CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22518Orig1s000

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-518**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**05/22/09**
PRODUCT:	**DULERA (Mometasone Furoate/Formoterol Fumarate)**
INTENDED CLINICAL POPULATION:	**Asthma**
SPONSOR:	**Shering Corporation 2000 Galloping Hill Road Kenilworth, NJ 07033**
DOCUMENTS REVIEWED:	**Electronic Submission**
REVIEW DIVISION:	**Division of Pulmonary and Allergy Products (HFD-570)**
PHARM/TOX REVIEWER:	**Timothy W. Robison**
ACTING PHARM/TOX SUPERVISOR:	**Jean Wu**
DIVISION DIRECTOR:	**Badrul Chowdhury**
PROJECT MANAGER:	**Eunice Chung**
Date of review submission to DARRTS:	**January 19, 2010**

TABLE OF CONTENTS

EXECUTIVE SUMMARY 3

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW 5

2.6.1 INTRODUCTION AND DRUG HISTORY 5

2.6.2 PHARMACOLOGY 9
2.6.2.1 Brief summary 9
2.6.2.2 Primary pharmacodynamics 10
2.6.2.3 Secondary pharmacodynamics 14
2.6.2.4 Safety pharmacology 14
2.6.2.5 Pharmacodynamic drug interactions 14

2.6.3 PHARMACOLOGY TABULATED SUMMARY 14

2.6.4 PHARMACOKINETICS/TOXICOKINETICS 14
2.6.4.1 Brief summary 14
2.6.4.2 Methods of Analysis 14
2.6.4.3 Absorption 14
2.6.4.4 Distribution 15
2.6.4.5 Metabolism 15
2.6.4.6 Excretion 15
2.6.4.7 Pharmacokinetic drug interactions 15
2.6.4.8 Other Pharmacokinetic Studies 15
2.6.4.9 Discussion and Conclusions 15
2.6.4.10 Tables and figures to include comparative TK summary 15

2.6.5 PHARMACOKINETICS TABULATED SUMMARY 15

2.6.6 TOXICOLOGY 15
2.6.6.1 Overall toxicology summary 15
2.6.6.2 Single-dose toxicity 19
2.6.6.3 Repeat-dose toxicity 19
2.6.6.4 Genetic toxicology 19
2.6.6.5 Carcinogenicity 18
2.6.6.6 Reproductive and developmental toxicology 20
2.6.6.7 Local tolerance 20
2.6.6.8 Special toxicology studies 20
2.6.6.9 Discussion and Conclusions 20
2.6.6.10 Tables and Figures 20

2.6.7 TOXICOLOGY TABULATED SUMMARY 21

OVERALL CONCLUSIONS AND RECOMMENDATIONS 21

APPENDIX/ATTACHMENTS 25

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability
From a nonclinical standpoint, the application is recommended for approval.

B. Recommendation for nonclinical studies
None

C. Recommendations on labeling
Recommendations for nonclinical sections of the labeling will follow in a separate labeling review.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings
The nonclinical safety program for the MF/F MDI is based upon the complete toxicology programs conducted for both individual active drugs. The nonclinical programs for the individual active drugs include single dose, chronic, reproductive toxicology, genotoxicity, and carcinogenicity studies. The sponsor conducted 13-week inhalation bridging toxicology studies with the combination of mometasone furoate (MF) and formoterol fumarate (F) in rats and dogs to assess for potential additive or synergistic toxic effects.

In 13-week inhalation bridging toxicology studies, rats were exposed by nose-only inhalation and dogs were exposed by mouth-only inhalation to aerosols of MDI formulations of MF + F containing oleic acid, ethanol, and HFA-227. In order to conduct a safety assessment of the three different clinical dosage strengths in terms of additive or synergistic effects, rats and dogs were exposed to 3 doses of the 50 to 5 ratio product and 1 dose of the 200 to 5 ratio product. Use of the 50 to 5 and 200 to 5 ratio products was intended to cover the range of clinical doses and maximize the potential to observe any interactions between mometasone and formoterol.

Toxicities observed in 3-month bridging studies with MF + F in rats and dogs appeared to be primarily attributable to the pharmacological effects of mometasone. In addition, tachycardia, attributable to formoterol, was observed in dogs. NOAELs were not identified in studies with rats and dogs based upon histopathological findings in all MF/F groups. There was no evidence of additive or synergistic toxic effects with the combination of mometasone and formoterol. There was no evidence of any interactions on toxicokinetic parameters in rats or dogs.

B. Pharmacologic activity

Mometasone furoate is a corticosteroid demonstrating potent anti-inflammatory activity. Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have been shown to have a wide range of inhibitory effects on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation and in the asthmatic response. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.

Formoterol fumarate is a long-acting selective $beta_2$-adrenergic receptor agonist ($beta_2$-agonist). Inhaled formoterol fumarate acts locally in the lung as a bronchodilator. The pharmacologic effects of $beta_2$-adrenoceptor agonist drugs, including formoterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

C. Nonclinical safety issues relevant to clinical use

None

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

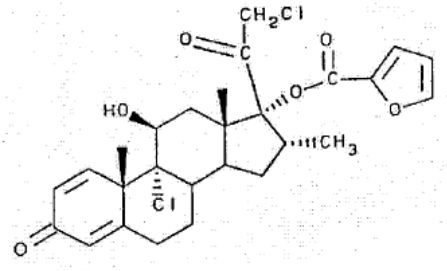
2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-518
Review number: #01
Sequence number/date/type of submission: #000
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Shering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033
Manufacturer for drug substance: Schering Corporation and Novartis

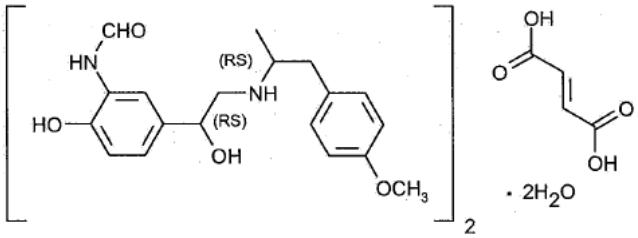
Reviewer name: Timothy W. Robison, Ph.D., D.A.B.T.
Division name: Pulmonary and Allergy Products
HFD #: 570
Review completion date: January 19, 2010

Drug:

Trade name: DULERA®
Generic name: Mometasone Furoate + Formoterol Fumarate
Code name: SCH418131 (Mometasone Furoate + Formoterol Fumarate)
Chemical name:
Mometasone furoate: 9α,21-dichloro-11β,17α-dihydroxy-16α-methyl-pregna-1,4-diene-3,20-dione17-(2')-furoate.
Formoterol fumarate dihydrate: (±)-2-hydroxy-5-[(1RS)-1-hydroxy-2-((1RS)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]formanilide fumarate dihydrate
Molecular formula/molecular weight:
Mometasone furoate, $C_{27}H_{30}O_6Cl_2$ / 521.4 g/mole
Formoterol fumarate dihydrate, $C_{42}H_{52}N_4O_{12} \cdot 2\ H_2O$ / 840.9 g/mole
Structure:
Mometasone furoate:



Formoterol fumarate:



Relevant INDs/NDAs/DMFs:
Mometasone from Schering: IND 24,088, (b) (4) (b) (4), IND 46,216, IND 52,214, IND 55,108, NDA 19-543, NDA 19-625, NDA 19-796, NDA 20-762 (b) (4) (b) (4) NDA 21-067, (b) (4)

Formoterol from Novartis: NDA 20-831

Drug class:
Mometasone furoate: glucocorticoid
Formoterol: β_2-adrenergic agonist

Intended clinical population: DULERA is indicated for (b) (4) twice-daily (b) (4) treatment of asthma, (b) (4) in adults and children 12 years of age and older.

Clinical formulation: The drug products contain the drug substances, Mometasone Furoate Anhydrous and Formoterol Fumarate Dihydrate. The drug products are white suspensions containing (b) (4) alcohol dehydrated/ethanol anhydrous (USP-NF), (b) (4) oleic acid (b) (4) (USP-NF), and (b) (4) HFA 227 (b) (4) (b) (4).

The drug products are formulated in (b) (4) strengths each designed to deliver a minimum of 120 actuations as shown in Table 1. One therapeutic dose is obtained from two single actuations of the drug products.

Table 1 Description of the Drug Products

Drug Product (Strength)	Strength of Mometasone Furoate (mcg per actuation ex-actuator)	Strength of Formoterol Fumarate (mcg per actuation ex-actuator)
(b) (4)		
Mid	100	5
High	200	5

The compositions of the drug products are presented in Table 2 to Table 4.

(b) (4)

[redacted]

Table 3 Composition of the 100/5 mcg per Actuation Drug Product

Ingredient	Theoretical Quantity					Function	Reference to Standards
	mg/metered actuation*	mg/mL	mg/g	% w/w	mg/filled canister		
Mometasone Furoate	[redacted]				(b) (4)	Drug substance	USP, Anhydrous Micronized (Inhalation Grade)
Formoterol Fumarate						Drug substance	USP
Ethanol					(b) (4)	and co-solvent	USP-NF
Oleic Acid						Surfactant	USP-NF
HFA 227						Propellant	(b) (4)
Total							

(b) (4)

[redacted]

Table 4 Composition of the 200/5 mcg per Actuation Drug Product

Ingredient	Theoretical Quantity					Function	Reference to Standards
	mg/metered actuation*	mg/mL	mg/g	% w/w	mg/filled canister		
Mometasone Furoate	[redacted]				(b) (4)	Drug substance	USP, Anhydrous Micronized (Inhalation Grade)
Formoterol Fumarate						Drug substance	USP
Ethanol					(b) (4)	and co-solvent	USP-NF
Oleic Acid						Surfactant	USP-NF
HFA 227						Propellant	(b) (4)
Total							

(b) (4)

[redacted]

Route of administration: Oral inhalation

Best Available Copy

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance: Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 22-518 are owned by Schering Corporation or are data for which Schering has obtained a written right of reference. Any information or data necessary for approval of NDA 22-518 that Schering Corporation does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Schering Corporation does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22-518.

Studies reviewed under NDA 22-518 or IND 70,283 for the combination of mometasone furoate and formoterol:

Study Title	Report Number	Location of Review
PHARMACOLOGY:		
Effect of Intratracheal (I.T.) SCH 32088 (Mometasone Furoate - MF) and Formoterol (F) on the Improvement in Lung Function in Allergen Challenged Brown Norway Rats	54911	NDA 22-518
The Effects of Intratracheal (IT) SCH32088 (MF) and Formoterol (F) on Antigen-Induced Pulmonary Inflammation and Cytokine Release in Allergic Brown Norway Rats	54919	NDA 22-518
Effect of the combination of formoterol together with mometasone on the glucocorticoid receptor binding to glucocorticoid response element in vitro	55130	NDA 22-518
TOXICOLOGY:		
Two-Week Nose-Only Inhalation Toxicity and Toxicokinetic Study of SCH32088 with Formoterol Aerosols in the Rat	99454	Summary in IND 70,283
Thirteen-Week Nose-Only Inhalation Toxicity Study of SCH 418131 (SCH 32088 with Formoterol) Aerosol in the Rat	99457	IND 70,283
Two-Week Inhalation Toxicity and Toxicokinetic Study of SCH 32088 with Formoterol Aerosols in the Dog	99455	Summary in IND 70,283
Thirteen-Week Oral Inhalation Toxicity Study of SCH418131 (SCH32088 with Formoterol) Aerosols in the Dog	99458	IND 70,283

Studies previously reviewed under other NDAs for Mometasone Furoate:
1. Three-Month Nose-Only Inhalation Study of SCH 32088 MDI (HFA-227 Propellant) Aerosol in Rats (Report Number P-6488). See NDAs 20-762 and 21-067
2. Three-Month Inhalation Toxicity Study of SCH 32088 Metered Dose Inhaler (HFA-227 Propellant) in the Dog (Report Number 95008). See NDAs 20-762 and 21-067

Studies not reviewed: None

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

The sponsor has developed a combination drug product consisting of mometasone furoate and formoterol fumarate for the treatment of asthma.

Mometasone furoate:
Mometasone furoate is a corticosteroid demonstrating potent anti-inflammatory activity. The precise mechanism of corticosteroid action on asthma is not known. Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have been shown to have a wide range of inhibitory effects on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation and in the asthmatic response. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.

Mometasone furoate has been shown *in vitro* to exhibit a binding affinity for the human glucocorticoid receptor, which is approximately 12 times that of dexamethasone, 7 times that of triamcinolone acetonide, 5 times that of budesonide, and 1.5 times that of fluticasone. The clinical significance of these findings is unknown.

Formoterol:
Formoterol fumarate is a long-acting selective $beta_2$-adrenergic receptor agonist ($beta_2$-agonist). Inhaled formoterol fumarate acts locally in the lung as a bronchodilator. In vitro studies have shown that formoterol has more than 200-fold greater agonist activity at $beta_2$-receptors than at $beta_1$-receptors. Although $beta_2$-receptors are the predominant adrenergic receptors in bronchial smooth muscle and $beta_1$-receptors are the predominant receptors in the heart, there are also $beta_2$-receptors in the human heart comprising 10%-50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective $beta_2$-agonists may have cardiac effects.

The pharmacologic effects of $beta_2$-adrenoceptor agonist drugs, including formoterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that formoterol is an inhibitor of the release of mast cell mediators, such as histamine and leukotrienes, from the human lung. Formoterol also inhibits histamine-induced plasma albumin extravasation in anesthetized guinea pigs and

inhibits allergen-induced eosinophil influx in dogs with airway hyper-responsiveness. The relevance of these in vitro and animal findings to humans is unknown.

Mometasone + Formoterol:
The combination of MF and F reversed antigen challenge-induced reductions of lung function in rats at all time points. Further, the combination was more effective at reversing deficits of lung function at all time points than either compound alone. Ovalbumin (OVA) challenge of sensitized rats significantly increased total cells, eosinophils, and neutrophils in the BAL fluid. Treatment of OVA-sensitized rats with MF alone inhibited increases of total cells and eosinophils at all doses and increases of neutrophils at the highest dose. Treatment of OVA-sensitized rats with F alone inhibited increases of total cells at all doses and increases of eosinophils at higher doses; however, neutrophil counts were not affected in a dose-related manner. Combinations of MF and F were significantly more effective in inhibiting increases of total numbers of cells than either MF or F alone. The combination was more effective in inhibiting increases of eosinophils than MF alone, but not F alone. One dose of the combination was more effective in inhibiting increases of neutrophils as compared to either MF or F alone. With respect to cytokines (IL-4, IL-5, IL-13 and TNFα), the combination did not show a significant improvement over MF or F alone at most doses.

2.6.2.2 Primary pharmacodynamics

See NDAs 20-762 and 21-067 and NDA 20-831 for reviews of studies conducted with mometasone and formoterol, respectively.

Drug activity related to proposed indication:

Effect of Intratracheal (I.T.) SCH 32088 (Mometasone Furoate - MF) and Formoterol (F) on the Improvement in Lung Function in Allergen Challenged Brown Norway Rats (Study Report 54911): Ovalbumin-sensitized male Brown Norway rats were exposed to aerosolized antigen bronchoprovocation. Forced vital capacity (FVC) was measured by whole body plethysmography. Mometasone furoate (MF) and Formoterol (F) were micronized, admixed with micronized lactose, and administered by the intratracheal route. The compounds (or lactose vehicle) were given 24 hr after the antigen challenge, a point at which animals had significant airflow obstructions. Lung function was measured 5 hr after MF dosing and 1 hr after F dosing. One hour after intratracheal administration of F alone (1, 10, and 100 µg/kg), reductions of FVC induced by antigen challenge were reversed. An intratracheal dose of 1 µg/kg partially (42 ± 14% reversal) attenuated the effects of antigen and this dose was selected for the combination study. Intratracheal administration of MF alone (0.1, 1.0, and 3.0 mg/kg) also dose-dependently attenuated reductions of FVC induced by antigen challenge. An intratracheal dose of 1 mg/kg partially (29 ± 6% reversal) attenuated the effects of antigen and this dose was selected for the combination study. In the combination study, the effects of an intratracheal administration of MF (1 mg/kg) alone, F (1 µg/kg) alone, and the combination were measured at 1, 5, and 24 hr postdose. The combination of MF and F reversed antigen challenge-induced reductions of lung

function at all time points. Further, the combination was more effective at reversing deficits of lung function at all time points than either compound alone. With F alone, significant effects were observed at 1 and 5 hr, but not at 24 hr. With MF alone, significant effects were observed at 5 and 24 hr only. With the combination, significant efficacy was observed at all time points and there was significantly improved efficacy at 5 hr relative to individual compounds.

Table 3 Reversal of allergen-induced reductions in FVC 1, 5 and 24 hrs after intratracheal administration of Formoterol alone, Mometasone alone and the combination of Mometasone and Formoterol.

Variable	Alum + Vehicle	OVA + Vehicle	OVA + Formoterol (1 µg/kg)	OVA + Mometasone (1 mg/kg)	OVA + Combination
n =	8	8	8	7	8
FVC + 1 hr (ml)	4.01 ± 0.19*	2.69 ± 0.20	3.12 ± 0.13*	2.94 ± 0.10	3.50 ± 0.21*@
FVC + 1 hr (% Reversal)	-	-	32 ± 10	19 ± 7	61 ± 16
FVC + 5 hrs (ml)	4.24 ± 0.03*	2.36 ± 0.22	2.99 ± 0.14*	3.20 ± 0.12*	4.06 ± 0.15*#@
FVC + 5 hrs (% Reversal)	-	-	33 ± 7	45 ± 7	91 ± 8
FVC + 24 hrs (ml)	4.40 ± 0.12*	2.12 ± 0.18	2.65 ± 0.32	3.76 ± 0.27*	3.74 ± 0.32*#
FVC + 24 hrs (% Reversal)	-	-	23 ± 14	72 ± 12	71 ± 14

*$p \leq 0.05$ compared to vehicle-treated OVA group,
#$p \leq 0.05$ compared to Formoterol alone group,
@$p \leq 0.05$ compared to Mometasone alone group,
Values expressed as mean ± SEM
Data in NB # 400052 pages 323-333 and NB#304126 pages 126-167.

<u>The Effects of Intratracheal (IT) SCH32088 (MF) and Formoterol (F) on Antigen-Induced Pulmonary Inflammation and Cytokine Release in Allergic Brown Norway Rats</u> (Study Report 54919): The combination of mometasone furoate (MF) and Formoterol (F) was compared to MF and F with respect to inhibition of antigen challenge-induced inflammatory cell infiltration and cytokine production in ovalbumin sensitized male Brown Norway rats. MF alone, F alone, MF + F, or lactose vehicle were administered by the intratracheal route 5 hr before aerosolized ovalbumin challenge. Animals were sacrificed 24 hr after challenge and bronchoalveolar lavage fluid isolation was performed. Number of eosinophils and neutrophils in the BAL were determined. In addition, cytokines, IL-1β, GRO/KC, IL-4, IL-5, TNFα, IFNγ and IL-13, from the supernatants of BAL samples were measured.

OVA challenge of sensitized rats significantly increased total cells, eosinophils, and neutrophils in the BAL fluid 24 hr after challenge. Treatment of OVA-sensitized rats with MF alone (0.03-0.3 mg/kg, IT) inhibited increases of total cells and eosinophils at all doses and increases of neutrophils at a dose of 0.3 mg/kg. Treatment of OVA-sensitized rats with F alone (1.0-10.0 mg/kg, IT) inhibited increases of total cells at all doses and increases of eosinophils at doses ≥3 µg/kg; however, neutrophil counts were not affected in a dose-related manner. Combinations of MF and F containing 0.1 mg/kg MF dose were significantly more effective in inhibiting increases of total numbers of cells than either MF or F alone. The combination was more effective in inhibiting increases of eosinophils than MF alone, but not F alone. One dose of the combination was more effective in inhibiting increases of neutrophils as compared to either MF or F alone.

Of the cytokines measured, only IL-4, IL-5, IL-13 and TNFα showed significant differences between positive and negative controls and thus only these cytokines were included in the subsequent analysis. Each of the four selected cytokines was significantly decreased in each of the four combination groups when compared to the positive control group. The combination did not show a significant improvement over MF or F alone at most doses.

Table 3. Effect of i.t. MF, F and MFF on BAL inflammatory cells 24 hr after antigen challenge to BN rats. Data were generated over three separate weeks of studies with each group represented in each study week.

Treatment	n	Total Cells (10^3/ml)	Total Cells (% inhib)	Eosinophils (10^3/ml)	Eosinophils (% inhib)	Neutrophils (10^3/ml)	Neutrophils (% inhib)
Alum + Vehicle	9	102 ± 15	-	29 ± 12	-	11 ± 3	-
Ova + Vehicle	15	371 ± 34	-	156 ± 22	-	123 ± 15	-
SCH 32088 (0.03 mg/kg)	9	246 ± 14*	46.5	83 ± 9*	57.7	95 ± 5	25.2
SCH 32088 (0.1 mg/kg)	9	265 ± 23*	39.4	101 ± 17	43.4	94 ± 7	25.9
SCH 32088 (0.3 mg/kg)	9	188 ± 19*	68.0	50 ± 11*	84.0	78 ± 8*	40.7
Formoterol (1 µg/kg)	8	260 ± 38*	41.3	107 ± 31	38.7	86 ± 13	33.0
Formoterol (3 µg/kg)	9	240 ± 26*	48.7	50 ± 7*	83.9	119 ± 16	3.6
Formoterol (10 µg/kg)	9	231 ± 24*	52.0	72 ± 19*	66.4	86 ± 8	33.5
SCH 32088 (0.03 mg/kg) Formoterol (1 µg/kg)	11	208 ± 20*	60.6	56 ± 9*#	79.1	84 ± 9	35.4
SCH 32088 (0.03 mg/kg) Formoterol (3 µg/kg)	9	230 ±23*	52.4	85 ± 19*	55.8	86 ± 10	33.6
SCH 32088 (0.1 mg/kg) Formoterol (1 µg/kg)	9	168 ± 28*#^	75.7	51 ± 23*#^	83.3	61 ± 8*#	55.3
SCH 32088 (0.1 mg/kg) Formoterol (3 µg/kg)	11	174 ± 22*#^	73.2	37 ± 10*#	93.7	84 ± 10*	35.3

*$p \leq 0.05$ compared to vehicle-treated OVA group. Values expressed as mean ± SEM.
#$p \leq 0.05$ compared to corresponding dose of MF alone. Values expressed as mean ± SEM.
^ $p \leq 0.05$ compared to corresponding dose of F alone. Values expressed as mean ± SEM.
Data in notebook number 400052, pages 211-228

Best Available Copy

Table 4. Effect of i.t. MF, F and MFF on pulmonary cytokine production 24 hr after antigen challenge to BN rats. These data were generated from the supernatant saved from the same BAL studies shown in Table 3.

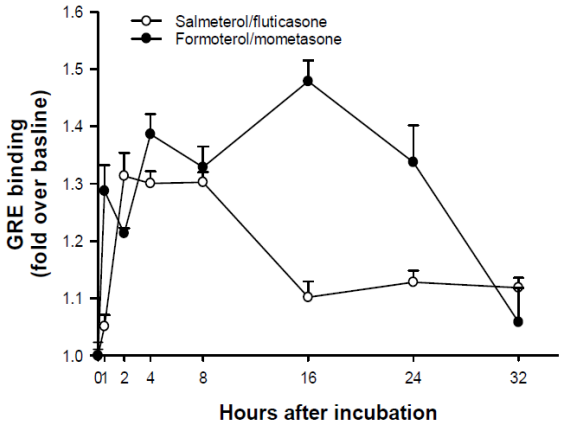
Treatment	n	IL-4 (10^2 ECL units)	IL-4 (% Inhib)	IL-5 (10^2 ECL units)	IL-5 (% Inhib)	IL-13 (10^2 ECL units)	IL-13 (% Inhib)	TNFα (10^2 ECL units)	TNFα (% Inhib)
Alum + Vehicle	9	4.6 ± 0.2	-	2.5 ± 0.3	-	16 ± 2	-	4.5 ± 0.2	-
Ova + Vehicle	15	15.0 ± 4.0	-	27.0 ± 8.2	-	84 ± 17	-	15.3 ± 2.0	-
SCH32088 (0.03 mg/kg)	9	9.0 ± 1.7*	59.9	19.8 ± 7.4	29.4	70 ± 20	21.4	17.4 ± 4.4	-19.1
SCH32088 (0.1 mg/kg)	9	7.2 ± 1.3*	76.0	7.1 ± 3.3*	81.1	32 ± 11*	76.9	9.3 ± 1.5*	55.8
SCH32088 (0.3 mg/kg)	9	5.5 ± 0.8*	91.8	5.1 ± 2.3*	89.4	18 ± 2*	98.0	6.0 ± 0.7*	85.8
Formoterol (1 µg/kg)	8	9.7 ± 2.7	53.2	17.1 ± 7.5*	40.5	53 ± 12	46.7	13.1 ± 2.4	20.3
Formoterol (3 µg/kg)	9	9.3 ± 2.4	56.3	8.5 ± 3.3*	75.8	32 ± 9*	76.6	12.1 ± 3.2	30.0
Formoterol (10 µg/kg)	9	5.4 ± 0.2*	92.8	4.0 ± 0.5*	94.1	23 ± 4*	89.8	10.3 ± 1.4	46.3
SCH32088 (0.03 mg/kg) Formoterol (1 µg/kg)	11	6.5 ± 0.8*	82.6	5.2 ± 0.9*	89.2	29 ± 6*#	81.4	9.1 ± 1.4*	57.6
SCH32088 (0.03 mg/kg) Formoterol (3 µg/kg)	9	7.1 ± 0.8*	77.5	6.9 ± 1.5*	82.0	45 ± 10*	57.3	10.2 ± 1.2*	47.0
SCH32088 (0.1 mg/kg) Formoterol (1 µg/kg)	9	6.3 ± 1.7*	84.8	6.3 ± 2.9*	84.5	26 ± 11*	85.8	8.5 ± 3.2*	63.2
SCH32088 (0.1 mg/kg) Formoterol (3 µg/kg)	11	4.6 ± 0.2*	100.1	2.6 ± 0.2*	99.6	15 ± 2*#	101.5	6.2 ± 0.7*	84.1

*$p \leq 0.05$ compared to vehicle-treated OVA group, Values expressed as mean ± SEM,
#$p \leq 0.05$ compared to corresponding dose of MF alone, Values expressed as mean ± SEM,
^ $p \leq 0.05$ compared to corresponding dose of F alone, Values expressed as mean ± SEM,
Data in notebook number 64380, pages 38-46, 51-52

Best Available Copy

Effect of the combination of formoterol together with mometasone on the glucocorticoid receptor binding to glucocorticoid response element in vitro (Study report 55130): Glucocorticoids have been shown to bind to glucocorticoid receptors in the cytoplasm which then dimerize and translocate to the nucleus, where they bind to glucocorticoid response elements (GRE) on glucocorticoid-responsive genes, resulting in down regulation of pro-inflammatory gene transcription or up regulation of anti-inflammatory genes The in vitro duration of action of the formoterol/mometasone combination was assessed by measuring the binding of the glucocorticoid receptor to its binding elements and compared with the salmeterol/fluticasone combination. In differentiated U937 cells, both combinations were able to induce binding of the glucocorticoid receptor to its response elements. However, the effect of the salmeterol/fluticasone combination was persisted up to 8 hr while the effect of the formoterol/mometasone combination lasted up to 24 hr.

Figure 3-1 Comparison of the glucocorticoid response elements (GRE) binding over time for the formoterol/mometasone and salmeterol/fluticasone combinations



Differentiated U397 cells were incubated with 100 nM of the beta2 agonist (salmeterol or formoterol) and 1 nM of the steroid (fluticasone or mometasone) and harvested at different time points for measurement of the glucocorticoid receptor binding to the glucocorticoid response elements. Data are expressed as mean ± standard error of the mean of triplicate determinations.

2.6.2.3 Secondary pharmacodynamics

See NDAs 20-762 and 21-067 and NDA 20-831 for reviews of studies conducted with mometasone and formoterol, respectively.

2.6.2.4 Safety pharmacology

See NDAs 20-762 and 21-067 and NDA 20-831 for reviews of studies conducted with mometasone and formoterol, respectively.

2.6.2.5 Pharmacodynamic drug interactions

See NDAs 20-762 and 21-067 and NDA 20-831 for reviews of studies conducted with mometasone and formoterol, respectively.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

Not provided.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

See NDAs 20-762 and 21-067 and NDA 20-831 for reviews of studies conducted with mometasone and formoterol, respectively.

2.6.4.1 Brief summary

Toxicokinetic parameters of SCH418131 (mometasone + formoterol) were assessed in 3-month bridging studies with rats and dogs and were described in the review of the initial submission of IND 70,283.

