. The 10 mcg MDI dose is equivalent to the 12 mcg DPI dose (emitted dose: 10 mcg) when assessed by the FEV1 AUC, according to the

results of Study P06144. In this trial, the Applicant concluded that the lowest dose, 6 mcg, was substandard, and the highest dose of 24 mcg offered no significant advantages (see Figure 1).



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A12=Foradil Aerolizer 12 mcg, A24=Foradil Aerolizer 24 mcg, H6=F MDI 6 mcg, H12=F MDI 12 mcg, and H24=F MDI 24 mcg

Figure 1 12-hour profile of LS mean FEV1 over time (Study P06144)

Additional comparison of the PD profiles was performed in Study P05643 (see figure 2). The complete study reports of these two studies are included in the NDA. Exploration of alternative dosing regimens besides BID dosing was not performed in the MF/F program.

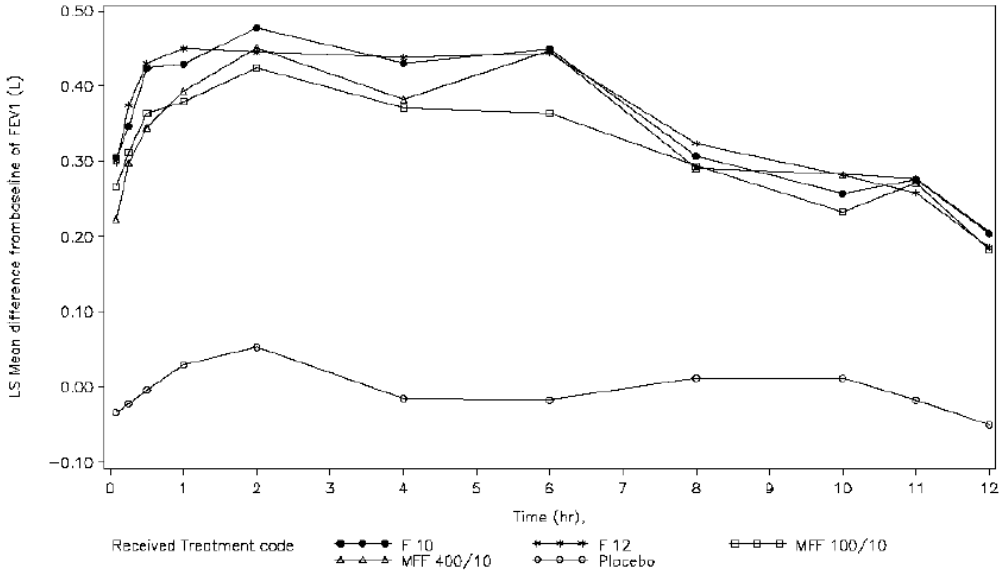

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Figure 2. 12 hour profile for least-squares mean change from baseline for FEV1 (L) (Study 05643)

Mometasone

Dose selection for mometasone was based on trials performed in the separate MF MDI monotherapy program, (b) (4) The selection is based on the results from study C97-208, C97-225, I97-200 and C97-224.

Reviewer's comments:
The sponsor indicated that the dosing regimens of MF and F used in the (b) (4) Dulera dosages were selected to be comparable to the dosing regimens approved and marketed as individual treatments for asthma (e.g., Asmanex® and Foradil®, respectively) as well as the dosing regimens approved and marketed in other combination products (e.g., Advair® and Symbicort®). The dose selection strategy adopted by the sponsor did not include full characterization of the individual components (MF and F in Dulera device) to establish the appropriate dose and dosing interval for each component. Instead, the sponsor relies on linking MF and F to the marketed MF and F products in terms of PK and PD without exploring alternate dosing regimen.

Dulera is a new drug product, with a new formulation, delivered via a different device than the marketed products. Therefore, this development program must include full characterization (dose-ranging) of the individual components (MF and F) to establish the appropriate dose for each component, before proceeding to studies with the combination product in the Phase 3 studies. Essentially, both components should be developed in a manner that would support the marketing of each as single drug products. Then the individual single-ingredient products may be combined at the appropriate doses established as safe and effective in the single-ingredient development program as a matter of convenience.

2.2.3 What is previously known about the pharmacokinetics of MF and F?

1) Mometasone furoate (Asmanex)

The pharmacokinetics information previously known for Mometasone furoate is obtained from the Asmanex label and the original NDA submission for Asmanex (NDA #21067).

Following an inhaled single 400 mcg dose of ASMANEX®TWISTHALER® treatment to 24 healthy subjects, plasma concentrations for most subjects were near or below the lower limit of quantitation for the assay (50 pcg/mL). The mean absolute systemic bioavailability of the above single inhaled 400 mcg dose, compared to an intravenous 400 mcg dose of mometasone furoate, was determined to be less than 1%. Following administration of the recommended highest inhaled dose (400 mcg twice daily) to 64 patients for 28 days, concentration-time profiles were discernible, but with large intersubject variability. The coefficient of variation for Cmax and AUC ranged between approximately 50 to 100%. The mean peak plasma concentrations at steady state ranged from approximately 94 to 114 pcg/mL and the mean time to peak levels ranged from approximately 1.0 to 2.5 hours.

Following an intravenous 400 mcg dose of mometasone furoate, the plasma concentrations showed a biphasic decline, with a mean terminal half-life of about 5 hours and the mean steady-state volume of distribution of 152 liters. The in vitro protein binding for mometasone furoate was reported to be 98 to 99% (in a concentration range of 5 to 500 ng/ml).

Studies have shown that mometasone furoate is primarily and extensively metabolized in the liver of all species investigated and undergoes extensive metabolism to multiple metabolites. In-vitro studies have confirmed the primary role of CYP 3A4 in the metabolism of this compound, however, no major metabolites were identified.

Following the inhaled dose of tritiated 1000 mcg mometasone furoate, the radioactivity is excreted mainly in the feces (a mean of 74%), and to a small extent in the urine (a mean of 8%) up to 7 days. No radioactivity was associated with unchanged mometasone furoate in the urine.

2) Formoterol fumarate (Foradil)

The pharmacokinetics information for formoterol fumarate is obtained from Foradil® label.

Following inhalation of a single 120 μg dose of formoterol fumarate by 12 healthy subjects, formoterol was rapidly absorbed into plasma, reaching a maximum drug concentration of 92 pg/mL within 5 minutes of dosing. Urinary excretion of unchanged formoterol was used as an indirect measure of systemic exposure since plasma formoterol concentrations parallel urinary concentrations.

The *in vitro* human plasma protein binding of formoterol was approximately 61 to 64% at concentrations from 0.1 to 100 ng/mL, while in vitro human serum albumin binding was approximately 31 to 38% over a concentration range of 5 to 500 ng/mL. The concentrations of formoterol used to assess the plasma protein binding were higher than those achieved in plasma following inhalation of a single 120 μg dose.

Formoterol is mainly metabolized by glucuronidation at the phenolic (primary route) or aliphatic hydroxyl group. A second major route of metabolism involves O-demethylation followed by glucuronide conjugation at either phenolic hydroxyl groups by CYP2D6, CYP2C19, CYP2C9, and CYP2A6. Minor pathways of metabolism include sulfate conjugation and deformylation. Formoterol did not inhibit CYP450 enzymes at therapeutically relevant concentrations.

After oral administration of 80 μg radio labeled formoterol fumarate, 59 to 62% was eliminated in the urine and 32 to 34% was eliminated in the feces after 104 hours. Renal clearance was approximately 150 mL/min. After administration of 120 μg, from plasma concentration data, the mean terminal elimination half-life was approximately 10 hours.

2.2.4 What is the new pharmacokinetic information gathered for both MF and F from the Dulera program?

Mometasone

Following single-dose administration of Dulera MF/F 800/20 mcg in healthy subjects (Study 04275), the arithmetic mean (CV%) Cmax and AUC0-12h values for MF were 67.8 (49) pg/mL

and 650 (51) pg.hr/mL, respectively while the corresponding estimates following BID dosing of Dulera MF/F 800/20 mcg at steady-state (Day 5) were 241 (36) pg/mL and 2200 (35) pg.hr/mL. In healthy subjects, geometric mean steady state (Day 5) plasma Cmax and AUC0-12h values for MF at MF/F 800/20 mcg BID dose were 227 pg/mL and 2060 pg•h/mL, respectively (Study P04275). Following inhalation of multiple doses of Dulera 400/10 mcg BID (Study P03705) in asthma patients, geometric mean steady-state plasma Cmax and AUC value for mometasone furoate were 57 pg/mL and 542 pg•h/mL, respectively (Table 6).

Geometric mean pharmacokinetic parameters of MF after dosing with MF/F BID for 42 days are respectively summarized in Table 6**.** Geometric means with 90% CI for MF Cmax and AUCτ showed increases in exposure with dose and with repeated dosing. With a large intersubject variability in each treatment group and sample sizes of 13 to 17 subjects, 90% confidence intervals around the geometric mean ratios for Cmax and AUC0-12h between MF/F 200/10 mcg vs. 400/10 mcg after BID dosing were large (Table 7).

By comparing the single dose and multiple dose data in both healthy and asthma patients, the reviewer found that the accumulation is different between the test MF/F MDI and the reference MF DPI Asmanex. In healthy subjectis, the accumulation for AUC (0-12) is 3.38 for MDI and 2.22 for DPI, and accumulation for Cmax is 3.55 for MDI and 2.08 for DPI. In asthma patients, the accumulation for AUC (0-12) is 3.39 for MDI and 2.45 for DPI, and accumulation for Cmax is 3.00 for MDI and 2.17 for DPI (Tables 8 and 9). Because the submission lacked PK information comparing the test product MF/F MDI to the reference MF DPI Asmanex, the data was borrowed from the previous submission for Asmanex.

Mean MF plasma concentration–time plots for each treatment and day showed rapid absorption and dose- and dose-by-day–related increases on exposure after repeated dosing (Figure 3).

Table 6 Geometric Means and 90% Confidence Intervals for MF Pharmacokinetic Parameters Following Inhalation of 200 µg or 400 µg MF BID from MF/F MDIs

Protocol No. P03705

Dosage	Day	n	Cmax (pg/mL)	90% Confidence Interval (pg/mL)	AUCτ (pg·hr/mL)	90% Confidence Interval (pg·hr/mL)
MF/F 200 µg/10 µg BID	1	15	11.4	9.33–14.0	75.4	56.7–100
	42	13	19.4	12.8–29.4	174	116–260
MF/F 400 µg/10 µg BID	1	17	16	12.3–20.8	127	92.9–173
	42	15	56.8	48.7–66.1	542	460–637

AUCτ=area under the concentration–time curve from 0 hr to 12 hr; Cmax=maximum plasma concentration; MF/F MDI=mometasone furoate/formoterol fumarate metered-dose inhaler; MF/F 100 µg/10 µg BID=2 puffs BID from metered-dose inhaler delivering mometasone furoate/formoterol fumarate 100 µg/5 µg per actuation; MF/F 400 µg/10 µg BID=2 puffs BID from metered-dose inhaler delivering mometasone furoate/formoterol fumarate 200 µg/5 µg per actuation.

Table 7 Geometric Mean Ratios and 90% Confidence Intervals for Dose-Normalized MF AUCτ and Cmax

Protocol No. P03705

	Comparison (sample sizes)	Parameter	Ratio (%)	90% CI[a]
Day 1	MF 200 µg BID (A)/MF 400 µg BID (B)	AUCτ	119	78.7–180
	(n=15/n=17)	Cmax	143	103–198
Day 42	MF 200 µg BID (A)/MF 400 µg BID (B)	AUCτ	64.1	43.1–95.2
	(n=13/n=15)	Cmax	68.4	45.9–102

AUCτ=area under the plasma concentration–time curve from 0 hr to 12 hr; CI=confidence interval; Cmax=maximum plasma concentration; MF 200 µg BID=mometasone furoate/formoterol fumarate 200 µg/10 µg [2 puffs of 100 µg/5 µg MF/F metered-dose inhaler] BID; MF 400 µg BID=mometasone furoate/formoterol fumarate 200 µg/10 µg [2 puffs of 100 µg/5 µg MF/F metered-dose inhaler] BID.

Table 8 Dose normalized arithmetic mean (CV%) MF exposures following single-dose and multiple-dose inhalations from MF/F MDIs and F Asmanex DPI in healthy subjects

Parameters*	Single-dose		Multiple-dose		Accumulation Index
	MDI	DPI	MDI	DPI	
AUC (0-t)	**325 (51)**	**635 (33)**	**1100 (35)**	**1410 (22)**	**3.38 (MDI) 2.22 (DPI)**
Cmax	**33.9 (49)**	**92 (36)**	**120.5 (36)**	**191.5 (23)**	**3.55 (MDI) 2.08 (DPI)**

*The PK parameters are dose normalized to 400 mcg/10 mcg BID, and 400 mcg single dose

Table 9 Dose normalized arithmetic mean (CV%) MF exposures following single-dose and multiple-dose inhalations from MF/F MDIs and F Asmanex DPI in asthma patients

Parameters*	Single-dose		Multiple-dose		Accumulation Index
	MDI	DPI	MDI	DPI	
AUC (0-t)	**170 (94)**	**259 (125)**	**577 (40)**	**634 (66)**	**3.39 (MDI) 2.45 (DPI)**
Cmax	**20.0 (88)**	**52.6 (112)**	**60.0 (36)**	**114 (52)**	**3.00 (MDI) 2.17 (DPI)**

*The PK parameters are dose normalized to 400 mcg/10 mcg BID, and 400 mcg single dose

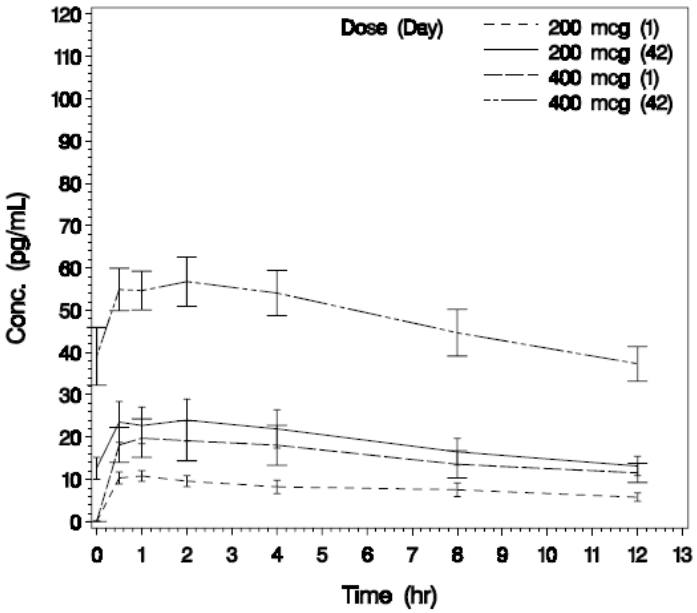

Figure 3 Mean (SD) MF Plasma Concentrations on Days 1 and 42 following BID Inhalation of 400 µg or 200 µg MF from MF/F MDIs. Subjects received MF/F 200/10 µg; or MF/F 400/10 µg via oral inhalation BID for 42 days

Formoterol

In a single-dose study with healthy subjects dosed with MF/F MDI combination, Cmax and AUC for formoterol 20 mcg and 40 mcg were 34.56 and 74.96 pmol/L and 192.3 and 445.3 pmol•h/L, respectively (Study P05644, geometric mean). Following single inhaled F doses ranging from 10 mcg to 40 mcg in healthy subjects from the MF/F MDI (Study 05644), the mean total amount of formoterol excreted within 48 hours ranged from 6.2 to 6.8 % across the three dose levels (Table 10). The mean elimination t1/2 for F was 12 hours for the MF/F 400/40 µg and MF/F 400/10 µg doses and 11 hours for the MF/F 400/20 µg dose.

In patients with asthma, the steady state Cmax and AUC for formoterol at MF/F 400/10 mcg BID dose, ranged from 28.3 to 36 pmol/L and 153 to 203 pmol•h/L, respectively (Study P03705).

Table 10 Summary statistics for urinary excretion derived parameters for formoterol

Treatment		Ae_{0-3} (nmol)	Ae_{0-12} (nmol)	Ae_{0-24} (nmol)	Ae_{0-36} (nmol)	Ae_{0-48} (nmol)	Ae_{0-48} (%dose)	ER_{max} (nmol/h)	t_{max} [(a)] (h)	$t_{1/2}$ (h)
MDI MF/F 400µg/10µg	N	24	24	24	24	24	24	24	24	23
	Mean	0.48	1.06	1.30	1.42	1.47	6.20	0.162	1.50 (1.50-7.50)	12.1
	SD	0.25	0.42	0.49	0.53	0.54	2.26	0.079	-	2.59
MF/F MDI 400µg/20µg	N	23	24	24	24	24	24	23	23	24
	Mean	1.08	2.31	2.85	3.10	3.22	6.76	0.348	1.50 (1.50-7.50)	11.0
	SD	0.48	0.84	1.01	1.09	1.13	2.37	0.159	-	2.09
MF/F MDI 400µg/40µg	N	23	24	24	24	24	24	23	23	24
	Mean	2.15	4.69	5.72	6.22	6.45	6.78	0.719	1.50 (1.25-7.50)	12.0
	SD	1.04	1.62	1.81	1.87	1.89	1.99	0.347	-	2.60

(a) median (min-max), ND not determined

ER_{max} Maximum (peak) observed excretion rate of drug into urine

A summary of urinary excretion parameters of the (-) (R,R) and (+) (S,S)- enantiomers is presented in Table 11 and Table 12, respectively. The elimination t½ determined from the urinary excretion rate vs. time profiles was approximately 13 hours and 10 hours for the (-) (R,R)-enantiomer and the (+) (S,S)-enantiomers, respectively. The relative proportion of the two enantiomers remained constant over the dose range studied: The (-) (R,R)-enantiomer accounted for 2.45%, 2.75% and 2.83% of the formoterol dose for the MF 400 µg/F 10 µg, MF 400 µg/F 20 µg and MF 400 µg/ F 40 µg dose levels, respectively; The (+) (S,S)-enantiomer accounted for 4.04% and 4.52% and 4.94% of the dose for the MF 400 µg/F 10 µg, MF 400 µg/F 20 µg and MF 400 µg/ F 40 µg dose levels, respectively.

