CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-067

Pharmacology Review(s)

PHARMACOLOGY/TOXICOLOGY REVIEW

Labeling Review

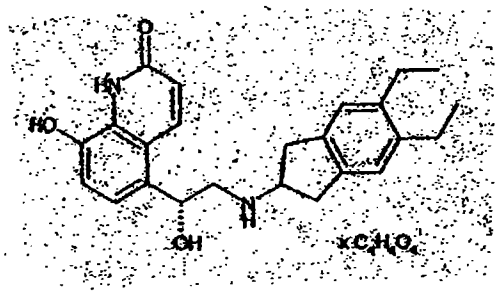
NDA number: NDA 21-067
Review number: 002
Serial number/date/type of submission: 000/November 14/2003/AZ
000/February 18, 2004/BL
000/ April12, 2004/BL

Information to sponsor: Yes (x) No ( )
Sponsor and/or agent: Schering Plough Corporation
Manufacturer for drug substance: Schering Plough Corporation LTD, Singapore

Reviewer name: Virgil Whitehurst, PhD
Division name: Division of Pulmonary and Allergy Drug Products
HFD #: HFD 570
Review completion date: April 27, 2004

Drug:

Trade name: Asmanex Twisthaler, 220 mcg
Generic name (list alphabetically): Mometasone furoate inhalation powder
Code name: SCH 32088
Chemical name: 9, 21-dichloro-11ß, 17-dihydroxy-16á-methylpregna-1, 4-diene-3, 20-dione 17-(2-fuorate)
CAS registry number: 83919-23-7
Mole file number: NA
Molecular formula/molecular weight: $C_{27}H_{30}CL_2O_6$/521.44
Structure:



Relevant INDs/NDAs/DMFs: NDAs 19-543, 19-625, 19-796 and 20-762/ INDs [ ] 46, 216, 52, 214 and 55, 108

Drug class: Corticosteroid, anti-inflammatory

Indication: Maintenance treatment of asthma as prophylactic therapy, recommended daily dose is [ ] µg/day for patients 12 years of age and older.

Clinical formulation:

Ingredient	200 µg/unit dose inhaler		400 µg/unit dose inhaler	
	µg/ unit dose[1]	mg/inhaler[2]	µg/ unit dose[1]	mg/inhaler[2]
Mometasone Furoate	200	—	400	—
Lactose, anhydrous,	[			]
Total	[			]

1 Unit dose is defined as single inhalation

2 Both 200 µg and 400 µg strength inhalers have identical target fills of — mg of mometasone furoate: lactose anhydrous [ ]

Route of administration: Oral inhalation

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

Introduction and drug history: The initial review for this NDA was conducted by Dr. Misoon Chun (August 1999) and recommended that the application be approved from the preclinical. Additionally, two Memoranda were written by Dr. Robin Huff. The first, dated October 1, 1999, addressed issues regarding the impurity [ ] This issue has been resolved as the sponsor has reduced the specifications for this impurity. The second, dated November 6, 2000, provided revisions to the product label that were communicated to the sponsor in the Approvable letter of December 4, 2000. The current review focuses on the currently proposed product label.

IND 46, 216 was originally submitted (9/13/1994) for the dry powder inhaler with pure mometasone furoate powder without excipient or vehicle. Preclinical studies in this submission include an acute study in the dog and 2 and 3 months studies in the rat and the dog. In addition, one and three month inhalation studies were conducted in mice and rats with SCH 32088 in CFC inhaler as well as a 3 month study in the dog with SCH 32088 pure powder. The genotoxicity, carcinogenicity and reproductive toxicity for mometasone furoate were reviewed in NDA 20-762 (Nasonex Aqueous Nasal Spray, approved October 6, 1997). The chronic toxicity studies with mometasone furoate (two-6 month studies, one in the rat and the other in the dog and a 12 month study in the dog) were reviewed in NDA 21-067. The pharmacodynamic and safety pharmacology studies of mometasone furoate have been reviewed in prior INDs [

] or NDAs (20-762 Nasonex Aqueous Nasal Spray). No preclinical data were reviewed in this review.

The preliminary labeling comments for Asmanex Twisthaler (mometasone furoate inhalation powder) were provided in the October 1, 1999 action letter with a further revision provided in the December 4, 2000. The reviewed submissions contain updated labeling for Asmanex which are reviewed below.

Studies reviewed within this submission: NA

Studies not reviewed within this submission: NA

DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Summaries of the pharmacology, pharmacokinetic/toxicokinetic, safety pharmacology, general toxicology, genetic toxicology, carcinogenicity and reproductive sections were taken directly from the pharmacology review #1 dated August 27, 1999.