2.6.4.2 Methods of Analysis

See attached review of IND 70,283 (3-month inhalation toxicology studies with the combination of mometasone furoate and formoterol in rats and dogs).

2.6.4.3 Absorption
See NDAs 20-762 and 21-067 and NDA 20-831 for reviews of studies conducted with mometasone and formoterol, respectively.

2.6.4.4 Distribution
See NDAs 20-762 and 21-067 and NDA 20-831 for reviews of studies conducted with mometasone and formoterol, respectively.

2.6.4.5 Metabolism
See NDAs 20-762 and 21-067 and NDA 20-831 for reviews of studies conducted with mometasone and formoterol, respectively.

2.6.4.6 Excretion
See NDAs 20-762 and 21-067 and NDA 20-831 for reviews of studies conducted with mometasone and formoterol, respectively.

2.6.4.7 Pharmacokinetic drug interactions
See NDAs 20-762 and 21-067 and NDA 20-831 for reviews of studies conducted with mometasone and formoterol, respectively.

2.6.4.8 Other Pharmacokinetic Studies
See NDAs 20-762 and 21-067 and NDA 20-831 for reviews of studies conducted with mometasone and formoterol, respectively.

2.6.4.9 Discussion and Conclusions
In the 13-week inhalation toxicology studies with the combination of mometasone and formoterol in rats and dogs, there was no substantial evidence that either component of the combination affected the toxicokinetic parameters of the other component.

2.6.4.10 Tables and figures to include comparative TK summary
Toxicokinetic data provided for combination product was limited. In general, for rats, dogs, and humans, there was no substantial evidence that either component of the combination affected the toxicokinetic parameters of the other component.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY
Not provided

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology:
Rats were exposed by nose-only inhalation to aerosols of MDI formulation of three dose levels of SCH418131 (mometasone furoate [SCH32088 or MF] in combination with formoterol [F]) at a 50:5 ratio, one level of SCH418131 (MF/F) at a 200:5 ratio, SCH32088 (MF) alone, or formoterol (F) alone. A vehicle-control group was exposed by

nose-only inhalation to aerosols of a MDI formulation comprised of oleic acid, ethanol, and HFA-227 propellant. An air-control group was exposed to by nose-only inhalation to HEPA-filtered and charcoal-filtered room air. Body weight gains were significantly decreased in all treatment groups receiving mometasone furoate. Target organs of toxicity were the lung, trachea, nose/turbinates, thymus, spleen, lymph nodes (mesenteric, bronchial, mandibular, and mediastinal), mammary gland, bone marrow, ovary, and vagina. Histopathological changes were generally observed in all treatment groups that received mometasone furoate (MF). Findings in the lungs consisted of BALT (bronchial-associated lymphoid tissue) depletion, accumulation of alveolar macrophages, and pigmented macrophages. BALT depletion was observed in all treatment groups that received mometasone. Accumulation of alveolar macrophages was observed in mid and high dose MF/F, the 200:5 MF/F group, and the MF only group. Findings in the trachea consisted of decreased globule leukocytes in all treatment groups that received MF. Thymus involution/atrophy was observed in all treatment groups that received MF. Lymphoid depletion was observed in the nose/turbinates, spleen, lymph nodes (mesenteric, bronchial, mandibular, and mediastinal). Increased incidences of lymphoid depletion in the nose/turbinates, mesenteric lymph nodes, bronchial lymph nodes, mandibular lymph nodes, and mediastinal lymph nodes occurred in all treatment groups that received mometasone. Lymphoid depletion in the spleen occurred in the mid and high dose MF/F groups, the 200:5 MF/F group, and the MF only group. Infiltration of mast cells was observed in the mesenteric lymph nodes for all treatment groups that received MF. Abnormal lobuloalveolar development of the mammary gland occurred for females all treatment groups that received MF as well as the F only group. Elevated incidences of increased marrow fat in the bone marrow were observed for all treatment groups that received MF. Increased incidences of decreased corpora lutea in the ovaries occurred in all female treatment groups that received MF as well as the F only group. Abnormal mucification of the vagina was observed in all treatment groups that received MF. A NOAEL was not established based upon histopathological findings in all MF treatment groups. Histopathological findings were attributable to the action of MF. There was no evidence of additive or synergistic toxic effects with the combination of mometasone and formoterol.

Dogs (4/sex/group) were exposed by mouth-only inhalation to aerosols of MDI formulations of 3 dose levels of SCH418131 (MF/F) at a 50:5 ratio, one dose level of SCH418131 at a 200:5 ratio, SCH32088 alone, or formoterol fumarate alone. Decreased lymphocyte and eosinophil counts were observed in treatment groups that received mometasone. Cortisol levels in response to challenge with exogenous ACTH were decreased for all male and female treatment groups that received mometasone. Increases of alkaline phosphate activities and levels of cholesterol and triglyceride in treatment groups that received mometasone may have correlated to histopathological findings of cytoplasmic vacuolation in the liver. Decreased duration of RR intervals (i.e., increased heart rate) was observed for treatment groups that received formoterol. This effect was attributed to formoterol. There was no evidence of additive or synergistic effects between mometasone and formoterol on the duration of the RR interval (i.e., heart rate). Histopathological changes were observed in the lung, thymus, adrenal

gland, cecum, colon, duodenum, ileum, jejunum, larynx, axillary LN, bronchi LN, mandibular LN, mediastinal LN, mesenteric LN, nose/turbinates, pharynx, rectum, spleen, stomach, salivary gland, ovary, uterus, mammary gland, liver, femur, rib, and sternum. In general, these histopathological changes were attributable to the actions of mometasone. In the lungs, increased incidences of hyperplasia of bronchioloalveolar cells and bronchial inflammation were observed for male and female treatment groups, although dose-response relationships were not generally evident. Vacuolization and/or atrophy of the adrenal cortex were observed for all male and female treatment groups that received mometasone furoate. Lymph depletion was observed in the thymus, cecum, colon, duodenum, ileum, jejunum, larynx, axillary LN, bronchi LN, mandibular LN, mediastinal LN, mesenteric LN, nose/turbinates, pharynx, rectum, spleen, and stomach. Incidences of lymphoid depletion in these tissues and organs were generally increased for all male and female treatment groups that received mometasone furoate. Incidences of sinus erythrophagocytosis in the mesenteric lymph nodes were increased for male and female treatment groups that received mometasone furoate. Hypoplasia of the ovaries and uterus was observed for females in the low and mid dose MF/F groups and 200:5 ratio MF/F group. For the high dose MF/F group, only 1 of 4 females was observed with hypoplasia of the uterus and there were no findings in the ovaries. Cytoplasmic vacuolation in the liver was observed for males and females in the high dose MF/F, 200:5 ratio MF/F, and MF alone groups. Fibrosis of the liver was observed for 1 of 4 females in the 200:5 ratio MF/F group. Increased fat deposition was observed in femur, rib, and sternum. These findings were observed in all treatment groups that received mometasone furoate. Epithelial vacuolization of the mammary gland was observed for females in the 200:5 ratio MF/F, MF alone, and formoterol alone groups, although a clear relationship to mometasone or formoterol was not evident. Slightly increased incidences of infiltration of adipocytes were observed in the salivary glands for the mid dose MF/F, 200:5 ratio MF/F, MF alone, and formoterol alone groups, although a relationship to treatment was unclear. There was no evidence of additive or synergistic toxic effects with the combination of mometasone and formoterol.

Genetic toxicology:

Mometasone:
Mometasone furoate increased chromosomal aberrations in an *in vitro* Chinese hamster ovary cell assay, but did not have this effect in an *in vitro* Chinese hamster lung cell assay. Mometasone furoate was not mutagenic in the Ames test or mouse lymphoma assay, and was not clastogenic in an *in vivo* mouse micronucleus assay, a rat bone marrow chromosomal aberration assay, or a mouse male germ-cell chromosomal aberration assay. Mometasone furoate also did not induce unscheduled DNA synthesis *in vivo* in rat hepatocytes.

Formoterol:
Formoterol fumarate was not mutagenic or clastogenic in the following tests: mutagenicity tests in bacterial and mammalian cells, chromosomal analyses in mammalian cells, unscheduled DNA synthesis repair tests in rat hepatocytes and

human fibroblasts, transformation assay in mammalian fibroblasts and micronucleus tests in mice and rats.

Carcinogenicity:

Mometasone:
In a 2-year carcinogenicity study in Sprague Dawley® rats, mometasone furoate demonstrated no statistically significant increase in the incidence of tumors at inhalation doses up to 67 µg/kg.

In a 19-month carcinogenicity study in Swiss CD-1 mice, mometasone furoate demonstrated no statistically significant increase in the incidence of tumors at inhalation doses up to 160 µg/kg.

Formoterol:
The carcinogenic potential of formoterol fumarate has been evaluated in 2-year drinking water and dietary studies in both rats and mice. In rats, the incidence of ovarian leiomyomas was increased at doses of 15 mg/kg and above in the drinking water study and at 20 mg/kg in the dietary study, but not at dietary doses up to 5 mg/kg. In the dietary study, the incidence of benign ovarian theca-cell tumors was increased at doses of 0.5 mg/kg and above. This finding was not observed in the drinking water study, nor was it seen in mice (see below).

In mice, the incidence of adrenal subcapsular adenomas and carcinomas was increased in males at doses of 69 mg/kg and above in the drinking water study, but not at doses up to 50 mg/kg in the dietary study. The incidence of hepatocarcinomas was increased in the dietary study at doses of 20 and 50 mg/kg in females and 50 mg/kg in males, but not at doses up to 5 mg/kg in either males or females. Also in the dietary study, the incidence of uterine leiomyomas and leiomyosarcomas was increased at doses of 2 mg/kg and above. Increases in leiomyomas of the rodent female genital tract have been similarly demonstrated with other beta-agonist drugs.

Reproductive toxicology:

Mometasone:
In reproductive studies in rats, impairment of fertility was not produced by subcutaneous doses up to 15 µg/kg.

In mice, mometasone furoate caused cleft palate at subcutaneous doses of 60 µg/kg and above. Fetal survival was reduced at 180 µg/kg. No toxicity was observed at 20 µg/kg.

In rats, mometasone furoate produced umbilical hernia at topical dermal doses of 600 µg/kg and above. A dose of 300 µg/kg produced delays in ossification, but no malformations. When rats received subcutaneous doses of mometasone furoate throughout pregnancy or during the later stages of pregnancy, 15 µg/kg caused

prolonged and difficult labor and reduced the number of live births, birth weight, and early pup survival. Similar effects were not observed at 7.5 µg/kg.

In rabbits, mometasone furoate caused multiple malformations (e.g., flexed front paws, gallbladder agenesis, umbilical hernia, hydrocephaly) at topical dermal doses of 150 µg/kg and above. In an oral study, mometasone furoate increased resorptions and caused cleft palate and/or head malformations (hydrocephaly and domed head) at 700 µg/kg. At 2800 µg/kg most litters were aborted or resorbed. No toxicity was observed at 140 µg/kg.

Formoterol:
Reproduction studies in rats revealed no impairment of fertility at oral doses up to 3 mg/kg.

Formoterol fumarate administered throughout organogenesis did not cause malformations in rats or rabbits following oral administration. However, formoterol fumarate was found to be teratogenic in rats (umbilical hernia) and rabbits (subcapsular cysts) from other testing laboratories. When given to rats throughout organogenesis, oral doses of 0.2 mg/kg and above delayed ossification of the fetus, and doses of 6 mg/kg and above decreased fetal weight. Formoterol fumarate has been shown to cause stillbirth and neonatal mortality at oral doses of 6 mg/kg and above in rats receiving the drug during the late stage of pregnancy. These effects, however, were not produced at a dose of 0.2 mg/kg.

Special toxicology:
See NDAs 20-762 and 21-067 and NDA 20-831 for reviews of studies conducted with mometasone and formoterol, respectively.

2.6.6.2 Single-dose toxicity
See NDAs 20-762 and 21-067 and NDA 20-831 for reviews of studies conducted with mometasone and formoterol, respectively.

2.6.6.3 Repeat-dose toxicity
See the attached reviews of 3-month inhalation toxicology studies conducted with the combination of mometasone and formoterol in rats and dogs under IND 70,283. See NDAs 20-762 and 21-067 and NDA 20-831 for reviews of studies conducted with mometasone and formoterol, respectively.

2.6.6.4 Genetic toxicology
See NDAs 20-762 and 21-067 and NDA 20-831 for reviews of studies conducted with mometasone and formoterol, respectively.

2.6.6.5 Carcinogenicity
See NDAs 20-762 and 21-067 and NDA 20-831 for reviews of studies conducted with mometasone and formoterol, respectively.

2.6.6.6 Reproductive and developmental toxicology

See NDAs 20-762 and 21-067 and NDA 20-831 for reviews of studies conducted with mometasone and formoterol, respectively.

2.6.6.7 Local tolerance

See NDAs 20-762 and 21-067 and NDA 20-831 for reviews of studies conducted with mometasone and formoterol, respectively.

2.6.6.8 Special toxicology studies

See NDAs 20-762 and 21-067 and NDA 20-831 for reviews of studies conducted with mometasone and formoterol, respectively.

2.6.6.9 Discussion and Conclusions

For the combination SCH418131 drug product (Mometasone Furoate + Formoterol Fumarate), 3-month inhalation bridging toxicology studies with rats and dogs were provided. Toxicities observed in 3-month bridging studies with SCH418131 in rats and dogs appeared to be primarily attributable to the pharmacological effects of mometasone (i.e., class effects of glucocorticoids). Target organs of toxicity in rats and dogs are shown in the table below. In addition, tachycardia, attributable to formoterol, was observed in dogs. There was no evidence in these studies of additive or synergistic toxic effects between mometasone and formoterol. There was no evidence of any interactions on toxicokinetic parameters in rats or dogs.

2.6.6.10 Tables and Figures

Target organs of toxicity observed in rats and dogs treated with SCH418131

Organ/Tissue	Rat	Dog
Lungs	BALT (bronchial-associated lymphoid tissue) depletion, accumulation of alveolar macrophages, and pigmented macrophages.	Hyperplasia of bronchioloalveolar cells and bronchial inflammation
Thymus	Involution/atrophy	Lymphoid depletion
Nose/Turbinates	Lymphoid depletion	Lymphoid depletion
Spleen	Lymphoid depletion	Lymphoid depletion
Mesenteric LN	Lymphoid depletion and infiltration of mast cells	Lymphoid depletion and erythrophagocytosis
Bronchial LN	Lymphoid depletion	Lymphoid depletion
Mandibular LN	Lymphoid depletion	Lymphoid depletion
Mediastinal LN	Lymphoid depletion	Lymphoid depletion
Mammary gland	Abnormal lobule development	
Bone marrow	Increased marrow fat	
Ovaries	Decrease corpora lutea	Hypoplasia
Vagina	Abnormal mucification	
Adrenal gland		Vacuolization and/or atrophy of the adrenal cortex
Cecum		Lymphoid depletion
Colon		Lymphoid depletion
Duodenum		Lymphoid depletion

Ileum		Lymphoid depletion
Jejunum		Lymphoid depletion
Larynx		Lymphoid depletion
Axillary LN		Lymphoid depletion
Pharynx		Lymphoid depletion
Rectum		Lymphoid depletion
Stomach		Lymphoid depletion
Salivary gland		Infiltration of adipocytes
Uterus		Hypoplasia
Liver		Cytoplasmic vacuolation
Femur		Increased fat deposition
Rib		Increased fat deposition
Sternum		Increased fat deposition
Trachea		Decreased globule leukocytes

2.6.7 TOXICOLOGY TABULATED SUMMARY

Not provided.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

The sponsor has developed a mometasone furoate/formoterol fumarate combination (MF/F) metered dose inhaler (MDI) for the (b) (4) twice-daily (b) (4) treatment of asthma, (b) (4) in adults and children 12 years of age and older. The nonclinical safety program for the MF/F MDI is based upon the complete toxicology programs conducted for both individual active drugs (NDAs 21-067 for mometasone furoate and NDA 20-831 for formoterol). The nonclinical programs for the individual active drugs include single dose, chronic, reproductive toxicology, genotoxicity, and carcinogenicity studies. The current nonclinical safety program for the MF/F MDI product consists of 2- and 13-week inhalation bridging toxicology studies with rats and dogs.

In 13-week inhalation bridging toxicology studies, rats were exposed by nose-only inhalation and dogs were exposed by mouth-only inhalation to aerosols of MDI formulations of SCH418131 containing oleic acid, ethanol, and HFA-227. In order to conduct a safety assessment of the three different dosage strengths in terms of additive or synergistic effects, rats and dogs were exposed to 3 doses of the 50 to 5 ratio product and 1 dose of the 200 to 5 ratio product. Mono-product comparator groups were exposed to mometasone or formoterol alone. Vehicle-control groups were exposed to an aerosol of a MDI formulation comprised of oleic acid, ethanol, and HFA-227 propellant. The aerosol of the vehicle-control group was generated to match the concentration of oleic acid in the high dose SCH418131 group at a 50:5 ratio.

Use of the 50 to 5 and 200 to 5 ratio products was intended to cover the range of clinical doses and maximize the potential to observe any interactions between mometasone and formoterol.

Toxic effects observed in rats and dogs were primarily attributed to mometasone (class effects of glucocorticoids). Body weight gains were significantly decreased in all rat treatment groups that received mometasone furoate. White blood cell counts were decreased in rats and dogs from treatment groups that received mometasone furoate. Decreases were primarily attributed to declines of lymphocyte counts in rats and lymphocyte and eosinophil counts in dogs. Adrenal suppression was evident in dogs from all treatment groups that received mometasone furoate. For dogs, increased heart rate was observed in all treatment groups that received formoterol. There were multiple target organs of toxicity in rats and dogs. In general, histopathological findings were evident in all treatment groups that received mometasone furoate. Lymphoid depletion was observed in lung, nose/turbinates, spleen, lymph nodes (mesenteric, bronchial, mandibular, mediastinal and axillary), cecum, colon, duodenum, ileum, jejunum, larynx, pharynx, rectum, spleen, and stomach. In the lungs, there were accumulations of alveolar macrophages in rats and bronchioloalveolar hyperplasia and bronchial inflammation in dogs. In the trachea for rats, there were decreased globule leukocytes. In the adrenal gland for dogs, there was cortical atrophy and vacuolization. In the thymus for rats, there was involution/atrophy. In the bone marrow for rats and dogs, there was increased fat deposition. In the mammary gland, there was abnormal lobuloalveolar development for rats and epithelial vacuolization for dogs. In the ovaries for rats, there were decreased corpora lutea. In the vagina for rats, there was abnormal mucification. Hypoplasia of the ovary and uterus was observed for dogs. In the liver for dogs, there was cytoplasmic vacuolization. In the salivary gland for dogs, there was adipocyte infiltration, although its relationship to treatment was questionable.

NOAELs were not identified in studies with rats and dogs based upon histopathological findings in all MF/F groups. Toxicities observed in 3-month bridging studies with SCH418131 in rats and dogs appeared to be primarily attributable to the pharmacological effects of mometasone. In addition, tachycardia, attributable to formoterol, was observed in dogs. There was no evidence of additive or synergistic toxic effects with the combination of mometasone and formoterol.

There was no evidence of any interactions on toxicokinetic parameters in rats or dogs. For rats, it was noted that exposures to mometasone were greater for the high dose 50 to 5 ratio group as compared to the 200 to 5 ratio group and exposures to formoterol were greater for the high dose 50 to 5 ratio group as compared to the formoterol only group; however, there differences were primarily attributed to variations in the delivered dose. These studies are still considered valid to assess any interactions between mometasone and formoterol.

With regard to systemic toxicity, exposure (i.e., AUC) values for mometasone and formoterol achieved in inhalation toxicology studies with rats and dogs were comparable to or greater than exposures obtained with the highest clinical dose of 400/10 µg BID.

Exposure margins for clinical doses based upon systemic exposures from the 13-week inhalation toxicology study with rats

MF/F µg/kg/day	MF AUC pg·hr/mL	F AUC pg·hr/mL	Clinical dose of 800 µg MF + 20 µg F	
			MF 16 µg/kg 1150 pg·hr/mL	F 0.4 µg/kg 156 pg·hr/mL
3.3/0.3	11550	490.5	10.0	3.1
6.6/0.6	26800	1345	23.3	8.6
13.2/1.2	54300	2320	47.2	14.9
13.2/0.3	38550	469	33.5	3.0
13.2 MF only	34850	-	30.3	-
1.2 F only	-	1185	-	7.6

Dose in µg achieved by 2 puffs of 200 µg/5 µg MF/F-MDI by oral inhalation BID for 42 days; steady-state AUC(0-24 hr) = AUC(0-12 hr) x 2 from P03705.

Exposure margins for clinical doses based upon systemic exposures from the 13-week inhalation toxicology study with dogs

MF/F µg/kg/day	MF AUC pg·hr/mL	F AUC pg·hr/mL	Clinical dose of 800 µg MF + 20 µg F	
			MF 16 µg/kg 1150 pg·hr/mL	F 0.4 µg/kg 156 pg·hr/mL
28/2.8	1015	674.5	0.9	4.3
56/5.6	2240	1415	1.9	9.1
111/11	4305	2610	3.7	16.7
111/2.8	1795	ND	1.6	-
111 MF only	2545	-	2.2	-
11 F only	-	2005	-	12.9

Dose in µg achieved by 2 puffs of 200 µg/5 µg MF/F-MDI by oral inhalation BID for 42 days; steady-state AUC(0-24 hr) = AUC(0-12 hr) x 2 from P03705.
With regard to local toxicity in the lung, pulmonary deposited doses of mometasone and formoterol achieved in rats and dogs do not provide exposure margins of at least 10 or 6 for the highest clinical dose of 400/10 µg BID, respectively.

Exposure margins for clinical doses based upon pulmonary deposited doses from the 13-week inhalation toxicology study with rats

MF/F µg/kg/day	Clinical dose of 400 µg MF + 20 µg F		Clinical dose of 800 µg MF + 20 µg F	
	MF 8 µg/kg/day	F 0.4 µg/kg	MF 16 µg/kg	F 0.4 µg/kg
3.3/0.3	0.41	0.75	0.21	0.75
6.6/0.6	0.83	1.5	0.41	1.5
13.2/1.2	1.65	3	0.825	3
13.2/0.3	1.65	0.75	0.825	0.75
13.2 MF only	1.65	-	0.825	-
1.2 F only	-	3	-	3

Exposure margins for clinical doses based upon pulmonary deposited doses from the 13-week inhalation toxicology study with dogs

MF/F µg/kg/day	Clinical dose of 400 µg MF + 20 µg F		Clinical dose of 800 µg MF + 20 µg F	
	MF 8 µg/kg/day	F 0.4 µg/kg	MF 16 µg/kg	F 0.4 µg/kg
28/2.8	3.5	0.75	1.75	0.75
56/5.6	7	1.5	3.5	1.5
111/11	13.9	3	7	3
111/2.8	13.9	0.75	7	0.75
111 MF only	13.9	-	7	-
11 F only	-	3	-	3

NOAELs were not identified in nonclinical studies with SCH418131 given that rats and dogs are known to be significantly more sensitive to the toxic effects of glucocorticoids as compared to humans. These findings are in concordance with previous inhalation toxicology studies conducted with mometasone in rats and dogs. Previous clinical experience with the mometasone supports clinical doses of mometasone in the combination (i.e., SCH418131).

The DULERA drug product contains the propellant, HFA-227, and two excipients, dehydrated alcohol and oleic acid. HFA-227, dehydrated alcohol, and oleic acid are all found in approved inhalation drug products. In 13-week inhalation bridging toxicology studies with rats and dogs, there was no evidence of toxicity in vehicle-control groups that were exposed to HFA-227, dehydrated alcohol, and oleic acid.

The daily dose of HFA-227 in the DULERA drug product is [redacted] (b) (4). For Symbicort HFA pMDI (NDA 21-929; AstraZeneca), the daily dose of HFA-227 is [redacted] (b) (4) which is slightly [redacted] (b) (4) than the proposed dose in the present IND. Extensive nonclinical toxicology studies have been conducted with HFA-227 by [redacted] (b) (4) for which the sponsor has rights of reference. These studies were reviewed under DMF [redacted] (b) (4) (See reviews dated October 2, 1996 and January 28, 1997). HFA-227 is considered reasonably safe for inhalation use in the DULERA drug product.

The daily doses of ethanol/dehydrated alcohol and oleic acid in the DULERA drug product are [redacted] (b) (4) respectively. For the approved drug product, Proventil-HFA, daily doses of ethanol/dehydrated alcohol and oleic acid ranged from [redacted] (b) (4), respectively. These doses are [redacted] (b) (4) than those found in the DULERA drug product.

From the vehicle-control groups in 13-week inhalation bridging toxicology studies with rats and dogs, pulmonary deposited doses of oleic acid were 0.63 and 5.05 µg/kg/day, respectively. Safety margins for the clinical dose of oleic acid (0.28 µg/kg/day) are 2.25- and 18-fold, respectively.

Unresolved toxicology issues (if any): None.

Recommendations: From a nonclinical perspective, the application is recommended for approval.

Suggested labeling: Recommendations for nonclinical sections of the labeling will follow in a separate labeling review.

Signatures (optional):

Reviewer signature: _____
Timothy W. Robison, Ph.D.

Supervisor signature: Concurrence - _____
Jean Wu, M.D., Ph.D.

cc: list:
NDA 22-518, HFD-570
ChungE, HFD-570
SeymourS, HFD-570
WuJ, HFD-570
RobisonT, HFD-570

APPENDIX/ATTACHMENTS

Appendix 1: Pharmacology/Toxicology Review of IND 70,283 Review #01 dated January 9, 2007

Appendix 1: Pharmacology/Toxicology Review of IND 70,283 Review #01 dated January 9, 2007

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

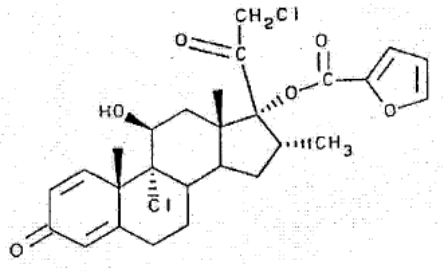
2.6.1 INTRODUCTION AND DRUG HISTORY

IND number: 70,283
Review number: #01
Sequence number/date/type of submission: #000/May 26, 2006/Initial Submission
#009/October 12, 2006/Amendment
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Shering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033
Manufacturer for drug substance: Schering Corporation and Novartis

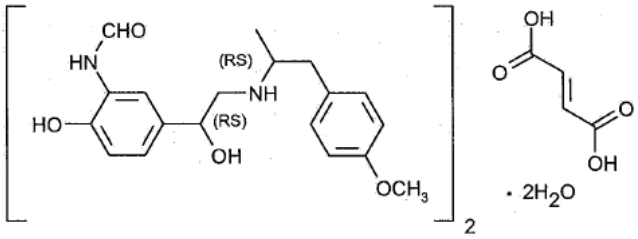
Reviewer name: Timothy W. Robison, Ph.D., D.A.B.T.
Division name: Pulmonary and Allergy Products
HFD #: 570
Review completion date: January 9, 2007

Drug:

Generic name: Mometasone Furoate + Formoterol Fumarate
Code name: SCH418131 (Mometasone Furoate + Formoterol Fumarate)
Chemical name:
Mometasone furoate: 9α,21-dichloro-11β,17α-dihydroxy-16α-methyl-pregna-1,4-diene-3,20-dione17-(2')-furoate.
Formoterol fumarate dihydrate: (±)-2-hydroxy-5-[(1RS)-1-hydroxy-2-((1RS)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]formanilide fumarate dihydrate
Molecular formula/molecular weight:
Mometasone furoate, $C_{27}H_{30}O_6Cl_2$ / 521.4 g/mole
Formoterol fumarate dihydrate, $C_{42}H_{52}N_4O_{12} \cdot 2\ H_2O$ / 840.9 g/mole
Structure:
Mometasone furoate:



Formoterol fumarate:



Relevant INDs/NDAs/DMFs:
Mometasone from Schering: IND 24,088, (b) (4), (b) (4), IND 46,216, IND 52,214, IND 55,108, NDA 19-543, NDA 19-625, NDA 19-796, NDA 20-762, (b) (4) NDA 21-067, (b) (4)

Formoterol from Novartis: NDA 20-831

Drug class:
Mometasone furoate: glucocorticoid
Formoterol: β_2-adrenergic agonist

Intended clinical population: Treatment of patients with asthma (b) (4)

Clinical formulation: Micronized mometasone and formoterol are being combined in an oral inhalation pressurized metered dose inhaler (MDI). The MDI device contains 120 actuations for inhalation. (b) (4) dosage strengths are being developed. Targeted delivery per actuation (ex-actuator) is nominally (b) (4) 100, or 200 µg/actuation of mometasone furoate, combined in each case with 5 µg/actuation of formoterol fumarate dihydrate. One complete dose is composed of two actuations from the combination inhaler. The (b) (4) drug product combinations of mometasone and formoterol contain the propellant, HFA-227, and two excipients, dehydrated alcohol and oleic acid. The container closure system is comprised of a 16 mL (b) (4) aluminum canister with a (b) (4) metering valve. A (b) (4) actuator is provided with the pressurized canister.