Table 11 Urinary excretion parameters of (-) (R,R)- enantiomer of formoterol

	Mometasone Furoate 400µg/Formoterol 10µg		Mometasone Furoate 400µg/Formoterol 20µg		Mometasone Furoate 400µg/Formoterol 40µg	
(-)(R,R)-enantiomer	Ae_{0-48} (%dose)	$t_{1/2}$ (h)	Ae_{0-48} (%dose)	$t_{1/2}$ (h)	Ae_{0-48} (%dose)	$t_{1/2}$ (h)
N	24	20	24	23	24	23
Mean	2.45	12.9	2.75	13.2	2.83	13.1
SD	1.01	2.16	1.06	2.07	0.92	2.49

Table 12 Urinary excretion parameters of (+) (S,S)- enantiomer of formoterol

	Mometasone Furoate 400µg/Formoterol 10µg		Mometasone Furoate 400µg/Formoterol 20µg		Mometasone Furoate 400µg/Formoterol 40µg	
	Ae_{0-48} (%dose)	$t_{1/2}$ (h)	Ae_{0-48} (%dose)	$t_{1/2}$ (h)	Ae_{0-48} (%dose)	$t_{1/2}$ (h)
N	24	18	24	24	24	23
Mean	4.04	9.70	4.52	9.46	4.94	9.95
SD	1.48	1.91	1.47	1.73	1.51	1.82

From the 42-day dedicated HPA-axis study (study P03705), mean (SD) formoterol plasma concentration-time profiles for each treatment and day showed rapid absorption (Figure 4). Mean concentration plots give the same ranking of exposure between treatment groups and day as did the geometric mean Cmax and AUCτ values (Table 13). Geometric means with 90% CI for formoterol Cmax and AUCτ showed increases in exposure with repeated dosing. The steady state Cmax and AUC for formoterol 10 mcg ranged from 28.3 to 36 pmol/L and 153 to 203 pmol•h/L, respectively (Table 13). Cmax and AUCτ values for formoterol indicate that exposures on Day 1 for the MF/F 400/10 µg dosage group tended to be lower than those for the MF/F 200/10 µg dosage group, and exposures for the MF/F 400/10 µg dosage on Day 42 tended to be higher than those for the MF/F 200/10 µg dosage group. Day 1 and Day 42 formoterol Cmax values for the MF/F 200/10 µg dosage were respectively 120% and 78.6% of the corresponding values for the MF/F 400/10 µg dosage (Table 14). The mean formoterol AUCτ values for the MF/F 200/10 µg dosage on Day 1 and Day 42 were respectively 121% and 75.1% of the values for the 400/10 µg dosage. With large intersubject variability in each treatment group and sample sizes of 13 to 15 subjects, the 90% CI values were large.

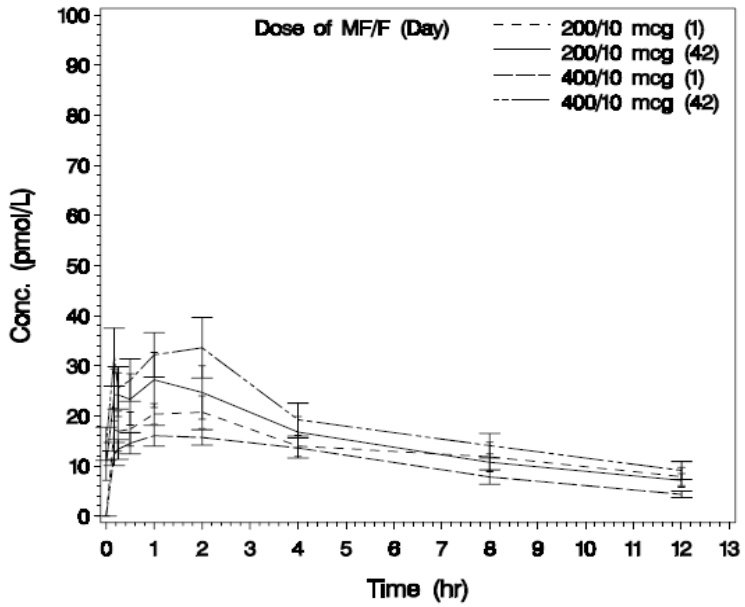

Figure 4 Mean Plasma Formoterol Concentrations with Standard Deviations on Days 1 and 42 following BID F 10 µg and MF 200 µg or 400 µg via MF/F FDC MDIs. Subjects received MF/F 200 µg/10 µg or MF/F 400 µg/10 µg via oral inhalation BID for 42 days.

Table 13 Geometric Means and 90% Confidence Intervals for Formoterol Pharmacokinetic Parameters following Inhalation of 10 µg Formoterol Fumarate from a MF/F 100/5 µg or MF/F 200/5 µg MDI.

Protocol No. P03705

Dosage	Day	n	Cmax (pmol/L)	90% CI (pmol/L)	AUCτ (pmol·hr/L)	90% CI (pmol·hr/L)
MF/F 200 µg/10 µg MDI BID	1	15	25.6	20.9–31.5	141	112–178
	42	13	28.3	21.4–37.5	153	111–209
MF/F 400 µg/10 µg MDI BID	1	15	21.4	18.7–24.6	116	97–139
	42	13	36	28.4–45.6	203	163–253

AUCτ=area under the concentration–time curve from 0 hr to 12 hr; CI=confidence interval; Cmax=maximum plasma concentration; MDI=metered-dose inhaler; MF/F 200 µg/10 µg MDI BID=2 puffs inhaled BID from mometasone furoate/formoterol fumarate 100 µg/5 µg fixed-dose combination metered-dose inhaler; MF/F 400 µg/10 µg MDI BID=2 puffs inhaled BID from mometasone furoate/formoterol fumarate 200 µg/5 µg fixed-dose combination metered-dose inhaler.

Table 14 Geometric Mean Ratios and 90% Confidence Intervals for Formoterol Exposure Parameters AUCτ and Cmax.

Protocol No. P03705

	Comparison (Sample Sizes)	Parameter	Ratio	90% CI[a]
Day 1	MF/F 200 µg/10 µg BID:MF/F 400 µg/10 µg BID (n=15/n=15)	AUCτ	121	91.4–161
		Cmax	120	94.1–152
Day 42	MF/F 200 µg/10 µg BID:MF/F 400 µg/10 µg BID (n=13/n=13)	AUCτ	75.1	51.9–109
		Cmax	78.6	55.3–112

AUCτ=area under the plasma concentration–time curve from 0 hr to 1 hr postdose; Cmax=maximum plasma concentration MF 200 µg/10 µg F=mometasone furoate/formoterol fumarate 100 µg/5 µg fixed-dose combination metered-dose inhaler (subjects inhaled 2 puffs BID); MF 400 µg/10 µg F=mometasone furoate/formoterol fumarate 200 µg/5 µg fixed-dose combination metered-dose inhaler (subjects inhaled 2 puffs BID)

Reviewer's Comments

The age group for the dedicated HPA-axis study is 18-64 yrs. There is no PK information for subjects 12-17 yrs of age.

Although both MF and formoterol showed dose-related differences in exposure between the low and high dosages of MF/F, dose-normalized values of Cmax and AUCτ were higher for MF/F 200 µg/10 µg than for MF/F 400 µg/10 µg on Day 1, but lower on Day 42. This is mainly due to the high intrasubject variability of exposure values.

2.2.5 What is the impact of chronic Dulera dosing on cortisol suppression?

Cortisol suppression data following chronic twice daily administration of Dulera was obtained from two separate studies: 1) Study P03705 (dedicated HPA-axis study) and 2) P04139 (long-term safety study).

1) Study P03705 was a randomized, open-labeled, placebo- and active-controlled, parallel group, 6-week study to evaluate the effect of corticosteroids on the hypothalamicpituitary-adrenal (HPA) axis. Two strengths of MF/F (200/10 µg and 400/10 µg) were compared to placebo as

well as to treatment with Advair® (fluticasone propionate/salmeterol) 460/42 µg as a positive control.

Subjects (asthma patients, age 18-64 yrs) were to be assigned to one of the following 4 treatments:

Treatment A (n=13): Mometasone furoate (MF)/formoterol fumarate (F) 200/10 µg (2 puffs of MF/F 100/5 µg MDI) by oral inhalation BID for 42 days, to be administered at the same time on study Days 1 through 42.

Treatment B (n=15): MF/F 400/10 µg (2 puffs of MF/F 200/5 µg MDI) by oral inhalation BID for 42 days, to be administered at the same time on study Days 1 through 42.

Treatment C (n=16): Fluticasone propionate (FP)/salmeterol (S) 460/42 µg (2 puffs of FP/S 230/21 µg MDI) by oral inhalation BID for 42 days, to be administered at the same time on study Days 1 through 42.

Treatment D (n=16): Placebo (2 puffs from an inhaler matching MF/F MDI) by oral inhalation BID for 42 days, to be administered at the same time on Day 1 through Day 42.

At day 1, mean plasma cortisol AUC (0-24 hr) values at baseline ranged from 1570 to 1700 ng. hr/mL and were similar for all the treatment groups. Following multiple BID oral inhalations of MF/F 200/10 µg or placebo, mean cortisol AUC (0-24 hr) values were similar (<10% change from baseline) (Table 15).

Table 15 Plasma cortisol parameters in asthmatic subjects following BID oral inhalation of MF/F 200/10 µg, MF/F 400/10 µg, FP/S, or placebo via MDI

Protocol No. P03705

Treatment	Day –1 Mean (% CV)		Day 42 Mean (% CV)	
	AUC(0-24 hr) (ng·hr/mL)	Ctrough (ng/mL)	AUC(0-24 hr) (ng·hr/mL)	Ctrough (ng/mL)
MF/F 200 µg/10 µg BID (Treatment A[a]) (MF 400 µg/F 20 µg total daily dose; n=15)	1620 (19)	23.6 (40)	1670 (29)[b]	24.1 (57)[b]
MF/F 400 µg/10 µg BID (Treatment B[a]) (MF 800 µg/F 20 µg total daily dose; n=16)	1570 (22)	20.3 (37)	1390 (49)[c]	14.9 (50)[c]
FP/S 460 µg/42 µg BID (Treatment C[a]) (FP 920 µg/ S 84 µg total daily dose; n=16)	1680 (31)	20.4 (44)	1240 (46)	16.4 (90)
Placebo BID (Treatment D[a]) (n=17)	1700 (38)	21.5 (61)	1830 (39)[d]	22.9 (71)[d]

* Numbers are baseline unadjusted

a: subjects received treatment A (MF/F 200/10 µg), treatment B (MF/F 400/10 µg), treatment C (FP/S 460/42 µg), or treatment D (placebo) by oral inhalation BID for 42 days

b: n=13, c: n=15, d: n=16

Table 16 Statistical comparison of plasma cortisol by treatment

Protocol No. P03705

Treatment (Total Daily Dose)	n[b]	Least-Square Mean[a] (90% CI) Day 42/Day –1 Ratio (%)	Treatment Comparison Ratio[a]		
			Label	Geometric Mean Ratio (%)	90% CI (%)
AUC(0-24 hr)					
Treatment A: MF/F 200 mcg/10 mcg BID (MF/F 400 mcg/20 mcg daily)	13	99 (87–113)	A vs D	92	78–110
Treatment B: MF/F 400 mcg/10 mcg BID (MF/F 800 mcg/20 mcg daily)	15	84 (75–95)	B vs D	78	66–92
Treatment C: FP/S 460 mcg/42 mcg BID (FP/S 920 mcg/84 mcg daily)	16	71 (63–80)	C vs D	66	56–78
Treatment D: Placebo BID	16	107 (96–120)	B vs C	119	101–140
			A vs C	140	118–166
			B vs A	85	71–101
Ctrough					
Treatment A: MF/F 200 mcg/10 mcg BID (MF/F 400 mcg/20 mcg daily)	13	95 (75–120)	A vs D	96	70–132
Treatment B: MF/F 400 mcg/10 mcg BID (MF/F 800 mcg/20 mcg daily)	15	68 (54–84)	B vs D	68	50–93
Treatment C: FP/S 460 mcg/42 mcg BID (FP/S 920 mcg/84 mcg daily)	16	63 (51–78)	C vs D	64	47–86
Treatment D: Placebo BID	16	99 (80–123)	B vs C	107	79–146
			A vs C	150	109–207
			B vs A	71	52–99

* Numbers are baseline adjusted
a: Model-based (least-squares) mean
b: Subjects missing Day 42 cortisol samples were excluded

MF/F 200 mcg/10 mcg BID and placebo Baseline (Day –1) to Day 42 log plasma cortisol AUC (0-24 hr) ratios were comparable. Day 42:Day –1 AUC(0-24 hr) ratios for MF/F 400 mcg/10 mcg and FP/S 460 mcg/42 mcg BID treatments were respectively 22% lower and 34% lower than with placebo treatment (Table 16). Note: the HPA axis study (29 days) results for the approved MF (Asmanex®) 440 mcg QD is plasma cortisol AUC (0-24h) decreased 18% from placebo on day 28. Therefore, the results for MF/F MDI from study P03705 generally showed similar trend as seen with the reference drug, Asmanex MF DPI.

2) The effect of inhaled mometasone furoate administered via DULERA on adrenal function was also evaluated in a safety study (Study P04139) in patients with asthma.

Study P04139 is a randomized, parallel-group, multi-center, open-label, evaluator-blind/third party dispenser study in adults and adolescents 12 years of age and older with persistent asthma, evaluating the safety of MF/F 200/10 mcg BID, and MF/F 400/10 mcg BID vs fluticasone propionate/salmeterol (F/SC) 250/50 mcg BID, and F/SC 500/50 mcg BID. Twenty-four-hour plasma cortisol samples were collected from 66 subjects across the four treatment groups; MF/F 200/10 (n=18),, MF/F 400/10 (n=20), F/SC 250/50 (n=8), and F/SC 500/50 (n=11). Results of baseline plasma cortisol 24-hour AUC and change from baseline at Week 26, Week 52 and endpoint are summarized in Table 17. At Week 52, the mean plasma cortisol AUC(0-24 hr) was 2.2%, 29.6%, 16.7%, and 32.2% lower from baseline for the MF/F 200/10, MF/F 400/10, F/SC 250/50, and F/SC 500/50 treatment groups, respectively.

Table 17 Plasma Cortisol 24-Hour AUC (mcg/dL*hr) Analysis Results - Change From Baseline

Protocol No. P04139

	MF/F MDI 200/10 mcg			MF/F MDI 400/10 mcg			F/SC MDI 250/50 mcg			F/SC MDI 500/50 mcg		
	BID (A)			BID (B)			BID (C)			BID (D)		
		LS	(Mean%		LS	(Mean%		LS	(Mean%		LS	(Mean%
	N	Mean[a]	Change)[b]	N	Mean[a]	Change)	N	Mean[a]	Change)	N	Mean[a]	Change)
Baseline	18	210.5	NA	20	188.8	NA	8	189.2	NA	11	238.3	NA
Change From Baseline												
Week 26	18	-82.0	(-37.5%)	18[c]	-81.2	(-33.3%)	7[c]	-65.0	(-28.8%)	10	-52.3	(-22.3%)
Week 52	17	-28.0	(-2.2%)	19	-74.8	(-29.6%)	8	-47.1	(-16.7%)	10	-66.3	(-32.2%)
Endpoint	**18**	**-34.9**	**(-6.4%)**	**20**	**-75.6**	**(-30.9%)**	**8**	**-46.0**	**(-16.7%)**	**11**	**-70.4**	**(-33.9%)**

		Model P-Values		Pairwise Comparisons P-Values					
	Pstd[a]	Trt	Base	A-B	A-C	A-D	B-C	B-D	C-D
Change From Baseline									
Week 26	41.9	0.272	<.001	0.954	0.368	0.082	0.391	0.097	0.548
Week 52	63.8	0.166	<.001	0.034	0.491	0.143	0.307	0.741	0.538
Endpoint	**64.9**	**0.232**	**<.001**	**0.061**	**0.689**	**0.162**	**0.281**	**0.836**	**0.431**

	95% Confidence Interval					
	A-B	A-C	A-D	B-C	B-D	C-D
Change From Baseline						
Week 26	(-29.1, 27.5)	(-54.6, 20.6)	(-63.4, 4.0)	(-53.8, 21.4)	(-63.3, 5.5)	(-54.9, 29.5)
Week 52	(3.6, 90.0)	(-36.2, 74.3)	(-13.4, 89.8)	(-81.7, 26.3)	(-60.4, 43.2)	(-43.0, 81.3)
Endpoint	**(-1.9, 83.4)**	**(-44.5, 66.8)**	**(-14.8, 85.9)**	**(-84.1, 24.9)**	**(-55.6, 45.1)**	**(-37.3, 86.1)**

a: LS Means and Pstd (pooled standard deviations) are obtained from the ANCOVA model with effects for treatment and Baseline (Base) as a covariate; b: Mean percent changes are raw means; c: Subjects must have had both a 0 and 24-hour evaluation to be included in this analysis. Two subjects (No. 330 in high MF/F dose level and No. 34 in medium F/SC dose level had their Week 26 cortisol data edge-imputed as it was missing. These subjects were NOT included in the Week 26 data. This is the reason that N is higher at Week 52 than at Week 26.

Reviewer's comments:

Where there is lack of robust PK data, a dedicated HPA axis study is needed. For the dedicated the HPA axis study, there are some deficiencies: 1) the number of subjects per treatment arm (n<20) is considered less than ideal (n~35-40); and 2) open label study design instead of desirable double-blind study design. This reviewer concludes that the HPA axis study design is less than ideal. However, the cortisol suppression data from the proposed product, the reference MF monotherapy drug (Asmanex®), as well as the positive control (Advair) were all showing the expected trend. Particularly, the positive and the negative controls did show similar data as has been obtained in previous submissions for these reference products.

2.3 General Biopharmaceutics

2.3.1 What is the relative bioavailability between the proposed fixed dose combination and the approved single-ingredient drug products?

In healthy subjects, the exposure of MF from the MF/F MDI differed from the marketed MF DPI (Asmanex® Twisthaler®). Systemic exposures to MF (based on AUC) were approximately 52%

and 25% lower on Day 1 and Day 5 following MDI administration compared with DPI administration (Table 18 and Table 19).

Study P04275 was a Phase 1, open-label, multiple-dose relative bioavailability study to compare the test combination product with the marketed MF DPI (Asmanex®) in healthy subjects. Subjects received twice daily doses of MF 800 µg via dry powder inhaler (MF-DPI) oral inhalation or via metered-dose inhaler (MF/F-MDI) oral inhalation for 5 days. A total of 12 healthy subjects were enrolled and completed the study.

Mean pharmacokinetic parameters of MF in healthy subjects on Days 1 and 5 after dosing with MF 800 µg administered in combination with F 20 µg (MDI) or MF 800 µg administered alone (DPI) are summarized in Table 18.

Table 18 Mean (CV%) Pharmacokinetic Parameters of MF on Days 1 and 5 After MDI Administration of MF 800 µg/F 20 µg BID or DPI Administration of MF 800 µg BID in Healthy Subjects

Parameter	n	Serum MF concentration (pg/ml)							
		MF 800 µg/F 20 µg MDI				MF 800 µg DPI			
		Day 1		Day 5		Day 1		Day 5	
		Mean	CV (%)	Mean	CV (%)	Mean	CV (%)	Mean	CV (%)
Tmax* (hr)	12	4.0	0.5-6.0	1.0	0.5-4.0	1.0	0.5-2.0	1.0	0.5-1.5
Cmax (pg/mL)	12	67.8	49	241	36	184	36	383	23
AUC (0-12 h) (pg.hr/mL)	12	650	51	2200	35	1270	33	2820	22

*** Median (range)**

The mean AUC (0-12 hr) ratio estimates were approximately 52% and 25% lower on Days 1 and 5 following MDI administration, respectively.

Table 19 Relative Systemic Exposures of MF on Days 1 and 5 After MDI Administration of MF 800 µg/F 20 µg or DPI Administration of MF 800 µg in Healthy Subjects

Protocol No. P04275

Parameters	Day	Ratio Estimate[a] (%)	90% CI
Cmax (pg/mL)	1	35.4	29 to 43
	5	60.6	49 to 75
AUC(0-12 hr) (pg·hr/mL)	1	48.2	39 to 59
	5	74.7	61 to 91

a: Ratio of MDI/DPI.

Systemic exposures to MF based on AUC (0-12hr) were lower following MDI administration compared with DPI administration on Days 1 and 5 (Table 18). The ratios of geometric means (90% CI) for Cmax and AUC (0-12 hr) values on Day 1 were 35.4% (29% to 43%) and 48.2% (39% to 59%) after MDI relative to DPI administration, respectively. Corresponding ratios (90%

CI) for Cmax and AUC (0-12 hr) on Day 5 were 60.6% (49% to 75%) and 74.7% (61% to 91%), respectively (Table 19).