PHARMACOLOGY:

Many pharmacodynamic studies for mometasone furoate have been included in INDs [46216 & [ ] for different formulations and extensively reviewed for NDA 20-762. The current NDA 21-067 contains an overview of four additional pharmacodynamic studies of mometasone furoate not previously submitted. Mometasone furoate (or fluticasone propionate) was the most potent glucocorticoids followed by budesonide, triamcinolone and dexamethasone for its antiinflammatory effects by: 1) inhibiting basophil histamine release, 2) inhibiting TNF-α induced VCAM-1 expression on human bronchial epithelial cell line and 3) reducing eosinophil survival. Mometasone furoate has a high affinity for the glucocorticoid (IC_{50} = 10.7 nM) and/or progesterone (IC_{50} = 4.39 nM) receptors and is the most potent of the glucocorticoids in activating the glucocorticoid and/or progesterone receptors (EC_{50} = 0.21 nM and EC_{50} = 0.07 nM, respectively). The ratio of glucocorticoid to progesterone receptor activation demonstrates that mometasone furoate is in the same range of activity as the other glucocorticoids.

PHARMACOKINETICS/TOXICOKINETICS:

The pharmacokinetics, toxicokinetics and metabolic disposition of mometasone furoate (MF, SCH 32088) were extensively studied in mice, rats, rabbits and dogs following single- and/or multiple-dose administration by different routes and formulations. Several toxicokinetic studies were conducted with MF/lactose (1:5.8) in rats and dogs during the repeat dose toxicology studies, one-month to either 6-month nose-only (rats) or12-month mouth only (dogs) inhalation studies. MF/lactose formulation was administered to rats via nose-only inhalation for 1 hr/day at toxicological exposure concentrations of 0.13, 0.5 and 2.0 mg/L or by mouth-only inhalation for 30 min/day to dogs at toxicological exposure concentrations of 0.1, 0.5, 1, 4 and 16 mg/L. In addition, inhalation studies with MF/lactose (1:19) for up to 3 months and with aerosolized MF pure powder for 3-months were conducted to correlate the systemic exposure achieved during the safety studies in rats and dogs with the exposure concentration or dose. The highest concentrations were observed within 15 minutes to 30 minutes after the end of exposure. Tmax normally occurred at the first sampling time, which was within ~5-15 minutes following cessation of exposure, demonstrating a rapid, initial absorption phase of lung deposited MF available for systemic circulation. In real time, this corresponded to ~1.25 hr (rats) and ~45 min (dogs) from the start of exposure. Plasma MF concentrations were gender independent, increased in an exposure concentration-related manner and showed no evidence of accumulation over the duration of the studies.

Toxicokinetic and ADME/AME studies have been completed with various formulations including the lactose-containing DPI formulation. ADME/AME studies completed with various formulations have demonstrated the similarity of the metabolic profiles across all of these formulations irrespective of dose route and/or MF formulation.

Mometasone furoate is rapidly absorbed from the lungs, attaining relatively high plasma drug concentrations, and rapidly cleared via biotransformation to a large number of polar metabolic products, one of which is 6β-hydroxy-mometasone furoate (SCH 471567), and excreted into the feces via the bile, irrespective of the animal species. Mometasone furoate was found to be a weak inducer of hepatic drug metabolizing enzymes when administered orally to rats at high doses, but did not show any induction potential in either rats or dogs following daily administration of the powder formulation by inhalation. *In vitro Metabolism study* showed that SCH 32088 was metabolized extensively in the liver, moderately in the GI tract, and minimally in the lung. Metabolism across species is qualitatively similar but quantitatively different. It was found that CYP3A4 enzyme plays the primary role in the metabolism of this compound.

SAFETY PHARMACOLOGY:

There were no special safety concerns with mometasone furoate from the pharmacokinetics and metabolic disposition in laboratory animals. Mometasone furoate is rapidly absorbed from the lungs, attaining relatively high plasma drug concentrations, and rapidly cleared via biotransformation to a large number of polar metabolic products, and excreted into the feces via the bile, irrespective of the animal species. There was no single major metabolite; however, one of the metabolites is 6β-hydroxy-mometasone furoate (SCH 471567) for which CYP 450 3A4 plays primary role in the liver. Plasma concentrations of mometasone furoate determined during the safety evaluation and toxicokinetic studies were dose-dependent but gender independent in all animal species studied. Mometasone furoate was found to be a weak inducer of hepatic drug metabolizing enzymes when administered orally to rats at high doses, but did not show any induction potential in either rats or dogs following daily administration of the powder formulation by inhalation.