(b) (4)

Table 3.2-2 Composition of Mometasone Furoate 100 mcg, Formoterol Fumarate 5 mcg (Delivered Dose) Pressurized Metered Dose Inhaler

Ingredient	Theoretical amount [mg/metered dose]	[mg/mL]	[% w/w]	Function
Mometasone furoate anhydrous			(b) (4)	Drug substance
Formoterol fumarate dihydrate				Drug substance
(b) (4) (HFA 227)				Propellant
Ethanol / Dehydrated alcohol				Co-solvent
Oleic acid				Surfactant
Total				

* Corresponding to a delivered dose of 0.100 mg/actuation mometasone furoate anhydrous

** Corresponding to a delivered dose of 0.005 mg/actuation formoterol fumarate dihydrate.

Table 3.2-3 Composition of Mometasone Furoate 200 mcg, Formoterol Fumarate 5 mcg (Delivered Dose) Pressurized Metered Dose Inhaler

Ingredient	Theoretical amount [mg/metered dose]	[mg/mL]	[% w/w]	Function
Mometasone furoate anhydrous			(b) (4)	Drug substance
Formoterol fumarate dihydrate				Drug substance
(b) (4) (HFA 227)				Propellant
Ethanol / Dehydrated alcohol				Co-solvent
Oleic acid				Surfactant
Total				

* Corresponding to a delivered dose of 0.200 mg/actuation mometasone furoate anhydrous

** Corresponding to a delivered dose of 0.005 mg/actuation formoterol fumarate dihydrate.

(b) (4)

Table 3.3-2 Composition of Mometasone Furoate 100 mcg (Delivered Dose) Comparator Pressurized Metered Dose Inhaler

Ingredient	Theoretical amount [mg/metered dose]	[mg/mL]	[% w/w]	Function
Mometasone furoate anhydrous			(b) (4)	Drug substance
(b) (4)(HFA 227)				Propellant
Ethanol/Dehydrated alcohol				Co-solvent
Oleic acid				Surfactant
Total				

* Corresponding to a delivered dose of 0.100 mg/actuation mometasone furoate anhydrous.

Table 3.3-3 Composition of Mometasone Furoate 200 mcg (Delivered Dose) Comparator Pressurized Metered Dose Inhaler

Ingredient	Theoretical amount [mg/metered dose]	[mg/mL]	[% w/w]	Function
Mometasone furoate anhydrous			(b) (4)	Drug substance
(b) (4)(HFA 227)				Propellant
Ethanol/Dehydrated alcohol				Co-solvent
Oleic acid				Surfactant
Total				

* Corresponding to a delivered dose of 0.200 mg/actuation mometasone furoate anhydrous.

Route of administration: Oral inhalation

Proposed clinical protocol:

Protocol provided in the initial submission dated May 26, 2006

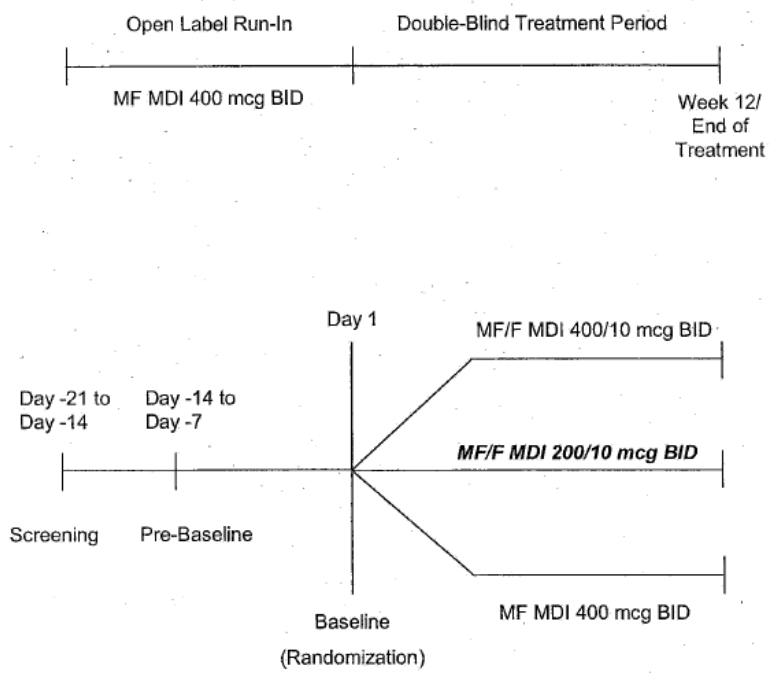
Protocol No. P04431: A 12-Week Efficacy and Safety Study of Two Doses of Mometasone Furoate/Formoterol Combination Formulation Compared with Mometasone Furoate Monotherapy, in Persistent Asthmatics Previously Treated with High-Dose Inhaled Glucocorticosteroids.

The sponsor has proposed a randomized, multicenter, double-blind, parallel-group, 12-week study with a preceding 2 to 3 week open-label run-in period with mometasone furoate (MF) MDI 400 µg BID in adult and adolescent subjects (male or female ≥12

years of age) with asthma previously treated with high doses of inhaled corticosteroids. A total of approximately 621 subjects are expected to be randomized to double-blind treatment. Subjects will be randomized to one of three treatment groups as shown in the table below. There will be 207 subjects per treatment group. Female subjects of childbearing potential must be using a medically acceptable, adequate form of birth control. The primary efficacy variable is the AUC(0-12hr) of the change from baseline to week 12 FEV_1.

Treatment Group	Description	Total daily dose
1	MF/F MDI 400/10 µg BID (two inhalations of a 200/5 µg inhaler twice daily)	800 µg MF 20 µg F
2	MF/F MDI 200/10 µg BID (two inhalations of a 100/5 µg inhaler twice daily)	400 µg MF 20 µg F
3	MF MDI 400 µg BID (two inhalations of a 200 µg inhaler twice daily)	800 µg MF

MF = mometasone furoate and F = formoterol



Protocols submitted in Amendment #009 dated October 12, 2006:

Protocol No. P04073: A 26-Week Placebo-Controlled Efficacy and Safety Study of Mometasone Furoate/Formoterol Fumarate Combination Formulation Compared with Mometasone Furoate and Formoterol Monotherapy in Subjects with Persistent Asthma Previously Treated with Low-Dose Inhaled Glucocorticosteroids.

The sponsor has proposed a randomized, multi-center, double-blind, double-dummy, placebo-controlled, parallel group study to determine the efficacy of MF/F MDI 100/10

µg BID as compared with MF MDI 100 µg BID alone or F MDI 10 µg BID alone, in order to assess the added benefit of F MDI 10 µg BID or MF MDI 100 µg BID, respectively, to the combination. Male and female adolescent and adult subjects >12 years of age with a diagnosis of asthma and using a low daily dose of ICS (either alone or in combination with a LABA) will be eligible for enrollment in the study. Subjects will randomized to 26 weeks of double-blind treatment in one of the four treatment groups as shown in the table below. Approximately 676 subjects or 169 subjects per group will be randomized into the study to ensure that at least 135 subjects per group complete the 26-week treatment period.

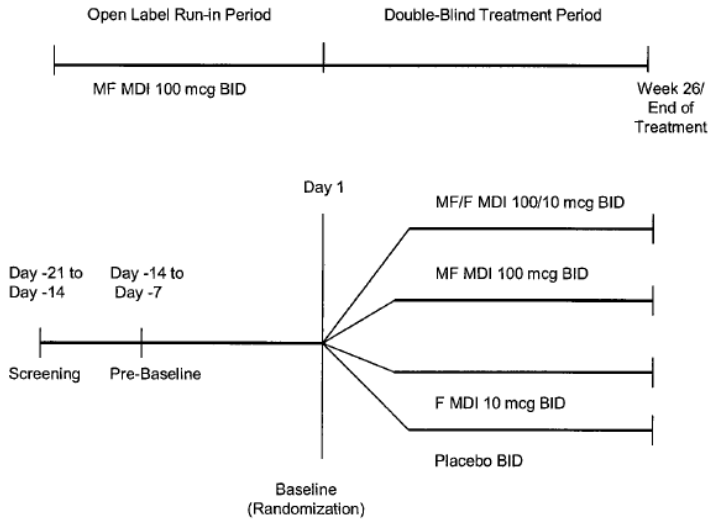


Table 2 Double-Blind Treatment Arms

Protocol No. P04073

Treatment Group	Inhaler	AM	PM	Treatment Regimen
1	A	MF/F MDI 50/5 mcg x 2 inhalations	MF/F MDI 50/5 mcg x 2 inhalations	MF/F MDI 100/10 mcg BID
	B	Placebo F MDI x 2 inhalations	Placebo F MDI x 2 inhalations	
2	A	MF MDI 50 mcg x 2 inhalations	MF MDI 50 mcg x 2 inhalations	MF MDI 100 mcg BID
	B	Placebo F MDI x 2 inhalations	Placebo F MDI x 2 inhalations	
3	A	Placebo MF/F MDI x 2 inhalations	Placebo MF/F MDI x 2 inhalations	F MDI 10 mcg BID
	B	F MDI 5 mcg x 2 inhalations	F MDI 5 mcg x 2 inhalations	
4	A	Placebo MF/F MDI x 2 inhalations	Placebo MF/F MDI x 2 inhalations	Placebo BID
	B	Placebo F MDI x 2 inhalations	Placebo F MDI x 2 inhalations	

Protocol No. P04334: A 26-Week Placebo-Controlled Efficacy and Safety Study of Mometasone Furoate/Formoterol Fumarate Combination Formulation Compared with Mometasone Furoate and Formoterol Monotherapy in Subjects with Persistent Asthma Previously Treated with Medium-Dose Inhaled Glucocorticosteroids.

The sponsor has proposed a randomized, multi-center, double-blind, double-dummy, placebo-controlled, parallel group study to determine the efficacy of MF/F MDI 200/10 µg BID as compared with MF MDI 200 µg BID alone or F MDI 10 µg BID alone, in order

to assess the added benefit of F MDI 10 µg BID or MF MDI 200 µg BID, respectively, to the combination. Male and female adolescent and adult subjects >12 years of age with a diagnosis of asthma and using a medium daily dose of ICS (either alone or in combination with a LABA) will be eligible for enrollment in the study. Subjects will randomized to 26 weeks of double-blind treatment in one of the four treatment groups as shown in the table below. Approximately 676 subjects or 169 subjects per group will be randomized into the study to ensure that at least 135 subjects per group complete the 26-week treatment period.

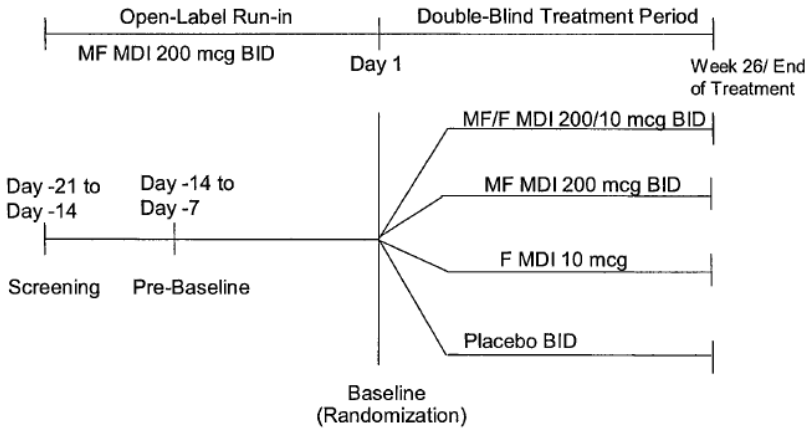


Table 2 Double-Blind Treatment Arms

Protocol No. P04334

Treatment Group	Inhaler	AM	PM	Treatment Regimen
1	A	MF/F MDI 100/5 mcg x 2 inhalations	MF/F MDI 100/5 mcg x 2 inhalations	MF/F MDI 200/10 mcg BID
	B	Placebo F MDI x 2 inhalations	Placebo F MDI x 2 inhalations	
2	A	MF MDI 100 mcg x 2 inhalations	MF MDI 100 mcg x 2 inhalations	MF MDI 200 mcg BID
	B	Placebo F MDI x 2 inhalations	Placebo F MDI x 2 inhalations	
3	A	Placebo MF/F MDI x 2 inhalations	Placebo MF/F MDI x 2 inhalations	F MDI 10 mcg BID
	B	F MDI 5 mcg x 2 inhalations	F MDI 5 mcg x 2 inhalations	
4	A	Placebo MF/F MDI x 2 inhalations	Placebo MF/F MDI x 2 inhalations	Placebo BID
	B	Placebo F MDI x 2 inhalations	Placebo F MDI x 2 inhalations	

Protocol No. P04229: A Randomized Placebo-Controlled Efficacy and Safety Study of 1-Year Treatment Duration with High- and Medium-Dose Inhaled Mometasone Furoate/Formoterol Combination Formulation Compared with Formoterol and High-Dose Inhaled Mometasone Furoate Monotherapy in Subjects with Moderate to Severe COPD.

The sponsor has proposed a randomized, multi-center, double-blind, placebo-controlled, parallel group study to determine the efficacy of MF/F MDI 400/10 µg BID as compared with MF MDI 400 µg BID alone in order to assess the added benefit of F MDI 10 µg BID to the combination. Further, the sponsor plans to determine the efficacy of MF/F MDI 400/10 µg BID and MF/F MDI 200/10 µg BID compared to F MDI 10 µg BID

in order to assess the benefit of the steroid component to the combination. Male and female adult subjects ≥40 years of age with a diagnosis of moderate to severe COPD will be eligible for enrollment in the study. Subjects will randomized to 1 year of double-blind treatment in one of the five treatment groups as shown in the table below. Approximately 1500 subjects or 300 subjects per group will be randomized into the study.

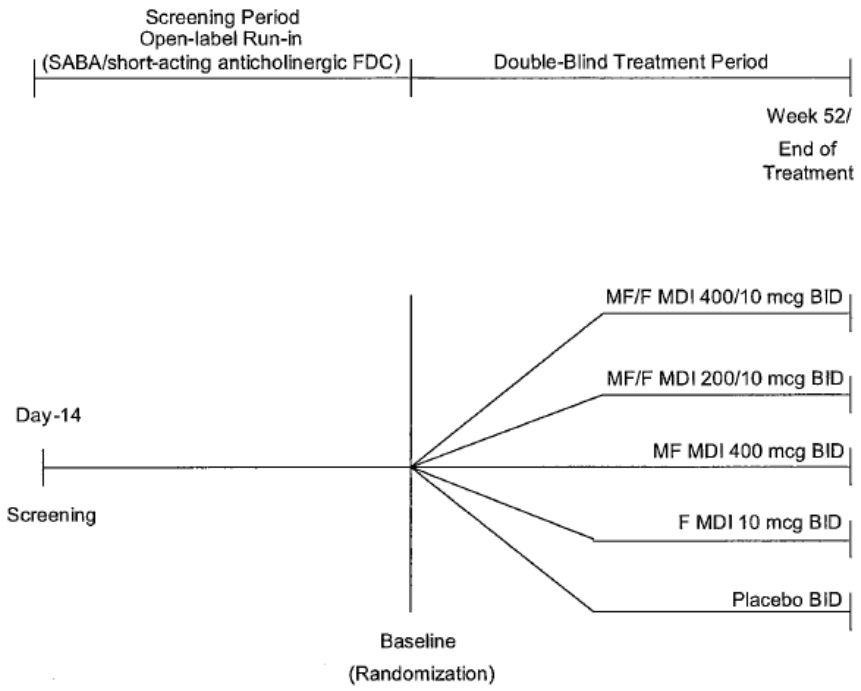


Table 2 Double-Blind Treatment Arms

Protocol No. P04229

Treatment Group	Inhaler	AM	PM	Treatment Regimen
1	A	MF/F MDI 200/5 mcg x 2 inhalations	MF/F MDI 200/5 mcg x 2 inhalations	MF/F 400/10 mcg BID
	B	Placebo F MDI x 2 inhalations	Placebo F MDI x 2 inhalations	
2	A	MF/F MDI 100/5 mcg x 2 inhalations	MF/F MDI 100/5 mcg x 2 inhalations	MF/F 200/10 mcg BID
	B	Placebo F MDI x 2 inhalations	Placebo F MDI x 2 inhalations	
3	A	MF MDI 200 mcg x 2 inhalations	MF MDI 200 mcg x 2 inhalations	MF 400 mcg BID
	B	Placebo F MDI x 2 inhalations	Placebo F MDI x 2 inhalations	
4	A	Placebo MF/F MDI x 2 inhalations	Placebo MF/F MDI x 2 inhalations	F 10 mcg BID
	B	F MDI 5 mcg x 2 inhalations	F MDI 5 mcg x 2 inhalations	
5	A	Placebo MF/F MDI x 2 inhalations	Placebo MF/F MDI x 2 inhalations	Placebo BID
	B	Placebo F MDI x 2 inhalations	Placebo F MDI x 2 inhalations	

Protocol No. 04230: A Randomized Placebo-Controlled Efficacy and Safety Study of 1-Year Treatment Duration with High- and Medium-Dose Inhaled Mometasone Furoate/Formoterol Combination Formulation Compared with Formoterol and High-

Dose Inhaled Mometasone Furoate Monotherapy in Subjects with Moderate to Severe COPD.

Protocol No. 04230 is essentially identical to Protocol No. P04229. The sponsor has proposed a randomized, placebo-controlled, parallel group, multi-site, double-blind study to determine the efficacy of MF/F MDI 400/10 µg BID compared with MF MDI 400 µg BID in order to assess the added benefit of F MDI 10 µg BID to the combination. Further, the sponsor plans to determine the efficacy of MF/F MDI 400/10 µg BID and MF/F MDI 200/10 µg BID compared to F MDI 10 µg BID in order to assess the benefit of the steroid component to the combination. Male and female adult subjects ≥40 years of age with a diagnosis of moderate to severe COPD will be eligible for enrollment in the study. Subjects will randomized to 1 year of double-blind treatment in one of the five treatment groups as shown in the table below. Approximately 1500 subjects or 300 subjects per group will be randomized into the study.

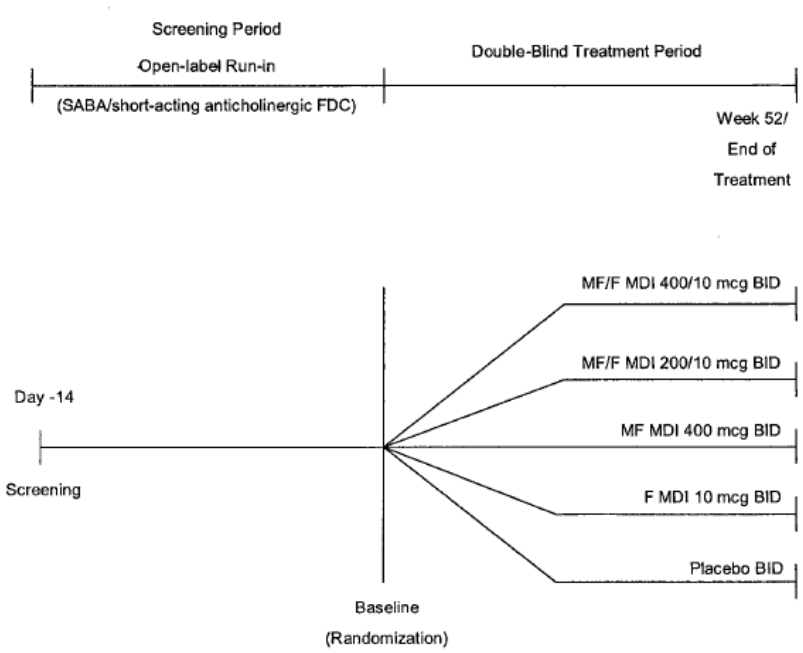


Table 2 Double-Blind Treatment Arms

Protocol No. P04230

Treatment Group	Inhaler	AM	PM	Treatment Regimen
1	A	MF/F MDI 200/5 mcg x 2 inhalations	MF/F MDI 200/5 mcg x 2 inhalations	MF/F 400/10 mcg BID
	B	Placebo F MDI x 2 inhalations	Placebo F MDI x 2 inhalations	
2	A	MF/F MDI 100/5 mcg x 2 inhalations	MF/F MDI 100/5 mcg x 2 inhalations	MF/F 200/10 mcg BID
	B	Placebo F MDI x 2 inhalations	Placebo F MDI x 2 inhalations	
3	A	MF MDI 200 mcg x 2 inhalations	MF MDI 200 mcg x 2 inhalations	MF 400 mcg BID
	B	Placebo F MDI x 2 inhalations	Placebo F MDI x 2 inhalations	
4	A	Placebo MF/F MDI x 2 inhalations	Placebo MF/F MDI x 2 inhalations	F 10 mcg BID
	B	F MDI 5 mcg x 2 inhalations	F MDI 5 mcg x 2 inhalations	
5	A	Placebo MF/F MDI x 2 inhalations	Placebo MF/F MDI x 2 inhalations	Placebo BID
	B	Placebo F MDI x 2 inhalations	Placebo F MDI x 2 inhalations	

Previous clinical experience: Monoproducts, mometasone and formoterol, are approved drug products.

ASMANEX TWISTHALER inhaler is indicated for the maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older. The ASMANEX TWISTHALER inhaler is also indicated for asthma patients who require oral corticosteroid therapy, where adding ASMANEX TWISTHALER therapy may reduce or eliminate the need for oral corticosteroids. ASMANEX TWISTHALER is NOT indicated for the relief of acute bronchospasm.

RECOMMENDED DOSAGES FOR ASMANEX TWISTHALER TREATMENT

Previous Therapy	Recommended Starting Dose	Highest Recommended Daily Dose
Bronchodilators alone	220 mcg QD PM *	440 mcg **
Inhaled corticosteroids	220 mcg QD PM *	440 mcg **
Oral corticosteroids **/*	440 mcg BID	880 mcg

* When administered once daily ASMANEX TWISTHALER should only be taken in the PM.

** The 440 mcg daily dose may be administered in divided doses of 220 mcg twice daily or as 440 mcg once daily.
NOTE: In all patients, it is desirable to titrate to the lowest effective dose once asthma stability is achieved.

/* **For Patients Currently Receiving Chronic Oral Corticosteroid Therapy: Prednisone should be reduced no faster than 2.5 mg/day on a weekly basis, beginning after at least 1 week of ASMANEX TWISTHALER therapy. Patients should be carefully monitored for signs of asthma instability, including serial objective measures of airflow, and for signs of adrenal insufficiency (see **WARNINGS**). Once prednisone reduction is complete, the dosage of mometasone furoate should be reduced to the lowest effective dosage.

FORADIL AEROLIZER is indicated for long-term, 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, who require regular treatment with inhaled, short-acting, beta$_2$-agonists. It is not indicated for patients whose asthma can be managed by occasional use of inhaled, short-acting,

beta$_2$-agonists. FORADIL AEROLIZER is also indicated for the acute prevention of exercise-induced bronchospasm (EIB) in adults and children 5 years of age and older, when administered on an occasional, as-needed basis. FORADIL AEROLIZER can be used to treat asthma concomitantly with short-acting beta$_2$-agonists, inhaled or systemic corticosteroids, and theophylline therapy (see PRECAUTIONS , Drug Interactions). A satisfactory clinical response to FORADIL AEROLIZER does not eliminate the need for continued treatment with an anti-inflammatory agent. FORADIL AEROLIZER is indicated for the long-term, twice daily (morning and evening) administration in the maintenance treatment of bronchoconstriction in patients with Chronic Obstructive Pulmonary Disease including chronic bronchitis and emphysema.

For Maintenance Treatment of Asthma in adults and children 5 years of age and older, the usual dosage is the inhalation of the contents of one 12-µg FORADIL capsule every 12 hours using the AEROLIZER® Inhaler. For Prevention of Exercise-Induced Bronchospasm (EIB) in adults and children 5 years of age or older, the usual dosage is the inhalation of the contents of one 12-µg FORADIL capsule at least 15 minutes before exercise administered on an occasional as-needed basis. For Maintenance Treatment of Chronic Obstructive Pulmonary Disease (COPD), the usual dosage is the inhalation of the contents of one 12 µg FORADIL capsule every 12 hours using the AEROLIZER® inhaler. A total daily dose of greater than 24 mcg is not recommended.

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission:

1. Thirteen-Week Nose-Only Inhalation Toxicity Study of SCH 418131 (SCH 32088 with Formoterol) Aerosol in the Rat (Schering-Plough Study No.: 99457).
2. Thirteen-Week Oral Inhalation Toxicity Study of SCH418131 (SCH32088 with Formoterol) Aerosols in the Dog (Schering-Plough Study No.: 99458).

(b) (4)

TABLE OF CONTENTS

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW 1

2.6.1 INTRODUCTION AND DRUG HISTORY 1

2.6.6 TOXICOLOGY 13

2.6.6.1 Overall toxicology summary 13
2.6.6.3 Repeat-dose toxicity 15
2.6.6.9 Discussion and Conclusions 60
2.6.6.10 Tables and Figures 60

OVERALL CONCLUSIONS AND RECOMMENDATIONS 61

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology:

Rats were exposed by nose-only inhalation to aerosols of MDI formulation of three dose levels of SCH418131 (mometasone furoate [SCH32088 or MF] in combination with formoterol [F]) at a 50:5 ratio, one level of SCH418131 (MF/F) at a 200:5 ratio, SCH32088 (MF) alone, or formoterol (F) alone. A vehicle-control group was exposed by nose-only inhalation to aerosols of a MDI formulation comprised of oleic acid, ethanol, and HFA-227 propellant. An air-control group was exposed to by nose-only inhalation to HEPA-filtered and charcoal-filtered room air. Body weight gains were significantly decreased in all treatment groups receiving mometasone furoate. Target organs of toxicity were the lung, trachea, nose/turbinates, thymus, spleen, lymph nodes (mesenteric, bronchial, mandibular, and mediastinal), mammary gland, bone marrow, ovary, and vagina. Histopathological changes were generally observed in all treatment groups that received mometasone furoate (MF). Findings in the lungs consisted of BALT (bronchial-associated lymphoid tissue) depletion, accumulation of alveolar macrophages, and pigmented macrophages. BALT depletion was observed in all treatment groups that received mometasone. Accumulation of alveolar macrophages was observed in mid and high dose MF/F, the 200:5 MF/F group, and the MF only group. Findings in the trachea consisted of decreased globule leukocytes in all treatment groups that received MF. Thymus involution/atrophy was observed in all treatment groups that received MF. Lymphoid depletion was observed in the nose/turbinates, spleen, lymph nodes (mesenteric, bronchial, mandibular, and mediastinal). Increased incidences of lymphoid depletion in the nose/turbinates, mesenteric lymph nodes, bronchial lymph nodes, mandibular lymph nodes, and mediastinal lymph nodes occurred in all treatment groups that received mometasone. Lymphoid depletion in the spleen occurred in the mid and high dose MF/F groups, the 200:5 MF/F group, and the MF only group. Infiltration of mast cells was observed in the mesenteric lymph nodes for all treatment groups that received MF. Abnormal lobuloalveolar development of the mammary gland occurred for females all treatment groups that received MF as well as the F only group. Elevated incidences of increased marrow fat in the bone marrow were observed for all treatment groups that received MF. Increased incidences of decreased corpora lutea in the ovaries occurred in all female treatment groups that received MF as well as the F only group. Abnormal mucification of the vagina was observed in all treatment groups that received MF. A NOAEL was not established based upon histopathological findings in all treatment groups with the exception of the formoterol only group. Histopathological findings were attributable to the action of MF. There was no evidence of additive or synergistic toxic effects with the combination of mometasone and formoterol.