In COPD patients, mean MF Cmax and AUC (0-12 hr) following inhalation of MF/F 400/10 µg MDI BID for 5 days were respectively 44% and 23% lower than MF 400 µg DPI (Asmanex®) BID for 5 days (Study P04689). Study P04689 is an open-label, multiple-dose, cross-over study to compare the systemic exposure of MF after MF/F MDI 400 µg/10 µg vs 400 mcg MF DPI in 14 subjects with moderate to severe COPD. Mean pharmacokinetic parameters of MF in COPD subjects on Days 5 after dosing with MF/F 400 µg/10 µg (MDI) or MF 400 µg administered alone (DPI) are summarized in Table 20.

In asthma patients, Sponsor did not perform the relative bioavailability study comparing the test MF/F MDI product to the reference F DPI Asmanex®. After abstracting the multiple dose MF PK data from the approved drug Asmanex® and comparing the MF PK data from the HPA axis study in this application, the reviewer found that the mean MF Cmax and AUC (0-12 hr) following MF/F 400/10 µg MDI BID were lower than the MF 400 µg DPI (Asmanex®) BID (9.0% and 47.4% lower for Cmax and AUC (0-12 hr), respectively, Table 20). However, for the asthma patients, this is the cross study and cross development comparison with different bioanalytical methodologies. In order to know whether it is reasonable to abstract the data from the MF PK data from the approved drug Asmanex®, the accumulation was calculated in healthy subjects and asthma patients (Table 8 and Table 9). The single-dose and multiple-dose PK data in asthma patients were taken from the previous submission for Asmanex®. The accumulations for AUC (0-12) and Cmax in healthy subjects were similar to those in asthma patients for both MDI formulation and DPI formulation (the accumulations for AUC (0-12) were 3.38 for MDI and 2.22 for DPI in healthy subjects, and 3.39 for MDI and 2.45 for DPI in asthma patients; accumulations for Cmax were 3.55 for MDI and 2.08 for DPI in healthy subjects, and 3.00 for MDI and 2.17 for DPI in asthma patients). The results indicate that the cross study and cross development comparison is reasonable.

Table 20 Dose normalized MF exposures following multiple-dose inhalations from MF/F MDIs and F Asmanex DPI

Parameters *	Healthy subject		Asthma patients		COPD patients	
	MDI (5 days) (Study P04275)	DPI (5 days) (Study P04275)	MDI (42 days) (Study P03705)	DPI (28 days) (Asmanex®)	MDI (Study P04689)	DPI (Study P04689)
AUC (pg hr/mL)	**1100 (35)**	**1410 (22)**	**577 (40)**	**634 (66)**	**484 (56)**	**646 (47)**
Cmax (pg/mL)	**120.5 (36)**	**191.5 (23)**	**60.0 (36)**	**114 (52)**	**49.2 (55)**	**90.2 (48)**

*The PK parameters are dose normalized to 400 mcg/10 mcg BID

2. Systemic exposure to F from the MF/F MDI product is similar to that from the marketed F DPI product (Foradil® Aerolizer®).

Study P05643 was a randomized, single-dose, double-blind, placebo-controlled, 5 period, crossover study in 25 subjects with mild to moderate asthma. Plasma and Urine Pharmacokinetic Parameters for Formoterol were summarized in Table 21. Systemic formoterol exposures were similar following administration of MF/F 100/10 mcg, MF/F 400/10 mcg, or F 10 mcg alone delivered via F 12 mcg (10 mcg emitted dose) delivered via F DPI (Foradil® Aerolizer®)(Table 21 and Table 22).

Table 21 Plasma and Urine Pharmacokinetic Parameters for Formoterol

Protocol No. P05643 (H2201)

Treatment	Tmax (hr) Median (Range)	Cmax (pmol/mL) Mean[a] ± SD	AUC(0-2 hr) (pmol·hr/L) Mean[a] ± SD	Ae(0-24 hr) (nmol) Mean[a] ± SD
MDI MF/F 100 mcg/10 mcg (n=24)	1.00 (0.17–2.08)	23.8 ± 13.0[b]	31.6 ± 15.0[c]	1.58 ± 0.78[b]
MDI MF/F 400 mcg/10 mcg (n=24)	0.58 (0.13–2.08)[b]	23.4 ± 7.3[b]	33.9 ± 10.7	1.63 ± 0.65
F MDI 10 mcg (n=24)	1.08 (0.05–2.08)	22.3 ± 6.1	33.7 ± 11.8	1.76 ± 0.75[b]
F Aerolizer® 12 mcg (n=24)	0.58 (0.05–2.08)[b]	21.6 ± 8.5[b]	29.6 ± 11.7[b]	1.42 ± 0.54

Ae(0-24hr)=amount excreted in urine during the interval 0 hr to 24 hr. AUC(0-2 hr)=area under the plasma concentration–time curve from 0 to 2 hr postdose; Cmax=maximum observed plasma concentration
a: Arithmetic mean.
b: n=25.
c: n=23.

Table 22 Geometric Mean Ratios (90% Confidence Intervals) for Formoterol Ae and Cmax

Comparison	**Cmax**	**Ae (0-24 hr)**
MDI MF/F 100 mcg/10 mcg (n=24) vs. F Aerolizer 12 mcg (n=24)	104.41 (91.66-118.93)	106.62 (94.52-120.26)
MDI MF/F 400 mcg/10 mcg (n=24) vs. F Aerolizer 12 mcg (n=24)	108.50 (95.26-123.60)	112.50 (99.89-126.70)

2.3.2 Is there any drug-drug and/or formulation interaction between the MF and F when delivered via the new MDI device?

No. There is no significant pharmacokinetic drug interaction between mometasone furoate (MF) and formoterol (F).

Study P03658 was an open-label, single-dose, 4 period crossover study in 27 healthy subjects to explore the potential for drug interaction as well as effects of combined administration on exposure. This study helped evaluate both drug-drug intraction (coadministration vs. single-ingredient in the same device) as well as formulation interaction (coadministration vs. combination).

The treatment arms in this study are as follows:
Treatment A: Mometasone furoate 800 µg via MF MDI device as a single dose.
Treatment B: Formoterol fumarate 20 µg via F MDI device as a single dose.

Treatment C: Mometasone furoate 800 µg via MF MDI device + Formoterol fumarate 20 µg via F MDI as a single dose.
Treatment D: Mometasone furoate 800 µg /formoterol fumarate 20 µg via MF/F MDI combination product device as a single dose.

The mean plasma MF and F concentration–time profiles in subjects receiving MF 800 mcg and/or F 20 mcg were in Figure 5. Following inhalation of a single dose of 20 µg F and/or 800 µg MF via MDI, F and MF were both rapidly absorbed in most subjects (Figure 5). Mean plasma concentration-time profiles showed no major difference between treatments in rate of absorption or elimination of MF or F.

Mean pharmacokinetic parameters and statistical comparisons for MF and F are summarized in Table 23 and Table 24.

The mean AUC and Cmax for MF and F are comparable when MF and F are administered from the new fixed-dose combination MDI device (MF/F MDI) vs coadministration from single-ingredient MDI devices (MF MDI + F MDI). Systemic exposure of MF and F is similar when the coadministration from the single ingredients vs the individual drug administered alone (Table 23 and Table 24). These data indicates that there are no drug-drug interaction and formulation effects.

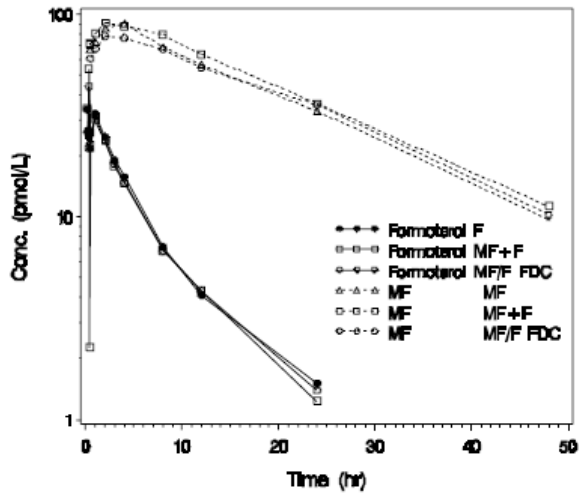

Figure 5 Mean Plasma MF and Formoterol Concentration–Time Profiles in Subjects Receiving MF 800 mcg and/or F 20 mcg (Protocol No. P03658).

Table 23 Statistical Group Comparisons of MF Pharmacokinetic Parameters

Protocol No. P03658

Parameter	Least-Squares Geometric Mean[b] (90% CI) MF (n=17[a,c])	MF+F (n=18[a,c])	MF/F(n=18[a,c])	Intrasubject CV (%)	Treatment Comparison	Geometric Mean Ratio (%)	90% CI (%)
AUC(0-tf)	906	885	837	25	MF+F vs MF	98	85–113
(pg·hr/mL)	(685–1199)	(670–1170)	(633–1106)		MF/F vs MF+F	95	82–109
Cmax	46	41	38	26	MF+F vs MF	91	78–106
(pg/mL)	(34–61)	(31–55)	(29–51)		MF/F vs MF+F	93	80–108

a: Values for Subject No. 112 following MF and Subject No. 122 following all 3 treatments were excluded from analyses because of anomalously low MF exposure values likely due to poor inhalation technique.
b: Model-based (least-squares) geometric mean: ANOVA extracting the effects due to treatment, period, sequence and subject.
c: Values from Subjects Nos. 105, 110, 115, 120, 125, and 127 were excluded from analysis because of predose values >5% of Cmax. Subject No. 107 withdrew early following treatment with MF/F, and Subject No. 123 withdrew following MF treatment; thus values from these subjects also were excluded.

Table 24 Statistical Group Comparisons of F Pharmacokinetic Parameters

Parameter	Least-Squares Geometric Mean[a] (n^b) 90% CI (%) F	MF+F	MF/F	Intrasubject CV (%)	Treatment Comparison	Geometric Mean Ratio (%)	90% CI (%)
AUC(0–tf)	145 (n=23)	141 (n=24)	152 (n=24)	48	MF+F vs F	98	77–124
(pmol·hr/L)	109–192	107–188	115–202		MF/F vs MF+F	108	85–136
AUC(0–12 hr)	138 (n=22)	134 (n=23)	133 (n=24)	41	MF+F vs F	97	79–120
(pmol·hr/L)	110–173	107–167	107–165		MF/F vs MF+F	99	81–122
Cmax	31.9 (n=24)	33.6 (n=24)	32.7 (n=24)	46	MF+F vs F	106	84–132
(pmol/L)	24.4–41.6	25.7–44	25.0–42.7		MF/F vs MF+F	97	78–122
Ae(0-48 hr)	1.63 (n=22)	1.32 (n=21)	1.69 (n=24)	59	MF+F vs F	81	59–111
(nmol)	1.17–2.28	0.94–1.85	1.22–2.34		MF/F vs MF+F	128	94–175

a: Model-based (least-squares) mean: ANOVA extracting effects due to treatment, period, sequence and subject.
b: Three subjects were excluded due to early withdrawal from the study. Subject No. 102 discontinued after MF+F and MF /F; Subject No. 107 discontinued after treatment with MF/F, and Subject No. 123 discontinued after treatment with F alone.

2.4 Analytical Section

2.4.1 What bioanalytical methods are used to assess concentrations?

Formoterol and Mometasone furoate in human plasma was analyzed by a validated liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) method developed and qualified (b) (4). Validated bioanalytical methods were used for quantification of MF in serum and/or plasma and formoterol in plasma and urine (DM27263, DM27484, DMPK R0500473, P860, P883, P868, R00-1844-02).

Table 25 provides the analytical ranges, linearity, precision, and accuracy values for each assay, which is within the acceptable range. The results of sample analysis in individual study are acceptable as evidenced by QC sample precision and accuracy within ± 15% (±20% at the LLOQ if included as a QC sample).

Table 25 Validation Summary for Assays Used to Determine Concentrations of Mometasone Furoate in Human Serum and Plasma, Formoterol in Human Plasma, and Formoterol, R,R-Formoterol, and S,S-Formoterol in Human Urine

Analyte[a]	Matrix	Validation Report	Range (pg/mL)[b]	Precision (CV, %)	Accuracy (%Bias)	Studies Supported
MF	Serum	DM27263	5.00 to 250	2.18 to 6.96	-4.22 to 0.115	P04275, P05642 (H2101)
	Plasma	DM27484	0.250 to 25.0	2.81 to 11.6	-7.29 to -3.26	P03658, P03705, P04689, P05644 (H2104)
Formoterol	Plasma	DMPK R0500473	3.44 to 551	3.0 to 12.1	-2.9 to 4.8	P05642 (H2101), P05643 (H2201)
		P860	0.499 to 250	4.27 to 11.7	0.343 to 11.7	P03658, P03705, P04689, P05644 (H2104)
	Urine	DMPK R0500473	6.99 to 1860	2.1 to 8.4	0.0 to 6.1	P05642 (H2101), P05643 (H2201)
		P883	5.99 to 1200	4.34 to 13.0 1.86 to 5.62[c]	0.138 to 8.07 -0.597 to 5.91[c]	P03658, P03705, P05644 (H2104)
		DMPK(F) R00-1844-02	12.3 to 12300	1.6 to 10.3	-4.9 to 2.3	P06144 (I2201)
R,R-Formoterol	Urine	P868	5.99 to 1200	2.95 to 8.05	0.663 to 7.77	P05644 (H2104)
S,S-Formoterol	Urine	P868	5.99 to 1200	3.01 to 8.62	0.445 to 17.8	P05644 (H2104)

a: MF = mometasone furoate
b: Lower limit of quantitation is the lowest value in the range of the assay.
c: Precision and accuracy from a set of freshly prepared QC standards.

3 PRELIMINARY LABELING RECOMMENDATIONS

Here are some high-level labeling comments. Line-by-line label edits will be done at a later date.

1) The proposed label does not include drug-drug interaction with ketoconazole as an item under warnings and precautions. According to this reviewer, interaction with ketoconazole should be viewed as a global interaction potential with strong CYP3A4 inhibitors and hence this needs to be included in several sections including warnings and precautions, drug interactions as well as under PK.

2) The results from the dedicated HPA axis study should be interpreted with caution due to major deficiencies in study design. To compensate for this, the cortisol suppression data from the original Asmanex NDA submission should be included in the label along with recently obtained cortisol suppression data from the present submission with a caveat that the HPA-axis study was not adequately designed.

Presented below are preliminary labeling comments from the Clinical Pharmacology perspective. The ***blue bolded italic*** words indicate the addition text, and the ~~**bold strike through**~~ words indicate the deletion.

5. Warnings and precautions

5.8 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of DULERA with ketoconazole, and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) because adverse effects related to increased systemic exposure to mometasone may occur [see Drug Interactions (7.1), ClinicalPharmacology (12.3)]

7. Drug Interactions

(b) (4)

7.1 Inhibitors of Cytochrome P4503A4

The main route of metabolism of corticosteroids, including mometasone, a component of DULERA, is via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4). After oral administration of ketoconazole, a strong inhibitor of CYP3A4, the mean plasma concentration of orally inhaled mometasone increased. Concomitant administration of CYP3A4 inhibitors may inhibit the metabolism of, and increase the systemic exposure to, mometasone. Caution should be exercised when considering the coadministration of DULERA with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin), [see Warnings and Precautions (b) (4) ***Clinical Pharmacology: Pharmacokinetics (12.3)].*** [4]

7.5 Monamine oxidase inhibitors, tricyclic antidepressants, and drugs known to prolong the QTc interval:
Formoterol, as with other beta$_2$-agonists, should be administered with extreme caution to patients being treated with monamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval ***or within 2 weeks of discontinuation of such agents***, because the action of (b) (4) ***formoterol, a component of DULERA***, on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias. [1]

7.6 Beta-adrenergic receptor antagonists:
Beta-adrenergic receptor antagonists (beta-blockers) and formoterol may inhibit the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of beta$_2$-agonists, such as formoterol, ***a component of DULERA***, but may produce severe bronchospasm in (b) (4) patients ***with asthma***. Therefore, patients with asthma should not normally be treated with beta-blockers (including eye drops). However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution. [1]

12. Clinical pharmacology

12.2 Pharmacodynamics
HPA-axis effects:

(b) (4)

In a 42-day, open-label, placebo and active-controlled study 60 patients with asthma 18 years of age and older were randomized to receive two inhalations twice daily of 1 of the following treatments: DULERA 100/5, DULERA 200/5 , fluticasone propionate/salmeterol xinafoate 230 mcg/21 mcg, or placebo. At Day 42, the mean change from baseline plasma cortisol AUC(0-24 hr) was 8%, 22% and 34% lower compared to placebo for the DULERA 100/5 (n=13), DULERA 200/5 (n=15) and fluticasone propionate/salmeterol xinafoate 230 mcg/21 mcg (n=16) treatment groups, respectively.[52]

(b) (4)

(b) (4)

In a 52-week safety study, primary analysis of the plasma cortisol 24-hour AUC was performed on 57 patients with asthma who received 2 inhalations twice daily of DULERA 100/5, DULERA 200/5, fluticasone propionate/salmeterol 250/50, or fluticasone propionate/salmeterol 500/50. At Week 52, the mean plasma cortisol AUC (0-24 hr) was 2.2%, 29.6%, 16.7%, and 32.2% lower from baseline for the DULERA 100/5 (n=18), DULERA 200/5 (n=20), fluticasone propionate/salmeterol 250/50 (n=8), and fluticasone propionate/salmeterol 500/5 (n=11) treatment groups, respectively. [53]

25 PAGES OF DRAFT LABELING HAVE BEEN WITHHELD IMMEDIATELY FOLLWING THIS PAGE AS B4 CCI/TS

Annotations References

1. Foradil USPI
2. Clinical Overview 2.5 – Section 7.3 Benefit Risk Discussion
3. Summary of Clinical Efficacy 2.7.3
4. Asmanex USPI
5. Module 3 - 3.2.P.1 Description/Composition of the Drug Product – Section 1 Description of the Dosage Form
6. Module 3 – 3.2.P.2.4 Container Closure System – Section 10 Priming and Re-priming – 10.1 Summary
7. Module 3 – 3.2.P.2.4 Container Closure System – Section 9 Effect of Shaking on Product Performance – 9.1 Summary

(b) (4)

9. Summary of Clinical Efficacy 2.7.3 – 2.2 Results of Study P04334
10. Summary of Clinical Efficacy 2.7.3 – 2.3 Results of Study P04431
11. National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program, Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, Full Report 2007.
12. Integrated Analysis of Safety 5.3.5.3 – 2.1.5.5 Hypersensitivity events
13. Integrated Analysis of Safety 5.3.5.3 – 2.1.1.2.1 All Phase 3 Studies Pooled
14. Integrated Analysis of Safety 5.3.5.3 – 2.1.5.3 Eye Events

(b) (4)