TOXICOLOGY:

General Toxicology:

The toxicity profile of inhalation of SCH 32088/lactose formulations in animals was typical of dose-related corticosteroid effects. In general, rats tolerated the mometasone furoate (SCH 32088)/lactose mix aerosol up to 2 μg/L, and dogs tolerated up to14 μg/L of SCH 32088 which correspond to estimated doses of 60 and 110 μg/kg/day, respectively. After multiple exposures, significant reductions in body weight and/or body weight gain (30-50%) were observed in rats, but less effect on body weights were noted in dogs. Changes in clinical pathology included increased total protein, cholesterol and glucose levels in rats and decreases in plasma cortisol levels and increases in glucose levels in dogs. At very high doses (110 μg/kg/day) in 14-day study in dogs, disturbances in electrolyte balance was also noted. Target organs were thymus and adrenal glands with reduced weights accompanied by histopathological changes of lymphoid depletion and adrenal atrophy in rats and dogs. Lymphoid depletion was also seen in various lymph nodes and gut-associated lymphoid tissues. There were minimal increased bone marrow adipose tissues in high dose groups of both rats and dogs. In addition, vacuolization of hepatocytes in the liver was observed in all treated dogs with increased hepatic glycogen at ≥ 4 μg/L. Such change in the liver was not observed in rats. Effects on reproductive organs were more pronounced in dogs with focal prostatic atrophy and testicular atrophy in the males and slight effects on uterus and ovary in females. The morphologic changes in the ovaries and mammary glands are the typical glucocorticoid effects of the hypothalamic/adrenal/ovarian axis. Enhanced lobuloalveolar development and secretion in mammary glands of female rats at the

high dose level were progestational-like changes in combination with other hormones including glucocorticoid. In general, the severity of changes increased with increased exposure concentrations and duration of the exposure. NOAELs for glucocorticoid effects was 0.1 µg/L for dogs but could not be determined in rats based on decreased tracheal globule leukocytes observed at all dose levels. NOAELs for progestational-like effects were < 0.13 µg/L for female rats and ≥ 2.0 µg/L for male rats. For dogs, there was no progestational-like effect at ≥ 4 µg/L up to 14 µg/L SCH 32088. In general, the effects on body weights and clinical pathology appeared to be more pronounced in those rats exposed to 2.0 µg/L SCH 32088 (1:5.8) than 2.0 µg/L SCH 32088 (1:19). This finding correlates with slightly higher plasma levels observed from the 1:5.8 formulation than from the 1:19 formulation at high doses. However, the effects from both SCH 32088 (1:5.8 and 1:19) formulations were similar in dogs.

Genetic Toxicology:

A total of 10 genetic toxicology studies with SCH 32088 were conducted. MF was non-mutagenic in the mouse lymphoma assay (P-5011) and the bacteria/mammalian microsome mutagenicity assay (P-4988, P-5969), and was negative in the mouse bone marrow erythrocyte micronucleus assay (P-5050), rat bone marrow clastogenicity assay (D-23508), UDS assay in rat hepatocytes (P-6017), and mouse spermatogonial cell assay (D-23580). It was positive at cytotoxic doses for chromosome aberrations in Chinese hamster ovary (CHO) cell cultures continuously exposed (10 hrs) in the nonactivation phase but not in the presence of rat liver S9 fraction (D-20741). MF was negative for chromosomal aberrations in CHO cell cultures under metabolic activation conditions or at lower concentrations of MF (D-23296). MF was positive under non-activation conditions in this test system only at toxic dose levels (D-23579). However, chromosomal abnormalities have been observed with other glucocorticoids at high concentrations. MF Degradation Product [ ] was negative either with or without activation.

The genetic toxicology studies indicate that MF and/or metabolites are not genotoxic or clastogenic, since negative results were seen in 8 out of 10 genetic toxicology studies. The chromosomal aberrations observed at cytotoxic dose levels in the nonactivation phase of the CHO assay were not detected in three *in vivo* clastogenesis assays (mouse micronucleus, rat bone marrow cytogenetics or mouse spermatogonial cytogenetics) or in cultured mouse lymphoma or in Chinese Hamster Lung (CHL) cells.