Dogs (4/sex/group) were exposed by mouth-only inhalation to aerosols of MDI formulations of 3 dose levels of SCH418131 (MF/F) at a 50:5 ratio, one dose level of

SCH418131 at a 200:5 ratio, SCH32088 alone, or formoterol fumarate alone. Decreased lymphocyte and eosinophil counts were observed in treatment groups that received mometasone. Cortisol levels in response to challenge with exogenous ACTH were decreased for all male and female treatment groups that received mometasone. Increases of alkaline phosphate activities and levels of cholesterol and triglyceride in treatment groups that received mometasone may have correlated to histopathological findings of cytoplasmic vacuolation in the liver. Decreased duration of RR intervals (i.e., increased heart rate) was observed for treatment groups that received formoterol. This effect was attributed to formoterol. There was no evidence of additive or synergistic effects between mometasone and formoterol on the duration of the RR interval (i.e., heart rate). Histopathological changes were observed in the lung, thymus, adrenal gland, cecum, colon, duodenum, ileum, jejunum, larynx, axillary LN, bronchi LN, mandibular LN, mediastinal LN, mesenteric LN, nose/turbinates, pharynx, rectum, spleen, stomach, salivary gland, ovary, uterus, mammary gland, liver, femur, rib, and sternum. In general, these histopathological changes were attributable to the actions of mometasone. In the lungs, increased incidences of hyperplasia of bronchioloalveolar cells and bronchial inflammation were observed for male and female treatment groups, although dose-response relationships were not generally evident. Vacuolization and/or atrophy of the adrenal cortex were observed for all male and female treatment groups that received mometasone furoate. Lymph depletion was observed in the thymus, cecum, colon, duodenum, ileum, jejunum, larynx, axillary LN, bronchi LN, mandibular LN, mediastinal LN, mesenteric LN, nose/turbinates, pharynx, rectum, spleen, and stomach. Incidences of lymphoid depletion in these tissues and organs were generally increased for all male and female treatment groups that received mometasone furoate. Incidences of sinus erythrophagocytosis in the mesenteric lymph nodes were increased for male and female treatment groups that received mometasone furoate. Hypoplasia of the ovaries and uterus was observed for females in the low and mid dose MF/F groups and 200:5 ratio MF/F group. For the high dose MF/F group, only 1 of 4 females was observed with hypoplasia of the uterus and there were no findings in the ovaries. Cytoplasmic vacuolation in the liver was observed for males and females in the high dose MF/F, 200:5 ratio MF/F, and MF alone groups. Fibrosis of the liver was observed for 1 of 4 females in the 200:5 ratio MF/F group. Increased fat deposition was observed in femur, rib, and sternum. These findings were observed in all treatment groups that received mometasone furoate. Epithelial vacuolization of the mammary gland was observed for females in the 200:5 ratio MF/F, MF alone, and formoterol alone groups, although a clear relationship to mometasone or formoterol was not evident. Slightly increased incidences of infiltration of adipocytes were observed in the salivary glands for the mid dose MF/F, 200:5 ratio MF/F, MF alone, and formoterol alone groups, although a relationship to treatment was unclear. There was no evidence of additive or synergistic toxic effects with the combination of mometasone and formoterol.

2.6.6.3 Repeat-dose toxicity

Rats

Study title: **13-Week Nose-Only Inhalation Toxicity Study of SCH418131 (SCH32088 with Formoterol) Aerosols in the Rat.**

Key study findings:

● Rats were exposed by nose-only inhalation to aerosols of MDI formulation of three dose levels of SCH418131 (mometasone furoate [SCH32088 or MF] in combination with formoterol [F]) at a 50:5 ratio, one level of SCH418131 (MF/F) at a 200:5 ratio, SCH32088 (MF) alone, or formoterol (F) alone. A vehicle-control group was exposed by nose-only inhalation to aerosols of a MDI formulation comprised of oleic acid, ethanol, and HFA-227 propellant. An air-control group was exposed by nose-only inhalation to HEPA-filtered and charcoal-filtered room air.

● Body weight gains were significantly decreased in all treatment groups receiving mometasone furoate.

● Target organs of toxicity were the lung, trachea, nose/turbinates, thymus, spleen, lymph nodes (mesenteric, bronchial, mandibular, and mediastinal), mammary gland, bone marrow, ovary, and vagina. Histopathological changes were generally observed in all treatment groups that received mometasone furoate (MF).

● Findings in the lungs consisted of BALT (bronchial-associated lymphoid tissue) depletion, accumulation of alveolar macrophages, and pigmented macrophages. BALT depletion was observed in all treatment groups that received mometasone. Accumulation of alveolar macrophages was observed in mid and high dose MF/F, the 200:5 MF/F group, and the MF only groups.

● Findings in the trachea consisted of decreased globule leukocytes in all treatment groups that received MF.

● Thymus involution/atrophy was observed in all treatment groups that received MF.

● Lymphoid depletion was observed in the nose/turbinates, spleen, lymph nodes (mesenteric, bronchial, mandibular, and mediastinal). Increased incidences of lymphoid depletion in the nose/turbinates, mesenteric lymph nodes, bronchial lymph nodes, mandibular lymph nodes, and mediastinal lymph nodes occurred in all treatment groups that received mometasone. Lymphoid depletion in the spleen occurred in the mid and high dose MF/F groups, the 200:5 MF/F group, and the MF only group.

● Infiltration of mast cells was observed in the mesenteric lymph nodes for all treatment groups that received MF.

● Abnormal lobuloalveolar development of the mammary gland occurred for all female treatment groups that received MF as well as the F only group.

● Elevated incidences of increased marrow fat in the bone marrow were observed for all treatment groups that received MF.

● Increased incidences of decreased corpora lutea in the ovaries occurred in all female treatment groups that received MF as well as the F only group.

● Abnormal mucification of the vagina was observed in all treatment groups that received MF.

● A NOAEL was not established based upon histopathological findings in all treatment groups with the exception of the formoterol only group. Histopathological findings were attributable to the action of MF.

● There was no evidence of additive or synergistic toxic effects with the combination of mometasone and formoterol.

Study no.: Schering-Plough Study No. 99457 / (b) (6) Study No. N104545
Volume #, and page #: Volumes 17-20, Pages 1-1275
Conducting laboratory and location: (b) (6)

Date of study initiation: June 15, 2004 (Dosing initiated on July 27, 2004)
GLP compliance: Yes
QA report: yes (X) no ( )
Drug, lot #, and % purity:
SCH 418131 (SCH 32088 [mometasone furoate (MF)] and formoterol fumarate [F]) at a 50:5 or 200:5 ratio in a metered dose inhaler (MDI) formulation. Other components in the MDI were oleic acid, ethanol, and HFA-227. Batch numbers PB171103 (50:5 ratio) and PB041203 (200:5 ratio).

Formoterol fumarate in a MDI formulation. Other components in the MDI were oleic acid, ethanol, HFA-134a, and lactose. Batch number Y1670903

SCH32088 [Mometasone Furoate (MF)] in a MDI Formulation. Other components in the MDI were oleic acid, ethanol, and HFA-227. Batch number 58364-026

The vehicle consisted of oleic acid, ethanol, and HFA-227. Batch number GH061103

Methods
Doses: Rats were exposed by nose-only inhalation to aerosols of metered dose inhaler (MDI) formulations of three dose levels of SCH 418131 (SCH 32088 in combination with formoterol fumarate, MF/F) at a 50:5 ratio, one dose level of SCH 418131 at a 200:5 ratio, SCH 32088 alone, or formoterol fumarate alone. A vehicle group was exposed by

nose-only inhalation to aerosols of a metered dose inhaler formulation comprised of oleic acid, ethanol, and HFA-227 propellant. The aerosol of the vehicle-control group was generated to match the concentration of oleic acid in the high dose SCH 418131 group at a 50:5 ratio. An air control group (10/sex) was exposed by nose-only inhalation to HEPA-filtered and charcoal-filtered room air.

Overall Group Mean Estimated Doses of SCH 32088/Formoterol

Group	Mean Aerosol Concentration µg/L	Mean BW g	Minute Volume mL/min	Duration min	Dose µg/kg/day	Deposited Dose µg/kg/day
Males						
Air Control	0.00/0.00	419.70	224.4	64	NC/NC	NC/NC
Vehicle	0.00/0.00	425.86	183.9	64	NC/NC	NC/NC
Low Dose MF/F	1.09/0.12	377.09	161.8	64	29.93/3.30	3.0/0.3
Mid Dose MF/F	2.22/0.24	343.08	156.4	64	64.77/7.00	6.5/0.7
High Dose MF/F	4.68/0.50	305.53	158.0	64	154.89/16.55	15.5/1.6
200:5 Ratio MF/F	4.12/0.11	326.65	167.0	64	135.21/3.61	13.5/0.36
SCH 32088	4.15/0.00	340.10	140.1	64	109.41/NC	10.9/NC
Formoterol fumarate	0.00/0.40	418.46	229.8	64	NC/14.06	NC/1.4
Females						
Air Control	0.00/0.00	243.71	173.5	64	NC/NC	NC/NC
Vehicle	0.00/0.00	248.98	149.0	64	NC/NC	NC/NC
Low Dose MF/F	1.08/0.11	216.28	128.6	64	41.10/4.19	4.1/0.4
Mid Dose MF/F	2.20/0.23	197.31	122.0	64	87.06/9.10	8.7/9.1
High Dose MF/F	4.64/0.49	193.86	117.9	64	180.60/19.07	18.1/1.9
200:5 Ratio MF/F	4.11/0.11	196.51	125.1	64	167.45/4.48	16.7/0.45
SCH 32088	4.15/0.00	184.86	110.8	64	159.19/NC	15.9/NC
Formoterol fumarate	0.00/0.40	261.50	162.8	64	NC/15.94	NC/1.6

Six exposure system were used in the study: one for the low-, mid-, and high-dose SCH 418131 groups, one for the 200:5 ratio SCH 418131 group, one for the SCH 32088 alone group, one for the formoterol fumarate alone group, one for the vehicle-control group, and one for the air-control group. Daily exposure duration was held constant for all groups. Different aerosol concentration levels were achieved by adjusting the number of MDIs that were used in the generation system. The air-control, vehicle-control, SCH 32088, and formoterol systems were each designed to expose up to 48 animals (1 chamber with 6 levels and 8 ports/level). The low-, mid-, and high-dose SCH418131 system and the 200:5 ratio SCH 418131 system were dual chamber systems designed to expose up to 96 animals.

A single MDI generation module, capable of actuating a maximum of 15 MDI units, was placed on top of the aerosol plenum for each system (except for the air-control system).

Pneumatic cylinders were used to activate the MDIs at a rate of approximately 1.7 times per minute.

HEPA- and charcoal-filtered room air was added to the generation plenum to achieve an initial aerosol concentration. The initial aerosol concentration test atmosphere was directed into a delivery manifold where it was diluted with filtered room air again creating the target test atmosphere aerosol concentration. Each exposure port had a positive airflow of 0.5 L/min that placed the test atmosphere into the animal-breathing zone. Total airflow for the 48 port chamber was 24 L/min and for the 96 port chamber was 48 L/min. All exposure systems had at least one reference port for aerosol and/or particle size distribution sampling.

During exposures, animals were restrained in polycarbonate exposure tubes with one end tapered to fit the shape of the animal's head.

Aerosol concentrations within the exposure atmosphere were gravimetrically measured daily using glass fiber filters to collect samples of the test atmosphere from the breathing zone. Filters were chemically analyzed at a minimum of once per week for SCH 32088 and formoterol and subsets of the filters or other collected filters were analyzed for oleic acid and lactose (formoterol alone group).

Overall mean estimated oleic acid deposited doses

Group	Group Mean Aerosol Concentration µg/L	Oleic acid Inhaled Dose µg/kg/day	Oleic acid Deposited Dose µg/kg/day
Males			
Air Control	0.00	NC	NC
Vehicle	0.19	5.25	0.525
Low Dose MF/F	0.06	1.65	0.165
Mid Dose MF/F	0.13	3.79	0.379
High Dose MF/F	0.24	7.94	0.794
200:5 Ratio MF/F	0.06	1.97	0.197
SCH 32088	0.30	7.91	0.791
Formoterol	0.11	3.87	0.387
Females			
Air Control	0.00	NC	NC
Vehicle	0.19	7.28	0.728
Low Dose MF/F	0.06	2.28	0.228
Mid Dose MF/F	0.13	5.14	0.514
High Dose MF/F	0.24	9.34	0.934
200:5 Ratio MF/F	0.06	2.44	0.244
SCH 32088	0.30	11.51	1.151
Formoterol	0.11	4.38	0.438

Overall group mean estimated lactose deposited doses

Group	Group Mean Aerosol Concentration µg/L	Oleic acid Inhaled Dose µg/kg/day	Oleic acid Deposited Dose µg/kg/day
Males			
Air Control	0.00	NC	NC
Formoterol	7.96	279.76	27.976
Females			
Formoterol	7.98	317.95	23.819

One liter foil gas sample collection bags were used to collect a sample of the plenum atmosphere for chemical analysis of HFA-227 and ethanol.

Table 4 Overall Group Mean HFA-227 and Ethanol Concentration in the Exposure Atmosphere (ppm)

Dose Group		HFA-227 PPM	ETOH PPM
Air Control (1)	Mean	ND	ND
	SD	ND	ND
	% RSD	ND	ND
Vehicle (2)	Mean	1397	89.16
	SD	89.6	10.61
	% RSD	6	12
Low Dose MF/F (3)	Mean	308.7	21.34
	SD	37.4	4.43
	% RSD	12	21
Mid Dose MF/F (4)	Mean	616.4	41.12
	SD	68.1	8.07
	% RSD	11	20
High Dose MF/F (5)	Mean	1056	67.74
	SD	284.5	21.36
	% RSD	27	32
200:5 Ratio MF/F (6)	Mean	306.9	21.83
	SD	22.2	3.14
	% RSD	7	14
SCH 32088 (7)	Mean	715.7	63.54
	SD	97.1	9.86
	% RSD	14	16
Formoterol Fumarate (8)	Mean	0.0	42.16
	SD	0.0	5.97
	% RSD	--	14

ND = Not detected

On-line aerosol monitoring was conducted using an aerosol monitor.

Aerosol particle size distribution was measured using Mercer-style In-Tox Products brand cascade impactors. There were eight stages in each impactor with effective cutoff diameters ranging from 0.5 to approximately 10 µm. Filters collected for particle size distribution were chemically analyzed for SCH 32088, formoterol fumarate, oleic acid, and/or lactose at a minimum of once per week.

Mean Particle Size Distribution (µm)										
	Total Mass		SCH 32088		Formoterol Fumarate		Oleic Acid		Lactose	
Dose Group	MMAD	GSD	MMAD	GSD	MMAD	GSD	MMAD	GSD	MMAD	GSD
Vehicle	1.43	3.55	NA	NA	NA	NA	0.74	2.10	NA	NA
Low-Dose MF/F	3.05	1.78	2.87	1.78	2.81	1.51	0.94	2.26		
Mid-Dose MF/F	2.75	2.01	2.86	1.79	2.75	1.54	0.92	2.38		
High-Dose MF/F	2.69	1.96	3.00	1.83	2.77	1.63	0.94	2.36		
200:5 Ratio MF/F	3.22	1.73	3.24	1.69	2.97	1.52	1.10	2.83		
SCH 32088	3.13	1.85	3.31	1.72	NA	NA	1.30	2.27		
F	2.07	1.83	NA	NA	2.60	1.65	1.98	1.98	1.89	1.76
NA = Not applicable										

Species/strain: Male and Female Sprague-Dawley (Crl:CD®(SD)IGS BR VAF/Plus) rats were obtained from [redacted] (b) (4)
Number/sex/group or time point (main study): 10 rats/sex/group
Route, formulation, volume, and infusion rate: Rats were exposed by nose-only inhalation.
Satellite groups used for toxicokinetics or recovery: 48 rats/sex/group for toxicokinetic assessment
Age: At the start of dosing, animals were 6 to 8 weeks old.
Weight: At the start of dosing, body weight ranges were 216.00 to 295.00 g for main study males, 142.80 to 199.50 g for main study females, 186.50 to 271.80 g for TK study males, and 136.90 to 223.00 g for TK study females.
Unique study design or methodology (if any): Dose selection was based upon a 2-week nose-only inhalation toxicity and toxicokinetic study of SCH32088 with formoterol aerosols in the rat. Rats were exposed via nose-only inhalation to aerosols of metered dose inhaler (MDI) formulations containing SCH32088 (mometasone furoate or MF) with formoterol fumarate (F) in a 50:5 ratio or formoterol fumarate-only for 60 min daily for 14 consecutive days. Nominal doses of MF/F for males and females combined in the low, mid, and high dose groups were 37/3.7 µg/kg/day, 88.7/8.8 µg/kg/day, and 140.6/14.1 µg/kg/day, respectively. Deposited doses were 3.7/0.37 µg/kg/day, 8.9/0.9 µg/kg/day, and 14.1/1.4 µg/kg/day, respectively. Nominal and deposited doses for the formoterol only group were 23.1 and 2.3 µg/kg/day, respectively. White blood cell counts were slightly decreased for females in the low, mid, and high MF/F groups. RBC counts, hemoglobin levels, and hematocrit were slightly increased for females in the low, mid, and high dose MF/F groups. Mean platelet volumes were slightly decreased for females in the low, mid, and high dose MF/F groups. Glucose levels were increased for males in the low, mid, and high dose MF/F groups. Absolute and relative thymus weights were decreased for males and females in the low, mid, and high dose MF/F groups, which appeared to correlate with histopathological findings of thymic atrophy/involution. The target organ of toxicity was the thymus. Potential treatment-related histopathological findings were also evident in the lungs and thyroid gland. Thymus atrophy/involution was observed for males in the mid and high dose MF/F groups and females in the low, mid, and high dose MF/F groups. Increased incidences of thymic cysts were observed for the high dose MF/F group; however, the low and mid dose MF/F groups were not examined. Incidences of increased alveolar macrophages

were observed for the high dose MF/F and F alone groups; however, the low and mid dose MF/F groups were not examined.

Observation and Times:
Clinical signs: Animals were examined at least twice per day for moribundity/mortality. Main study animals were examined at least once daily within 45 min post-exposure.
Body weights: Body weights of main study animals were recorded on day 1 prior to exposure, once weekly thereafter, and on the day before and on the day of scheduled necropsy (fasted).
Food consumption: Food consumption (g/day) for main study animals was measured weekly during the study.
Ophthalmoscopy: Ophthalmic examination for main study animals were conducted pretest and on day 85.
EKG: Not performed.
Hematology: Blood samples for measurement of hematology and coagulation parameters were collected on day 92.
Clinical chemistry: Blood samples for measurement of serum chemistry parameters were collected on day 92. Analyses included corticosterone and Troponin T.
Urinalysis: Urine samples for measurement of urinalysis parameters were collected from days 91 through 92 (4 and 24 hr from initiation).
Gross pathology: Rats were sacrificed on day 92 and submitted to necropsy examinations.
Organ weights: Absolute and relative organ weights were determined for the adrenal glands, brain, epididymides, heart, kidneys, liver, lungs plus bronchi, ovaries, pituitary gland, prostate, spleen, salivary gland (mandibular), testes, thymus, thyroid gland/parathyroid gland, and uterus with cervix.
Histopathology: Organ/tissues collected from all rats were processed to slides and stained with hematoxylin and eosin. The testes were stained with Periodic Acid-Schiff (PAS) for histopathologic examination. All organ/tissues processed in the air-control, vehicle-control, high dose SCH 418131, 200:5 ratio SCH 418131, SCH 32088 alone, and formoterol alone groups were examined by light microscopy. All gross lesions were examined. Organs identified as potential target organs (adrenal gland, bone marrow, larynx, bronchial, mandibular, mediastinal, and mesenteric lymph nodes, lung, nasal turbinates (nose), trachea, thymus, spleen, ovary, and vagina) from rats in the low and mid dose SCH418131 groups and the mammary glands from females in the low and mid dose SCH 418131 groups were examined by light microscopy.
Toxicokinetics: Blood samples were for measurement of plasma concentrations of mometasone and formoterol were collected from TK rats in the low, mid, and high dose SCH 418131 groups, the 200:5 ratio SCH 418131 group, the SCH 32088 alone group, and the formoterol fumarate alone group on days 1 and 64 at 0.25, 0.5, 1, 4, 8, 12, and 23 hr post-exposure. For each time point, blood samples were collected from 12 rats/sex/group. Urine (non-fasted) was collected from main study rats over a 24 ± 2 hr period on days 1 and 64 for determination of formoterol concentration. Plasma and urine samples were shipped to the analytical laboratory. Schering-Plough Research Institute measured plasma concentrations of mometasone. Novartis Pharma SAS, France measured plasma and urine concentrations of formoterol. Plasma

concentrations of SCH 32088 were measured using a liquid chromatographic-tandem mass spectrometric (LC-MS/MS) method. Plasma and urine concentrations of formoterol were measured using a validated LC-MS/MS method.
Respiratory measurements: Measurements of respiratory rate, tidal volume, and minute volume were conducted weekly using plethysmographs. For weeks 1 and 10, data were collected from 4 TK rats/sex/group from the low, mid, and high dose SCH 418131 groups, the 200:5 ratio SCH 418131 group, the SCH 32088 alone group, and the formoterol fumarate alone group. For weeks 2-9 and 11-13, data were collected from 4 main study rats/sex/group from the low, mid, and high dose SCH 418131 groups, the 200:5 ratio SCH 418131 group, the SCH 32088 alone group, and the formoterol fumarate alone group. For air-control and vehicle-control groups, data were collected weekly from 4 main study rats/sex/groups.

Results:

Mortality: Two animals [one high dose MF/F male (#502) on day 90 and one MF alone female (#756) on day 64] were found dead during the treatment period.

The cause of death for the male (#502) in the high dose MF/F group was attributed to lymphoma.

The female (#756) in the MF alone group was found with several histopathological findings that included lymphoid depletion of the bronchial-associated lymphoid tissue, fibrosis of lung serosa, lymphoid depletion in the bronchial, mediastinal, and mesenteric lymph nodes, infiltration of mast cells in the mesenteric lymph nodes, alterations of lobuloalveolar development in the mammary gland, infiltration of mononuclear cells, acinar atrophy, and chronic, active inflammation in the pancreas, lymphoid depletion and hemosiderosis in the spleen, involution/atrophy of the thymus, and decreased globule leukocytes in the trachea. This animal had the only findings of fibrosis of the lung serosa.

Clinical signs: Clinical signs were observed for two rats (#502 and #510) in the high dose SCH 418131 group.

Clinical signs

Clinical sign	#Observations/#Animals	Days Observed
Lethargic	29/1 (#502)	Days 61-89
Rough coat	43/2 (#502 and #510)	Days 61-85
Ataxic incoordination	25/1 (#502)	Days 61-85
Hindlimb weakness	4/1 (#502)	Days 86-89
Labored respiration	25/1 (#502)	Days 61-85

Body weights: Body weight gains were decreased for male and female rats in the low, mid, and high dose SCH 418131 groups, the 200:5 ratio SCH 418131 group, and the SCH 32088 alone group. Decreased body weight gain was attributed to the pharmacological properties of mometasone.

Body weight gains from days 0 to 91 expressed as a percent of the air-control group

Sex	AC	VC	MF/F				MF	F
			LD 50:5	MD 50:5	HD 50:5	200:5		
Males	100%	100.2%	71.85%	54.4%	33.8%	42.7%	47.2%	97.9%
Females	100%	102.3%	66.6%	36.1%	32.6%	34.8%	54.7%	107.6%

Food consumption: Food consumption from days 1 to 91 was decreased for male and female rats in the low, mid, and high dose SCH 418131 groups, the 200:5 ratio SCH 418131 group, and the SCH 32088 alone group. Decreased food consumption was attributed to the pharmacological properties of mometasone.

Body weight gains from days 0 to 91 expressed as a percent of the air-control group

Sex	AC	VC	MF/F				MF	F
			LD 50:5	MD 50:5	HD 50:5	200:5		
Males	100% (333.9 g)	100.1%	92.5%	89.1%	83.7%	86.7%	87.4%	100.9%
Females	100% (230%)	100.4%	87.6%	86.8%	89.3%	85.8%	80.7%	105.8%

Ophthalmoscopy: There were no apparent treatment-related ophthalmic findings on day 85.

Hematology: White blood cell counts were decreased for all groups that received mometasone. This finding is commonly attributed to the pharmacological properties of corticosteroids.

White blood cell (WBC) counts were decreased for male and female rats in the low, mid, and high dose MF/F groups, the 200:5 MF/F group, and the MF alone group. Decreased WBC counts were attributed to lower lymphocyte, eosinophil, and basophil counts.

Neutrophil and monocyte counts were slightly increased for male and/or female rats in the low, mid, and high dose MF/F groups the 200:5 MF/F group, and the MF alone group.

Red blood cell (RBC) counts and hemoglobin levels were slightly increased for male rats in the low, mid, and high dose MF/F groups, the 200:5 MF/F group, and the MF alone group. RBC counts, hemoglobin levels, and hematocrit were slightly increased for female rats in the mid and/or high dose MF/F groups. Reticulocyte counts were slightly decreased for male and female rats in the low, mid, and high dose MF/F groups, the 200:5 MF/F group, the MF alone group, and the formoterol alone group. These findings appear to have minimal toxicological significance.

Hematology parameters on day 92

Parameter	Sex	AC	VC	Low MF/F	Mid MF/F	High MF/F	200:5 MF/F	MF	F
WBC K/µL	M	11.47	11.90	8.84* (77%)	7.71* (67%)	6.19* (54%)	5.83* (51%)	5.47* (48%)	11.28
	F	7.98	6.79	6.63	5.16* (65%)	4.63* (63%)	4.99* (63%)	4.04* (51%)	7.44
RBC M/µL	M	8.87	8.76	9.65* (113%)	10.06* (112%)	9.95* (113%)	9.99* (108%)	9.54* (108%)	9.07
	F	8.69	8.37	8.49	8.99	9.32* (107%)	8.60	8.33*	8.54
Hemoglobin g/dL	M	16.3	17.7	17.3* (106%)	18.0* (110%)	18.2* (112%)	18.2* (112%)	17.4* (107%)	16.7
	F	16.1	15.9	16.0	17.0* (106%)	17.9* (111%)	16.3	16.0	16.2
Hematocrit %	M								
	F	50.1	48.6	49.2	51.8	54.0* (108%)	50.1	48.2*	50.3
MCV fL	M	58.5	57.4	57.8	56.6* (97%)	56.7	57.5	57.2	59.1
	F								
Neutrophils %	M	15.2	12.8	21.0 (138%)	27.7* (182%)	37.1* (244%)	32.6* (215%)	33.1* (218%)	11.5
	F	10.0	11.9	11.1	22.5* (225%)	32.2* (322%)	27.7* (277%)	28.3 (283%)	9.4
Neutrophils K/µL	M	1.68	1.55	1.86 (111%)	2.10 (125%)	2.25* (134%)	1.86 (111%)	1.79 (107%)	1.2
	F	0.78	0.80	0.73	1.12 (144%)	1.49* (191%)	1.38* (177%)	1.16* (149%)	0.69
Lymphocytes %	M	80.8	83.2	73.9 (91%)	66.9* (83%)	55.3* (68%)	61.7* (76%)	60.2* (75%)	84.8
	F	85.4	83.2	83.8	69.8* (82%)	59.9* (70%)	64.8 (76%)	64.0* (75%)	86.5
Lymphocytes K/µL	M	9.33	9.87	6.53* (70%)	5.19* (56%)	3.47* (37%)	3.63* (39%)	3.32* (36%)	9.57
	F	6.84	5.67	5.56	3.64* (53%)	2.77* (40%)	3.23* (47%)	2.57* (38%)	6.46
Monocytes %	M	2.6	2.7	3.7* (142%)	4.1* (158%)	6.3* (242%)	5.0* (192%)	5.6* (215%)	2.4
	F	3.2	3.3	3.7	6.3* (197%)	6.3* (197%)	6.0* (188%)	6.4 (200%)	2.7
Monocytes K/µL	F	0.25	0.22	0.24	0.33* (132%)	0.30 (120%)	0.31* (124%)	0.26	0.19
Eosinophils %	M	1.1	1.0	1.1	1.0	1.1	0.6 (55%)	0.8 (73%)	1.0
	F								
Eosinophils K/µL	M	0.12	0.12	0.10	0.08	0.06	0.03* (25%)	0.04* (33%)	0.11
	F	0.08	0.09	0.07	0.06	0.07	0.06	0.04 (50%)	0.07
Basophils %	M	0.4	0.3	0.3	0.4	0.2* (50%)	0.1* (25%)	0.3	0.4
Basophils	M	0.05	0.04	0.03*	0.03*	0.02*	0.01*	0.01*	0.04

K/µL	F			(60%)	(60%)	(40%)	(20%)	(20%)	
Reticulocytes %	M	2.4	2.3	1.6* (67%)	1.8 (75%)	1.6* (67%)	1.5* (63%)	1.4* (58%)	2.0
	F	2.0	1.9	1.9	1.5* (75%)	2.2	1.6	1.7	1.8
Reticulocytes K/µL	M	214.43	198.92	152.57* (71%)	180.56* (84%)	156.71* (73%)	145.62* (68%)	133.12* (62%)	176.80* (83%)
	F	173.02	155.90	156.81	133.12* (77%)	206.52 (119%)	139.25 (80.0)	137.11 (79%)	148.65 (86%)

*p≤0.05

Clinical chemistry: Several differences in serum biochemistry parameters were observed between control and treatment groups. Most of these differences appeared to be associated with the pharmacological actions of mometasone. There were no corresponding treatment-related histopathological findings in the liver or kidneys.