16. CSR P04334 – Section 11.2 Demographic and Other Baseline Characteristics - Table 5 [Summary of Demographic Data and Baseline Characteristics (All Treated Subjects)]
17. CSR P04431 – Section 11.2 Demographic and Other Baseline Characteristics - Table 5 [Summary of Demographic Data and Baseline Characteristics (All Treated Subjects)]
18. CSR P04139 – Section 11.2 Demographic and Other Baseline Characteristics - Table 5 (Summary of Demographic Data and Baseline Characteristics)
19. (b) (4)
20. CSR P04334 – Section 12.2.1.3 Treatment-Related Adverse Events
21. CSR P04431– Section 12.2.1.3 Treatment-Related Adverse Events
22. Integrated Analysis of Safety 5.3.5.3 – 2.1.1.2 Treatment-Related Adverse Events
23. Integrated Analysis of Safety 5.3.5.3 – 2.1.1.2.4 Long-Term 52-Week Safety Study (P04139)
24. Integrated Analysis of Safety 5.3.5.3 – 2.1.2 Deaths
25. Integrated Analysis of Safety 5.3.5.3 – 2.1.3.5.1 Serious Asthma Exacerbations
26. CSR P04139 12.5.3.1 Ophthalmologic Examinations
27. CSR P04139 12.6 Safety Conclusions
28. Integrated Analysis of Safety 5.3.5.3 – 3.1.3 Long-Term 52-Week Safety Study (P04139)
29. Integrated Analysis of Safety 5.3.5.3 – 4.1.3 Long-Term 52-Week Safety Study (P04139)
30. Integrated Analysis of Safety 5.3.5.3 – 6 Post-Marketing Data
31. Integrated Analysis of Safety 5.3.5.3 – 5.3 Drug Interactions

32. CSR P04705 – Section 11.2 Demographic and Other Baseline Characteristics - Table 5 [Summary of Demographic Data and Baseline Characteristics (All Treated Subjects)]

33. Integrated Analysis of Safety 5.3.5.3 – 5.1.1 Effects of Age, Sex, Race, and BMI on Occurrence of Adverse Events

34. Module 3 - 3.2.S.4 Control of Drug Substance – Introduction

35. Module 3 – 3.2.P.2.4 Container Closure System- 3.1 Mouthpiece Retention – Table 3

36. Module 3 – 3.2.P.5.1 Specification(s) – Table 1

37. CSR P05643 (CFOR258H2201) – 9.1 Overall study design and plan

38. CSR P05643 (CFOR258H2201) – 11.4.2 Analysis of Pharmacodynamics FEV1

39. CSR P05643 (CFOR258H2201) – 12.4.2 Evaluation of each laboratory parameters

40. CSR P05643 (CFOR258H2201) 12.5 Vital signs, physical findings, and other observations related to safety

41. CSR P05644 (CFOR258H2104) – 9.1 Overall study design and plan

42. CSR P05644 (CFOR258H2104) – 12.4.2 Evaluation of each laboratory parameter

43. CSR P05644 (CFOR258H2104) – 12.5 Vital signs, ECG, physical findings, and other observations related to safety

44. Integrated Analysis of Safety 5.3.5.3 – 3.1.1 Placebo-Controlled 26-Week Efficacy and Safety Studies ((b) (4) and P04334)

45. CSR P04431 – 12.4.2.1 Summary of Hematology, Blood Chemistry, and Urinalysis

46. Integrated Analysis of Safety 5.3.5.3 – 3.1.3 Long-Term 52-Week Safety Study (P04139)

47. Integrated Analysis of Safety 5.3.5.3 – 4.1.1 Placebo Controlled 26-Week Efficacy and Safety Studies (b) (4) and P04334)

48. CSR P04431 – 12.5.1 Vital Signs

49. CSR P04431 – 12.5.2 Electrocardiograms

50. Integrated Analysis of Safety 5.3.5.3 – 4.1.3 Long-Term 52-Week Safety Study (P04139)

51. Clinical Overview 2.5 – 6.3 Effect on HPA-Axis

52. Summary of Clinical Pharmacology 2.7.2 – 2.6 Study P03705: Evaluation of Extrapulmonary Effects of MF from a Combination MDI formulation versus Fluticasone Propionate from a Fluticasone Propionate/Salmeterol Combination Comparator on HPA-Axis Function.

53. Integrated Summary of Safety 5.3.5.3 – 3.3 Plasma Cortisol Results

54. Summary of Clinical Pharmacology Studies 2.7.2 – 3.2 Pharmacokinetics of Mometasone Furoate

55. CSR P03705 11.4.1.2.1 Mometasone Furoate Pharmacokinetic Results – Table 17 Geometric Means and 90% Confidence Intervals for MF Pharmacokinetic Parameters Following inhalation of 200 mcg and 400 mcg of MF/F MDIs

56. CSR P04275 14.2 Pharmacokinetic Data: Summary Tables and Figures – Table 2 Individual and Mean (CV) Pharmacokinetic Parameters of MF on Days 1 and 5 After MDI Administration of MF 800 mcg in Healthy Subjects

57. Summary of Clinical Pharmacology Studies 2.7.2 – 3.5 Conclusions

58. Summary of Clinical Pharmacology Studies 2.7.2 – 3.1 Pharmacokinetics of Formoterol Fumarate

59. CSR P05644 (CFOR258H2104) – Table 16.2.5-2.8 Individual and summary statistics for plasma pharmacokinetic parameters of formoterol after administration of Treatment 1 (MDI MF/F 400/40 mcg)

60. CSR P05644 (CFOR258H2104) – Table 16.2.5-2.9 Individual and summary statistics for plasma pharmacokinetic parameters of formoterol after administration of Treatment 2 (MDI MF/F 400/20 mcg)

61. CSR P05644 (CFOR258H2104) – 14.2 Efficacy and other non-safety data Table 14.2-1.8 Summary statistics for formoterol PK parameter

62. Summary of Clinical Pharmacology Studies 2.7.2 – 1.2 Overview of Conclusions of the Clinical Pharmacology Program

63. CSR P05644 (CFOR258H2104) – Table 16.2.5-2.20 Individual and summary statistics for Ae, AUC and renal clearance derived from these parameters for Treatment 2 (MDI MF/F 400/20 mcg)

64. CSR P05644 (CFOR258H2104) – Table 16.2.5-2.21 Individual and summary statistics for Ae, AUC and renal clearance derived from these parameters for Treatment 2 (MDI MF/F 400/40 mcg)

65. CSR P05644 (CFOR258H2104) – Table 16.2.5-2.14 Individual cumulative amounts of formoterol (nmol) excreted in urine and summary statistics following administration of Treatment 1 (MDI MF/F 400/40 mcg)

66. CSR P05644 (CFOR258H2104) – Table 16.2.5-2.15 Individual cumulative amounts of formoterol (nmol) excreted in urine and summary statistics following administration of Treatment 2 (MDI MF/F 400/20 mcg)

67. CSR P05644 (CFOR258H2104) – Table 16.2.5-2.16 Individual cumulative amounts of formoterol (nmol) excreted in urine and summary statistics following administration of Treatment 3 (MDI MF/F 400/10 mcg)

68. CSR P05644 (CFOR258H2104) – Table 16.2.5-4.4 Individual cumulative amounts of the (-)R,R-enantiomer (nmol) of formoterol excreted in urine and summary statistics following administration of Treatment 1 (MDI MF/F 400/40 mcg)

69. CSR P05644 (CFOR258H2104) – Table 16.2.5-4.5 Individual cumulative amounts of the (-)R,R-enantiomer (nmol) of formoterol excreted in urine and summary statistics following administration of Treatment 2 (MDI MF/F 400/20 mcg)

70. CSR P05644 (CFOR258H2104) – Table 16.2.5-4.6 Individual cumulative amounts of the (-)R,R-enantiomer (nmol) of formoterol excreted in urine and summary statistics following administration of Treatment 3 (MDI MF/F 400/10 mcg)

71. CSR P05644 (CFOR258H2104) – Table 16.2.5-5.4 Individual cumulative amounts of the (+)S,S-enantiomer (nmol) of formoterol excreted in urine and summary statistics following administration of Treatment 1 (MDI MF/F 400/40 mcg)

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73. CSR P05644 (CFOR258H2104) – Table 16.2.5-5.6 Individual cumulative amounts of the (+)S,S-enantiomer (nmol) of formoterol excreted in urine and summary statistics following administration of Treatment 3 (MDI MF/F 400/10 mcg)

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4.2 Individual Study Review

4.2.1 Study P04275 SCH 418131: A Study to evaluate the relative bioavailability of mometasone furoate after administration from an MF-DPI vs MF/F-MDI for formulation device in healthy subjects

Objective(s):
1. To determine whether the extent of absorption of mometasone furoate (MF) administered from a new metered-dose inhaler combination product containing MF and formoterol (F) (MF/F-MDI) was comparable to that of MF administered from a single-ingredient dry powder inhaler device (MF-DPI).

2. To assess the safety and tolerability of multiple doses of MF and F administered from the combination drug product.

Methodology: This randomized, open-label, multiple-dose, two-period, two-treatment crossover study. Treatments A and B were administered by inhalation twice daily every 12 hours:

Treatment A: MF 800 µg via DPI oral inhalation (four puffs from an Asmanex® Twisthaler® 200 µg per burst) BID for 5 days (nine doses; AM dose only on Day 5).

Treatment B: MF 800 µg/F 20 µg via MDI oral inhalation (four puffs from a MF 200 µg/F 5 µg per burst combination product) BID for 5 days (nine doses; AM dose only on Day 5).
Each treatment was separated by a washout interval of at least 7 days.

Blood samples for MF pharmacokinetics were drawn predose (0 hour) on Day 1 and at 0.5, 1, 1.5, 2, 4, 6, 8, and 12 hours after the first dose and predose (0 hour) on Day 5 and at 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, and 24 hours postdose during each period of the crossover. Serum MF concentrations were determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay with a lower limit of quantitation (LLOQ) of 5.0 pg/mL.

Number of Subjects: Twelve subjects were randomized and completed the treatment phase.

Diagnosis and Criteria for Inclusion: Healthy nonsmoking adult male and female volunteers were selected for the study. Subjects were between the ages of 18 and 65 years inclusive with a body mass index (BMI) of 18 to 29 kg/m^2.

Duration of Treatment: Five days (nine doses) per treatment on two separate occasions with each treatment separated by at least 7 days for a total of 10 days (18 doses).

Results:

Mean pharmacokinetic parameters of MF in healthy subjects on Days 1 and 5 after dosing with MF 800 µg administered in combination with F 20 µg (MDI) or MF 800 µg administered alone (DPI) are summarized in Table 1.

Table 1 Mean Pharmacokinetic Parameters of MF on Days 1 and 5 After MDI Administration of MF 800 µg/F 20 µg or DPI Administration of MF 800 µg in Healthy Subjects

Protocol No. P04275

Parameter	n	Serum MF Concentration (pg/mL)							
		MF 800 µg/F 20 µg MDI				MF 800 µg DPI			
		Day 1		Day 5		Day 1		Day 5	
		Mean	CV (%)	Mean	CV (%)	Mean	CV (%)	Mean	CV (%)
Tmax[a] (hr)	12	4.00	0.500–6.00	1.00	0.500–4.00	1.00	0.500–2.00	1.00	0.500–1.50
Cmax (pg/mL)	12	67.8	49	241	36	184	36	383	23
AUC(0-12 hr) (pg·hr/mL)	12	650	51	2200	35	1270	33	2820	22
R	12	–	–	3.81	37	–	–	2.34	21

Tmax = time of observed maximum serum concentration; Cmax = maximum observed serum concentration; AUC (0-12 hr) = area under the concentration-time curve from 0 to 12 hours; R = accumulation index.
a: Median (range).

Systemic exposures to MF based on AUC (0-12hr) were lower following MDI administration compared with DPI administration on Days 1 and 5 (Table 2). The mean AUC (0-12 hr) ratio estimates were approximately 52% and 25% lower on Days 1 and 5 following MDI administration, respectively.

Table 2 Relative Systemic Exposures of MF on Days 1 and 5 After MDI Administration of MF 800 µg/F 20 µg or DPI Administration of MF 800 µg in Healthy Subjects

Protocol No. P04275

Parameters	Day	Ratio Estimate[a] (%)	90% CI
Cmax (pg/mL)	1	35.4	29 to 43
	5	60.6	49 to 75
AUC(0-12 hr) (pg·hr/mL)	1	48.2	39 to 59
	5	74.7	61 to 91

Cmax = maximum observed serum concentration; AUC (0-12 hr) = area under the concentration-time curve from 0 to 12 hours; CI = confidence intervals.
a: Ratio of MDI/DPI.

Conclusion:

Systemic exposures to MF (based on AUC) were approximately 52% to 25% lower following MDI administration compared with DPI administration. The ratios of geometric means (90% CI) for Cmax and AUC (0-12 hr) values on Day 1 were 35.4% (29% to 43%) and 48.2% (39% to 59%) after MDI relative to DPI administration, respectively. Corresponding ratios (90% CI) for Cmax and AUC (0-12 hr) on Day 5 were 60.6% (49% to 75%) and 74.7% (61% to 91%), respectively.

4.2.2 Study P03658 SCH 418131: Evaluation of the Potential for a Pharmacokinetic Interaction between Mometasone Furoate (SCH 032088) and Formoterol after Single Dose in Healthy Subjects

Objectives

1. To evaluate the potential for a pharmacokinetic drug interaction between mometasone furoate (MF) and formoterol fumarate (F) as determined by the coadministration from separate single-ingredient MDI formulation devices compared to each drug administered alone.

2. To determine whether the extent of systemic exposure to each active ingredient from the fixed-combination drug product device (MF/F MDI) is comparable to that for each active ingredient administered concurrently from separate single-ingredient MDI formulation devices.

Methodology: This was a randomized, open-label, single-dose, 4-period crossover study.

On Day 1 of each treatment period of the crossover, subjects were to be assigned to one of the following 4 treatments:

Treatment A: Mometasone furoate 800 µg (4 puffs x 200 µg/oral inhalation) via MF MDI device as a single dose.

Treatment B: Formoterol fumarate 20 µg (4 puffs x 5 µg/oral inhalation) via F MDI device as a single dose.

Treatment C: Mometasone furoate 800 µg (4 puffs x 200 µg/oral inhalation) via MF MDI device + Formoterol fumarate 20 µg (4 puffs x 5 µg/oral inhalation) via F MDI as a single dose.

Treatment D: Mometasone furoate 800 µg /formoterol fumarate 20 µg (4 puffs x 200 µg/5 µg MF/F per oral inhalation) via MF/F MDI combination product device as a single dose. All treatments were to be administered by oral inhalation in the morning. A 1 week washout period separated each treatment.

Blood samples were to be collected for plasma mometasone furoate and formoterol pharmacokinetic evaluations. Urine samples were to be collected for evaluation of unchanged "racemic" formoterol and (-) R,R and (+)S,S enantiomers.

Number of Subjects: Twenty-seven subjects were randomized; 3 subjects discontinued; and 24 subjects completed treatment. Healthy adult female and male subjects aged 18–55 years.

Results:

Following inhalation of a single dose of 20 µg F and/or 800 µg MF via MDI, formoterol was rapidly absorbed in most subjects, whereas absorption of MF was prolonged (Figure 1). Mean

plasma concentration-time profiles showed no major difference between treatments in rate of absorption or elimination of MF or formoterol.

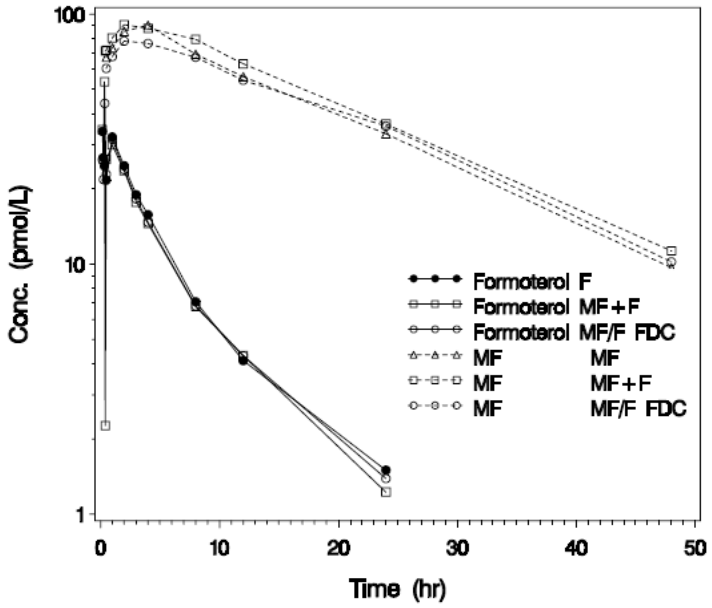

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Figure 1. Mean Plasma Concentration-Time Profiles for MF and Formoterol in Subjects Receiving 800 µg MF and/or 20 µg of F

Mean pharmacokinetic parameters and statistical comparisons for MF and formoterol are summarized in Table 2 and Table 3. The mean AUC and Cmax for MF and F are comparable when MF and F are administered from the new fixed-dose combination MDI device (MF/F MDI) vs coadministration from single-ingredient MDI devices (MF MDI + F MDI). Systemic exposure of MF and F is similar when the coadministration from the single ingredients vs the individual drug administered alone (Table 2 and Table 3). These data indicates there is no drug-drug interaction and formulation effect.

Table 2 Statistical Group Comparisons of MF Pharmacokinetic Parameters

Protocol No. P03658

Parameter	Least-Squares Geometric Mean[b] (90% CI) MF (n=17[a,c])	MF+F (n=18[a,c])	MF/F(n=18[a,c])	Intrasubject CV (%)	Treatment Comparison	Geometric Mean Ratio (%)	90% CI (%)
AUC(0-tf)	906	885	837	25	MF+F vs MF	98	85–113
(pg·hr/mL)	(685–1199)	(670–1170)	(633–1106)		MF/F vs MF+F	95	82–109
Cmax	46	41	38	26	MF+F vs MF	91	78–106
(pg/mL)	(34–61)	(31–55)	(29–51)		MF/F vs MF+F	93	80–108

a: Values for Subject No. 112 following MF and Subject No. 122 following all 3 treatments were excluded from analyses because of anomalously low MF exposure values likely due to poor inhalation technique.
b: Model-based (least-squares) geometric mean: ANOVA extracting the effects due to treatment, period, sequence and subject.
c: Values from Subjects Nos. 105, 110, 115, 120, 125, and 127 were excluded from analysis because of predose values >5% of Cmax. Subject No. 107 withdrew early following treatment with MF/F, and Subject No. 123 withdrew following MF treatment; thus values from these subjects also were excluded.

Table 3 Statistical Group Comparisons of F Pharmacokinetic Parameters

Parameter	Least-Squares Geometric Mean[a] (n^b) 90% CI (%)			Intrasubject	Treatment	Geometric Mean Ratio	90% CI
	F	MF+F	MF/F	CV (%)	Comparison	(%)	(%)
AUC(0–tf)	145 (n=23)	141 (n=24)	152 (n=24)	48	MF+F vs F	98	77–124
(pmol·hr/L)	109–192	107–188	115–202		MF/F vs MF+F	108	85–136
AUC(0–12 hr)	138 (n=22)	134 (n=23)	133 (n=24)	41	MF+F vs F	97	79–120
(pmol·hr/L)	110–173	107–167	107–165		MF/F vs MF+F	99	81–122
Cmax	31.9 (n=24)	33.6 (n=24)	32.7 (n=24)	46	MF+F vs F	106	84–132
(pmol/L)	24.4–41.6	25.7–44	25.0–42.7		MF/F vs MF+F	97	78–122
Ae(0-48 hr)	1.63 (n=22)	1.32 (n=21)	1.69 (n=24)	59	MF+F vs F	81	59–111
(nmol)	1.17–2.28	0.94–1.85	1.22–2.34		MF/F vs MF+F	128	94–175

a: Model-based (least-squares) mean: ANOVA extracting effects due to treatment, period, sequence and subject.
b: Three subjects were excluded due to early withdrawal from the study. Subject No. 102 discontinued after MF+F and MF /F; Subject No. 107 discontinued after treatment with MF/F, and Subject No. 123 discontinued after treatment with F alone.