Carcinogenicity:

Two twenty-four month nose only inhalation oncogenicity studies in rats (P-6005) and in mice (P-6006) were conducted with MF aerosol with CFC propellant and surfactant (MMAD 2.1-3.1 µm) at chamber concentrations of 0.25, 0.5, 1.0, and 2.0 µg/L. No statistically significant increases in tumors were noted in Sprague Dawley rats in doses up to 0.68 times the clinical dose and in Swiss CD-1 mice up to 0.82 times the clinical dose on a surface area basis. However, when AUC values at each top doses were compared, these studies were conducted at 8 times and 12 times human dose multiples. There was no significant dose-response relationship for any tumor types in rats or mice. It was concluded that there was no human risk of carcinogenicity associated with the therapeutic use of the DPI MF: lactose (1:5.8) formulation. The conclusion was based upon the lack of a dose response

Reproductive and Developmental Toxicology:
Reproduction studies were performed in rats, mice, and rabbits by oral, dermal and subcutaneous routes of administration. The review in NDA 20-762 states that subcutaneous administration of SCH 32088 produced more maternal and fetal toxicity when compared with the animals treated through dermal or oral routes of administration. In rodents (s.c.), malformations and reduced survival were noted in doses lower than the clinical dose (based on body surface area comparisons). In rabbits (oral), malformations and effects on fetal growth were noted at doses well above the clinical dose. No changes in fertility were noted in an oral rat multigenerational study, although changes such as prolonged gestation and labor and reduced body weight gain were observed at doses slightly below the clinical dose (on a body surface area basis). However, when AUC values from the scanty data are compared, the exposure multiples of animals-to-humans were slightly higher than the body surface comparisons.

General Toxicology Issues: None at this time.

Recommendations:

This application is recommended for approval from a nonclinical perspective.

The sponsor's proposed nonclinical product label is also acceptable. A period (.) should be placed at the last sentence of paragraph 3 of the Pregnancy section.

Labeling with basis for findings:

Initial labeling comments were communicated to the sponsor following the first review cycle. In an effort to update the steroid label so that they reflected current labeling practices, the nonclinical portions of the label for mometasone furoate were revised (see memorandum by Dr. Robin Huff, dated November 6, 2000, communicated via Division Approvable letter of December 4, 2000). The recommended wording for the genetic toxicology findings was as follows:

"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 *in vivo* mouse [ ] micronucleus assays or [ ] Mometasone furoate also did not induce unscheduled DNA synthesis *in vivo* in rat hepatocytes."

In a labeling review for NDA 20-762 (Nasonex, Schering Plough) dated December 14, 2001, similar recommendations were made. However, in a fax to the sponsor dated April 9, 2002, the text regarding the genetic toxicology section was revised as follows:

"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".

An examination of the original genotoxicity assays (N20-762) reveals that the April 9, 2002 revision contains the more accurate description of the conducted studies and should be included in the labeling for Asmanex Twisthaler.

The sponsor's proposed nonclinical labeling is shown below and is considered to be acceptable. The only edit (denoted by an underline) is the addition of a period (.) at the end of the last sentence of the third paragraph of the Pregnancy section.

Carcinogenesis, Mutagenesis, Impairment of Fertility: 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 mcg/kg (approximately 8 times the maximum recommended daily inhalation dose in adults on an AUC basis). 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 mcg/kg (approximately 10 times the maximum recommended daily inhalation dose in adults on an AUC basis).

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.

In reproductive studies in rats, impairment of fertility was not produced by subcutaneous doses up to 15 mcg/kg (approximately 6 times the maximum recommended daily inhalation dose in adults on an AUC basis).

Pregnancy: ***Teratogenic Effects: Pregnancy Category*** **C**: When administered to pregnant mice, rats and rabbits, mometasone furoate increased fetal malformations. The doses that produced malformations also decreased fetal growth, as measured by lower fetal weights and/or delayed ossification. Mometasone furoate also caused dystocia and related complications when administered to rats during the end of pregnancy.

In mice, mometasone furoate caused cleft palate at subcutaneous doses of 60 mcg/kg and above (less than the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis). Fetal survival was reduced at 180 mcg/kg (approximately equal to the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis). No toxicity was observed at 20 mcg/kg (less than the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis).

In rats, mometasone furoate produced umbilical hernia at topical dermal doses of 600 mcg/kg and above (approximately 6 times the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis). A dose of 300 mcg/kg (approximately 3 times the maximum recommended

daily inhalation dose in adults on a mcg/m^2 basis) produced delays in ossification, but no malformations.