Triglyceride and cholesterol levels were increased for males in the mid and high dose MF/F group, the 200:5 MF/F group, and the MF alone group. Cholesterol levels were increased for females in the low, mid, and high dose MF/F groups, the 200:5 MF/F group, the MF alone group, and the formoterol alone group.

Total protein, albumin, and globulin levels were slightly increased for males in the low, mid, and high dose MF/F groups, the 200:5 MF/F group, and the MF alone group. These changes appeared to be associated with the presence of mometasone. However, total protein, albumin and globulin levels were slightly increased for females in the 200:5 MF/F group, the MF alone group, and the formoterol alone group, where a direct association with mometasone was not evident. The albumin to globulin ratio was decreased for females in the high dose MF/F group.

Glucose levels were decreased for males and females in the high dose MF/F and 200:5 MF/F groups, which appeared to be associated with a high dose of mometasone.

Phosphate levels were slightly decreased for males in the high dose MF/F group. Calcium levels were decreased for females in the high dose MF/F and 200:5 MF/F groups.

ALT and AST activities were increased for females in the mid dose MF/F group; however, there was no evidence of a dose-response relationship as no changes were evident in the high dose MF/F group.

Corticosterone and Troponin T values were highly variable and no inferences about the effects of treatment on these parameters could be made.

Serum chemistry parameters on day 92

Parameter	Sex	AC	VC	Low MF/F	Mid MF/F	High MF/F	200:5 MF/F	MF	F
Total protein g/dL	M	7.0	6.8	7.5* (107)	7.8* (111%)	7.7* (110%)	7.9* (113%)	8.0* (114%)	6.8
	F	7.8	8.2	8.3	8.6* (110%)	8.3	9.1* (117%)	9.0* (115%)	8.7* (112%)
Albumin g/dL	M	4.5	4.4	4.9* (109%)	4.9* (109%)	4.9* (109%)	5.0* (110%)	5.1* (113%)	4.4
	F	5.6	6.0	6.0	6.1	5.5	6.5* (116%)	6.4* (114%)	6.2* (111%)
Globulin g/dL	M	2.5	2.4	2.7	2.9* (116%)	2.8* (112%)	3.0* (120%)	2.9* (116%)	2.4
	F	2.3	2.3	2.3	2.5	2.8* (122%)	2.6 (113%)	2.6 (113%)	2.5 (109%)
A/G ratio	F	2.51	2.71	2.62	2.46	2.03* (81%)	2.53	2.54	2.58
Glucose mg/dL	M	107	105	105	104	83 (78%)	83 (78%)	114	118
	F	98	98	91	83	67* (68%)	78 (80%)	92	87
Triglyceride mg/dL	M	61	54	59	104* (171%)	97 (159%)	82 (134%)	90 (148%)	37 (61%)
	F	40	45	43	47	65* (163%)	43	37	36
Cholesterol mg/dL	M	95	87	92	113 (119%)	120 (126%)	109 (115%)	128* (135%)	77 (81%)
	F	105	125	135 (129%)	160* (152%)	136 (130%)	178* (170%)	146* (139%)	136 (130%)
Phosphate mg/dL	M	10.1	9.9	10.7	10.1	8.8 (87%)	10.3	9.5	10.3
	F								
Calcium mg/dL	F	98	98	91	83	67* (68%)	78 (80%)	92	87
ALT U/L	M	39	44	40	50 (128%)	42	47 (121%)	46 (118%)	43
	F	67	64	65	156 (233%)	48	94 (140%)	94 (140%)	77 (115%)
AST U/L	M	91	105*	123*	117*	103	133* (146%)	103	97
	F	141	173	184	235 (167%)	114	151	166	236 (167%)

*p≤0.05

Urinalysis: Differences in urinalysis parameters between control and treatment groups were observed for phosphorus, calcium, sodium, potassium, chloride, osmolality, creatinine, and creatinine clearance. There were no treatment-related histopathological findings in the kidneys suggesting these differences had little or no toxicological significance. Further, observed differences were generally confined to male treatment groups, which places more doubt on their significance. Phosphorus concentrations were decreased for males in the high dose MF/F, 200:5 MF/F, and MF alone groups; however, elevations were observed for females in the MF alone and F alone groups.

Calcium concentrations were decreased for all male treatment groups. Sodium concentrations were decreased for males in all treatment groups that received MF. Potassium concentrations were decreased for males in the high dose MF/F group. Smaller decreases of the potassium concentrations were evident for all other male treatment groups. Chloride concentrations were significantly decreased for males in the high dose MF/F and 200:5 MF/F groups. Smaller decreases of chloride concentrations were evident for all other male treatment groups. Creatine concentrations and osmolality were significantly decreased for males in the high dose MF/F, 200:5 MF/F, and MF alone groups. Creatinine clearances were decreased for males in the 200:5 MF/F and MF alone groups. Incidences of occult blood were increased for males in treatment groups that received MF.

Urinalysis parameters on day 91/92

Parameter	Sex	AC	VC	Low MF/F	Mid MF/F	High MF/F	200:5 MF/F	MF	F
Phosphorus mg/dL	M F	106.8 121.4	111.0	82.9	100.5	70.7 (66%)	64.8 (61%)	87.5 (82%) 172.2 (142%)	107.9 210.9 (174%)
Calcium mg/dL	M	6.3	4.8 (76%)	4.2 (67%)	3.6 (57%)	4.1 (65%)	3.5 (56%)	3.9 (62%)	3.5 (56%)
Sodium mEq/L	M	48	40	31 (65%)	31 (65%)	26* (54%)	29 (60%)	21* (44%)	43
Potassium mEq/L	M	134.5	116.5 (87%)	93.0 (69%)	102.0 (76%)	67.1* (50%)	80.0 (60%)	96.0 (71%)	93.6 (70%)
Chloride mEq/L	M	59	45 (76%)	35 (59%)	31 (53%)	25* (42%)	21* (36%)	33 (56%)	35 (59%)
Osmolality mOsm/kg	M	977	913	788 (81%)	870 (89%)	624 (64%)	688 (70%)	717 (73%)	891 (91%)
Creatinine mg/dL	M F	104.0 80.6	105.3 109.9	97.5 100.0	96.6 64.4 (80%)	63.4* (61%) 65.5 (81%)	74.0 (71%) 84.5	78.9 (76%) 92.5	116.3 126.8
Creatinine CL mL/min	M	2.0	2.1	1.9	1.6	1.9	1.4* (70%)	1.6 (80%)	2.2
Occult blood	M	10 at 0	9 at 0 1 at 1	2 at 0 6 at 1	3 at 0 4 at 1 1 at 2	5 at 0 4 at 1	2 at 0 8 at 1	1 at 0 7 at 1 1 at 2	6 at 0 1 at 1 1 at 3

*p≤0.05

Gross pathology: There were observations of small thymus for males in the high dose MF/F and MF alone groups and females in the low, mid, and high dose MF/F groups, the 200:5 MF/F group, and the MF alone group. These observations correlated with histopathological findings of thymic involution/atrophy. There were observations of lung foci for males and females in the high dose MF/F and 200:5 MF/F groups and males in the MF alone group. These observations correlated with histopathological findings of alveolar macrophage accumulation.

Organ weights: Differences of organ weights between air-control and treatment groups were observed for the thymus, spleen, adrenal glands, prostate, lung, ovary, heart,

pituitary, thyroid, and uterus. Organ to body weight percentages were increased for treatment groups that received mometasone due to severe decreases of body weights. Therefore, organ to body weight percentages were not used in the current assessment.

Absolute and relative thymus weights were decreased for treatment groups that received mometasone, which appear to correlate with histopathological effects of thymic involution/atrophy.

Absolute and relative spleen weights were decreased for treatment groups that received mometasone, which may correlate with histopathological findings of lymphoid depletion.

Absolute and relative adrenal gland weights were decreased for male treatment groups that received mometasone, which generally appeared to correlate with histopathological findings of atrophy of the zona fasciculata.

Relative prostate weights were decreased for male rats in the mid and high dose MF/F groups and the 200:5 MF/F group; however, there were no corresponding histopathological findings.

Absolute and relative ovary weights were decreased for female rats in the mometasone only group; however, there were no corresponding histopathological findings.

Absolute and relative lung, heart weights, pituitary, thyroid, and uterus weights were increased for female rats in the formoterol only group; however, there were no corresponding histopathological findings.

Uterus weights were decreased for females in the high dose MF/F group; however, there were no corresponding histopathological findings.

Absolute and relative organ weights for male and female rats at the end of the treatment period

Organ	Sex	AC	VC	LD MF/F	MD MF/F	HD MF/F	200:5 MF/F	MF	F
Thymus g	M	0.474	0.408	0.337* (71%)	0.273* (58%)	0.187* (40%)	0.296* (63%)	0.282* (59%)	0.443
	F	0.349	0.317	0.224* (64%)	0.138* (40%)	0.130* (37%)	0.164* (47%)	0.118* (34%)	0.360
Thymus %BrW	M	23.64	19.50 (82%)	16.77 (71%)	13.59 (58%)	9.68 (41%)	14.95 (63%)	14.00 (59%)	21.95 (93%)
	F	18.73	16.73	12.20 (65%)	7.50 (40%)	6.88 (37%)	9.11 (49%)	6.38 (34%)	19.45
Spleen g	M	0.836	0.779	0.658* (79%)	0.580* (69%)	0.471* (56%)	0.457* (55%)	0.505* (60%)	0.749
	F	0.464	0.505	0.414	0.331* (71%)	0.307* (66%)	0.335* (72%)	0.292* (63%)	0.489
Spleen %BrW	M	41.67	37.34	32.52 (78%)	29.05 (70%)	24.40 (59%)	22.61 (54%)	24.99 (60%)	36.95 (89%)
	F	24.97	26.70	22.50	18.01 (72%)	16.44 (66%)	18.50 (74%)	15.84 (63%)	26.43

Adrenals g	M	0.0676	0.0705	0.0600 (90%)	0.0514* (76%)	0.0473* (70%)	0.0436* (65%)	0.0429* (64%)	0.0611
Adrenals %BrW	M	3.351	3.379	2.974 (89%)	2.576 (77%)	2.444 (73%)	2.168 (65%)	2.122 (63%)	3.011 (70%)
Prostate g	M	0.981	0.859	0.820	0.664* (68%)	0.666* (68%)	0.739* (75%)	0.843	0.818
Prostate %BrW	M	48.87	41.09 (84%)	40.44 (83%)	33.31 (68%)	34.42 (70%)	36.74 (75%)	41.70 (85%)	40.31 (82%)
Lung g	M F	3.061 2.063	2.990	2.690	2.693	2.572	2.814	2.263* (74%)	2.828 2.615* (127%)
Lung %BrW	F	111.31							140.84 (127%)
Ovary g	F	0.117	0.117	0.091* (78%)	0.094 (80%)	0.115	0.092* (79%)	0.078* (67%)	0.102
Ovary %BrW	F	6.25	6.19	4.93 (79%)	5.09 (81%)	6.15	5.10 (81%)	4.24 (68%)	5.49 (88%)
Uterus %BrW	F	31.14	40.00	34.18	28.36	24.66 (79%)	27.84	26.29	36.19 (116%)
Heart g	F	0.961	1.027	1.021	0.992	1.035	0.990	0.916	1.178* (123%)
Heart %BrW	F	51.59	54.31	55.52	54.08	55.11	54.71	49.56	63.70 (123%)
Pituitary g	F	0.0205							0.0333* (162%
Pituitary %BrW	F	1.100	1.219	1.303	1.123	1.081	1.064	1.268	1.802 (164%)
Thyroid g	F	0.0282							0.0429 (152%)
Thyroid %BrW	F	1.512							2.327 (154%)

*p≤0.05

Histopathology: Target organs of toxicity were the lung, trachea, nose/turbinates, thymus, spleen, lymph nodes (mesenteric, bronchial, mandibular, and mediastinal), mammary gland, bone marrow, ovary, and vagina. In general, histopathological findings were evident in all treatment groups that received mometasone furoate.

Findings in the lungs consisted of BALT (bronchial-associated lymphoid tissue) depletion, accumulation of alveolar macrophages, and pigmented macrophages. BALT depletion was observed in all treatment groups that received mometasone. Accumulation of alveolar macrophages was observed in mid and high dose MF/F, the 200:5 MF/F group, and the MF only group.

Findings in the trachea consisted of decreased globule leukocytes in all treatment groups that received mometasone.

Thymus involution/atrophy was observed in all treatment groups that received mometasone.

Lymphoid depletion was observed in the nose/turbinates, spleen, lymph nodes (mesenteric, bronchial, mandibular, and mediastinal). Increased incidences of lymphoid depletion in the nose/turbinates, mesenteric lymph nodes, bronchial lymph nodes, mandibular lymph nodes, and mediastinal lymph nodes occurred in all treatment groups that received mometasone. Lymphoid depletion in the spleen occurred in the mid and high dose MF/F groups, the 200:5 MF/F group, and the MF only group.

Infiltration of mast cells was observed in the mesenteric lymph nodes for all treatment groups that received mometasone.

Abnormal lobuloalveolar development of the mammary gland occurred for females all treatment groups that received mometasone as well as the formoterol only group.

Elevated incidences of increased marrow fat in the bone marrow were observed for all treatment groups that received mometasone.

Increased incidences of decreased corpora lutea in the ovaries occurred in all female treatment groups that received mometasone as well as the formoterol only group.

Abnormal mucification of the vagina was observed in all treatment groups that received mometasone.

An increased incidence of atrophy of the zona fasciculata of the adrenal gland was observed for males in the 200:5 MF/F group.

Histopathological findings in rats after exposure for 13 weeks

Organ	Sex	AC	VC	MF/F				MF	F
				LD	MD	HD	200:5		
Lung									
-depletion, lymphoid, BALT	M	0/10	0/10	8/10	10/10	9/10	8/10	10/10	0/10
	F	0/10	0/10	8/10	7/10	10/10	10/10	10/10	0/10
-accumulation, alveolar macrophages	M	0/10	0/10	0/10	5/10	7/10	5/10	5/10	0/10
	F	0/10	0/10	0/10	4/10	6/10	4/10	3/10	0/10
-pigmented (macrophages)	M	0/10	1/10	2/10	1/10	1/10	2/10	3/10	0/10
	F	0/10	0/10	0/10	0/10	1/10	0/10	0/10	0/10
Trachea									
-globule leukocytes decreased	M	0/10	0/10	10/10	10/10	10/10	10/10	10/10	0/10
	F	1/10	0/10	10/10	10/10	10/10	10/10	10/10	0/10
Thymus									
-involution/atrophy	M	1/10	0/10	3/10	4/10	8/10	10/10	9/10	0/10
	F	0/10	0/10	5/10	9/10	10/10	9/9	10/10	0/10
Nose/Turbinates									
-depletion lymphoid	M	0/10	0/10	4/10	8/10	9/10	10/10	10/10	1/10
	F	0/10	0/10	3/10	6/10	8/10	4/10	8/10	0/10
Spleen									
-depletion, lymphoid	M	0/10	0/10	0/10	2/10	7/10	6/10	5/10	0/10
	F	1/10	1/10	0/10	9/10	9/10	8/10	10/10	0/10

Mesenteric LN									
-depletion, lymphoid	M	1/10	1/10	0/10	3/10	8/10	6/10	7/10	0/10
	F	0/10	0/10	3/10	5/10	10/10	9/10	10/10	0/10
-infiltration, mast cells	M	0/10	0/10	3/10	5/10	4/10	7/10	7/10	0/10
	F	0/10	0/10	2/10	4/10	4/10	8/10	4/10	0/10
Bronchial LN									
-depletion, lymphoid	M	0/9	0/7	0/9	2/6	6/8	6/7	6/7	1/8
	F	0/9	1/10	4/10	3/7	7/7	6/7	7/7	1/10
Mandibular LN									
-depletion lymphoid	M	1/10	0/10	3/9	2/10	9/10	8/10	8/9	0/10
	F	0/10	2/10	4/10	6/10	8/10	6/10	7/10	0/10
Mediastinal LN									
-depletion, lymphoid	M	0/9	0/10	2/8	3/8	5/7	2/7	3/10	0/10
	F	3/10	1/9	3/9	6/10	6/10	4/9	7/9	0/8
Mammary gland									
-lobuloalveolar development	M	0/9	0/10	-	-	0/10	0/10	0/10	0/10
	F	0/10	0/10	5/10	5/10	6/10	9/10	10/10	3/10
Bone marrow									
-increased marrow fat	M	1/10	4/10	8/10	10/10	9/10	10/10	10/10	2/10
	F	1/10	0/10	2/10	7/10	8/10	8/10	2/10	0/10
Ovary									
-decreased corpora lutea	F	0/10	3/10	7/10	6/10	2/10	8/10	8/10	9/10
Vagina									
-abnormal mucification	F	0/10	0/10	4/10	3/10	1/10	8/10	6/10	0/9
Adrenal gland									
-atrophy, zona fasciculata	M	1/10	0/10	0/10	0/10	1/10	3/10	0/10	0/10
	F	0/10	0/10	0/10	0/10	0/10	0/10	1/10	0/10

Toxicokinetics: For male and female rats in the low, mid, and high dose MF/F groups, C_{max} and AUC values for MF and formoterol increased in an approximate dose proportional manner. C_{max} and AUC values for MF and formoterol on day 64 were generally greater than those on day 1 suggesting some accumulation of MF and formoterol as the treatment period progressed. There was no evidence of sex-related differences in toxicokinetic parameters for MF or formoterol. C_{max} and AUC values for MF in the high dose MF/F group were greater than those for the 200:5 MF/F and MF alone groups, which was in general agreement with pulmonary deposited doses for MF in these groups. C_{max} and AUC values for formoterol in the high dose MF/F group were greater than those for the 200:5 MF/F and F alone groups, which was in general agreement with pulmonary deposited doses for formoterol in these groups. For the low, mid, and high dose MF/F groups, recovery of formoterol in the urine increased with elevating dose of formoterol. Urinary excretion of formoterol appeared to be independent of sex. Urinary excretion values on day 64 were generally greater as compared to day 1. There was no evidence of any interactions on toxicokinetic parameters.

Table 1 SCH 32088 Toxicokinetic Parameters on Days 1 and 64 Following a 64-Minute Inhalation (Nose-Only) Administration of SCH 32088 Alone or in Combination with Formoterol Fumarate to Male and Female Rats

Group	Estimated Deposited Dose[a] (µg/kg)	Sex	Cmax (pg/mL)	Tmax (hr)	AUC(0-24hr) (pg·hr/mL)	AUC(0-24hr) Normalized (pg·hr/mL) / (µg/kg)
			Day 1			
3	64.59	Female	1260	2.07	6540	101
	51.54	Male	2510	1.18	9050	176
4	102.80	Female	3420	1.12	14800	144
	92.68	Male	2590	1.12	13000	140
5	197.62	Female	6530	1.12	25300	128
	169.44	Male	5710	1.12	24400	144
6	145.58	Female	3160	1.57	20300	139
	164.79	Male	3480	1.17	17300	105
7	182.00	Female	1840	1.14	12900	70.9
	135.14	Male	1960	1.57	12600	93.4
			Day 64			
3	29.96	Female	2470	1.57	11300	376
	25.40	Male	2460	1.14	11800	464
4	62.90	Female	5450	2.07	26000	413
	54.04	Male	6880	1.15	27600	510
5	201.45	Female	17300	1.11	62300	309
	139.98	Male	10700	1.14	46300	331
6	164.73	Female	6880	2.07	33700	205
	128.94	Male	7090	1.16	43400	337
7	118.35	Female	3850	2.07	31600	267
	105.60	Male	4110	2.07	38100	361

a: EDD calculated using the group mean aerosol concentration, group mean body weight of the toxicokinetic animals, an overall group mean minute volume measured in four toxicokinetic animals, and a 64-minute exposure period on the respective day of exposure. Dose was calculated from the deposition model based on Raabe.[1]

Table 2 Formoterol Toxicokinetic Parameters on Days 1 and 64 Following a 64-Minute Inhalation (Nose-Only) Administration of Formoterol Fumarate Alone or in Combination with SCH 32088 to Male and Female Rats

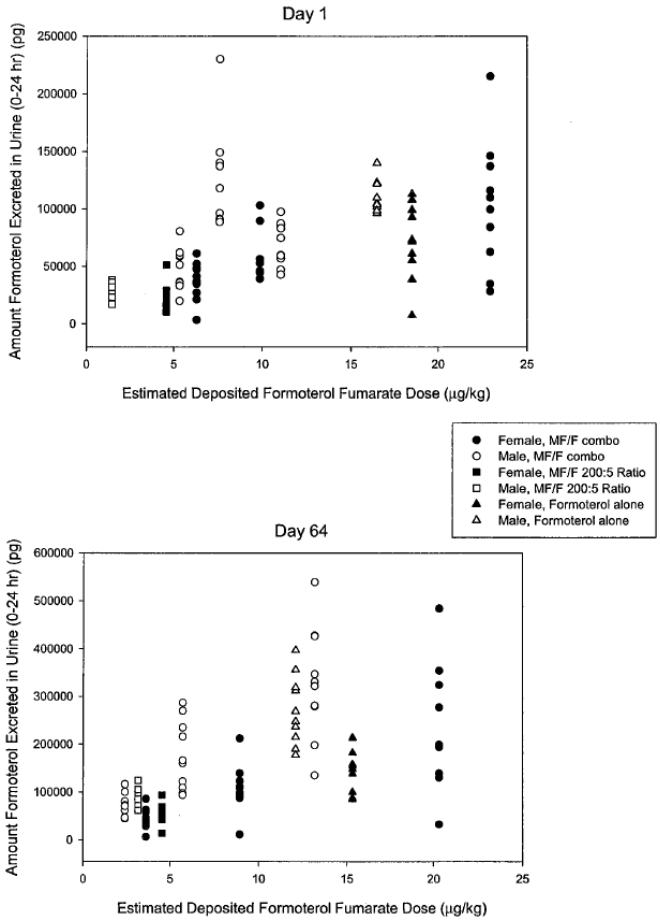
Formoterol										
Group	Estimated Deposited Dose[a] (µg/kg)	Sex	Cmax (pg/mL)	Tmax (hr)	tf (hr)	AUC(tf) (pg·hr/mL)	AUC(0-24hr) (pg·hr/mL)	AUC(0-24hr) normalized (pg·hr/mL) / (µg/kg)	AUC(tf) normalized (pg·hr/mL) / (µg/kg)	AE(0-24 hr)[b] (pg)
Day 1										
3	6.30	Female	204	1.11	5.07	338	368	58.4	53.7	37300 (45)
	5.33	Male	198	1.14	2.07	NC[c]	NC	NC	NC	49900 (36)
4	9.87	Female	392	1.12	5.07	559	589	59.7	56.6	58200 (39)[d]
	11.03	Male	414	1.11	5.07	619	665	60.3	56.1	69400 (27)
5	22.97	Female	832	1.11	5.07	1490	1590	69.3	64.8	103000 (54)
	7.60	Male	841	1.14	13.07	1420	1470	194	186	128000 (34)
6	4.57	Female	103	1.11	2.07	NC	NC	NC	NC	24900 (44)
	1.47	Male	93.5	1.23	2.07	NC	NC	NC	NC	30000 (22)
8	18.49	Female	496	1.17	5.07	804	868	46.9	43.5	72000 (46)
	16.48	Male	284	1.23	24.07	903	903	54.8	54.8	111000 (12)
Day 64										
3	3.63	Female	344	1.09	5.07	481	517	142	132	42500 (51)
	2.42	Male	282	1.11	5.07	418	464	192	173	74200 (29)
4	8.95	Female	1050	1.07	9.07	1360	1370	154	152	108000 (46)
	5.72	Male	861	1.09	9.07	1270	1320	230	223	176000 (41)
5	20.32	Female	1290	1.11	13.07	2080	2130	105	102	237000 (58)[d]
	13.14	Male	1610	1.11	13.07	2560	2680	204	195	329000 (36)
6	4.55	Female	341	1.09	5.07	458	490	108	101	53100 (39)
	3.16	Male	279	1.09	5.07	411	448	142	130	85400 (22)
8	15.32	Female	824	1.09	13.07	1470	1510	98.8	95.7	148000 (32)
	12.05	Male	462	1.14	5.07	792	860	71.4	65.8	272000 (27)

a: EDD calculated using the group mean aerosol concentration, group mean body weight of the toxicokinetic animals, an overall group mean minute volume measured in four toxicokinetic animals, and a 64 minute exposure period on the respective day of exposure. Dose was calculated from the deposition model based on Raabe.[1]

b: AE (0-24 hr) = amount excreted in urine over 24 hours from individual core rats; data are mean (CV); N = 10

c: NC = Not calculated; measurable plasma concentrations at only 3 sampling timepoints

d: N = 9



Best Available Copy

Figure 1 Amount of Formoterol Excreted in Urine Over 24 hours on Days 1 and 64 Following a 64-Minute Inhalation (Nose-Only) Administration of Formoterol Fumarate Alone or in Combination with SCH 32088 to Male and Female Rats

Respiratory Parameters: Tidal volume and minute volume were decreased for male and female rats in treatment groups that received mometasone furoate (MF). These effects were attributed to body weight losses in treatment groups that received MF. Respiratory rate and minute volume were increased for females in the formoterol alone group at week 13.

Mean respiratory rate, tidal volume, and minute volume for male and female rats at week 13

Group	Males			Females		
	Resp Rate Breaths/min	Tidal Volume mL/Breath	Min. Volume mL/minute	Resp Rate Breaths/min	Tidal Volume mL/Breath	Min. Volume mL/minute
AC	127	1.8	217.6	108	1.4	149.3
VC	131	1.8	235.1	121	1.4	162.8
Low MF/F	102	1.9	181.2	111	1.3	141.2
Mid MF/F	147	1.3	177.3	114	1.0	115.8

High MF/F	133	1.3	170.3	109	1.1	113.7
200:5 MF/F	147	1.4	201.4	121	1.2	129.1
MF	124	1.3	147.7	96	1.1	102.2
F	137	1.9	254.4	150	1.7	250.2

Dogs

Study title: **13-Week Oral Inhalation Toxicity Study of SCH418131 (SCH32088 with Formoterol) Aerosols in the Dog.**

Key study findings:

● Dogs (4/sex/group) were exposed by mouth-only inhalation to aerosols of MDI formulations of 3 dose levels of SCH418131 (MF/F) at a 50:5 ratio, one dose level of SCH418131 at a 200:5 ratio, SCH32088 alone, or formoterol fumarate alone.

● Decreased lymphocyte and eosinophil counts were observed in treatment groups that received mometasone.

● Cortisol levels in response to challenge with exogenous ACTH were decreased for all male and female treatment groups that received mometasone.

● Increases of alkaline phosphate activities and levels of cholesterol and triglyceride in treatment groups that received mometasone may have corresponded to histopathological findings of cytoplasmic vacuolation in the liver.

● Decreased duration of RR intervals (i.e., increased heart rate) was observed for treatment groups that received formoterol. These effects were attributed to formoterol. There was no evidence of additive or synergistic effects between mometasone and formoterol on the duration of the RR interval (i.e., heart rate).

● Histopathological changes were observed in the lung, thymus, adrenal gland, cecum, colon, duodenum, ileum, jejunum, larynx, axillary LN, bronchi LN, mandibular LN, mediastinal LN, mesenteric LN, nose/turbinates, pharynx, rectum, spleen, stomach, salivary gland, ovary, uterus, mammary gland, liver, femur, rib, and sternum. In general, these histopathological changes were attributable to the actions of mometasone.

● In the lungs, increased incidences of hyperplasia of bronchioloalveolar cells and bronchial inflammation were observed for male and female treatment groups, although dose-response relationships were not generally evident.

● Vacuolization and/or atrophy of the adrenal cortex were observed for all male and female treatment groups that received mometasone furoate.

● Lymph depletion was observed in the thymus, cecum, colon, duodenum, ileum, jejunum, larynx, axillary LN, bronchi LN, mandibular LN, mediastinal LN, mesenteric LN, nose/turbinates, pharynx, rectum, spleen, and stomach. Incidences of lymphoid

depletion in these tissues and organs were generally increased for all male and female treatment groups that received mometasone furoate.