Conclusion and discussion:

Pharmacokinetic parameters of both mometasone furoate and formoterol appeared to be largely unaffected by coadministration, suggesting that interaction between these drugs does not a pose a concern. Therefore, it is unlikely that dose adjustment for either component would be indicated for the combination product.

The following conclusions can be drawn from this study:
• There is no significant pharmacokinetic drug interaction between mometasone furoate (MF) and formoterol.

• The systemic exposure to MF and formoterol is similar when MF and F are administered from the new fixed-dose combination MDI device (MF/F MDI) vs coadministration from single-ingredient MDI devices (MF MDI + F MDI), which indicates there is no formulation effect for the combination product.

4.2.3 Study P03705: Evaluation of the Extrapulmonary Effects of Mometasone Furoate From a Combination MDI Formulation (SCH 418131) Versus Fluticasone Propionate From a Fluticasone Propionate/Salmeterol Combination Comparator on HPA-Axis Function

Objectives:

1. To compare the extrapulmonary effects on hypothalamic–pituitary–adrenal (HPA) axis function of mometasone furoate administered from the MF/F (mometasone furoate/formoterol) MDI (metered-dose inhaler) combination formulation versus fluticasone propionate from a fluticasone propionate/salmeterol combination product.

2. To characterize the multiple-dose pharmacokinetics of mometasone furoate and formoterol in patients with asthma.

3. To explore the dose-response and time to maximum response of fractional exhaled nitric oxide (FENO).

4. To evaluate the safety and tolerability of the mometasone furoate/formoterol combination formulations after 6 weeks of treatment.

Methodology: This was a randomized, open-label, placebo-controlled, active-comparator, parallel-group, multiple-dose study.

Subjects (asthma patients, age 18-64 yrs) were to be assigned to one of the following 4 treatments:

Treatment A (n=13): Mometasone furoate (MF)/formoterol fumarate (F) 200 µg/10 µg (2 puffs of MF/F 100 µg/5 µg MDI) by oral inhalation BID for 42 days, to be administered at the same time on study Days 1 through 42.

Treatment B (n=15): MF/F 400 µg/10 µg (2 puffs of MF/F 200 µg/5 µg MDI) by oral inhalation BID for 42 days, to be administered at the same time on study Days 1 through 42.

Treatment C (n=16): Fluticasone propionate (FP)/salmeterol (S) 460 µg/42 µg (2 puffs of FP/S 230 µg/21 µg MDI) by oral inhalation BID for 42 days, to be administered at the same time on study Days 1 through 42.

Treatment D (n=16): Placebo (2 puffs from an inhaler matching MF/F MDI) by oral inhalation BID for 42 days, to be administered at the same time on Day 1 through Day 42.

Results:

At day 1, mean plasma cortisol AUC (0-24 hr) values at Baseline ranged from 1570 to 1700 ngxhr/mL and were similar for all the treatment groups. Following multiple BID oral inhalations of MF/F 200 µg/10 µg or placebo, mean cortisol AUC (0-24 hr) values were similar (<10% change from Baseline) (Table 1).

Table 1. Plasma cortisol parameters in asthmatic subjects following BID oral inhalation of MF/F 200/10 µg, MF/F 400/10 µg, FP/S, or placebo via MDI

Protocol No. P03705

Treatment	Day –1 Mean (% CV)		Day 42 Mean (% CV)	
	AUC(0-24 hr) (ng·hr/mL)	Ctrough (ng/mL)	AUC(0-24 hr) (ng·hr/mL)	Ctrough (ng/mL)
MF/F 200 µg/10 µg BID (Treatment A[a]) (MF 400 µg/F 20 µg total daily dose; n=15)	1620 (19)	23.6 (40)	1670 (29)[b]	24.1 (57)[b]
MF/F 400 µg/10 µg BID (Treatment B[a]) (MF 800 µg/F 20 µg total daily dose; n=16)	1570 (22)	20.3 (37)	1390 (49)[c]	14.9 (50)[c]
FP/S 460 µg/42 µg BID (Treatment C[a]) (FP 920 µg/ S 84 µg total daily dose; n=16)	1680 (31)	20.4 (44)	1240 (46)	16.4 (90)
Placebo BID (Treatment D[a]) (n=17)	1700 (38)	21.5 (61)	1830 (39)[d]	22.9 (71)[d]

* Numbers are baseline unadjusted
a: subjects received treatment A (MF/F 200/10 µg), treatment B (MF/F 400/10 µg), treatment C (FP/S 460/42 µg), or treatment D (placebo) by oral inhalation BID for 42 days
b: n=13, c: n=15, d: n=16

Table 2 Statistical comparison of plasma cortisol by treatment

Protocol No. P03705

Treatment (Total Daily Dose)	n[b]	Least-Square Mean[a] (90% CI) Day 42/Day –1 Ratio (%)	Treatment Comparison Ratio[a]		
			Label	Geometric Mean Ratio (%)	90% CI (%)
AUC(0-24 hr)					
Treatment A: MF/F 200 mcg/10 mcg BID (MF/F 400 mcg/20 mcg daily)	13	99 (87–113)	A vs D	92	78–110
Treatment B: MF/F 400 mcg/10 mcg BID (MF/F 800 mcg/20 mcg daily)	15	84 (75–95)	B vs D	78	66–92
Treatment C: FP/S 460 mcg/42 mcg BID (FP/S 920 mcg/84 mcg daily)	16	71 (63–80)	C vs D	66	56–78
Treatment D: Placebo BID	16	107 (96–120)	B vs C	119	101–140
			A vs C	140	118–166
			B vs A	85	71–101
Ctrough					
Treatment A: MF/F 200 mcg/10 mcg BID (MF/F 400 mcg/20 mcg daily)	13	95 (75–120)	A vs D	96	70–132
Treatment B: MF/F 400 mcg/10 mcg BID (MF/F 800 mcg/20 mcg daily)	15	68 (54–84)	B vs D	68	50–93
Treatment C: FP/S 460 mcg/42 mcg BID (FP/S 920 mcg/84 mcg daily)	16	63 (51–78)	C vs D	64	47–86
Treatment D: Placebo BID	16	99 (80–123)	B vs C	107	79–146
			A vs C	150	109–207
			B vs A	71	52–99

* Numbers are baseline adjusted
a: Model-based (least-squares) mean
b: Subjects missing Day 42 cortisol samples were excluded

MF/F 200 mcg/10 mcg BID and placebo Baseline (Day –1) to Day 42 log plasma cortisol AUC (0-24 hr) ratios were comparable. Day 42:Day –1 AUC(0-24 hr) ratios for MF/F 400 mcg/10 mcg and FP/S 460 mcg/42 mcg BID treatments were respectively 22% lower and 34% lower than with placebo treatment (Table 2). Note: the HPA axis study (29 days) results for the

approved MF (Asmanex®) 440 mcg QD is plasma cortisol AUC (0-24h) decreased 18% from placebo on day 28. Therefore, the results are comparable to the reference drug.

Geometric mean pharmacokinetic parameters of MF after dosing with MF/F BID for 42 days are respectively summarized in Table 3**.** Geometric means with 90% CI for MF Cmax and AUCτ showed increases in exposure with dose and with repeated dosing. With a large intersubject variability in each treatment group and sample sizes of 13 to 17 subjects, 90% confidence intervals were large (Table 4).

By comparing the single dose and multiple dose data in both healthy and asthma patients, the reviewer found that the accumulation is different between the test MF/F MDI and the reference MF DPI Asmanex. In healthy subjectis, the accumulation for AUC (0-12) is 3.38 for MDI and 2.22 for DPI, and accumulation for Cmax is 3.55 for MDI and 2.08 for DPI. In asthma patients, the accumulation for AUC (0-12) is 3.39 for MDI and 2.45 for DPI, and accumulation for Cmax is 3.00 for MDI and 2.17 for DPI (Table 5 and 6). Because the submission is lack of the PK information comparing the test product MF/F MDI to the reference MF DPI Asmanex, the data was subtracted from the previous submission for the Asmanex.

Mean MF plasma concentration–time plots for each treatment and day showed rapid and prolonged absorption and dose- and dose-by-day–related increases on exposure repeated dosing (Figure 1).

Table 3 Geometric Means and 90% Confidence Intervals for MF Pharmacokinetic Parameters Following Inhalation of 200 µg or 400 µg MF BID from MF/F MDIs

Protocol No. P03705

Dosage	Day	n	Cmax (pg/mL)	90% Confidence Interval (pg/mL)	AUCτ (pg·hr/mL)	90% Confidence Interval (pg·hr/mL)
MF/F 200 µg/10 µg BID	1	15	11.4	9.33–14.0	75.4	56.7–100
	42	13	19.4	12.8–29.4	174	116–260
MF/F 400 µg/10 µg BID	1	17	16	12.3–20.8	127	92.9–173
	42	15	56.8	48.7–66.1	542	460–637

AUCτ=area under the concentration–time curve from 0 hr to 12 hr; Cmax=maximum plasma concentration; MF/F MDI=mometasone furoate/formoterol fumarate metered-dose inhaler; MF/F 100 µg/10 µg BID=2 puffs BID from metered-dose inhaler delivering mometasone furoate/formoterol fumarate 100 µg/5 µg per actuation; MF/F 400 µg/10 µg BID=2 puffs BID from metered-dose inhaler delivering mometasone furoate/formoterol fumarate 200 µg/5 µg per actuation.

Table 4 Geometric Mean Ratios and 90% Confidence Intervals for Dose-Normalized MF AUCτ and Cmax

Protocol No. P03705

	Comparison (sample sizes)	Parameter	Ratio (%)	90% CI[a]
Day 1	MF 200 µg BID (A)/MF 400 µg BID (B)	AUCτ	119	78.7–180
	(n=15/n=17)	Cmax	143	103–198
Day 42	MF 200 µg BID (A)/MF 400 µg BID (B)	AUCτ	64.1	43.1–95.2
	(n=13/n=15)	Cmax	68.4	45.9–102

AUCτ=area under the plasma concentration–time curve from 0 hr to 12 hr; CI=confidence interval; Cmax=maximum plasma concentration; MF 200 µg BID=mometasone furoate/formoterol fumarate 200 µg/10 µg [2 puffs of 100 µg/5 µg MF/F metered-dose inhaler] BID; MF 400 µg BID=mometasone furoate/formoterol fumarate 200 µg/10 µg [2 puffs of 100 µg/5 µg MF/F metered-dose inhaler] BID.

Table 5 Dose normalized MF exposures following single-dose and multiple-dose inhalations from MF/F MDIs and F Asmanex DPI in healthy subjects

Parameters*	Single-dose		Multiple-dose		Accumulation
	MDI	DPI	MDI	DPI	
AUC (0-t)	**325 (51)**	**635 (33)**	**1100 (35)**	**1410 (22)**	**3.38 (MDI)** **2.22 (DPI)**
Cmax	**33.9 (49)**	**92 (36)**	**120.5 (36)**	**191.5 (23)**	**3.55 (MDI)** **2.08 (DPI)**

*The PK parameters are dose normalized to 400 mcg/10 mcg BID, and 400 mcg single dose

Table 6 Dose normalized MF exposures following single-dose and multiple-dose inhalations from MF/F MDIs and F Asmanex DPI in asthma patients

Parameters*	Single-dose		Multiple-dose		Accumulation
	MDI	DPI	MDI	DPI	
AUC (0-t)	**170 (94)**	**259 (125)**	**577 (40)**	**634 (66)**	**3.39 (MDI)** **2.45 (DPI)**
Cmax	**20.0 (88)**	**52.6 (112)**	**60.0 (36)**	**114 (52)**	**3.55 (MDI)** **2.17 (DPI)**

*The PK parameters are dose normalized to 400 mcg/10 mcg BID, and 400 mcg single dose

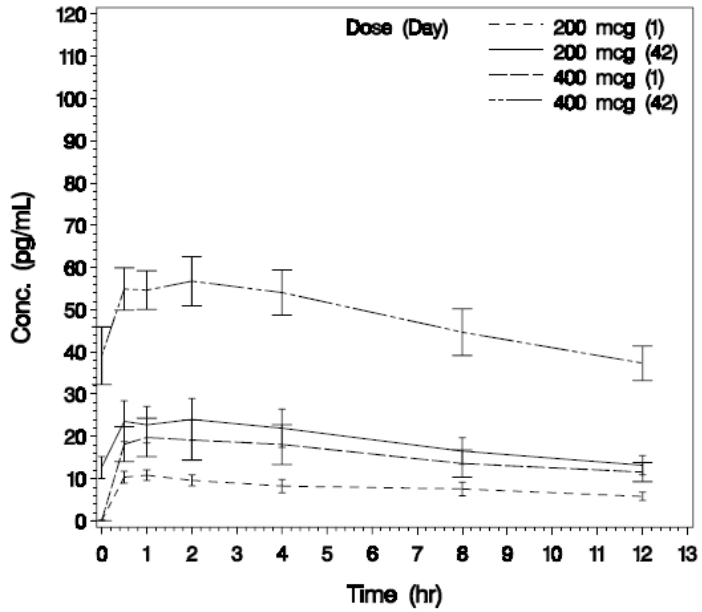

Figure 1 Mean (SD) MF Plasma Concentrations on Days 1 and 42 following BID Inhalation of 400 µg or 200 µg MF from MF/F MDIs. Subjects received MF/F 200 µg/10; or MF/F 400 µg/10 µg via oral inhalation BID for 42 days

Mean (SD) formoterol plasma concentration-time profiles for each treatment and day showed rapid and prolonged absorption (Figure 2). Mean concentration plots give the same ranking of exposure between treatment groups and day as did the geometric mean Cmax and AUCτ values (Table 7). Cmax and AUCτ values for formoterol indicate that exposures on Day 1 for the MF/F 400 µg/10 µg dosage group tended to be lower than those for the MF/F 200 µg/10 µg dosage

group, and exposures for the MF/F 400 µg/10 µg dosage on Day 42 tended to be higher than those for the MF/F 200 µg/10 µg dosage group. Day 1 and Day 42 formoterol Cmax values for the MF/F 200 µg/10 µg dosage were respectively 120% and 78.6% of the corresponding values for the MF/F 400 µg/10 µg dosage (Table 8). The mean formoterol AUCτ values for the MF/F 200 µg/10 µg dosage on Day 1 and Day 42 were respectively 121% and 75.1% of the values for the 400 µg/10 µg dosage. With large intersubject variability in each treatment group and sample sizes of 13 to 15 subjects, the 90% CI values were large.

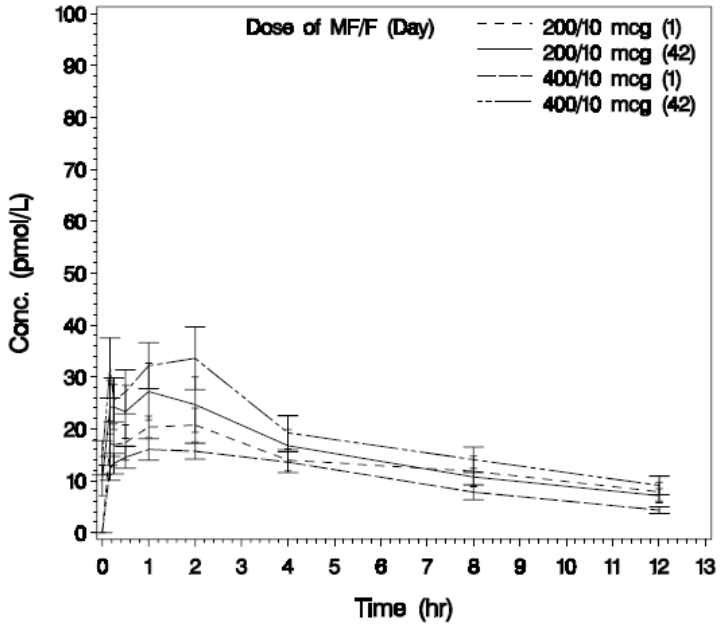

Figure 2 Mean (SD) Plasma Formoterol Concentrations with Standard Deviations on Days 1 and 42 following BID F 10 µg and MF 200 µg or 400 µg via MF/F FDC MDIs. Subjects received MF/F 200 µg/10 µg or MF/F 400 µg/10 µg via oral inhalation BID for 42 days

Table 7 Geometric Means and 90% Confidence Intervals for Formoterol Pharmacokinetic Parameters following Inhalation of 10 µg Formoterol Fumarate from a MF/F 100 µg/5 µg or MF/F 200 µg/5 µg MDI.

Protocol No. P03705

Dosage	Day	n	Cmax (pmol/L)	90% CI (pmol/L)	AUCτ (pmol·hr/L)	90% CI (pmol·hr/L)
MF/F 200 µg/10 µg MDI BID	1	15	25.6	20.9–31.5	141	112–178
	42	13	28.3	21.4–37.5	153	111–209
MF/F 400 µg/10 µg MDI BID	1	15	21.4	18.7–24.6	116	97–139
	42	13	36	28.4–45.6	203	163–253

Abbreviations: AUCτ=area under the concentration–time curve from 0 hr to 12 hr; CI=confidence interval; Cmax=maximum plasma concentration; MDI=metered-dose inhaler; MF/F 200 µg/10 µg MDI BID=2 puffs inhaled BID from mometasone furoate/formoterol fumarate 100 µg/5 µg fixed-dose combination metered-dose inhaler; MF/F 400 µg/10 µg MDI BID=2 puffs inhaled BID from mometasone furoate/formoterol fumarate 200 µg/5 µg fixed-dose combination metered-dose inhaler.

Table 8 Geometric Mean Ratios and 90% Confidence Intervals for Formoterol Exposure Parameters AUCτ and Cmax.

Protocol No. P03705

	Comparison (Sample Sizes)	Parameter	Ratio	90% CI[a]
Day 1	MF/F 200 µg/10 µg BID:MF/F 400 µg/10 µg BID (n=15/n=15)	AUCτ	121	91.4–161
		Cmax	120	94.1–152
Day 42	MF/F 200 µg/10 µg BID:MF/F 400 µg/10 µg BID (n=13/n=13)	AUCτ	75.1	51.9–109
		Cmax	78.6	55.3–112

AUCτ=area under the plasma concentration–time curve from 0 hr to 1 hr postdose; Cmax=maximum plasma concentration MF 200 µg/10 µg F=mometasone furoate/formoterol fumarate 100 µg/5 µg fixed-dose combination metered-dose inhaler (subjects inhaled 2 puffs BID); MF 400 µg/10 µg F=mometasone furoate/formoterol fumarate 200 µg/5 µg fixed-dose combination metered-dose inhaler (subjects inhaled 2 puffs BID)

FENO (fraction exhaled nitric oxide), a marker of airway inflammation, was evaluated in a subset of subjects. By Day 8 of treatment, all active treatments (MF/F 200 mcg/10 mcg [Treatment A], MF/F 400 mcg/10 mcg [Treatment B], and FP/S 460 mcg/42 mcg [Treatment C]) achieved near maximal reduction of FENO relative to Baseline and the placebo group as shown by comparisons of time-weighted average change in FENO; this effect was maintained throughout the treatment period (Figure 3). FENO levels were comparably lowered by repeated BID oral inhalation of MF/F 200 mcg/10 mcg, MF/F 400 mcg/10 mcg, or FP/S 460 mcg/42 mcg from Baseline and with respect to placebo. These effects with active treatment were apparent at Day 8 and were sustained throughout treatment, whereas subjects receiving placebo showed little change in FENO.