In rabbits, mometasone furoate caused multiple malformations (e.g., flexed front paws, gallbladder agenesis, umbilical hernia, hydrocephaly) at topical dermal doses of 150 mcg/kg and above (approximately 3 times the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis). In an oral study, mometasone furoate increased resorptions and caused cleft palate and/or head malformations (hydrocephaly and domed head) at 700 mcg/kg (less than the maximum recommended daily inhalation dose in adults on an AUC basis). At 2800 mcg/kg (approximately 2 times the maximum recommended daily inhalation dose in adults on an AUC basis) most litters were aborted or resorbed. No toxicity was observed at 140 mcg/kg (less than the maximum recommended daily inhalation dose in adults on an AUC basis).

When rats received subcutaneous doses of mometasone furoate throughout pregnancy or during the later stages of pregnancy, 15 mcg/kg (approximately 6 times the maximum recommended daily inhalation dose in adults on an AUC basis) 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 mcg/kg (approximately 3 times the maximum recommended daily inhalation dose in adults on an AUC basis).

There are no adequate and well-controlled studies in pregnant women. ASMANEX TWISTHALER, like other corticosteroids, should be used during pregnancy only if the potential benefits justify the potential risks to the fetus. Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

Reviewer signature: Virgil Whitehurst

Supervisor signature [concurrence]: Timothy J. McGovern

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

/s/

Virgil Whitehurst
4/28/04 11:00:15 AM
PHARMACOLOGIST

Timothy McGovern
4/28/04 01:17:02 PM
PHARMACOLOGIST
I concur.

Memorandum

To: NDA 21-067
From: Robin A. Huff, Ph.D., Supervisory Pharmacologist
Date: November 6, 2000
Re: Labeling Revisions

As part of an effort to update steroid labels so that they reflect current labeling practices, the label for mometasone furoate was reviewed. Most of the necessary revisions involve data organization and presentation style. In instances where revisions involve specific data items in the "Pregnancy" section, studies located in archival volumes were consulted to support the revisions. The "Carcinogenesis, Mutagenesis, Impairment of Fertility" and "Pregnancy" sections of labeling should be revised to read as follows:

Carcinogenesis, Mutagenesis, Impairment of Fertility: 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 mcg/kg (approximately 8 times the maximum recommended daily inhalation dose in adults on an AUC basis). 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 mcg/kg (approximately 10 times the maximum recommended daily inhalation dose in adults on an AUC basis).

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 *in vivo* mouse [ ] micronucleus assays or [ ]. Mometasone furoate also did not induce unscheduled DNA synthesis *in vivo* in rat hepatocytes.

In reproductive studies in rats, impairment of fertility was not produced by subcutaneous doses up to 15 mcg/kg (approximately 6 times the maximum recommended daily inhalation dose in adults on an AUC basis).

Pregnancy: ***Teratogenic Effects: Pregnancy Category C*:** When administered to pregnant mice, rats and rabbits, mometasone furoate increased fetal malformations. The doses that produced malformations also decreased fetal growth, as measured by lower fetal weights and/or delayed ossification. Mometasone furoate also caused dystocia and related complications when administered to rats during the end of pregnancy.

In mice, mometasone furoate caused cleft palate at subcutaneous doses of 60 mcg/kg and above (less than the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis). Fetal survival was reduced at 180-mcg/kg (approximately equal to the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis). No toxicity was

observed at 20 mcg/kg (less than the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis).

In rats, mometasone furoate produced umbilical hernia at topical dermal doses of 600 mcg/kg and above (approximately 6 times the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis). A dose of 300 mcg/kg (approximately 3 times the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis) produced delays in ossification, but no malformations.

In rabbits, mometasone furoate caused multiple malformations (e.g., flexed front paws, gallbladder agenesis, umbilical hernia, hydrocephaly) at topical dermal doses of 150 mcg/kg and above (approximately 3 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis). In an oral study, mometasone furoate increased resorptions and caused cleft palate and/or head malformations (hydrocephaly and domed head) at 700 mcg/kg (less than the maximum recommended daily inhalation dose in adults on an AUC basis). At 2800 mcg/kg (approximately 2 times the maximum recommended daily inhalation dose in adults on an AUC basis) most litters were aborted or resorbed. No toxicity was observed at 140 mcg/kg (less than the maximum recommended daily inhalation dose in adults on an AUC basis).

When rats received subcutaneous doses of mometasone furoate throughout pregnancy or during the later stages of pregnancy, 15 mcg/kg (approximately 6 times the maximum recommended daily inhalation dose in adults on an AUC basis) 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 mcg/kg (approximately 3 times the maximum recommended daily inhalation dose in adults on an AUC basis).