● Incidences of sinus erythrophagocytosis in the mesenteric lymph nodes were increased for male and female treatment groups that received mometasone furoate.

● Hypoplasia of the ovaries and uterus was observed for females in the low and mid dose MF/F groups and 200:5 ratio MF/F group. For the high dose MF/F group, only 1 of 4 females was observed with hypoplasia of the uterus and there were no findings in the ovaries.

● Cytoplasmic vacuolation in the liver was observed for males and females in the high dose MF/F, 200:5 ratio MF/F, and MF alone groups. Fibrosis of the liver was observed for 1 of 4 females in the 200:5 ratio MF/F group.

● Increased fat deposition was observed in femur, rib, and sternum. These findings were observed in all treatment groups that received mometasone furoate.

● Epithelial vacuolization of the mammary gland was observed for females in the 200:5 ratio MF/F, MF alone, and formoterol alone groups. A clear relationship to mometasone or formoterol was not evident.

● Slightly increased incidences of infiltration of adipocytes were observed in the salivary glands for the mid dose MF/F, 200:5 ratio MF/F, MF alone, and formoterol alone groups. A relationship to treatment was unclear.

● A NOAEL was not identified based upon histopathology findings in all treatment groups.

● There was no evidence of additive or synergistic toxic effects with the combination of mometasone and formoterol.

Study no.: Schering-Plough Study number 99458 / (b) (6) Study number N104546
Volume #, and page #: Volumes 25-28, Pages 1-1605
Conducting laboratory and location: (b) (6)

Date of study initiation: June 2, 2004 (June 29, 2004)
GLP compliance: Yes
QA report: yes (X) no ( )
Drug, lot #, and % purity:
SCH 418131 (SCH 32088 [Mometasone Furoate (MF)] and Formoterol Fumarate [F]) in 50:5 or 200:5 ratio in a Metered Dose Inhaler (MDI). Other components in the MDI were oleic acid, ethanol, and HFA-227.
Batch numbers GH241103 (50:5 ratio), DH271103 (50:5 ratio), TJ081203 (200:5 ratio)

Formoterol fumarate in a MDI formulation. Other components in the MDI were oleic acid, ethanol, HFA-134a, and lactose.
Batch number Y1670903

SCH 32088 [Mometasone Furoate (MF)] in a MDI formulation. Other components in the MDI were oleic acid, ethanol, and HFA-227
Batch number 58364-026

Vehicle (Oleic acid/Ethanol Formulated with HFA-227 Propellant for a MDI)
Batch number DH101103

Methods

Doses: Dogs were exposed by mouth-only inhalation to aerosols of MDI formulations of three doses of SCH 418131 [SCH 32088 in combination with formoterol fumarate (MF/F)] at a 50:5 ratio, one dose of SCH 418131 at a 200:5 ratio, SCH 32088 alone, or formoterol fumarate alone. A vehicle group was exposed by mouth-only inhalation to aerosols of a MDI formulation comprised of oleic acid, ethanol, and HFA-227 propellant. An air-control group was exposed by mouth-only inhalation to HEPA-filtered room air. The inhalation exposures were 30 min daily for 91 consecutive days.

Overall Group Mean Estimated Doses of SCH 32088/Formoterol

Group	Mean Aerosol Concentration µg/L	Mean BW g (Week 13)	Minute Volume mL/min (Week 13)	Duration min	Dose µg/kg/day
Males					
Air Control	0.00/0.00	9.6	2449	30	0.00/0.00
Vehicle	0.00/0.00	10.0	2573	30	0.00/0.00
Low Dose MF/F	2.78/0.28	9.3	3388	30	40.38/4.06
Mid Dose MF/F	5.57/0.59	9.7	4360	30	69.84/7.37
High Dose MF/F	10.97/1.17	9.4	2724	30	133.50/13.82
200:5 Ratio MF/F	11.86/0.29	9.2	1464	30	89.09/2.15
SCH 32088	12.26/0.00	9.0	2756	30	154.10/0
Formoterol fumarate	0.00/1.01	10.1	2863	30	0/9.99
Females					
Air Control	0.00/0.00	7.6	1863	30	0.00/0.00
Vehicle	0.00/0.00	7.6	1934	30	0.00/0.00
Low Dose MF/F	2.79/0.29	8.0	2727	30	41.63/4.17
Mid Dose MF/F	5.54/0.59	7.7	1833	30	69.35/7.21

High Dose MF/F	10.95/1.18	7.8	2551	30	146.07/15.40
200:5 Ratio MF/F	11.89/0.29	7.8	1831	30	109.72/2.63
SCH 32088	12.29/0.00	7.6	1568	30	94.29/0.00
Formoterol fumarate	0.00/0.99	8.3	2393	30	0/9.92

Multiple common plenum exposure systems were designed: one for the low, mid, and high dose SCH 418131 groups, one for the 200:5 ratio SCH 418131 group, one for the SCH 32088 alone group, one for the formoterol fumarate alone group, one for the vehicle group, and one for the air-control group. The exposure duration was held constant for all dose groups at 30 min. Aerosol concentration levels were achieved by adjusting the number of MDIs actuated, the frequency of the actuation, and the amount of dilution air added upstream of the animal's breathing zone. Each system was designed to expose up to 8 animals at a time.

Four MDI generation modules capable of actuating a maximum of 15 MDIs each were placed on top of each aerosol plenum (except for the air-control). HEPA- and charcoal-filtered room air was added to the plenum to achieve target aerosol concentrations. Each plenum contained 10 exposure ports available for animals and/or sampling. All exposure systems had two ports (reference ports) dedicated for aerosol and particle size distribution sampling. An additional non-exposure/sampling port was added to allow fine adjustment of the plenum aerosol concentration. Pneumatic cylinders were used to activate the MDIs at a rate of twice per min.

Dogs were restrained during the exposure in slings. Dogs were exposed to test atmospheres through a mouth-only exposure mask.

Aerosol concentrations with the exposure atmosphere was measured daily using glass fiber filters for gravimetric analysis. Subsets of filters were analyzed by a chemical method for SCH 32088 and formoterol and subsets of the filters or other collected filters were analyzed for oleic acid and lactose (formoterol alone group).

Estimated doses of oleic acid and lactose

Group	Accumulated inhaled volume, L/day		Oleic acid mass inhaled dose, µg/kg/day		Lactose mass inhaled dose, µg/kg/day	
	Males	Females	Males	Females	Males	Females
AC	99.49	65.14	0.00	0.00	-	-
VC	91.65	66.73	5.32	4.78	-	-
Low MF/F	131.53	112.14	2.22	2.28	-	-
Mid MF/F	118.17	90.87	3.90	3.84	-	-
High MF/F	105.67	99.24	7.18	7.86	-	-
200:5 ratio MF/F	65.23	70.26	1.30	1.59	-	-
MF alone	104.01	55.27	8.84	5.36	-	-
F alone	99.72	84.37	2.87	2.94	188.67	180.65

Aerosol particle size distribution was measured using Mercer-style In-Tox Products brand cascade impactors. There were 8 stages in each impactor with effective cut-off diameters ranging from 0.5 to 10 µm. Glass fiber filters were used as the collection media on each stage of the impactor. Specific impactor samples were designated for analysis of components of the atmosphere by validated chemical methods. MMAD and GSD were calculated.

Mean Particle Size Distribution (µm)										
	Total Mass		SCH 32088		Formoterol Fumarate		Oleic Acid		Lactose	
Dose Group	MMAD	GSD	MMAD	GSD	MMAD	GSD	MMAD	GSD	MMAD	GSD
Vehicle	1.06	2.79	NA	NA	NA	NA	0.83	1.82	NA	NA
Low-dose MF/F	2.85	1.79	2.95	1.75	2.94	1.54	1.18	2.36		
Mid-dose MF/F	2.75	1.86	2.95	1.76	2.91	1.58	1.20	2.21		
High-dose MF/F	2.83	1.81	3.00	1.75	2.97	1.56	1.19	2.16		
200:5 ratio MF/F	3.21	1.74	3.25	1.66	3.17	1.49	1.41	2.47		
SCH 32088	3.32	1.85	3.49	1.67	NA	NA	1.57	2.33		
F	2.34	1.78	NA	NA	2.93	1.60	2.16	1.96		
F (for lactose)	2.29	1.82	NA	NA	NA	NA	NA	NA	2.21	1.82

NA = Not applicable

One liter-volume foil gas sample collection bags were used to collect a sample of the plenum atmosphere for chemical analysis of volatile components of the formulations, HFA-227 and ethanol.

Dose Group	Mean HFA-227 Concentration (ppm)	Mean Ethanol Concentration (ppm)
Air Control	ND	ND
Vehicle	3927	315.1
Low-dose MF/F	1231	101.2
Mid-dose MF/F	2363	192.2
High-dose MF/F	4592	369.4
200:5 ratio MF/F	1238	103.3
SCH 32088	2393	245.5
F	ND	252.6

ND = Not Detected

On-line aerosol monitoring was conducted using a Casella UK Microduct Pro aerosol monitor.

Species/strain: Male and Female Beagle Dogs were obtained from (b) (4) .
Number/sex/group or time point (main study): 4 dogs/sex/group
Route, formulation, volume, and infusion rate: Dogs were exposed by mouth-only inhalation.
Satellite groups used for toxicokinetics or recovery: None
Age: At the start of treatment, dogs were 7 to 8 months old.

Weight: At the start of treatment, body weight ranges were 6.4 to 9.9 kg for males and 6.1 to 8.3 kg for females.
Unique study design or methodology (if any): Dose selection was based upon a 2-week inhalation toxicity and toxicokinetic study of SCH32088 with Formoterol Aerosols in the Dog (Schering Plough Study number 99455 / (b) (4) study number N104542). Dogs (4/sex/group) were exposed by mouth-only inhalation to aerosols of a MDI formulation containing SCH32088 (mometasone furoate or MF) with formoterol (F) in a 50:5 ratio or formoterol-fumarate only for 30 min/day for 14 days. Nominal doses of MF/F for males and females combined in the low, mid, and high dose groups were 44.3/4.25 µg/kg/day, 90.6/9 µg/kg/day, and 172/17.6 µg/kg/day, respectively. The nominal dose for the formoterol only group was 14.5 µg/kg/day. Deposition was assumed to be 100% based upon the use of mouth-only inhalation. Heart rates were increased for males in low and high dose MF/F groups and formoterol only group. Heart rates were increased for females in the low, mid, and high dose MF/F groups and formoterol only group. White blood cell counts were decreased for females in the high dose MF/F group. Lymphocyte counts were decreased for males in high dose MF/F group and females in the mid and high dose MF/F groups. Eosinophil counts were decreased for males and females in the low, mid, and high dose MF/F groups. Neutrophil counts were decreased for females in the high dose MF/F group. Red blood cell counts, hemoglobin levels, and hematocrit values were decreased for females in the mid and high dose MF/F groups. ALP activities were increased for males and females in the low, mid, and high dose MF/F groups and the formoterol only group. GGT activity was increased for males in the high dose MF/F group. Phosphorus and potassium levels were increased for all male treatment groups. Cholesterol levels were increased for males in the low, mid, and high dose MF/F groups. Differences in absolute and relative organ weights between air-control and treatment groups were observed for the liver, thymus, axillary lymph node, prostate, adrenal gland, uterus, ovary, and spleen, although there were generally no correlations to histopathological findings. Absolute and relative liver weights were increased for males and females in the mid and high dose MF/F groups. Absolute and relative thymus weights were decreased for males in the mid and high dose MF/F groups. Absolute and relative axillary lymph node weights were decreased for males in the low, mid, and high dose MF/F groups and females in the mid and high dose MF/F groups. Absolute and relative prostate weights were decreased for males in the high dose MF/F group. Absolute and relative adrenal gland weights were slightly decreased for males in the low, mid, and high dose MF/F groups. Absolute and relative uterus and ovary weights were decreased for females in the formoterol group. Absolute and relative spleen weights were decreased for females in the high dose MF/F group. Target organs of toxicity were the adrenal gland, heart, ileum, jejunum, lymph nodes, lung, and rectum. Atrophy and/or vacuolization of the adrenal cortex were observed for males and females in the low, mid, and high dose MF/F groups. Cardiac fibrosis was observed for females in the mid and high dose MF/F groups and the formoterol only group. Atrophy of lymphoid tissue in the ileum was observed for males and females in the low, mid, and high dose MF/F groups. Atrophy of lymphoid tissue in the jejunum was observed for males and females in the low, mid, and high dose MF/F groups, although a dose-response relationship was not observed for female treatment groups. Atrophy of lymphoid tissue in the axillary lymph nodes was observed for males in the low, mid, and

high dose MF/F groups and females in the mid and high dose MF/F groups, although a dose-response relationship was not observed for female treatment groups. Atrophy of lymphoid tissue in the mandibular lymph nodes was observed for males and females in the high dose MF/F group. Acute alveolar inflammation was observed for males in the low and mid MF/F groups and formoterol group and for females in all treatment groups, although dose-response relationships were not evident for either males or females. Atrophy of lymphoid tissue was observed for males in the high dose MF/F group and females in the low, mid, and high dose MF/F groups.

Observation and Times:

Clinical signs: Dogs were observed twice daily for moribundity/mortality. Clinical observations were conducted during the dosing phase were conducted at least once daily between 1-2 hr following dose administration.

Body weights: Body weights were measured during the pre-treatment period, on the day prior to the start of exposure, weekly during the treatment period, on the day before necropsy, and the day of necropsy (fasted).

Food consumption: Food consumption was assessed by visual examination on a daily basis.

Ophthalmoscopy: Ophthalmic examinations were conducted pretest and within 1 week of the final exposure.

EKG: ECG measurements were collected once pretest (Week -2), day 1 (within 30 min post-exposure), and weeks 4 and 12 (within 45 min post-exposure). Waveform tracings of leads I, II, III, aVR, aVL, aVF, RV2, V2, V4, and V10 were collected for each animal. ECG waveform tracings were evaluated for evidence of cardiac dysfunction through examination of rhythm, morphology, and rate. ECG waveform morphology (P, QRS, and T waves), measurement of interval duration (PR, QRS, RR, and QT), and calculation of QTc interval using Fridericia's formula were performed.

Hematology: Blood samples for measurement of hematology and coagulation parameters were collected at weeks -4, -2/-1, 4, and 12.

Clinical chemistry: Blood samples for measurement of serum chemistry parameters were collected at weeks -4, -2/-1, 4, and 12. These parameters included ACTH response test and serum Troponin T.

Urinalysis: Urine samples for analysis of urinalysis parameters were collected twice pretest (weeks -4 and -2/-1) and during weeks 4 and 12.

Gross pathology: Dogs were sacrificed on day 92 and submitted to necropsy examination.

Organ weights: Absolute and relative organ weights were determined for the adrenal glands, brain, epididymides, heart, kidneys, liver, lung plus bronchi, lymph nodes (axillary), ovaries, prostate, spleen, salivary gland, testes, thymus, thyroid gland, and uterus with cervix.

Histopathology: Organs/tissues collected from all dogs were processed to slides and stained with hematoxylin and eosin. The following processed organs/tissues were examined by the study pathologist:

- organ/tissues processed from the air-control, vehicle-control, high dose SCH 418131, 200:5 ratio SCH 418131, SCH 32088 alone, and formoterol alone groups

- all gross findings
- organs identified as potential target organs by the pathologist (adrenal gland, heart, lymphoid tissues, liver, mammary gland, ovary, uterus, and bone marrow) following microscopic examination of the high dose SCH 418131 group were examined in the low and mid dose SCH 418131 groups.

Toxicokinetics: Blood samples for measurement of plasma concentrations of SCH32088 and formoterol were collected from all dogs on days 1 and 57 at 0.25 (day 57 only), 0.50 (day 1 only), 2, 4, 6, and 12 hr and immediately prior to the next day's exposure (at least 23 hr post-dose). Urine (non-fasted) for measurement of formoterol concentrations was collected from dogs on days 1 and 57 over a 24-hr period. Plasma samples from the low, mid, and high dose SCH418131 groups, the 200:5 ratio SCH418131 group, and the SCH 32088 alone group were analyzed for SCH 32088 concentrations using a liquid chromatographic-tandem mass spectrometric (LC-MS/MS) method. Plasma and urine samples from the low, mid, and high dose SCH 418131 groups, the 200:5 ratio SCH 418131 group, and the formoterol alone group were analyzed for formoterol concentrations using a LC-MS/MS method. Plasma samples for SCH 32088 were analyzed by Schering-Plough Research Institute of Lafayette, NJ. Plasma and urine samples for formoterol were analyzed by Novartis, France.

Respiratory measurements: Respiratory rate, tidal volume, and minute volume were measured for each dog on a weekly basis.

Results:

Mortality: None.

Clinical signs: There were no treatment-related clinical signs.

Body weights: There were no treatment-related effects on body weight gain for males and females in the low, mid, and high dose MF/F groups, 200:5 ratio MF/F groups, and MF alone groups. Body weight gains were increased for males and females in the formoterol alone groups, which could be attributed to the pharmacological actions of formoterol.

Food consumption: There were no treatment-related effects on food consumption.

Ophthalmoscopy: There were no treatment-related ophthalmic findings on day 85.

EKG: Decreased duration of RR intervals (i.e., increased heart rate) was observed for treatment groups that received formoterol. Effects for male treatment groups were primarily observed on day 1. Effects for female treatment groups were observed on day 1 and weeks 4 and 12. These effects were attributed to formoterol. There was no evidence of additive or synergistic effects between mometasone and formoterol on the duration of the RR interval (i.e., heart rate). There were no treatment-related changes of other ECG parameters.

RR Interval (seconds)								
Males	AC	VC	LD 50:5	MD 50:5	HD 50:5	200:5	MF Only	F only
Week -2	0.746	0.597	0.646	0.805	0.596	0.701	0.737	0.678
Day 1	0.588	0.569	0.501 (85%)	0.411 (69%)	0.311 (53%)	0.479 (81%)	0.528 (90%)	0.312 (53%)
Week 4	0.528	0.619	0.551	0.593	0.454 (86%)	0.605	0.765	0.534
Week 12	0.502	0.504	0.502	0.658	0.392 (78%)	0.517	0.593	0.404 (80%)
Females	AC	VC	LD 50:5	MD 50:5	HD 50:5	200:5	MF Only	F only
Week -2	0.790	0.814	0.609	0.726	0.681	0.714	0.817	0.605
Day 1	0.490	0.616	0.439	0.309 (63%)	0.327 (67%)	0.347 (71%)	0.528	0.285 (58%)
Week 4	0.721	0.560 (78%)	0.492 (68%)	0.452 (63%)	0.445 (62%)	0.484 (67%)	0.594 (82%)	0.461 (64%)
Week 12	0.577	0.593	0.445 (77%)	0.352 (61%)	0.425 (74%)	0.488 (85%)	0.546	0.497 (86%)

Hematology: Observed changes of hematology parameters (i.e., decreases of white blood cell, lymphocyte, and eosinophil counts) were consistent with the pharmacological effects of mometasone.

White blood cell counts on day 78 were decreased for males in the high dose MF/F and 200:5 ratio MF/F groups and females in the 200:5 MF/F group. Lymphocyte percentages and counts on day 78 were decreased for females in the high dose MF/F group. Eosinophil percentages and counts on day 23 were decreased for males in the high dose MF/F and MF alone groups and females in the high dose MF/F, 200:5 MF/F, and MF alone groups. Eosinophil percentages and counts on day 78 were decreased for males and females in the mid and high dose MF/F groups, the 200:5 ratio MF/F group, and MF alone group.

Hematology parameters (PT1, PT2, D23, and D78)

Parameter	Day	Sex	AC	VC	MF/F			200:5 MF/F	MF	F
					Low	Mid	High			
WBC counts K/µL	78	M	10.78	9.92	11.17	10.90	7.78 (72%)	8.61 (80%)	10.60	11.31
		F	10.73	9.06	10.93	10.03	9.23	8.27 (77%)	9.57	8.98
Lymphocytes %	78	F	30.8	27.3	26.6	27.3	23.8 (77%)	34.9	31.1	32.7
Lymphocytes K/µL	78	F	3.28	2.45	2.89	2.67	2.19 (67%)	2.85	2.98	2.91
Eosinophils %	23	M	2.7	3.9	2.8	3.2	1.5 (56%)	2.9	1.3 (48%)	3.3
		F	4.9	1.8	3.6	2.3	1.1 (22%)	1.3 (27%)	1.0 (20%)	1.8
	78	M	2.4	3.9	2.2	1.5 (63%)	0.7 (29%)	0.7 (29%)	0.3 (13%)	3.0
		F	3.4	2.2	3.0	0.5 (15%)	0.3 (9%)	1.9 (56%)	1.3 (38%)	2.2
Eosinophils K/µL	23	M	0.27	0.40	0.32	0.43	0.14 (52%)	0.24	0.16 (59%)	0.46
		F	0.43	0.17	0.47	0.32	0.12* (28%)	0.14 (33%)	0.12* (28%)	0.19 (44%)
	78	M	0.25	0.39	0.25	0.16 (64%)	0.05* (20%)	0.05* (20%)	0.03* (12%)	0.32
		F	0.32	0.20	0.33	0.04 (13%)	0.03 (9%)	0.16 (50%)	0.15 (47%)	0.20

*p≤0.05

Clinical chemistry: Cortisol levels in response to challenge with exogenous adrenocorticotrophic hormone (ACTH) on days 23 and 78 were decreased for all male and female treatment groups that received mometasone (there was no summary of this data as only individual animal values were provided).

Differences in activities of alkaline phosphate (ALP) and levels of cholesterol and triglyceride between control and treatment groups may have corresponded to histopathological findings of cytoplasmic vacuolation in the liver. These histopathological changes in the liver as well as changes of ALP, cholesterol, and triglyceride concentrations appeared to result from the actions of mometasone. There were no histopathological findings in the kidneys that appeared to correspond to differences in concentrations of potassium, blood urea nitrogen, and creatinine between control and treatment groups.

ALP activities on days 23 and 78 were increased for males and females in the high dose MF/F group. Cholesterol levels on days 23 and 78 were increased for males in the mid and high dose MF/F groups, the 200:5 MF/F group, the MF alone group, and the formoterol alone group. Cholesterol levels on days 23 and 78 were increased for females in the low, mid, and/or high dose MF/F groups. Triglyceride levels on days 23

and 78 were increased for males in the mid and high dose MF/F groups and MF alone group. Triglyceride levels on day 78 were also increased for males in the formoterol alone group. Triglyceride levels on day 23 were increased for females in the 200:5 ratio MF/F and MF alone groups. Potassium levels on day 78 were increased for males in the high dose MF/F, 200:5 ratio MF/F, MF alone and formoterol alone groups. Blood urea nitrogen (BUN) levels on day 23 were slightly increased for females in the high dose MF/F, 200:5 ratio MF/F, MF alone and formoterol alone groups. BUN levels on day 78 were slightly increased for females in the high dose MF/F group and males and females in the formoterol only group. Creatinine levels on day 78 were increased for males in the formoterol only group. There were no treatment-related effects on Troponin T levels on days 23 or 78.

Serum chemistry parameters (PT1, PT2, D23, and D78)

Parameter	Day	Sex	AC	VC	MF/F			200:5 MF/F	MF	F
					Low	Mid	High			
ALP U/L	23	M	81	101 (125%)	123* (152%)	120 (148%)	142* (175%)	103 (127%)	112 (138%)	103 (127%)
		F	76	84	109* (143%)	128 (168%)	187 (246%)	97 (128%)	107 (141%)	103 (136%)
	78	M	68	89 (131%)	109 (160%)	90 (132%)	124 (182%)	88 (129%)	89 (131%)	103 (127%)
		F	67	123 (184%)	85	108	200 (298%)	81	84	88
Cholesterol mg/dL	23	M	169	165	172	216 (128%)	227* (134%)	203 (120%)	221* (131%)	200 (118%)
		F	168	194 (116%)	187	226 (135%)	243* (145%)	232 (138%)	186	183
	78	M	167	164	173	223 (134%)	235 (141%)	202 (121%)	237 (142%)	214 (128%)
		F	179	225	200	226	252 (141%)	266* (149%)	193	183
Triglyceride mg/dL	23	M	42	37	39	49 (117%)	59 (140%)	35	54 (129%)	42
		F	34	56 (165%)	52 (153%)	49 (144%)	41 (121%)	74* (218%)	66 (194%)	37
	78	M	46	44	42	64 (139%)	75 (163%)	39	68 (148%)	66 (144%)
		F	40	64	53	58	64	43	70	43
Potassium mEq/L	78	M	4.8	4.7	4.9	5.1	5.5* (115%)	5.3 (110%)	5.3 (110%)	5.4* (113%)
BUN mg/dL	23	F	16	16	16	17	19 (119%)	19 (119%)	18 (113%)	19 (119%)
	78	M	18	17	16	18	18	17	19	25 (139%)
		F	18	17	17	18	22 (122%)	18	20	24* (133%)
Creatinine mg/dL	78	M	0.8	0.9	0.8	0.8	0.8	0.8	0.8	1.1* (138%)

*p≤0.05

Urinalysis: Urinary volumes on days 23 and 78 were increased for male and female rats in most treatment groups that received mometasone. Given increased urinary volumes, osmolality on days 23 and 78 were decreased for male and female rats in most treatment groups that received mometasone. Further, concentrations of sodium, chloride, potassium, phosphorus, and calcium on days 23 and 78 were decreased for male and female rats in most treatment groups that received mometasone. Creatinine clearance on days 23 and 78 were slightly increased for males and females in most treatment groups that received mometasone. There were no treatment-related histopathological findings in the kidneys. These effects are attributed to the pharmacological actions of mometasone.

Serum chemistry parameters (PT1, PT2, D23, and D78)

Parameter	Day	Sex	AC	VC	MF/F			200:5 MF/F	MF	F
					Low	Mid	High			
Volume mL	23	M	208.8	185.3	173.8	272.8 (131%)	314.0 (150%)	424.8 (203%)	452.3 (217%)	164.5
		F	157.8	274.8	246.5	241.3	305.8 (194%)	496.5 (315%)	380.3 (241%)	203.5
	78	M	207.8	188.5	299.3 (144%)	369.3 (178%)	628 (302%)	423.0 (204%)	351.8 (169%)	359.5 (173%)
		F	352.3	207.3	719.3 (204%)	431.0 (122%)	399.8 (113%)	408.3 (116%)	489.3 (139%)	367.0
Osmolality mosm/kg	23	M	1390	1332	1657	1457	1134 (82%)	869 (63%)	999 (72%)	1334
		F	1372	1540	923 (67%)	953 (70%)	1168 (85%)	840 (61%)	1023 (75%)	1563
	78	M	1256	1465	1494	1193	665 (53%)	807 (64%)	853 (68%)	1182
		F	1043	1506	658 (63%)	877 (84%)	958 (92%)	826 (79%)	840 (80%)	1204
Sodium mEq/L	23	M	109	110	88	78	73	56 (51%)	74 (68%)	84 (77%)
		F	94	92	56 (60%)	47 (50%)	74 (79%)	51 (54%)	78 (83%)	119
	78	M	98	107	108	78 (80%)	49 (50%)	65 (66%)	63 (64%)	79 (81%)
		F	76	86	51 (67%)	73	85	64 (84%)	57 (75%)	97
Potassium mEq/L	23	M	171.4	152.5	186.5	184.6	127.5 (74%)	90.5 (53%)	104.7 (61%)	152.4
		F	154.0	175.1	107.1 (70%)	98.9 (64%)	131.5	85.6 (56%)	98.8 (64%)	178.0
	78	M	164.4	152.0	154.8	120.2	49.8 (30%)	53.6 (33%)	61.9 (38%)	107.7 (66%)
		F	102.7	154.7	63.2 (62%)	79.6 (78%)	85.6 (85%)	87.2 (85%)	97.7 (95%)	125.2
Chloride mEq/L	23	M	131	115	79 (60%)	86 (66%)	92 (70%)	45 (34%)	75 (57%)	107
		F	132	149	91 (69%)	76 (57%)	90 (68%)	53 (40%)	98	150

	78	M	120	116	118	88 (73%)	52 (43%)	67 (56%)	65 (54%)	101
		F	108	174	73 (68%)	70 (65%)	83 (77%)	70 (65%)	68 (63%)	109
Phosphorus mg/dL	23	M	195.5	187.0	261.5	241.9	191.3	135.4 (69%)	155.5 (80%)	203.5
		F	224.1	231.2	158.8	173.3	196.1	126.3 (56%)	154.8 (69%)	249.1
	78	M	198.8	199.7	219.5	181.1	100.2 (50%)	103.2 (52%)	123.3 (62%)	174.1
		F	164.6	251.9	106.7 (65%)	127.6 (78%)	120.0 (73%)	117.2 (71%)	137.0 (83%)	156.6
Calcium mg/dL	23	M	6.2	7.7	7.1	7.9	7.8	4.5 (73%)	5.8	11.3
		F	6.7	8.3	6.9	6.3	6.3	4.1 (61%)	5.4 (81%)	8.3
	78	F	8.2	14.9	8.0	6.6	6.8	5.7 (70%)	5.2 (63%)	7.0
Creatinine clearance mL/min	23	M	23.9	19.9	25.4	31.1 (130%)	27.3 (114%)	27.5 (115%)	31.6 (132%)	18.0
		F	17.5	23.7	16.5	20.6	25.8 (147%)	27.3 (156%)	25.4 (145%)	22.4 (128%)
	78	M	22.8	20.8	36.5 (160%)	36.5 (160%)	32.5 (143%)	21.7	22.8	27.9
		F	24.3	22.2	30.1	21.5	26.6	22.8	33.2 (137%)	27.4

Gross pathology: Gross pathological findings were evident in the adrenal glands, thymus, axillary lymph nodes, and uterus and attributed to the actions of mometasone. Small adrenal glands were observed for females in the low and mid dose MF/F groups and males and females in the high dose MF/F, 200:5 ratio MF/F, and MF alone groups. These finding corresponded to adrenal cortical atrophy and vacuolization. Small thymuses were observed for males and female in the low, mid, and high dose MF/F groups, females in the 200:5 ratio MF/F group, and males and females in the MF alone group. These findings corresponded to lymphoid depletion. Small axillary lymph nodes were observed for females in the high dose MF/F group and corresponded to lymphoid depletion. A small uterus was observed for one female in the high dose MF/F group and one female in the 200:5 MF/F group. This finding corresponded to endometrial atrophy.