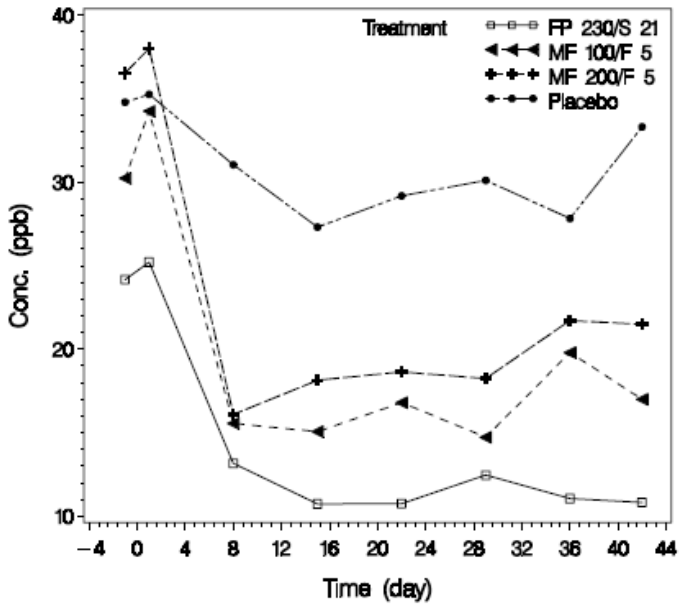

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Figure 3 Mean Fractional Exhaled Nitric Oxide (FENO) Concentration (ppb) vs. Time (day)

Reviewer's comments:
The age group for this study is 18-64 yrs. There is no information for subjects 12-17 yrs of age.

Although both MF and formoterol showed dose-related differences in exposure between the low and high dosages of MF/F, dose-normalized values of Cmax and AUCτ were higher for MF/F 200 μg/10 μg than for MF/F 400 μg/10 μg on Day 1, but lower on Day 42. This is mainly due to the high intrasubject variability of exposure values.

When there is no robust PK data, a dedicated HPA axis study was needed. For the dedicated the HPA axis study, there are some deficiencies in the study: 1) the number of subjects per treatment arm (n<20) is considered less than ideal (n~35-40); 2) open label study design instead of double-blind study design. In this point of view, the HPA axis study design was considered less than ideal. However, the cortisol suppression data from the proposed product, the reference MF monotherapy drug (Asmanex®), as well as the positive control (Advair) was showing an expected trend.

4.2.4 Study P06144: A randomized, multicenter, double-blind, double-dummy, placebo controlled, cross-over dose ranging study to evaluate the safety and efficacy of single doses of formoterol fumarate (6, 12 and 24 µg) via an HFA pMDI versus placebo and versus formoterol fumarate (12 and 24 µg) dry powder delivered via the Aerolizer™ in adolescent and adult patients with persistent asthma

Objectives:
1. To establish an optimal effective dose of formoterol delivered from the HFA pMDI by comparing the therapeutic safety and efficacy of three doses (6, 12 and 24µg) of formoterol fumarate with placebo in adult and adolescent patients with persistent asthma.

2. To compare the relative safety and tolerability, and efficacy of formoterol fumarate metered doses (6, 12 and 24µg) via an HFA pMDI with formoterol fumarate dry powder (12 and 24µg) delivered via the Aerolizer.

3. To assess the dose proportionality of the urinary excretion of formoterol after inhalation of three rising (6, 12 and 24µg) doses via HFA pMDI.

Methodology: This was a Phase II multicenter, randomized, double-blind, double-dummy, cross-over trial to establish the optimum dose of formoterol (6, 12 and 24µg) delivered via an HFA pMDI, in terms of the efficacy, safety and tolerability following a single inhalation compared to placebo and compared to formoterol dry powder capsules administered via the Aerolizer device (12 and 24µg) in male and female adult and adolescent patients with persistent asthma. Each patient was randomized to one of 6 treatment sequences and received each treatment (formoterol fumarate 6, 12 and 24µg given by pMDI, formoterol fumarate 12 and 24µg dry powder, and placebo) once. Treatment visits were separated by 2-7 day washout periods and each visit comprised 6 inhalations (4 from four separate pMDI followed by 2 from an Aerolizer device).

Number of patients: Planned: up to 28 patients (at least 24 patients who completed treatment). Either sex aged 13-75 years with asthma. All 26 patients randomized completed the trial and were included in both the safety and the efficacy analysis. Mean age (range) was 53 (18-67) years, and 15 (58%) of patients were male.

Duration of treatment: Run-in: 2 to 14 days. Treatment: Six treatment visits separated by 2-7 day washout periods (total duration approx. 5 weeks).

The primary pharmacodynamic variable was the AUC of FEV1 over the 12 hours postdose, standardized with respect to time. Least-squares means of the standardized AUC of FEV1 are presented in Table 1, with corresponding estimates of treatment contrasts in Table 2.

Table 1 Standardized AUC of FEV1: Least-Squares (Adjusted) Means, Intent-to-Treat Population

Protocol No. P06144 (I2201)

Treatment	Least-Squares Mean[a] (L)	Standard Error	n[b]
Placebo	2.17	0.023	26
HFA pMDI 6 mcg (H6)	2.33	0.023	27
HFA pMDI 12 mcg (H12)	2.41	0.023	26
HFA pMDI 24 mcg (H24)	2.45	0.024	25
Aerolizer 12 mcg (A12)	2.41	0.023	26
Aerolizer 24 mcg (A24)	2.46	0.023	26

A12=12 mcg formoterol fumarate delivered via the Aerolizer; A24=24 mcg formoterol fumarate delivered via the Aerolizer; ANCOVA=analysis of covariance; AUC=area under FEV1–time curve; FEV1=forced expiratory volume in 1 second; H6=formoterol fumarate 6 mcg delivered via the HFA pressurized metereddose inhaler (pMDI); H12=formoterol 12 mcg delivered via the HFA pMDI; H24=formoterol fumarate 24 mcg delivered via the HFA pMDI; HFA=hydrofluoroalkane (propellant).
a: Least-squares mean based on the ANCOVA model: AUC = patient + period + treatment + baseline FEV1.
b: n=number of subjects (one patient in the H6 treatment group was counted twice).

Table 2 Standardized AUC of FEV1: Estimates of Treatment Contrasts with Associated 95% Confidence Intervals, Intent-to-Treat Population.

Protocol No. P06144 (I2201)

Treatment Contrast	Estimate[a] (L)	95% CI	p–value
HFA pMDI 24 mcg vs Placebo	0.28	(0.22, 0.35)	<0.0001
HFA pMDI 12 mcg vs Placebo	0.24	(0.17, 0.30)	<0.0001
HFA pMDI 6 mcg vs Placebo	0.16	(0.10, 0.23)	<0.0001
HFA pMDI 24 mcg vs HFA pMDI 12 mcg	0.04	(–0.02, 0.11)	0.1953
HFA pMDI 24 mcg vs HFA pMDI 6 mcg	0.12	(0.05, 0.18)	0.0004
HFA pMDI 12 mcg vs HFA pMDI 6 mcg	0.08	(0.01, 0.14)	0.0215
HFA pMDI 24 mcg vs Aerolizer 24 mcg	–0.01	(–0.07, 0.06)	0.8500
HFA pMDI 12 mcg vs Aerolizer 24 mcg	–0.05	(–0.11, 0.02)	0.1344
HFA pMDI 6 mcg vs Aerolizer 24 mcg	–0.13	(–0.19, –0.06)	0.0002
HFA pMDI 24 mcg vs Aerolizer 12 mcg	0.04	(–0.02, 0.11)	0.2116
HFA pMDI 12 mcg vs Aerolizer 12 mcg	–0.00	(–0.07, 0.06)	0.9603
HFA pMDI 6 mcg vs Aerolizer 12 mcg	–0.08	(–0.14, –0.01)	0.0189
Aerolizer 24 mcg vs Placebo	0.29	(0.22, 0.35)	<0.0001
Aerolizer 12 mcg vs Placebo	0.24	(0.18, 0.30)	<0.0001

Aerolizer 12 mcg=12 mcg formoterol fumarate delivered via the Aerolizer; Aerolizer 24 mcg=24 mcg formoterol fumarate delivered via the Aerolizer; ANCOVA=analysis of covariance; AUC=area under FEV1– time curve; CI=confidence interval; FEV1=forced expiratory volume in 1 second; HFA pMDI 6 mcg=formoterol 6 mcg delivered via the HFA pressurized metered–dose inhaler (pMDI); HFA pMDI 12 mcg=formoterol 12 mcg delivered via the HFA pMDI; HFA pMDI 24 mcg=formoterol 24 mcg delivered via the HFA pMDI; HFA=hydrofluoroalkane (propellant).
a: Least-squares mean of the difference based on the ANCOVA model: AUC = patient + period + treatment + baseline FEV1. Data are reported to 2 significant figures.

For all F doses delivered by the F MDI device, the AUC of FEV1 was statistically superior to placebo (p<0.0001). Both F MDI 24 mcg (H24) and 12 mcg (H12) produced improvement over placebo that was considered to be clinically relevant (>0.2 L). Although there was no significant difference between the two higher doses of F MDI, the AUC for the 6 mcg dose was significantly inferior to both 12 mcg and 24 mcg doses. Estimates of treatment contrasts showed no statistically significant difference between the corresponding doses from the two devices. At both the F 12 mcg dose level and the F 24 mcg dose level, AUCs of FEV1 for MDI and

Aerolizer were similar, suggesting that the same dose from each of the two devices provided similar bronchodilation over the 12 hour period. Both doses from the Aerolizer achieved a statistically significant improvement over placebo, confirming the sensitivitiy of the trial.

FEV1 least-squares means at 2 and 12 hours postdose are presented in **Table 3**, with corresponding estimates of treatment contrasts at 12 hours postdose shown in **Table 4**.

Table 3. FEV1 at Selected Time Points (Last Observation Carried Forward): Least-Squares (Adjusted) Means, Intent-to-Treat Population.

Protocol No. P06144 (I2201)

	Least-Squares Mean[a] of FEV1 (L)					
Time Point	Placebo (n=26)	H6 (n=27[b])	H12 (n=26)	H24 (n=25)	A12 (n=26)	A24 (n=26)
2 hours postdose	2.24	2.43	2.50	2.58	2.53	2.58
12 hours postdose	2.07	2.17	2.29	2.28	2.26	2.31

A12=12 mcg formoterol fumarate delivered via the Aerolizer; A24=24 mcg formoterol fumarate delivered via the Aerolizer; ANCOVA=analysis of covariance; FEV1=forced expiratory volume in 1 second; H6=formoterol fumarate 6 mcg delivered via the HFA pressurized metered–dose inhaler (pMDI); H12=formoterol fumarate 12 mcg delivered via the HFA pMDI; H24=formoterol fumarate 24 mcg delivered via the HFA pMDI; HFA=hydrofluoroalkane (propellant).
a: Least-squares mean based on the ANCOVA model: FEV1 = patient + period + treatment + baseline FEV1.
b: One patient in the H6 treatment group was counted twice.

Table 4 Twelve Hour Postdose FEV1: Estimates of Treatment Contrasts with Associated 95% Confidence Intervals, Intent-to-Treat Population.

Protocol No. P06144 (I2201)

Treatment Contrast	Estimate[a] (L)	95% CI	p–value
HFA pMDI 24 mcg vs Placebo	0.21	(0.12, 0.29)	<0.0001
HFA pMDI 12 mcg vs Placebo	0.22	(0.13, 0.30)	<0.0001
HFA pMDI 6 mcg vs Placebo	0.10	(0.01, 0.18)	0.0253
HFA pMDI 24 mcg vs HFA pMDI 12 mcg	–0.01	(–0.10, 0.08)	0.8016
HFA pMDI 24 mcg vs HFA pMDI 6 mcg	0.11	(0.03, 0.20)	0.0104
HFA pMDI 12 mcg vs HFA pMDI 6 mcg	0.12	(0.04, 0.21)	0.0045
HFA pMDI 24 mcg vs Aerolizer 24 mcg	–0.03	(–0.11, 0.06)	0.5376
HFA pMDI 12 mcg vs Aerolizer 24 mcg	–0.02	(–0.10, 0.07)	0.7060
HFA pMDI 6 mcg vs Aerolizer 24 mcg	–0.14	(–0.22, –0.05)	0.0016
HFA pMDI 24 mcg vs Aerolizer 12 mcg	0.02	(–0.07, 0.10)	0.6891
HFA pMDI 12 mcg vs Aerolizer 12 mcg	0.03	(–0.06, 0.11)	0.5088
HFA pMDI 6 mcg vs Aerolizer 12 mcg	–0.09	(–0.18 , –0.01)	0.0279
Aerolizer 24 mcg vs Placebo	0.24	(0.15, 0.32)	<0.0001
Aerolizer 12 mcg vs Placebo	0.19	(0.11, 0.28)	<0.0001

Aerolizer 12 mcg=12 mcg formoterol fumarate delivered via the Aerolizer; Aerolizer 24 mcg=24 mcg formoterol fumarate delivered via the Aerolizer; ANCOVA=analysis of covariance; AUC=area under FEV1– time curve; CI=confidence interval; FEV1=forced expiratory volume in 1 second; HFA pMDI 6 mcg=formoterol 6 mcg delivered via the HFA pressurized metered–dose inhaler (pMDI); HFA pMDI 12 mcg=formoterol 12 mcg delivered via the HFA pMDI; HFA pMDI 24 mcg=formoterol 24 mcg delivered via the HFA pMDI; HFA=hydrofluoroalkane (propellant).
a: Least-squares mean of the difference based on the ANCOVA model: FEV1 = patient + period + treatment + baseline FEV1.

All doses of formoterol delivered by both devices provided statistically significant improvements compared to placebo at all time points over the 12 hour period. Analysis of the FEV1 values at

12 hours indicates that all doses of formoterol were statistically superior to placebo. Both the higher doses (12 mcg and 24 mcg) delivered by the F MDI device maintained clinically relevant improvements over placebo (defined as difference >0.2 L) for the full 12 hours, whereas the lowest dose did not. The estimated improvement in FEV1 for the 6 mcg dose was close to being clinically relevant for the first 6 to 8 hours, after which the treatment difference became smaller until, at 12 hours, the estimated difference was 0.10 L. This would suggest that although both F MDI 12 mcg [H12] and 24 mcg [H24] have a duration of action of at least 12 hours, the lowest dose from the F MDI has a shorter duration. There was no significant difference in terms of FEV1 at 12 hours between F MDI 12 mcg [H12] and 24 mcg [H24], the two doses providing similar and statistically significant increases in bronchodilation, in addition to clinically relevant benefit at all times up to 12 hours.

Conclusions:
Single doses of formoterol fumarate administered at doses of 6, 12 and 24 µg via a CFC-free pressured metered dose inhaler were more effective than placebo in terms of their effect on FEV1.

At the higher dose levels (12 and 24 µg), efficacy was achieved and maintained for at least 12 hours. However the duration of the lower dose was less than 12 hours.

Both higher dose levels (12 and 24 µg) were more effective than 6µg in terms of FEV1, with no differences shown between the 12 and 24µg doses.

No difference was shown in any of the efficacy parameters between the two administration devices.

4.2.5 Study 05644: A randomized, single dose, 3-period crossover study to evaluate the dosage form proportionality, dose proportionality and pharmacokinetics of mometasone furoate and formoterol fumarate from three combination MDI formulations

Objectives:
1. To examine dosage form proportionality of mometasone furoate and the dose proportionality of formoterol from the three combination MDI formulations (MF/F 50 µg/
5 µg, 100 µg/5 µg and 200 µg/5 µg) over a dose range (MF/F 400 µg/10 µg, 400 µg/20 µg and 400 µg/40 µg) that include clinically relevant doses.

2. To compare the single-dose extrapulmonary (systemic) effects and safety of mometasone furoate and formoterol from three different dosage strength combination MDI formulations, and to further evaluate plasma and urine pharmacokinetics of formoterol and urinary excretion of the (-) (R,R)- and (+) (S,S)- enantiomers.

Methodology:
This was a single centre, randomized, open-label, three-way crossover, single dose study in healthy volunteers. Each subject received all of the following 3 treatments in a randomized order: During each of the three treatment periods a single dose of MF/F was administered. 1) Mometasone Furoate 400 µg/Formoterol 40 µg, 2). Mometasone Furoate 400 µg/Formoterol 20 µg, and 3) Mometasone Furoate 400 µg/Formoterol 10 µg, delivered by MDI inhalers.

Following each dose of the assigned study treatment at each treatment visit, pharmacokinetic and safety assessments were made for up to 48 hours post first dose and subjects were domiciled until this point.

Number of patients (planned and analyzed):
As it was planned, a total of 24 subjects was enrolled and analyzed

Pharmacokinetics variables: PK samples were collected at pre-dose, 5, 10, 20 and 30 minutes, 1, 2, 3, 4, 8, 12, 16, 24, 36 and 48 hours post dose. Urine was collected pre-dose and during 0-3, 3-12, 12-24, 24-36 and 36-48 hour intervals post-dose. The following PK parameters were determined using non-compartmental method(s): plasma mometasone furoate and plasma formoterol: AUC0-tlast, Cmax and Tmax; AUC0-8, AUC0-∞ and t1/2 (formoterol only). Urine 'racemic' formoterol and (-) (R,R)- and (+) (S,S)-formoterol enantiomers: amount excreted (Ae), t1/2 (from excretion-rate time curves) and CL_R (formoterol only).

Results:
The main pharmacokinetic parameters are summarized in Table 1 and Table 2.

The mean terminal t1/2 of formoterol determined from plasma at the MF 400 µg/F 20 µg and MF 400 µg/ F 40 µg dose levels (9.75 and 11.5 hr, respectively) were in close agreement with the mean values derived from urinary excretion data for racemic formoterol (11 to 12 hr). The kinetic characteristics of the enantiomers were similar resulting in a mean terminal phase t1/2 of about 10 and 13 hr for the (+) (S,S) and (-) (R,R)-enantiomers, respectively. The (-) (R,R)-enantiomer accounted for 2.45%, 2.75% and 2.83% of the formoterol dose for the MF 400 µg/F

10 µg, MF 400 µg/F 20 µg and MF 400 µg/ F 40 µg dose levels, respectively. The (+) (S,S)-enantiomer accounted for 4.04% and 4.52% and 4.94% of the dose for the MF 400 µg/ F 10 µg, MF 400 µg/F 20 µg and MF 400 µg/ F 40 µg dose levels, respectively.

Dose proportionality assessments for formoterol are summarized in Table 3.