Organ weights: Differences of absolute and/or relative organ weights between treatment and air-control groups were observed for the adrenal glands, axillary LN, spleen, thymus, testis, uterus, ovary, salivary gland, and thyroid gland. Many of these differences could be attributed to the pharmacological action of mometasone as noted below.

Adrenal glands weights were decreased for treatment groups that received mometasone and appeared to correspond to histopathological findings of cortical atrophy. This finding is attributed to the pharmacological action of mometasone.

Axillary LN weights were decreased for males in the high dose MF/F, 200:5 ratio MF/F, and MF alone groups and females in the high dose MF/F group. Decreased weights appeared to correspond to histopathological findings of lymphoid depletion. This finding is attributed to the pharmacological action of mometasone.

Spleen weights were increased for males in the 200:5 ratio MF/F group and females in the high dose MF/F and MF alone groups. Increased weights do not appear to correspond to observed histopathological findings in the spleen (i.e., lymphoid depletion).

Thymus weights were decreased for males in the high dose MF/F and MF alone groups, which appear to correspond to histopathological findings in the thymus of lymphoid depletion. This finding is attributed to the pharmacological action of mometasone. Thymus weights were increased for males in the 200:5 ratio MF/F group and females in the MF alone; however, increased weights do not appear to correspond to histopathological findings.

Uterus and ovary weights were decreased for treatment groups that received mometasone. These findings appeared to correspond to histopathological findings of hypoplasia. These findings are attributed to the pharmacological action of mometasone.

Salivary gland weights were increased for females in the high dose MF/F group. This finding may correspond to histopathological findings of adipocyte infiltration. This finding is attributed to the pharmacological action of mometasone.

Testis weights were increased for males in the low, mid, and high dose MF/F groups, the MF alone group, and the formoterol alone group; however, they were no corresponding histopathological findings. These differences may be due to variations in sexual maturity.

Thyroid gland weights were increased for females in the MF alone group. There were no corresponding histopathological findings.

Absolute and relative organ weights

Organ/Tissue	Sex	AC	VC	MF/F			200:5 MF/F	MF	F
				Low	Mid	High			
Adrenals g	M	0.822	0.990	0.785	0.669 (81%)	0.532 (65%)	0.465 (57%)	0.584 (71%)	0.916
	F	0.766	0.937	0.639 (83%)	0.489 (64%)	0.483 (63%)	0.447 (58%)	0.469 (61%)	0.980
Adrenals %BW	M	0.0088	0.0099	0.0084	0.0068 (77%)	0.0056 (64%)	0.0052 (59%)	0.0065 (74%)	0.0091
	F	0.0099	0.0124	0.0079 (80%)	0.0063 (64%)	0.0063 (64%)	0.0058 (59%)	0.0061 (62%)	0.0119
Adrenals %BrW	M	1.02	1.32	1.02	0.88 (86%)	0.72 (71%)	0.62 (61%)	0.79 (77%)	1.23
	F	1.08	1.24	0.88 (81%)	0.67 (62%)	0.70 (65%)	0.60 (56%)	0.63 (58%)	1.36

Axillary LN g	M	0.6448	0.4837 (75%)	0.4640 (72%)	0.4374 (68%)	0.4103 (64%)	0.3487 (54%)	0.4363 (68%)	0.5261 (82%)
	F	0.4523	0.2514	0.3205	0.3111	0.1547 (62%)	0.3044	0.3537	0.3827
Axillary LN %BW	M	0.0072	0.0048	0.0050	0.0045	0.0043	0.0037 (51%)	0.0051	0.0053
	F	0.0059	0.0032	0.0040	0.0039	0.0020 (34%)	0.0040	0.0047	0.0046
Axillary LN %BrW	M	0.778	0.641	0.599	0.600	0.557 (72%)	0.457 (59%)	0.590 (76%)	0.704
	F	0.639	0.336	0.441	0.425	0.225 (35%)	0.411	0.475	0.532
Spleen g	M	60.64	63.96	63.62	59.38	53.57	78.61 (130%)	55.34	57.32
	F	43.36	49.59	49.65	46.80	53.63 (124%)	47.29	82.21 (190%)	43.15
Spleen %BW	M	0.643	0.629	0.687	0.600	0.540	0.864 (134%)	0.606	0.578
	F	0.559	0.640	0.611	0.598	0.691	0.621	1.048 (187%)	0.532
Spleen %BrW	M	75.2	84.6	82.0	80.5	72.0	105.8 (141%)	75.1	76.6
	F	61.1	65.2	69.2	63.5	77.6 (127%)	63.7	111.8 (183%)	60.3
Thymus g	M	4.85	8.15	5.32	4.11	2.76 (57%)	10.30 (212%)	2.90 (60%)	8.83
	F	5.65	4.53	6.86	5.19	6.91	5.44	9.43 (167%)	6.37
Thymus %BW	M	0.045	0.080	0.058	0.041	0.028 (62%)	0.117 (260%)	0.031 (69%)	0.085 (189%)
	F	0.072	0.059	0.085	0.066	0.087	0.073	0.123 (171%)	0.078
Thymus %BrW	M	6.3	10.8	6.8	6.1	3.7 (59%)	14.0 (222%)	3.9 (62%)	11.9
	F	7.9	6.1	10.1	7.1	10.2	7.4	12.8 (162%)	9.0
Uterus g	F	11.78	11.87	6.58 (47%)	5.54 (47%)	2.38 (20%)	7.07 (60%)	6.57 (56%)	15.64
Uterus %BW	F	0.145	0.156	0.069 (48%)	0.070 (48%)	0.032 (22%)	0.088 (61%)	0.085 (59%)	0.193
Uterus %BrW	F	16.5	15.8	8.3 (50%)	7.6 (46%)	3.4 (21%)	9.5 (58%)	8.7 (53%)	21.7
Ovary g	F	1.15	1.62	0.79 (69%)	0.81 (70%)	0.60 (52%)	0.92 (80%)	0.99 (86%)	1.45
Ovary %BW	F	0.014	0.021	0.010	0.010	0.008 (57%)	0.012	0.013	0.018
Ovary %BrW	F	1.6	2.2	1.1 (69%)	1.1 (69%)	0.9 (56%)	1.2 (75%)	1.3 (81%)	2.0)
Salivary g	F	7.493	8.460	8.562	8.825	9.549 (127%)	8.157	8.869	8.403
Salivary %BrW	F	10.55	11.16	11.98	12.03	13.79 (131%)	11.00	11.93	11.72
Thyroid %BW	F	0.0072	0.0078	0.0081	0.0092	0.0077	0.0084	0.0101 (140%)	0.0080
Testis	M	10.13	13.21	14.53.	15.09	11.79	10.75	14.85	12.64

g				(143%)	(149%)	(116%)		(147%)	(125%)
Testis %BW	M	0.106	0.134	0.155	0.154	0.124	0.114	0.162 (153%)	0.125
Testis %BrW	M	12.6	17.6	18.6	20.0 (159%)	15.9	14.2	20.0 (159%)	17.1
Thyroid %BrW	F	0.78	0.78	0.92	0.98	0.87	0.87	1.02 (131%)	0.88

Histopathology: Histopathological changes were observed in the lung, thymus, adrenal gland, cecum, colon, duodenum, ileum, jejunum, larynx, axillary LN, bronchi LN, mandibular LN, mediastinal LN, mesenteric LN, nose/turbinates, pharynx, rectum, spleen, stomach, salivary gland, ovary, uterus, mammary gland, liver, femur, rib, and sternum. In general, these histopathological changes were attributable to the actions of mometasone.

In the lungs, increased incidences of hyperplasia of bronchioloalveolar cells and bronchial inflammation were observed for male and female treatment groups, although dose-response relationships were not generally evident. Hyperplasia of bronchioloalveolar cells in the lung was observed for males in the low, mid, and high dose MF groups, the 200:5 ratio MF/F group, and the formoterol alone group. An increased incidence of hyperplasia of bronchioloalveolar cells was also observed for females in the mid dose MF/F group. Bronchial inflammation in the lung was observed for males in mid and high dose MF/F groups, the 200:5 ratio MF/F group, the MF alone group, and the formoterol alone group. Increased incidences of bronchial inflammation were observed for females in the mid dose MF/F, 200:5 ratio MF/F, and MF alone group; however, there were no findings in the high dose MF/F group.

Vacuolization and/or atrophy of the adrenal cortex were observed for all male and female treatment groups that received mometasone furoate.

Lymph depletion was observed in the thymus, cecum, colon, duodenum, ileum, jejunum, larynx, axillary LN, bronchi LN, mandibular LN, mediastinal LN, mesenteric LN, nose/turbinates, pharynx, rectum, spleen, and stomach. Incidences of lymphoid depletion in these tissues and organs were generally increased for all male and female treatment groups that received mometasone furoate

Incidences of sinus erythrophagocytosis in the mesenteric lymph nodes were increased for male and female treatment groups that received mometasone furoate.

Hypoplasia of the ovaries and uterus was observed for females in the low and mid dose MF/F groups and 200:5 ratio MF/F group. For the high dose MF/F group, only 1 of 4 females was observed with hypoplasia of the uterus and there were no findings in the ovaries.

Cytoplasmic vacuolation in the liver was observed for males and females in the high dose MF/F, 200:5 ratio MF/F, and MF alone groups. Fibrosis of the liver was observed for 1 of 4 females in the 200:5 ratio MF/F group.

Increased fat deposition was observed in femur, rib, and sternum. These findings were observed in all treatment groups that received mometasone furoate.

Epithelial vacuolization of the mammary gland was observed for females in the 200:5 ratio MF/F, MF alone, and formoterol alone groups. A clear relationship to mometasone or formoterol was not evident.

Slightly increased incidences of infiltration of adipocytes were observed in the salivary glands for the mid dose MF/F, 200:5 ratio MF/F, MF alone, and formoterol alone groups. A relationship to treatment was unclear.

Histopathological findings in dogs after exposure for 13 weeks

Organ	Sex	AC	VC	MF/F				MF	F
				Low	Mid	High	200:5		
Lung									
-hyperplasia,	M	0/4	0/4	2/4	2/4	2/4	2/4	0/4	1/4
bronchioloalveolar cells	F	1/4	1/4	1/4	3/4	1/4	1/4	0/4	0/4
-inflammation, bronchial	M	0/4	0/4	0/4	1/4	2/4	2/4	4/4	1/4
	F	1/4	1/4	0/4	2/4	0/4	3/4	3/4	0/4
Adrenal gland									
-vacuolization, cortex	M	1/4	0/4	0/4	2/4	3/4	4/4	4/4	0/4
	F	0/4	0/4	1/4	1/4	2/4	2/4	3/4	0/4
-atrophy, cortex	M	0/4	0/4	4/4	3/4	4/4	4/4	4/4	0/4
	F	0/4	0/4	2/4	4/4	4/4	4/4	4/4	0/4
Thymus									
-depletion, lymphoid	M	2/4	2/4	4/4	3/4	4/4	4/4	4/4	3/4
	F	1/4	1/4	3/4	4/4	4/4	3/4	4/4	2/4
Cecum									
-depletion, lymphoid	M	0/4	0/4	0/4	2/4	4/4	4/4	4/4	0/4
	F	0/4	0/4	1/4	4/4	3/4	4/4	4/4	0/4
Colon									
-depletion, lymphoid	M	0/4	0/4	1/4	1/4	0/4	2/4	1/4	0/4
	F	0/4	0/4	1/4	2/4	0/4	2/4	3/4	0/4
Duodenum									
-depletion, lymphoid	M	0/4	0/4	0/4	1/4	0/4	3/4	1/4	0/4
	F	0/4	0/4	1/4	2/4	0/4	1/4	1/4	0/4
Ileum									
-depletion, lymphoid	M	0/4	0/4	1/4	2/4	4/4	4/4	4/4	0/4
	F	0/4	0/4	1/4	4/4	4/4	4/4	4/4	0/4
Jejunum									
-depletion, lymphoid	M	0/4	0/4	1/4	2/4	4/4	4/4	3/4	0/4
	F	0/4	0/4	2/4	4/4	4/4	4/4	4/4	0/4
Larynx									
-depletion, lymphoid	M	0/4	0/4	1/4	1/4	1/4	4/4	4/4	0/4
	F	0/4	0/4	1/4	2/4	2/4	4/4	4/4	0/4
LN, Axillary									
-depletion, lymphoid	M	0/4	0/4	0/4	2/4	3/4	3/4	4/4	0/4
	F	1/4	0/4	2/4	4/4	4/4	4/4	4/4	1/4
LN Bronchi									
-depletion, lymphoid	M	0/4	0/4	0/4	2/4	4/4	4/4	4/4	0/4
	F	0/4	0/4	1/4	0/4	3/4	4/4	4/4	0/4
LN Mandibular									
-depletion, lymphoid	M	0/4	0/4	0/4	2/4	3/4	4/4	4/4	0/4
	F	0/4	0/4	2/4	3/4	4/4	4/4	4/4	0/4
LN Mediastinal									
-lymphoid, depletion	M	-	-	-	-	1/1	1/1	-	-
	F	-	-	-	-	1/1	1/1	-	-
-congestion and hemorrhage	M	-	-	-	-	-	-	-	-
	F	-	-	-	-	-	-	-	-
LN Mesenteric									
-erythrophagocytosis, sinus	M	1/4	1/4	2/4	3/4	4/4	3/4	3/4	0/4
	F	1/4	0/4	2/4	2/4	1/4	1/4	2/4	0/4

-depletion, lymphoid	M	0/4	0/4	0/4	2/4	4/4	3/4	4/4	0/4
	F	0/4	0/4	2/4	4/4	4/4	4/4	3/4	0/4
Nose/Turbinates									
-depletion, lymphoid	M	0/4	0/4	2/4	2/4	3/4	4/4	4/4	0/4
	F	0/4	0/4	2/4	4/4	3/4	2/4	3/4	0/4
Pharynx									
-lymphoid depletion	M	0/4	0/4	1/4	0/4	3/4	4/4	4/4	0/4
	F	0/4	0/4	1/4	2/4	2/4	0/4	1/4	0/4
Rectum									
-depletion, lymphoid	M	0/4	0/4	1/4	2/4	3/4	4/4	4/4	0/4
	F	0/4	0/4	1/4	4/4	4/4	3/4	4/4	0/4
Spleen									
-depletion, lymphoid	M	2/4	0/4	1/4	2/4	4/4	4/4	4/4	0/4
	F	0/4	0/4	2/4	4/4	3/4	4/4	4/4	0/4
-infiltration, granulocytic	M	0/4	1/4	0/4	1/4	3/4	0/4	1/4	1/4
	F	3/4	2/4	2/4	0/4	1/4	1/4	1/4	2/4
Stomach									
-depletion, lymphoid	M	0/4	0/4	0/4	0/4	3/4	4/4	0/4	0/4
	F	0/4	0/4	1/4	2/4	3/4	2/4	2/4	0/4
Salivary gland									
-infiltration, adipocyte	M	0/4	0/4	0/4	0/4	0/4	3/4	1/4	2/4
	F	1/4	1/4	0/4	2/4	1/4	2/4	1/4	1/4
Ovary									
-hypoplasia	F	0/4	0/4	3/4	3/4	0/4	3/4	0/4	0/4
Uterus									
-hypoplasia	F	0/4	0/4	3/4	3/4	1/4	4/4	0/4	0/4
Liver									
-cytoplasmic vacuolation	M	0/4	0/4	0/4	0/4	4/4	4/4	4/4	0/4
	F	0/4	0/4	0/4	0/4	4/4	4/4	4/4	0/4
-fibrosis	M	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
	F	0/4	0/4	0/4	0/4	0/4	1/4	0/4	0/4
Femur									
-increased fat deposition	M	0/4	0/4	0/4	2/4	4/4	4/4	4/4	0/4
	F	0/4	0/4	2/4	4/4	2/4	4/4	4/4	0/4
Rib									
-increased fat deposition	M	0/4	0/4	0/4	2/4	4/4	2/4	1/4	0/4
	F	0/4	0/4	1/4	3/4	2/4	2/4	1/4	0/4
Sternum									
-increased fat deposition	M	0/4	0/4	0/4	2/4	4/4	4/4	4/4	0/4
	F	0/4	0/4	2/4	4/4	2/4	4/4	4/4	0/4
Mammary gland									
-epithelial vacuolization	M	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
	F	0/4	0/4	0/4	0/4	0/4	2/4	1/4	2/4

Toxicokinetics: For the low, mid, and high dose MF/F groups on days 1 and 57, C_{max} and AUC values for mometasone (SCH32088) and formoterol generally increased in a dose proportional manner. It was noted on day 1, that C_{max} and AUC values for mometasone and formoterol in females from the mid dose MF/F group were equal to or greater than values for females in the high dose MF/F group. C_{max} and AUC values for mometasone and formoterol in the high dose MF/F group on both days 1 and were

greater than those for the 200:5 ratio MF/F group. C_{max} and AUC values for mometasone in the high dose MF/F group were greater than values for the mometasone only group. These findings are consistent with inhaled doses of mometasone and formoterol. There were no consistent differences between males and females with regard to C_{max} and AUC values for mometasone and formoterol.

For the low, mid, and high dose MF/F groups, urinary excretion of formoterol increased with elevating dose. For the high dose MF/F group, urinary excretion of formoterol was greater than for the 200:5 ratio MF/F group. Urinary excretion of formoterol for the formoterol alone group was greater than for high dose MF/F group.

There was no evidence of any interactions on toxicokinetic parameters.

Table 1 Mean (CV) SCH 32088 Toxicokinetic Parameters on Days 1 and 57 Following a 30-Minute Inhalation (Mouth-Only) Administration of SCH 32088 Alone or in Combination with Formoterol Fumarate to Male and Female Dogs

			SCH 32088							
Day	Group	Sex[a]	EDD[b] (µg/kg/day)	Cmax (pg/mL)	Tmax (hr)	tf (hr)	AUC(tf) (pg·hr/mL)	AUC(0-24 hr) (pg·hr/mL)	AUC(0-24 hr)/EDD (pg·hr/mL)/(µg/kg/day)	AUC(tf)/EDD (pg·hr/mL)/(µg/kg/day)
1	3	Female	32.7 (23)	140 (45)	0.64 (8)	10.00 (50)	645 (24)[c]	746 (24)[c]	21.1 (28)[c]	18.2 (28)[c]
		Male	22.6 (57)	89.4 (91)	0.67 (7)	6.50 (66)	499 (NC)[d,e]	566 (NC)[d]	20.6 (NC)[d]	17.9 (NC)[d]
	4	Female	126 (41)	723 (59)	0.66 (4)	19.63 (45)	3120 (70)	3130 (69)	28.8 (64)	28.7 (65)
		Male	49.1 (24)	283 (67)	0.65 (7)	15.75 (66)	1680 (42)[c]	1720 (38)[c]	37.6 (20)[c]	36.4 (25)[c]
	5	Female	127 (25)	462 (69)	0.70 (7)	18.16 (64)	3330 (44)[c]	3330 (44)[c]	24.5 (30)[c]	24.5 (30)[c]
		Male	191 (59)	626 (41)	0.66 (8)	24.00 (0)	3200 (64)	3200 (64)	23.8 (87)	23.8 (87)
	6	Female	96.2 (4)	355 (41)	0.68 (7)	24.00 (0)	2180 (35)	2180 (35)	22.8 (36)	22.8 (36)
		Male	66.2 (30)	207 (58)	0.64 (7)	15.38 (37)	1140 (73)	1220 (64)	17.4 (33)	16.0 (41)
	7	Female	92.3 (10)	255 (38)	0.69 (4)	24.00 (0)	2060 (47)	2060 (47)	22.0 (42)	22.0 (42)
		Male	114 (45)	459 (41)	0.65 (6)	24.00 (0)	3250 (35)	3250 (35)	29.8 (31)	29.8 (31)
57	3	Female	28.8 (74)	213 (62)	0.53 (2)	15.75 (66)	984 (35)[c]	1010 (29)[c]	33.1 (40)[c]	31.5 (41)[c]
		Male	32.5 (68)	241 (103)	0.52 (2)	14.75 (73)	1000 (76)[c]	1020 (72)[c]	22.7 (49)[c]	21.9 (57)[c]
	4	Female	35.9 (39)	534 (70)	0.52 (2)	21.13 (27)	2590 (82)	2620 (80)	68.3 (41)	67.1 (44)
		Male	66.2 (42)	517 (66)	0.53 (2)	21.13 (27)	1820 (48)	1860 (45)	28.4 (18)	27.5 (17)
	5	Female	172 (60)	1060 (45)	0.53 (3)	24.00 (0)	4050 (40)	4050 (40)	28.7 (55)	28.7 (55)
		Male	78.8 (33)	979 (59)	0.52 (0)	24.00 (0)	4560 (59)	4560 (59)	55.2 (40)	55.2 (40)
	6	Female	75.7 (38)	381 (67)	0.53 (2)	24.00 (0)	2090 (63)	2090 (63)	27.5 (59)	27.5 (59)
		Male	68.1 (24)	286 (23)	0.53 (3)	24.00 (0)	1500 (20)	1500 (20)	22.4 (19)	22.4 (19)
	7	Female	84.6 25)	328 (39)	0.53 (3)	24.00 (0)	1980 (33)	1980 (33)	24.9 (39)	24.9 (39)
		Male	123 (52)	552 (56)	0.53 (3)	24.00 (0)	3110 (35)	3110 (35)	27.2 (26)	27.2 (26)

a: n = 4/timepoint/sex/dose/day unless otherwise noted.

b: EDD = Estimated Deposited Dose. Individual estimated deposited dose data calculated based on the individual body weight and respiratory minute volume data collected on the study day, aerosol concentration measured on the study day and deposition data based on the ICRP Task Group on Lung Dynamics.[1]

c: n = 3

d: n = 2

e: NC = Not calculated when n<3.

Table 2 Mean (CV) Formoterol Toxicokinetic Parameters on Days 1 and 57 Following a 30-Minute Inhalation (Mouth-Only) Administration of Formoterol Fumarate Alone or in Combination with SCH 32088 to Male and Female Dogs

			Formoterol							
Day	Group	Sex[a]	EDD[b] (µg/kg/day)	Cmax (pg/mL)	Tmax (hr)	tf (hr)	AUC(tf) (pg·hr/mL)	AUC(0-24 hr) (pg·hr/mL)	AUC(0-24 hr)/EDD (pg·hr/mL)/(µg/kg/day)	AUC(tf)/EDD (pg·hr/mL)/(µg/kg/day)
1	3	Female	3.19 (23)	68.3 (49)	2.10 (140)	5.02 (59)	305 (9)[c]	365 (NC)[d,e]	112 (NC)[d]	89.0 (21)[c]
		Male	2.10 (57)	32.2 (125)	0.67 (NC)[f]	2.57 (NC)[f]	ND[g]	ND	ND	ND
	4	Female	12.2 (41)	358 (53)	0.66 (4)	13.38 (60)	2030 (31)[c]	2150 (30)[c]	214 (27)[c]	203 (33)[c]
		Male	4.67 (24)	126 (82)	0.67 (5)[c]	5.83 (20)[c]	668 (NC)[f]	747 (NC)[f]	155 (NC)[f]	139 (NC)[f]
	5	Female	12.4 (25)	206 (79)	2.50 (0)[c]	16.33 (41)[c]	1690 (46)[c]	1780 (40)[c]	137 (31)[c]	129 (36)[c]
		Male	18.8 (59)	433 (79)	0.66 (8)	9.50 (36)	1260 (64)	1410 (59)	105 (82)	94.9 (86)
	6	Female	2.16 (4)	83.0 (25)	1.13 (81)	5.00 (20)	290 (NC)[d]	346 (NC)[d]	162 (NC)[d]	135 (NC)[d]
		Male	1.52 (30)	47.9 (72)	0.64 (7)	2.56 (108)	261 (NC)[d]	334 (NC)[d]	153 (NC)[d]	120 (NC)[d]
	8	Female	12.0 (8)	873 (53)	1.10 (85)	15.38 (37)	3060 (31)	3240 (31)	275 (34)	260 (35)
		Male	11.3 (10)	511 (43)	0.69 (8)	11.00 (27)	1740 (29)	1930 (26)	170 (22)	153 (23)
57	3	Female	3.23 (74)	150 (71)	0.53 (2)	5.00 (60)	489 (46)[c]	576 (44)[c]	156 (23)[c]	132 (23)[c]
		Male	3.19 (68)	101 (96)	0.52 (2)[c]	4.51 (77)[c]	638 (NC)[f]	773 (NC)[f]	153 (NC)[f]	127 (NC)[f]
	4	Female	3.73 (39)	571 (118)	0.52 (2)	8.00 (38)	1190 (98)	1280 (92)	308 (51)	282 (56)
		Male	6.50 (42)	642 (82)	0.53 (2)	10.88 (80)	1480 (91)	1550 (84)	227 (50)	214 (55)
	5	Female	17.8 (60)	1200 (40)	0.53 (3)	11.00 (27)	2490 (42)	2660 (42)	173 (50)	162 (52)
		Male	8.66 (33)	1150 (86)	1.01 (98)	9.50 (36)	2410 (74)	2560 (70)	276 (60)	258 (65)
	6	Female	1.90 (39)	140 (82)	0.52 (2)[c]	3.83 (30)[c]	ND	ND	ND	ND
		Male	1.89 (24)	82.9 (52)	1.02 (97)	3.50 (33)	ND	ND	ND	ND
	8	Female	6.90 (24)	650 (39)	0.54 (2)	11.00 (27)	1530 (36)	1750 (40)	246 (20)	216 (15)
		Male	7.96 (47)	946 (58)	0.52 (2)	11.00 (27)	2030 (47)	2260 (46)	298 (48)	270 (52)

a: n = 4/timepoint/sex/dose/day unless otherwise noted.

b: EDD = Estimated Deposited Dose. Individual estimated deposited dose data calculated based on the individual body weight and respiratory minute volume data collected on the study day, aerosol concentration measured on the study day and deposition data based on the ICRP Task Group on Lung Dynamics.[1]

c: n = 3

d: n = 1

e: NC = Not calculated when n<3 or when n = 0.

f: n = 2

g: ND = Not determined

Table 3 Mean Amount of Formoterol Excreted in Urine on Days 1 and 57 Following a 30-Minute Inhalation (Mouth-Only) Administration of Formoterol Fumarate Alone or in Combination with SCH 32088 to Male and Female Dogs

Group	Sex[a]	Day 1 AE[b] (ng)	Day 57 AE (ng)
3	Female	1180 (37)[c]	422 (84)
	Male	280 (135)	881 (87)
4	Female	1340 (93)	841 (36)
	Male	900 (85)	1090 (57)
5	Female	2330 (78)	2790 (48)
	Male	2450 (47)	3320 (56)
6	Female	352 (29)	397 (47)
	Male	411 (78)	353 (35)
8	Female	3610 (22)	1130 (68)
	Males	2230 (28)	1570 (12)

a: n = 4/sex/group unless otherwise indicated.
b: AE = Amount excreted (0-24 hr) in urine
c: n = 3

Respiratory measurements: There was a high degree of variability in values for respiratory rate, tidal volume, and minute volume. No treatment-related changes could be discerned.