Table 1 Plasma pharmacokinetic parameters and urinary excretion for unchanged formoterol (Mean +/- SD)

Device	t_{max} (hr)[1]	C_{max} (pmol/L)	$AUC_{0\text{-tlast}}$ (pmol.hr/L)	$Ae_{0\text{-}48}$ (nmol)	$Ae_{0\text{-}48}$ (% of dose	CL_R mL/min
MF/F 400µg/10µg	0.50 (0.08-4.00)	15.4 ± 7.75	80.8 ± 41.2	1.47 ± 0.54	6.20 ± 2.26	ND[2]
MF/F 400µg/20µg	0.17 (0.08-2.00)	38.4 ± 19.6	216 ± 119	3.22 ± 1.13	6.76 ± 2.37	231 ± 55.0
MF/F 400µg/40µg	0.17 (0.08-2.00)	81.5 ± 32.9	474 ± 173	6.45 ± 1.89	6.78 ± 1.99	215 ± 59.7

[1] Median (min-max), [2] Not determined

Table 2 Pharmacokinetic parameters for mometasone furoate (Mean +/- SD)

Device	t_{max} (hr)[1]	C_{max} (pg/mL)	$AUC_{0\text{-tlast}}$ (pg.hr/L)
MF/F 400µg/10µg	1.00 (0.5-4.02)	17.6 ± 13.5	275 ± 266
MF/F 400µg/20µg	0.5 (0.50-8.00)	26.3 ± 13.6	376 ± 278
MF/F 400µg/40µg	0.5 (0.50-8.00)	36.4 ± 14.4	407 ± 221

[1] Median (min-max)

Table 3 Estimate of the slope for the linear regression between log-PK parameters and log-dose of formoterol

PK parameter of formoterol	Slope estimate	Lower 90% confidence limit for slope	Upper 90% confidence limit for slope	Dose proportionality across the whole dose range?
$AUC_{0\text{-}8}$	1.15	1.10	1.20	Yes
$AUC_{0\text{-tlast}}$	1.33	1.27	1.40	No
$AUC_{0\text{-}\infty}$	1.14	1.07	1.21	Yes
$Ae_{0\text{-}48}$ (primary parameter)	1.08	1.00	1.16	Yes

Dosage form proportionality assessments for mometasone furoate are summarized in Table 4. None of the treatment comparisons met the bioequivalence criterion.

Table 4 Geometric mean ratio and 90% confidence intervals for mometasone furoate AUC0-tlast (pg.h/mL)

Test MF/F dose (µg)	geometric mean for test dose	Reference MF/F dose (µg)	geometric mean for reference dose	Geometric mean ratio (test/ref.)	Lower 90% confidence limit	Upper 90% confidence limit
400/20	307.23	400/10	196.53	1.56	1.32	1.86
400/40	344.49	400/10	196.53	1.75	1.48	2.08
400/40	344.49	400/20	307.23	1.12	0.94	1.33

Conclusions:

• Dose proportionality based on formoterol urinary excretion (Ae0-48, the primary PK variable) can be concluded because the slope was close to 1 and 90% confidence interval for the slope was include 1.

• Dosage form proportionality for mometasone furoate systemic exposure (AUC0-tlast) can not be concluded because the 90% confidence intervals for the geometric mean ratios for AUC0-tlast were not contained wholly within the acceptance region (0.80, 1.25).

4.2.6 Study P04689: Evaluation of the Relative Bioavailability/Systemic Exposure of Inhaled Mometasone Furoate (MF) From an MF/F-MDI (SCH 418131) vs MF-DPI Formulation Device in COPD Patients (Protocol No. P04689)

Objectives

1. To characterize the pharmacokinetic profile and compare the systemic exposure of mometasone furoate (MF) after oral inhalation from a mometasone furoate/formoterol fumarate (MF/F) metered-dose inhaler (MDI) vs MF dry-power inhaler (DPI) device in patients with chronic obstructive pulmonary disease (COPD)

2. To assess the effects of a spacer device on the pharmacokinetic profile and systemic exposure of MF and formoterol fumarate (F) after oral inhalation from an MF/F MDI device in patients with COPD

3. To characterize the pharmacokinetic profile of formoterol after oral inhalation from an MF/F MDI device in patients with COPD

4. To assess the safety and tolerability of multiple doses of MF/F administered from the combination product in patients COPD.

Methodology: This was a randomized, open-label, multiple-dose, 3-period, 3-treatment crossover study.

On Day 1 of Period 1, each subject was randomly assigned a sequence for the following 3 treatments:

Treatment A: Mometasone furoate 400 µg/formoterol fumarate 10 µg via MDI oral inhalation (2 puffs x 200 µg/5 µg MF/F per burst combination product) BID for 5 days (9 doses; only the AM dose on Day 5)

Treatment B: Mometasone furoate 400 µg/formoterol fumarate 10 µg via MDI oral inhalation and in conjunction with a spacer device (2 puffs x 200 µg/5 µg MF/F per burst combination product) BID for 5 days (9 doses; only the AM dose on Day 5)

Treatment C: Mometasone furoate 400 µg via DPI oral inhalation (2 puffs x 200 µg MF per oral inhalation from an ASMANEX®TWISTHALER®) BID for 5 days (9 doses; only the AM dose on Day 5)

Doses for each treatment were administered every 12 hours at approximately 8 to 9 AM and 8 to 9 PM. Each treatment was separated by a washout of at least 7 days. Blood samples were collected for plasma mometasone furoate and formoterol pharmacokinetic evaluations.

Number of Subjects: Twelve subjects were to be enrolled

Diagnosis and Criteria for Inclusion: Adult subjects at least 40 years of age with a diagnosis of moderate to severe COPD were selected for the study.

Demographic and Baseline Characteristics: A total of 14 adult subjects (5 men and 9 women) aged 45 to 72 years (mean, 62.7 years) were treated and completed study procedures. Thirteen (93%) of the subjects were white; 1 (7%) was black/African-American.

Results:

Pharmacokinetics: Mean and individual MF plasma concentration–time profiles showed prolonged absorption, particularly following administration of MF from the MDI.

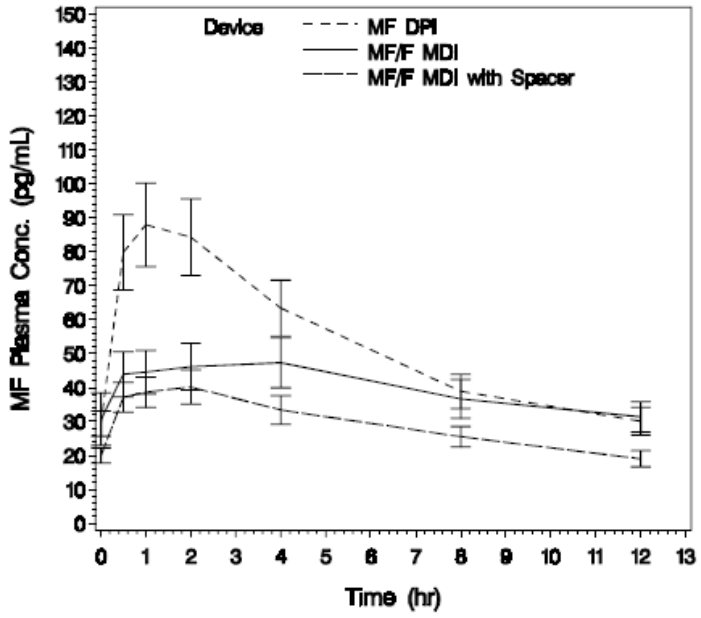

Figure 1 Plots of Mean Mometasone Furoate (MF) Plasma Concentration vs Time with Standard Deviations, by Treatment. Subjects received MF 400 µg via dry-powder inhaler (MF DPI); MF/formoterol fumarate (MF/F) via metered-dose inhaler alone (MF/F MDI), and mometasone furoate/formoterol fumarate via metered-dose inhaler in conjunction with a spacer device (MF/F MDI with Spacer).

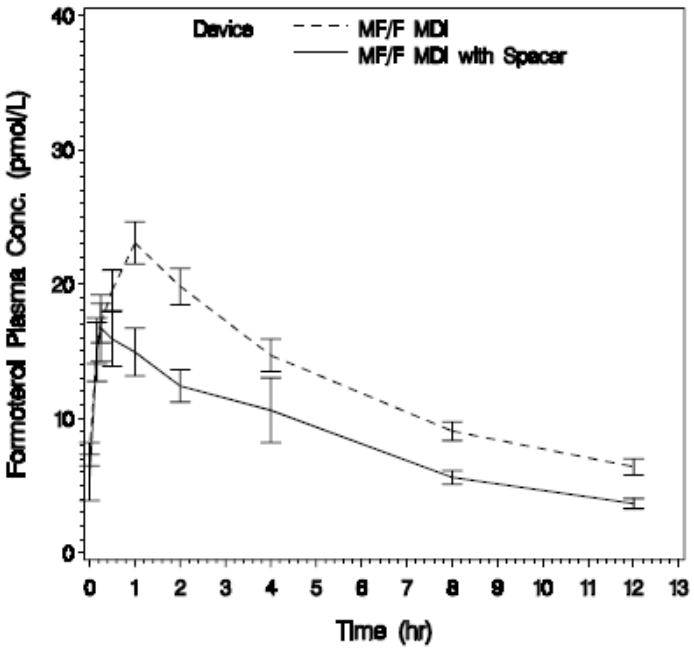

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Figure 2 Plots of Mean Formoterol (F) Plasma Concentration vs Time with Standard Deviations, by Treatment. Subjects received MF/formoterol fumarate (MF/F) via metered-dose inhaler alone (MF/F MDI), and mometasone furoate/formoterol fumarate via metered-dose inhaler in conjunction with a spacer device (MF/F MDI with Spacer).

Table 1 MF and Formoterol Day 5 Pharmacokinetic Parameters in Subjects with COPD following BID Administration of MF/F via MDI, With or W/O Spacer, or MF via DPI.

Protocol No. P04689

		MF 400 µg/F 10 µg MDI (Treatment A)		MF 400 µg/F 10 µg MDI + Spacer (Treatment B)		MF 400 µg DPI (Treatment C)
Parameter	n	MF	Formoterol	MF	Formoterol	MF
Tmax Median (Range)	14	3.00 hr (0.500–8.00)	1.02 hr (0.18–2.02)	2.00 hr (0.500–8.00)	0.52 hr (0.18–4.02)	1.00 hr (0.500–12.0)
Cmax Mean (CV [%])	14	49.2 (55) (pg/mL)	23.78 (24) (pmol/L)	41.1 (45) (pg/mL)	20.77 (47) (pmol/L)	90.2 (48) (pg/mL)
AUC(0-12 hr) Mean (CV [%])	14	484 (56) (pg·hr/mL)	152.9 (26) (pmol·hr/L)	353 (44) (pg·hr/mL)	101.1 (39) (pmol·hr/L)	646 (47) (pg·hr/mL)

AUC(0-12 hr)=area under the concentration–time curve from 0 hr to 12 hr on Day 5; Cmax=maximum plasma concentration; COPD=chronic obstructive pulmonary disease; CV=coefficient of variation; DPI=drypowder inhaler; F=formoterol fumarate; MDI=metered-dose inhaler; MF=mometasone furoate; Tmax=time to Cmax; Treatment A=mometasone furoate 400 µg/formoterol fumarate 10 µg inhaled orally BID via MDI; Treatment B=mometasone furoate 400 µg/formoterol fumarate 10 µg inhaled orally BID via MDI in conjunction with a spacer device; Treatment C=mometasone furoate 400 µg inhaled orally BID via DPI.

Median MF Tmax values were 3.00 hr, 2.00 hr, and 1.00 hr for Treatments A, B, and C, respectively (Table 1). Median formoterol Tmax values were 1.02 hr and 0.52 hr for Treatments A and B, respectively (Table 1). The distribution of individual MF and formoterol Tmax values at each timepoint is shown by treatment in Table 1. Tmax values ranged from 0.5 hr (first

sampling time) to 12 hr for MF and from 0.167 hr (first sampling time) to 4 hr for formoterol (Table 1).

For comparison of the MF exposure following inhalation of the DPI and MDI, the ANOVA model included all treatments. Intrasubject variabilities for MF AUC (0-12 hr) and Cmax of 44% and 47%, respectively, were obtained from the model (Table 2). Mean MF AUC (0-12 hr) following inhalation via MDI alone was 23% lower than the mean value following administration of MF from the DPI.

Table 2 Day 5 Exposures of MF in Subjects with COPD after MF/F MDI, With or Without Spacer, or MF DPI

Protocol No. P04689

	n	Least-Squares Geometric Means[a]					Ratio	90%
Parameter		MF/F MDI (A)	MF/F MDI + Spacer (B)	MF DPI (C)	Intrasubject CV (%)	Treatment Comparison	Estimate (%)	Confidence Interval
AUC(0-12 hr) (pg·hr/mL)	14	431	322	561	44%	B vs A	75	56–100
						A vs C	77	58–102
Cmax (pg/mL)	14	44	37	77	47%	B vs A	86	63–117
						A vs C	56	41–77

ANOVA=analysis of variance; AUC(0-12 hr)=area under the concentration–time curve from 0 hr to 12 hr posdose, Cmax=maximum plasma concentration; COPD=chronic obstructive pulmonary disorder; CV=coefficient of variation; DPI=dry-powder inhaler; MDI=metered-dose inhaler; MF=mometasone furoate; MF/F MDI (A)=mometasone furoate 400 µg/formoterol fumarate 10 µg BID via MDI oral inhalation; MF/F MDI + Spacer (B)=mometasone furoate 400 µg/formoterol fumarate 10 µg BID via MDI in conjunction with a spacer device; MF DPI (C)=mometasone furoate 400 µg BID via DPI oral inhalation.
a: Model-based (least squares) mean: ANOVA model extracting the effects due to treatment, sequence, period, and subject.

A secondary objective of the study was to compare MF and formoterol exposure following inhalation using the MDI with and without a spacer. Following inhalation with the spacer, MF exposures based on AUC (0-12) were lower (Table 2). However, because the larger intrasubject variability was related to the DPI treatment group, a reanalysis without DPI treatment group (Treatment C) showed that the Cmax and AUC (0-12 hr) values were 18% and 28% lower, respectively when spacer was used with the MDI than when the MDI was used alone (Table 3). Intrasubject variability for MF Cmax and AUC(0-12 hr) values in the original three-treatment ANOVA decreased from 47% and 44%, respectively, to 24% and 23%, when comparing only the MDI data.

Mean and individual plots of formoterol concentrations showed rapid and extended absorption of formoterol (Figure 3). For formoterol, Cmax and AUC (0-12 hr) values were 20% and 38% lower, respectively when the spacer was used (Table 4). The 90% CI for the ratio estimate for Cmax and AUC (0-12 hr) were 63%–101% and 52%-74%, respectively.

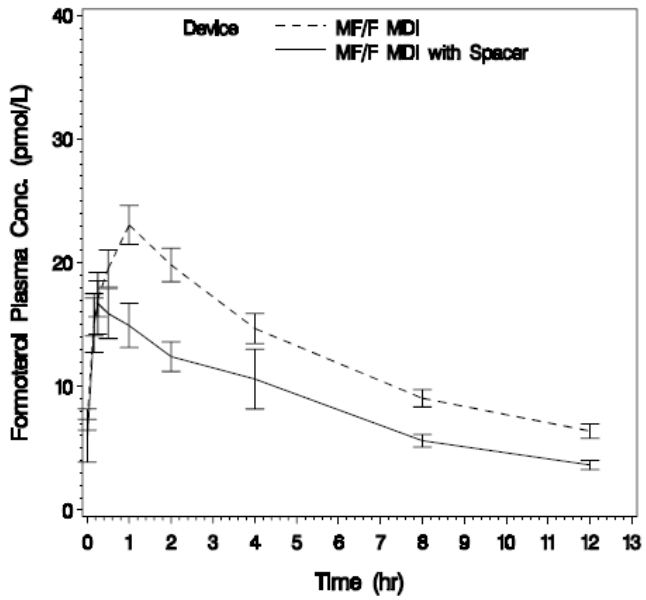

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Figure 3 Day 5 Mean Formoterol Plasma Concentration–Time Profiles in Subjects with COPD after MF/F MDI, With and Without a Spacer. Error bars depict standard deviation. Subjects received mometasone furoate/formoterol fumarate via metered-dose inhaler alone (MF/F MDI) and mometasone furoate/formoterol fumarate via metereddose inhaler in conjunction with a spacer device (MF/F MDI with Spacer).

Table 4 Day 5 Exposures of Formoterol in Subjects with COPD after Administration of MF/F via MDI, With or Without Spacer

Protocol No. P04689

		Least-Squares Geometric Means[a]				
Parameter	n	MF/F MDI – Spacer Treatment A	MF/F MDI + Spacer Treatment B	Treatment Comparison	Ratio Estimate (%)	90% Confidence Interval
AUC(0-12 hr) (pmol·hr/L)	14	150	93	B vs A	62	52–74
Cmax (pmol/L)	14	23.3	18.5	B vs A	80	63–101

ANOVA=analysis of varianc; Cmax=maximum observed plasma concentration; AUC(0-12 hr)=area under the concentration–time curve from 0 hr to 12 hr on Day 5 (steady state); MDI=metered-dose inhaler; MF/F=mometasone furoate/formoterol fumarate; MF/F MDI − Spacer (Treatment A)=mometasone furoate 400 µg/formoterol fumarate10 µg administered twice daily via metered-dose inhaler without a spacer; MF/F MDI + Spacer (Treatment B)=mometasone furoate 400 µg/formoterol fumarate 10 µg administered twice daily via metered-dose inhaler in conjunction with a spacer device; MF DPI (Treatment C)=mometasone furoate 400 µg administered twice daily via dry-powder inhaler.
a: Model-based (least-squares) geometric mean: ANOVA model extracting the effects due to treatment, sequence, period, and subject.

Conclusions:

• Based on AUC and Cmax, systemic MF exposures were lower following administration via MF/F MDI as compared with MF DPI administration.

• Based on AUC and Cmax, systemic exposures of MF and formoterol were lower following administration via MF/F MDI in conjunction with a spacer as compared with administration via MF/F MDI alone.

4.2.7 Study 05642: A randomized, open-label, 3-period crossover study to assess the cumulative dose response to formoterol fumarate alone and in combination with mometasone furoate in patients with mild to moderate persistent asthma

Title: Study 05642 is a randomized, open-label, 3-period crossover study to assess the cumulative dose response to formoterol fumarate alone and in combination with mometasone furoate in patients with mild to moderate persistent asthma.

Objective: The primary study objective is to assess comparability of the PD dose response of lung function parameters to formoterol fumarate alone and in combination with mometasone furoate in asthmatic subjects. The pharmacokinetic objective is to evaluate the systemic exposure and urinary excretion of formoterol alone and formoterol in the combination product.

Three study drugs were administered in this study and were given in a randomized order over three treatment visits. Each subject participated in three treatment visits. In each treatment visit, one of the following study drugs was assessed and subjects received cumulative doses of that study drug. Three doses were administered per treatment day, to provide a cumulative dose.

- Treatment A: Formoterol (FOR258) Aerolizer® 12 µg to 48 µg (Dose 1: 12 µg, Dose 2: 12 µg, Dose 3: 24 µg)
- Treatment B: MF/F MDI: mometasone furoate / formoterol fumarate (100/5 combination) 200 µg/10 µg to 800 µg/40 µg (Dose 1: 200/10 µg, Dose 2: 200/10 µg, Dose 3: 400/20 µg)
- Treatment C: MF/F MDI: mometasone furoate / formoterol fumarate (200/5 combination) 400 µg/10 µg to 1600 µg/40 µg. (Dose 1: 400/10 µg, Dose 2: 400/10 µg, Dose 3: 800/20 µg)

The individual PK parameters are summarized by Table 1 and Table 2.