Group	Respiratory Rate breaths/min		Tidal volume mL/Breath		Minute Volume mL/Minute	
	Week 1	Week 13	Week 1	Week 13	Week 1	Week 13
Males						
AC	21	16	149	166	2936	2449
VC	28	20	151	134	3995	2573
Low MF/F	23	29	123	114	2907	3388
Mid MF/F	21	26	165	190	3258	4350
High MF/F	23	21	248	140	5577	2724
200:5 ratio MF/F	15	13	150	124	2129	1464
MF	22	23	161	135	3370	2756
F	21	16	170	188	3263	2863
Females						
AC	23	17	141	111	3127	1863
VC	19	16	133	127	2266	1934
Low MF/F	21	23	164	132	3169	2727
Mid MF/F	26	12	221	159	5376	1833
High MF/F	20	19	149	130	2701	2551
200:5 ratio MF/F	16	16	179	120	2579	1831
MF	16	13	139	128	1959	1568
F	19	16	194	153	3368	2393

Histopathology inventory (optional)

Study	13-week nose-only inhalation	13-week mouth-only inhalation
Species	Rat	Dog
Adrenals	X*	X*
Aorta	X	X
Bone Marrow smear	X (not examined)	X (not examined)
Bone (femur)	X	X
Brain	X*	X*
Cecum	X	X
Cervix	X* (w/uterus)	X* (w/uterus)
Colon	X	X
Duodenum	X	X
Epididymis	X*	X*
Esophagus	X	X
Eye	X	X
Fallopian tube		
Gall bladder		X
Gross lesions	X	X
Harderian gland	X	
Heart	X*	X*
Ileum	X	X
Injection site		
Jejunum	X	X
Kidneys	X*	X*
Lachrymal gland		
Larynx	X	X
Liver	X*	X*
Lungs	X*	X*
Lymph nodes, axillary		X*
Lymph node, bronchial		X
Lymph nodes, cervical		
Lymph nodes mandibular	X	X
Lymph nodes, mediastinal	X	
Lymph nodes, mesenteric	X	X
Lymph nodes, tracheobronchial	X	
Mammary Gland	X	X
Nasal cavity	X (4 levels)	X (4 levels)
Optic nerves	X	X
Ovaries	X*	X*
Pancreas	X	X
Parathyroid	X* (w/thyroid)	X

Peripheral nerve		
Pharynx	X	X
Pituitary	X*	X
Prostate	X*	X*
Rectum	X	X
Salivary gland	X*	X*
Sciatic nerve	X	X
Seminal vesicles	X	
Skeletal muscle	X	X
Skin	X	X
Spinal cord	X	X
Spleen	X*	X*
Sternum		X
Stomach	X	X
Testes	X*	X*
Thymus	X*	X*
Thyroid	X* (w/parathyroid)	X*
Tongue	X	X
Trachea	X	X
Urinary bladder	X	X
Uterus	X* (w/cervix)	X* (w/cervix)
Vagina	X	X
Zymbal gland		

X, histopathology performed
*, organ weight obtained

2.6.6.9 Discussion and Conclusions

For the combination SCH418131 drug product (Mometasone Furoate + Formoterol Fumarate), 3-month inhalation bridging toxicology studies with rats and dogs were provided. Toxicities observed in 3-month bridging studies with SCH418131 in rats and dogs appeared to be primarily attributable to the pharmacological effects of mometasone (i.e., class effects of glucocorticoids). Target organs of toxicity in rats and dogs are shown in the table below. In addition, tachycardia, attributable to formoterol, was observed in dogs. There was no evidence in these studies of additive or synergistic toxic effects between mometasone and formoterol. There was no evidence of any interactions on toxicokinetic parameters in rats or dogs.

2.6.6.10 Tables and Figures

Target organs of toxicity observed in rats and dogs treated with SCH418131

Organ/Tissue	Rat	Dog
Lungs	BALT (bronchial-associated lymphoid tissue) depletion, accumulation of alveolar macrophages, and pigmented macrophages.	Hyperplasia of bronchioloalveolar cells and bronchial inflammation
Thymus	Involution/atrophy	Lymphoid depletion
Nose/Turbinates	Lymphoid depletion	Lymphoid depletion
Spleen	Lymphoid depletion	Lymphoid depletion

Mesenteric LN	Lymphoid depletion and infiltration of mast cells	Lymphoid depletion and erythrophagocytosis
Bronchial LN	Lymphoid depletion	Lymphoid depletion
Mandibular LN	Lymphoid depletion	Lymphoid depletion
Mediastinal LN	Lymphoid depletion	Lymphoid depletion
Mammary gland	Abnormal lobule development	
Bone marrow	Increased marrow fat	
Ovaries	Decrease corpora lutea	Hypoplasia
Vagina	Abnormal mucification	
Adrenal gland		Vacuolization and/or atrophy of the adrenal cortex
Cecum		Lymphoid depletion
Colon		Lymphoid depletion
Duodenum		Lymphoid depletion
Ileum		Lymphoid depletion
Jejunum		Lymphoid depletion
Larynx		Lymphoid depletion
Axillary LN		Lymphoid depletion
Pharynx		Lymphoid depletion
Rectum		Lymphoid depletion
Stomach		Lymphoid depletion
Salivary gland		Infiltration of adipocytes
Uterus		Hypoplasia
Liver		Cytoplasmic vacuolation
Femur		Increased fat deposition
Rib		Increased fat deposition
Sternum		Increased fat deposition
Trachea		Decreased globule leukocytes

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Summary:

The sponsor has proposed to develop SCH418131, a combination drug product consisting of mometasone furoate and formoterol fumarate, for the treatment of asthma (b) (4) There was a Pre-IND meeting between the Division and sponsor to discuss this drug product on June 11, 2003. The individual components, mometasone furoate and formoterol fumarate, are each found in approved drug products. Mometasone furoate is found in several approved drug products. With regard to the development of SCH418131, the Asmanex Twisthaler, is probably the most relevant. Formoterol fumarate is found in the Foradil® Aerolizer™ drug product.

(b) (4) dosage strengths of SCH418131 are being developed. Targeted delivery per actuation (ex-actuator) is nominally (b) (4) 100, or 200 µg/actuation of mometasone furoate, combined in each case with 5 µg/actuation of formoterol fumarate dihydrate. One complete dose is composed of two actuations from the combination inhaler. The (b) (4) drug product combinations of mometasone and formoterol contain the propellant, HFA-227, and two excipients, dehydrated alcohol and oleic acid.

In the present IND, the sponsor conducted 2-week dose range finding studies and 13-week inhalation bridging toxicology studies with combinations of mometasone furoate and formoterol fumarate dihydrate in rats and dogs to support clinical trials with duration of 12 weeks or greater.

In 13-week inhalation bridging toxicology studies, rats were exposed by nose-only inhalation and dogs were exposed by mouth-only inhalation to aerosols of MDI formulations of SCH418131 containing oleic acid, ethanol, and HFA-227. In order to conduct a safety assessment of the three different dosage strengths in terms of additive or synergistic effects, rats and dogs were exposed to 3 doses of the 50 to 5 ratio product and 1 dose of the 200 to 5 ratio product. Mono-product comparator groups were exposed to mometasone or formoterol alone. Vehicle-control groups were exposed to an aerosol of a MDI formulation comprised of oleic acid, ethanol, and HFA-227 propellant. The aerosol of the vehicle-control group was generated to match the concentration of oleic acid in the high dose SCH418131 group at a 50:5 ratio.

Use of the 50 to 5 and 200 to 5 ratio products was intended to cover the range of clinical doses and maximize the potential to observe any interactions between mometasone and formoterol (See Pre-IND minutes dated June 11, 2003). However, exposures to mometasone and formoterol were greater for the high dose 50 to 5 ratio group as compared to the 200 to 5 ratio group. These studies are still considered valid to assess any interactions between mometasone and formoterol.

Toxic effects observed in rats and dogs were primarily attributed to mometasone (class effects of glucocorticoids). Body weight gains were significantly decreased in all rat treatment groups that received mometasone furoate. White blood cell counts were decreased in rats and dogs from treatment groups that received mometasone furoate. Decreases were primarily attributed to declines of lymphocyte counts in rats and lymphocyte and eosinophil counts in dogs. Adrenal suppression was evident in dogs from all treatment groups that received mometasone furoate. For dogs, increased heart rate was observed in all treatment groups that received formoterol. There were multiple target organs of toxicity in rats and dogs. In general, histopathological findings were evident in all treatment groups that received mometasone furoate. Lymphoid depletion was observed in lung, nose/turbinates, spleen, lymph nodes (mesenteric, bronchial, mandibular, mediastinal and axillary), cecum, colon, duodenum, ileum, jejunum, larynx, pharynx, rectum, spleen, and stomach. In the lungs, there were accumulations of alveolar macrophages in rats and bronchioloalveolar hyperplasia and bronchial inflammation in dogs. In the trachea for rats, there were decreased globule leukocytes. In the adrenal gland for dogs, there was cortical atrophy and vacuolization. In the thymus for rats, there was involution/atrophy. In the bone marrow for rats and dogs, there was increased fat deposition. In the mammary gland, there was abnormal lobuloalveolar development for rats and epithelial vacuolization for dogs. In the ovaries for rats, there were decreased corpora lutea. In the vagina for rats, there was abnormal mucification. Hypoplasia of the ovary and uterus was observed for dogs. In the liver for dogs, there was cytoplasmic vacuolization. In the salivary gland for dogs, there was adipocyte infiltration, although its relationship to treatment was questionable.

NOAELs were not identified in studies with rats and dogs based upon histopathological findings in all MF/F groups. Toxicities observed in 3-month bridging studies with SCH 418131 in rats and dogs appeared to be primarily attributable to the pharmacological effects of mometasone. In addition, tachycardia, attributable to formoterol, was observed in dogs. There was no evidence of additive or synergistic toxic effects with the combination of mometasone and formoterol. There was no evidence of any interactions on toxicokinetic parameters in rats or dogs.

With regard to systemic toxicity, exposure (i.e., AUC) values for mometasone and formoterol achieved in inhalation toxicology studies with rats and dogs were greater than exposures obtained with the highest clinical dose of 400/10 µg BID.

Exposure margins for clinical doses based upon systemic exposures from the 13-week inhalation toxicology study with rats

MF/F µg/kg/day	MF AUC pg·hr/mL	F AUC pg·hr/mL	Clinical dose of 800 µg MF + 20 µg F	
			MF 16 µg/kg 484 pg·hr/mL	F 0.4 µg/kg 358 pg·hr/mL
3.3/0.3	11550	490.5	24	1.4
6.6/0.6	26800	1345	55.5	3.8
13.2/1.2	54300	2320	112	6.5
13.2/0.3	38550	469	80	1.3
13.2 MF only	34850	-	72	-
1.2 F only	-	1185	-	3.3

Exposure margins for clinical doses based upon systemic exposures from the 13-week inhalation toxicology study with dogs

MF/F µg/kg/day	MF AUC pg·hr/mL	F AUC pg·hr/mL	Clinical dose of 800 µg MF + 20 µg F	
			MF 16 µg/kg 484 pg·hr/mL	F 0.4 µg/kg 358 pg·hr/mL
28/2.8	1015	674.5	2.1	1.9
56/5.6	2240	1415	4.6	4
111/11	4305	2610	8.9	7.3
111/2.8	1795	ND	3.7	-
111 MF only	2545	-	5.3	-
11 F only	-	2005	-	5.6

With regard to local toxicity in the lung, pulmonary deposited doses of mometasone and formoterol achieved in rats and dogs do not provide exposure margins of at least 10 or 6 for the highest clinical dose of 400/10 µg BID, respectively.

Exposure margins for clinical doses based upon deposited doses from the 13-week inhalation toxicology study with rats

MF/F µg/kg/day	Clinical dose of 400 µg MF + 20 µg F		Clinical dose of 800 µg MF + 20 µg F	
	MF 8 µg/kg/day	F 0.4 µg/kg	MF 16 µg/kg	F 0.4 µg/kg
3.3/0.3	0.41	0.75	0.21	0.75
6.6/0.6	0.83	1.5	0.41	1.5
13.2/1.2	1.65	3	0.825	3
13.2/0.3	1.65	0.75	0.825	0.75
13.2 MF only	1.65	-	0.825	-
1.2 F only	-	3	-	3

Exposure margins for clinical doses based upon deposited doses from the 13-week inhalation toxicology study with dogs

MF/F µg/kg/day	Clinical dose of 400 µg MF + 20 µg F		Clinical dose of 800 µg MF + 20 µg F	
	MF 8 µg/kg/day	F 0.4 µg/kg	MF 16 µg/kg	F 0.4 µg/kg
28/2.8	3.5	0.75	1.75	0.75
56/5.6	7	1.5	3.5	1.5
111/11	13.9	3	7	3
111/2.8	13.9	0.75	7	0.75
111 MF only	13.9	-	7	-
11 F only	-	3	-	3

NOAELs were not identified in nonclinical studies with SCH 418131 given that rats and dogs are known to be significantly more sensitive to the toxic effects of glucocorticoids as compared to humans. These findings are in concordance with previous inhalation toxicology studies conducted with mometasone in rats and dogs. Previous clinical experience with the mometasone supports clinical doses of mometasone in the combination (i.e., SCH 418131).

The SCH 418131 drug product contains the propellant, HFA-227, and two excipients, dehydrated alcohol and oleic acid. HFA-227, dehydrated alcohol, and oleic acid are all found in approved inhalation drug products. In 13-week inhalation bridging toxicology studies with rats and dogs, there was no evidence of toxicity in vehicle-control groups that were exposed to HFA-227, dehydrated alcohol, and oleic acid.

The daily dose of HFA-227 in the SCH 418131 drug product is [redacted] (b) (4). For Symbicort HFA pMDI (NDA 21-929; AstraZeneca), the daily dose of HFA-227 is [redacted] (b) (4) [redacted] (b) (4), which is slightly [redacted] (b) (4) than the proposed dose in the present IND. Extensive nonclinical toxicology studies have been conducted with HFA-227 by [redacted] (b) (4), for which the sponsor has rights of reference. These studies were reviewed under DMF [redacted] (b) (4) (See reviews dated October 2, 1996 and January 28, 1997). HFA-227 is considered reasonably safe for inhalation use in the SCH 418131 drug product.

The daily doses of ethanol/dehydrated alcohol and oleic acid in the SCH 418131 drug product are [redacted] (b) (4), respectively. For the approved drug product, Proventil-HFA, daily doses of ethanol/dehydrated alcohol and oleic acid ranged from

(b) (4) respectively. These doses are (b) (4) than those found in the SCH 418131 drug product.

From the vehicle-control groups in 13-week inhalation bridging toxicology studies with rats and dogs, pulmonary deposited doses of oleic acid were 0.63 and 5.05 µg/kg/day, respectively. Safety margins for the clinical dose of oleic acid (0.32 µg/kg/day) are 2- and 15.8-fold, respectively.

Recommendation: From a nonclinical standpoint, the proposed clinical trials appear reasonably safe to proceed.

Reviewer signature: _____
Timothy W. Robison, Ph.D.

Supervisor signature: Concurrence - _____
C. Joseph Sun, Ph.D.,

cc: list:
IND 72,308, HFD-570
GarciaL, HFD-570
LimbS, HFD-570
SunC, HFD-570
RobisonT, HFD-570

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

/s/

Timothy Robison
1/9/2007 03:54:41 PM
PHARMACOLOGIST

Joseph Sun
1/12/2007 02:41:40 PM
PHARMACOLOGIST
I concur.

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/

TIMOTHY W ROBISON
01/19/2010

JEAN Q WU
01/19/2010

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW
CHEMISTRY CONSULT #2

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-518
Sponsor and/or agent: Shering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033
Manufacturer for drug substance: Same

Reviewer name: Timothy W. Robison, Ph.D., D.A.B.T.
Division name: Pulmonary and Allergy Products
HFD #: 570
Review completion date: January 15, 2010

Drug:

Trade name: DULERA®
Generic name: Mometasone Furoate + Formoterol Fumarate
Code name: SCH418131 (Mometasone Furoate + Formoterol Fumarate)
Chemical name:
Mometasone furoate: 9α,21-dichloro-11β,17α-dihydroxy-16α-methyl-pregna-1,4-diene-3,20-dione17-(2')-furoate.
Formoterol fumarate dihydrate: (±)-2-hydroxy-5-[(1RS)-1-hydroxy-2-((1RS)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]formanilide fumarate dihydrate

Relevant INDs/NDAs/DMFs:
Mometasone from Schering: IND 24,088, (b) (4), (b) (4), IND 46,216, IND 52,214, IND 55,108, NDA 19-543, NDA 19-625, NDA 19-796, NDA 20-762, (b) (4), NDA 21-067, (b) (4)

Formoterol from Novartis: NDA 20-831

Drug class:
Mometasone furoate: glucocorticoid
Formoterol: β_2-adrenergic agonist

Intended clinical population: DULERA is indicated for (b) (4) twice-daily (b) (4) treatment of asthma, (b) (4), in adults and children 12 years of age and older.

Clinical formulation: The drug products contain the drug substances, Mometasone Furoate Anhydrous and Formoterol Fumarate Dihydrate. The drug products are white suspensions containing (b) (6) alcohol dehydrated/ethanol anhydrous (USP-NF),

(b) (6) oleic acid (b) (4) (USP-NF), and (b) (6) HFA 227 (b) (6)

The drug products are formulated in (b) (4) strengths each designed to deliver a minimum of 120 actuations as shown in Table 1. One therapeutic dose is obtained from two single actuations of the drug products.

Table 1 Description of the Drug Products

Drug Product (Strength)	Strength of Mometasone Furoate (mcg per actuation ex-actuator)	Strength of Formoterol Fumarate (mcg per actuation ex-actuator)
(b) (4)		
Mid	100	5
High	200	5

The compositions of the drug products are presented in Table 2 to Table 4.

(b) (4)

Table 3 Composition of the 100/5 mcg per Actuation Drug Product

Ingredient	Theoretical Quantity					Function	Reference to Standards
	mg/metered actuation*	mg/mL	mg/g	% w/w	mg/filled canister		
Mometasone Furoate	(b) (4)					Drug substance	USP, Anhydrous Micronized (Inhalation Grade)
Formoterol Fumarate						Drug substance	USP
Ethanol						(b) (4) (b) co-solvent	USP-NF
Oleic Acid						Surfactant	USP-NF
HFA 227						Propellant	(b) (4)
Total							

(b) (4)

Best Available Copy

Table 4 Composition of the 200/5 mcg per Actuation Drug Product							
Ingredient	Theoretical Quantity					Function	Reference to Standards
	mg/metered actuation [a]	mg/mL	mg/g	% w/w	mg/filled canister		
Mometasone Furoate	(b) (4)					Drug substance	USP, Anhydrous Micronized (Inhalation Grade)
Formoterol Fumarate						Drug substance	USP
Ethanol						(b) (4) (b) co-solvent	USP-NF
Oleic Acid						Surfactant	USP-NF
HFA 227						Propellant	(b) (4)
Total							

(b) (4)

Route of administration: Oral inhalation

Response to Chemistry Consult Requested by Alan C. Schroeder, Ph.D.

Description of the Consult: Safety assessments for items listed below are provided in this consult. Additional information is provided in Appendix 1. Also, this consult provides a follow-up revision of the safety assessment for foreign particulates discussed in the consult review dated December 4, 2009.

(b) (4)

9 pages has been withheld in full as B(4) CCI/TS immediately following this page

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/

TIMOTHY W ROBISON
01/15/2010

JEAN Q WU
01/15/2010

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW
CHEMISTRY CONSULT #1

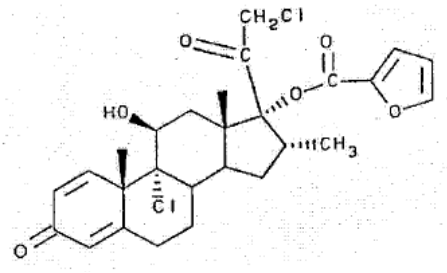
2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-518
Sponsor and/or agent: Shering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033
Manufacturer for drug substance: Same

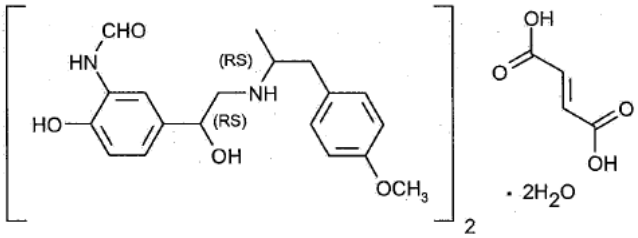
Reviewer name: Timothy W. Robison, Ph.D., D.A.B.T.
Division name: Pulmonary and Allergy Products
HFD #: 570
Review completion date: December 4, 2009

Drug:

Trade name: DULERA®
Generic name: Mometasone Furoate + Formoterol Fumarate
Code name: SCH418131 (Mometasone Furoate + Formoterol Fumarate)
Chemical name:
Mometasone furoate: 9α,21-dichloro-11β,17α-dihydroxy-16α-methyl-pregna-1,4-diene-3,20-dione17-(2')-furoate.
Formoterol fumarate dihydrate: (±)-2-hydroxy-5-[(1RS)-1-hydroxy-2-((1RS)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]formanilide fumarate dihydrate
Molecular formula/molecular weight:
Mometasone furoate, $C_{27}H_{30}O_6Cl_2$ / 521.4 g/mole
Formoterol fumarate dihydrate, $C_{42}H_{52}N_4O_{12} \cdot 2\ H_2O$ / 840.9 g/mole
Structure:
Mometasone furoate:



Formoterol fumarate:



Relevant INDs/NDAs/DMFs:
Mometasone from Schering: IND 24,088, (b) (4), (b) (4), IND 46,216, IND 52,214, IND 55,108, NDA 19-543, NDA 19-625, NDA 19-796, NDA 20-762, (b) (4) (b) (4) NDA 21-067, (b) (4)

Formoterol from Novartis: NDA 20-831

Drug class:
Mometasone furoate: glucocorticoid
Formoterol: β_2-adrenergic agonist

Intended clinical population: DULERA is indicated for (b) (4) twice-daily (b) (4) treatment of asthma, (b) (4), in adults and children 12 years of age and older.

Clinical formulation: The drug products contain the drug substances, Mometasone Furoate Anhydrous and Formoterol Fumarate Dihydrate. The drug products are white suspensions containing (b) (4) alcohol dehydrated/ethanol anhydrous (USP-NF), (b) (4) oleic acid (b) (4) (USP-NF), and (b) (4) HFA 227 (b) (4)

The drug products are formulated in (b) (4) strengths each designed to deliver a minimum of 120 actuations as shown in Table 1. One therapeutic dose is obtained from two single actuations of the drug products.

Table 1 Description of the Drug Products

Drug Product (Strength)	Strength of Mometasone Furoate (mcg per actuation ex-actuator)	Strength of Formoterol Fumarate (mcg per actuation ex-actuator)
(b) (4)		
Mid	100	5
High	200	5

The compositions of the drug products are presented in Table 2 to Table 4.

(b) (4)

[redacted]

Table 3 Composition of the 100/5 mcg per Actuation Drug Product

Ingredient	Theoretical Quantity					Function	Reference to Standards
	mg/metered actuation*	mg/mL	mg/g	% w/w	mg/filled canister		
Mometasone Furoate	[redacted]					Drug substance	USP, Anhydrous Micronized (Inhalation Grade)
Formoterol Fumarate	[redacted]					Drug substance	USP
Ethanol	[redacted]					[redacted] and co-solvent	USP-NF
Oleic Acid	[redacted]					Surfactant	USP-NF
HFA 227	[redacted]					Propellant	[redacted]
Total	[redacted]						

(b) (4)

Table 4 Composition of the 200/5 mcg per Actuation Drug Product

Ingredient	Theoretical Quantity	Function	Reference to Standards
	[redacted]		
Mometasone Furoate	[redacted]	Drug substance	USP, Anhydrous Micronized (Inhalation Grade)
Formoterol Fumarate	[redacted]	Drug substance	USP
Ethanol	[redacted]	[redacted] and co-solvent	USP-NF
Oleic Acid	[redacted]	Surfactant	USP-NF
HFA 227	[redacted]	Propellant	[redacted]
Total	[redacted]		

(b) (4)

Best Available Copy

Route of administration: Oral inhalation

Response to Chemistry Consult Requested by Alan C. Schroeder, Ph.D.

Description of the Consult: Safety assessments for items listed in the table below are provided in this consult. See the Request for Chemistry Consult in the Appendix.

(b) (4)

(b) (4)

19 pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/

ALAN C SCHROEDER
11/30/2009

PRASAD PERI
11/30/2009

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/

TIMOTHY W ROBISON
12/04/2009

JEAN Q WU
12/04/2009

NDA Pharmacology Fileability Check List

NDA No: 22-518

Date of submission: May 22, 2009

Date of Fileability meeting: July 6, 2009

Information to Sponsor Yes ( ) No (X**)**

Date of check list:
(1) On its face, is the Pharm/Tox section of the NDA organized in a manner to allow substantive review? Yes (X) No ( ) NA ( )

(2) On its face, is the Pharm/Tox section of the NDA legible for review?
Yes (X) No ( ) NA ( )

(3) Are final reports of all required and requested preclinical studies submitted in this NDA? Yes (X) No ( ) NA ( )

	Yes	No	NA
Pharmacology	(X)	( )	( )
ADME	(X)	( )	( )
Toxicology (duration, route of administration and species specified)			
acute	(X)	( )	( )
subchronic and chronic studies	(X)	( )	( )
reproductive studies	(X)	( )	( )
carcinogenicity studies	(X)	( )	( )
mutagenicity studies	(X)	( )	( )
special studies	(X)	( )	( )
others	(X)	( )	( )

(4) If the formulation to be marketed is different from the formulation used in the toxicology studies, is repeating or bridging the studies necessary? Yes ( ) No (X) NA ( )

If no, state why not?
The sponsor conducted 3-month bridging studies in rats and dogs using the to be marketed formulation.

If yes, has the applicant made an appropriate effort to repeat the studies using the to be marketed product, to bridge the studies or to explain why such repetition or bridging should not be required? Yes ( ) No ( ) NA (X)

(5) Are the proposed preclinical labeling sections (carcinogenesis, mutagenesis and impairment of fertility, pregnancy category and overdosage) appropriate (including human dose multiples expressed in either mg/m^2 or comparative systemic exposure levels) and in accordance with 201.57? Yes (X) No ( ).

(6) Has the applicant submitted all special studies/data requested by the Division prior to the submission including but not limited to pre-NDA discussion? Yes (X) No ( ) NA ( )

(7) On its face, does the route of administration used in the pivotal toxicity studies appear to be the same as the intended clinical route? Yes (X) No ( ) NA ( )

If not, has the applicant submitted a rationale to justify the alternative route?
Yes ( ) No ( ) NA

(8) Has the applicant submitted a statement(s) that all of the toxicity studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations? Yes (X) No ( ) NA ( )

(9) Has the applicant submitted any studies or data to address any impurity or extractable issues (if any)? Yes ( ) No (X) NA ( )

In the pre-NDA meeting, the sponsor was asked to address any issues regarding impurities, degradants, extractables, and/or leachables. Based upon the discussion at the July 6, 2009 filing meeting, the chemist plans to submit consult requests regarding levels of impurities, leachables, and extractables.

(10) Are there any outstanding preclinical issues? Yes ( ) No (X)
If yes, identify those below.

(11) From a preclinical perspective, is this NDA fileable? Yes (X) No ( )

If no, state below why it is not.

(12) Should any additional information/data be requested? Yes ( ) No (X)

NDA Planning Timeline

NDA No.: 22-518

Date of planning timeline: July 6, 2009

PDUFA Due Date: March 22, 2010

Projected review completion date: January 22, 2010

	Milestone Dates
Pharmacology and ADME	1-22-2010
Toxicology	
General toxicity studies	Completed
Carcinogenicity studies and mutagenicity studies	Completed
a. Statistical consult request for CA studies	Completed
b. Submission of CA studies for CAC concurrence	Completed
Reproductive studies	Completed
Special studies and Others	Completed
Labeling	12-16-2009

Signatures (optional):

Reviewer Signature _____
Timothy W. Robison, Ph.D.

Supervisor Signature _____
Jean Wu, Ph.D.

Concurrence Yes ___ **No** ___

cc:
NDA 22-518, HFD-570 Division Files
ChungE, HFD-570
WuJ, HFD-570
RobisonT, HFD-570

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

/s/

Timothy Robison
7/7/2009 04:31:19 PM
PHARMACOLOGIST

Jean Wu
7/7/2009 04:50:21 PM
PHARMACOLOGIST
I concur.