Table 1: Plasma pharmacokinetic parameters and urinary excretion for unchanged formoterol (Mean +/- SD)

Device	t_{max} (hr)[1]	C_{max} (pmol/L)	AUC (0-12) (pmol*hr/L)	AUC(0-t_{last}) (pmol*hr/L)	Ae(0-24) (% of dose)	CL_R mL/min
Aerolizer	2.17 (2.12-2.27)	106 ± 26.3	445 ± 63.1	472 ± 67.3	6.93 ± 2.29	246±84.4
MF/F 100/5	2.23 (2.10-4.07)	68.8 ± 23.6	358 ± 121	368 ± 146	6.85 ± 2.73	256±85.0
MF/F 200/5	2.18 (1.12-4.08)	58.7 ± 21.6	322 ± 117	327 ± 143	6.05 ± 2.06	259±90.4

[1] Median (min-max)

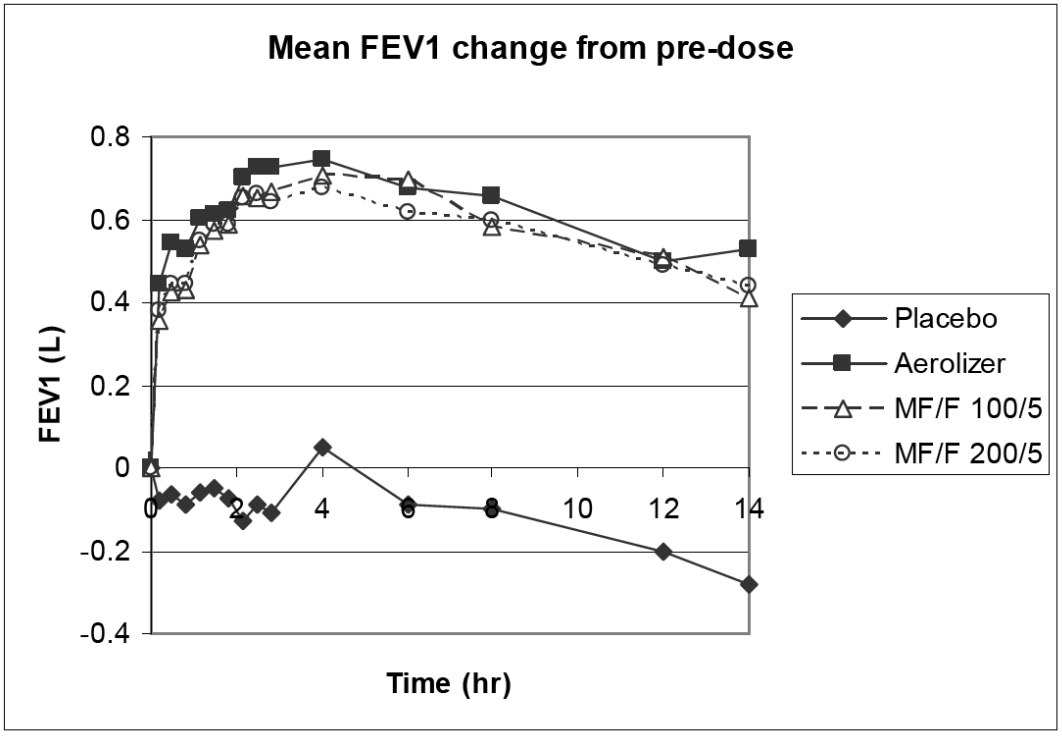
Table 2: Serum pharmacokinetic parameters for mometasone furoate (Mean +/- SD)

Device	t_{max} (hr)[1]	C_{max} (pg/mL)	AUC(0-24) (pg*hr/mL)
MF/F 100/5	2.17 (2.00-3.00)	49.0 ± 17.7	484 ± 195
MF/F 200/5	3.00 (2.00-10:00)	62.5 ± 19.9	787 ± 270

[1] Median (min-max)

The mean FEV1 and FEV1 change from baseline following formoterol via Aerolizer®, MF/F 100/5 MDI, MF/F 200/5 MDI were shown in Figure 1 and Table 3.

Figure 1: Mean FEV1 change from pre-dose over 14 hours and over first 4 hours



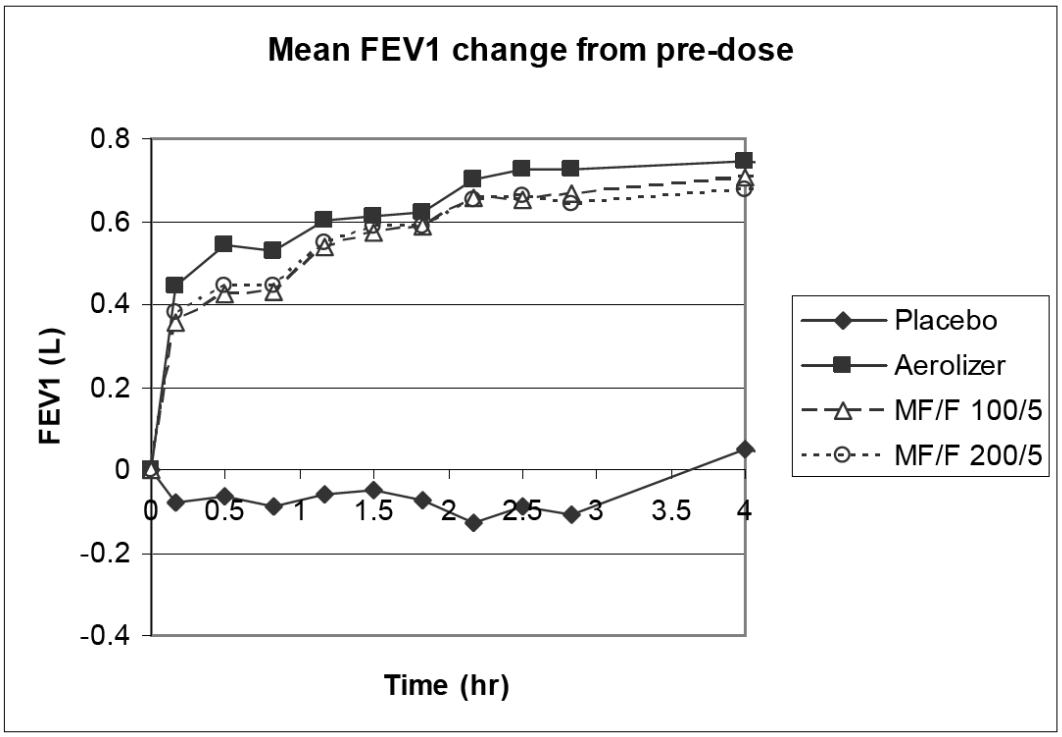


Table 3: FEV1 at 30 min post-dose –statistical analysis (N=18)

Parameter (unit)	Treatment	Arithmetic mean	Standard deviation	Percent difference	p-value	95% CI for difference of means
First dose (Step 1*)						
FEV_1 (L)	A: Formoterol Aerolizer®	3.326	0.535			
FEV_1 (L)	B: MF/F 100/5	3.230	0.553	-2.89	0.019	(-0.18, -0.02)
FEV_1 (L)	C: MF/F 200/5	3.272	0.543	-1.64	0.171	(-0.13, 0.03)
Change in FEV_1 (L)	A: Formoterol Aerolizer®	0.545	0.246			
Change in FEV_1 (L)	B: MF/F 100/5	0.423	0.283	-22.43	0.052	(-0.25, 0.00)
Change in FEV_1 (L)	C: MF/F 200/5	0.443	0.204	-18.65	0.104	(-0.23, 0.02)
Second dose (Step 2*)						
FEV_1 (L)	A: Formoterol Aerolizer®	3.391	0.496			
FEV_1 (L)	B: MF/F 100/5	3.378	0.545	-0.38	0.756	(-0.10, 0.07)
FEV_1 (L)	C: MF/F 200/5	3.415	0.534	0.70	0.563	(-0.06, 0.11)
Change in FEV_1 (L)	A: Formoterol Aerolizer®	0.610	0.341			
Change in FEV_1 (L)	B: MF/F 100/5	0.571	0.353	-6.38	0.600	(-0.19, 0.11)
Change in FEV_1 (L)	C: MF/F 200/5	0.587	0.255	-3.83	0.753	(-0.17, 0.13)
Third dose (Step 3*)						
FEV_1 (L)	A: Formoterol Aerolizer®	3.509	0.564			
FEV_1 (L)	B: MF/F 100/5	3.457	0.564	-1.49	0.203	(-0.13, 0.03)
FEV_1 (L)	C: MF/F 200/5	3.491	0.532	-0.52	0.651	(-0.10, 0.06)
Change in FEV_1 (L)	A: Formoterol Aerolizer®	0.728	0.351			
Change in FEV_1 (L)	B: MF/F 100/5	0.650	0.358	-10.76	0.311	(-0.23, 0.08)
Change in FEV_1 (L)	C: MF/F 200/5	0.663	0.281	-9.00	0.395	(-0.22, 0.09)

*Steps defined in Table 9-1

Source: Post-text table 14.2-5.1

Conclusion:

Pharmacokinetics: With or without dose normalization, systemic exposure to formoterol was lower for the MF/F MDI devices (total nominal dose of formoterol fumarate: 40 µg) than for the Aerolizer (total nominal dose of formoterol fumarate: 48 µg). Inter-subject variability in formoterol pharmacokinetics was lower for the Aerolizer® than for the MDI devices. A lag time to peak concentration was evident for the MDI devices. The increase in mometasone furoate systemic exposure appeared to be less than proportional to the 2-fold increase in MF dose.

Pharmacodynamics: Clinical benefits as measured by FEV1 changes were observed by the first post-dose measurement (10 min) for all devices tested. At 30 min following the first dose, the airways response (mean FEV1 and FEV1 change from baseline) to formoterol via Aerolizer®

was greater than following MF/F 100/5 MDI or MF/F 200/5 MDI. The difference in mean FEV1 was statistically significant for MF/F 100/5 MDI but not for MF/F 200/5.

4.2.8 Study 05643: A randomized, single dose, double-blind, placebo controlled crossover study to characterize the single dose pharmacodynamics of formoterol fumarate in combination with mometasone furoate and alone via MDI

Study 05643 is A randomized, single dose, double-blind, placebo controlled crossover study to characterize the single dose pharmacodynamics of formoterol fumarate in combination with mometasone furoate and alone via MDI.

The primary study objective is to evaluate the single dose duration of action of formoterol fumarate via MDI in combination with mometasone furoate in comparison to placebo. The pharmacokinetic objective is to characterize the single dose pharmacokinetics of formoterol fumarate via MDI alone and in combination with mometasone furoate.

This study was designed single dose and 5-period crossover study in subjects with mild to moderate persistent asthma using the following treatments:

- Treatment A: mometasone 100 µg/ formoterol 10 µg via and mometasone furoate (MF)/formoterol fumarate (F) MDI and Aerolizer® placebo
- Treatment B: mometasone 400 µg/formoterol 10 µg via MF/F MDI and Aerolizer® placebo
- Treatment C: formoterol 10 µg via MDI and Aerolizer® placebo
- Treatment D: formoterol 12 µg via Aerolizer® and placebo MDI
- Treatment E: placebo MDI and Aerolizer® placebo

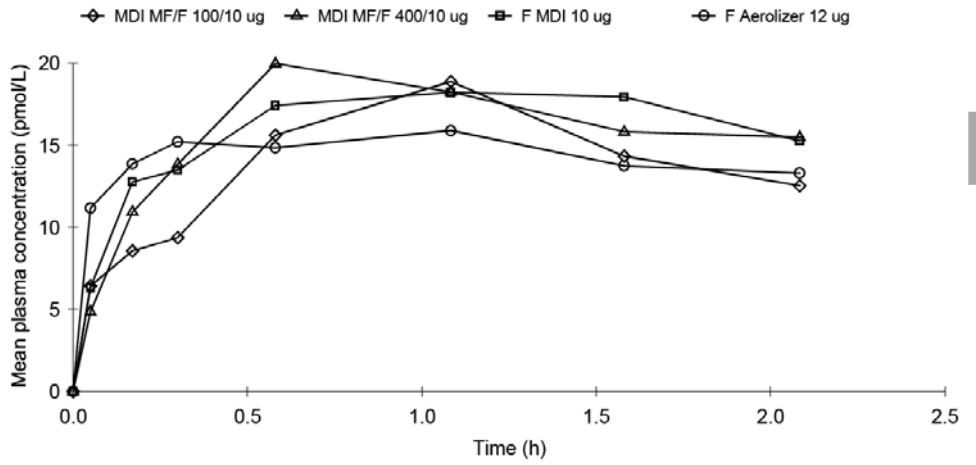
The individual PK parameters are summarized by Table 1 and Figure 1.

Table 1: Pharmacokinetic parameters for unchanged formoterol in plasma and urine (mean +/- SD)

Treatment	t_{max} [a] (h)	C_{max} (pmol/L)	AUC_{all} (pmol.hL/L)	Ae_{0-24} (nmol)	Ae_{0-24} (%dose) [b]
MDI MF/F 100/10 µg	1.00 (0.17-2.08) [1]	23.8 ± 13.0 [1]	31.6 ± 15.0 [3]	1.58 ± 0.78 [3]	6.66 ± 3.27 [3]
MDI MF/F 400/10 µg	0.58(0.13-2.08) [1]	23.4 ± 7.3 [1]	33.9 ± 10.7 [2]	1.63 ± 0.65 [2]	6.84 ± 2.75 [2]
F MDI 10 µg	1.08 (0.05-2.08) [2]	22.3 ± 6.1 [2]	33.7 ± 11.8 [2]	1.76 ± 0.75 [1]	7.41 ± 3.16 [1]
F Aerolizer® 12 µg	0.58 (0.05-2.08) [1]	21.6 ± 8.5 [1]	29.6 ± 11.7 [1]	1.42 ± 0.54 [2]	4.98 ± 1.90 [2]

[a] median (range); [b] % of the nominal dose
[1] N=25; [2] N=24 [3] N=23

Figure 1: Mean plasma concentration-time profiles of formoterol in patients with mild to moderate persistent asthma

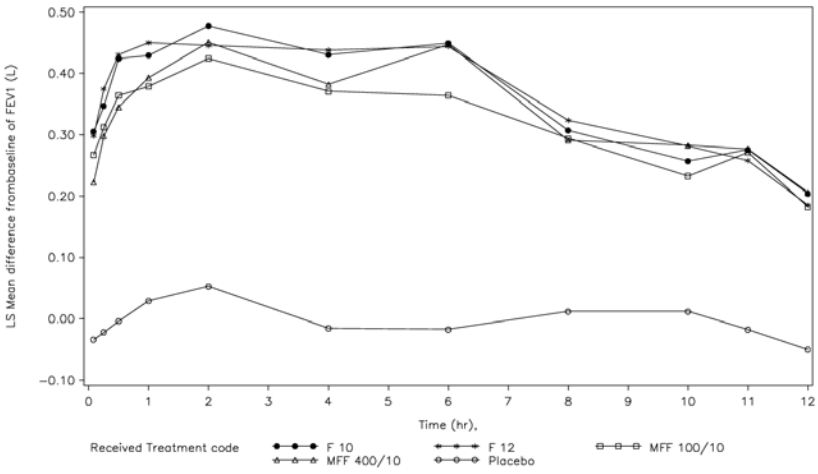


The FEV1 10-12 hour summary and estimates of contrasts with 95% confidence intervals of FEV1 10-12 hour with mixed effect ANCOVA were presented. Table 2 summarizes the 12-hour ANCOVA data. Figure 2 shows the 12 hour profile for LS mean difference of FEV1 from baseline.

Table 2: Estimates of contrasts with 95% confidence intervals of FEV1 10-12 hour (L) with mixed effect ANCOVA

Treatment contrast	LS Mean	95% confidence interval	p-value
MF/F 100/10 vs Placebo	0.23	(0.11 , 0.36)	0.0003
MF/F 400/10 vs Placebo	0.26	(0.13 , 0.38)	<.0001
F 10 vs Placebo	0.25	(0.13 , 0.38)	<.0001
F 12 vs Placebo	0.24	(0.11 , 0.36)	0.0002
MF/F 100/10 vs F 10	-0.02	(-0.14 , 0.10)	0.7306
MF/F 400/10 vs F 10	0.00	(-0.12 , 0.12)	0.9728
MF/F 100/10 vs F 12	-0.00	(-0.13 , 0.12)	0.9625
MF/F 400/10 vs F 12	0.02	(-0.10 , 0.14)	0.7403
MF/F 100/10 vs MF/F 400/10	-0.02	(-0.15 , 0.10)	0.7054
F 10 vs F 12	0.02	(-0.10 , 0.14)	0.7661

Figure 2: 12 hour profile for LS mean change from baseline for FEV1 (L)



Conclusion:

Pharmacokinetics: Even though the systemic exposure following formoterol 12 μg via Aerolizer® was slightly lower than those following the other three active treatments, systemic exposure to formoterol alone treatments were overall comparable to the systemic exposure for the MF/F combination treatments. Inter-subject variability in formoterol pharmacokinetics were also comparable cross all four active treatments.

Pharmacodynamics: With regard to single dose bronchodilator efficacy as measured by FEV1 changes, two MF/F combination treatment and two formoterol alone treatments generated indistinguishable efficacy effect. All of the active treatments are statistically superior to placebo treatment.

4.3 OCP Filing form

Office of Clinical Pharmacology *New Drug Application Filing Form*			
General Information About the Submission			
	Information		Information
NDA Number	**22-518**	**Brand Name**	**DULERA inhalation aerosol**
OCP Division	**DCP2**	**Generic Name**	**Mometasone furoate/formoterol furoate**
Medical Division	**DPAP (OND-570)**	**Drug Class**	
OCP Reviewer	**Ying Fan**	**Proposed Indication(s)**	**Asthma (b) (4) in adults and children 12 years of age and older**
OCP Team Leader	**Dakshina Chilukuri**	**Dosage Form**	**Inhalation aeroso (b) 100/5 and 200/5 mcg**
		Dosing Regimen	**Two inhalations twice daily (morning and evening)**
Date of Submission	**21 May 2009**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**22 December 2009**	**Sponsor**	**Schering-Plough and Novartis**
PDUFA Due Date	**22 March 2010**	**Priority Classification**	**Standard**
Division Due Date	**22 Jan 2010**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**x**			
Tabular Listing of All Human Studies	**x**			
HPK Summary	**x**			
Labeling	**x**			
Reference Bioanalytical and Analytical Methods	**x**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
5 Healthy Volunteers-				
single dose:				
multiple dose:				
6 Patients-				
single dose:	x	1		**Dose response-P05642**
multiple dose:	x	1		**P04689**
Dose proportionality -	**x**			
fasting / non-fasting single dose:	x	1		**P05644**
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -	**x**			
In-vivo effects on primary drug:				
In-vivo effects of primary drug:	x	1		**P03658**
In-vitro:				

Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:	**x**	**3**		**P05643** **P06144**
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	x	1		**P03705 HPA-axis**
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	x	1		**P04275**
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**8**		
7				

8 Filability and QBR comments		
9	**"X" if yes**	**10 Comments**
Application filable?	**x**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?		**The validation method can not be located in clin pharm studies** **Justify the reason not providing the population PK for the adolescents**
QBR questions (key issues to be considered)	**Are the proposed and marketed products comparable?** **Is there any drug-drug interaction between the MF and F?** **Is there any PK difference between the healthy and target population?** **What is the result for the HPA axis study?**	

APPEARS THIS WAY ON ORIGINAL

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22518	ORIG-1	SCHERING CORP	MOMETASONE FUROATE/FORMOTEROL FUMARATE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YING FAN
01/22/2010

LIANG ZHAO
01/22/2010

PARTHA ROY
01/22/2010