There are no adequate and well-controlled studies in pregnant women. ASMANEX TWISTHALER, like other corticosteroids, should be used during pregnancy only if the potential benefits justify the potential risk to the fetus. Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born to women receiving corticosteroids during pregnancy. Such infants should be carefully monitored.

cc: NDA 21-067 Division File
/HFD-570 Hilfiker
/HFD-570 Huff

Dunn

AUG 27 1999

DIVISION OF PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original Submission: Review #1

NDA 21-067

Reviewer: Misoon Y. Chun, Pharm.D., DABT
Date of Submission: December 1, 1998
Date of Review: June 21, 1999 (First draft)
August 27, 1999 (Final)

Information to be Conveyed to Sponsor: Yes ( ), No (x)

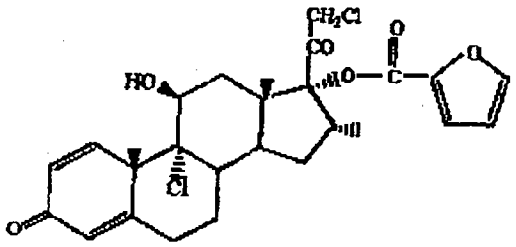
Sponsor: Schering Corporation
2000 Galloping Hill Rd
Kenilworth, NJ 07033

Drug Name: TRADEMARK 220 µg/
Mometasone Furoate Inhalation Powder

Chemical Name: 9,21-Dichloro-11β, 17-dihydroxy-16α -methylpregna-1,4-diene-3,20-dione 17-(2-fuorate)

CAS Number: 83919-23-7 Molecular Weight: 521.44

Molecular Formular and Structure: $C_{27}H_{30}Cl_2O_6$



Class of Drug: Corticosteroid, Anti-inflammatory

Indication: Maintenance treatment of asthma as prophylactic therapy

Propose Clinical Dose: 400µg bid by Oral Inhalation

Related NDAs/INDs:

NDA 19-543:	Elocon (Mometasone Furoate) Ointment, approved 04/30/87
NDA 19-625:	Elocon (Mometasone Furoate) Cream, approved 05/06/87
NDA 19-796:	Elocon (Mometasone Furoate) Lotion, approved 03/30/89
NDA 20-762:	Nasonex (Aqueous Nasal Suspension Spray), approved 12/29/97
IND [redacted]	[redacted]
IND [redacted]	[redacted]
IND 46,216:	Pure MF Dry Powder later changed to Lactose-containing MF DPI
IND 52,214:	MF/HFA-227 MDI
IND 55,108:	MF/HFA-227 Nasal Aerosol (Nasonex/HFA)

Introduction

The IND 46,216 was originally submitted (9/13/94) for the dry powder inhaler with pure mometasone furoate powder without excipient or vehicle. Preclinical testing with this pure dry powder includes acute study in dogs, 2-week and 3-month studies in both rats and dogs. In addition, one and three-month studies conducted in mice and rats with SCH 32088 in CFC MDI and a 3-month study in dogs by oral inhalation of SCH 32088 pure powder were reported in the original submission and reviewed by Dr. Virgil Whitehurst (10/13/94). Additional studies performed via intranasal, oral and intravenous administration of SCH 32088 were reported in various INDs.

The genotoxicity, carcinogenicity and reproductive toxicity for mometasone furoate have been assessed by Dr. Tom Du for NDA 20-762 (Nasonex Nasal Spray), which was approved October 6, 1997. The Review No.2 for IND 46,216 (Attachment No.1) by Dr. M. Chun contains reviews of those studies (two 2-week, two-1 month and two-3 month studies in rats and dogs) conducted with mometasone furoate powder containing lactose mixture and pharmacokinetic/ toxicokinetic studies for bridging between different formulations.

For this NDA 21-067, the additional toxicity studies with toxicokinetics (two-6 month studies in rats and dogs and one-12 month study in dog) conducted with the final clinical formulation plus four pharmacology and three ADME studies are reviewed.

Formulations:

a) *Various Formulations used in Toxicology study:*

Anhydrous Mometasone Furoate only (Pure powder)
Particle size at breathing zone from Toxicology Study:
Mometasone Furoate: MMAD = 1 Micron, GSD = 2-3

Anyhydrous Mometasone Furoate/ Lactose
Particle size at breathing zone from Toxicology Study:

Mometasone Furoate: MMAD = 3-5 Microns; GSD = 2-3
Lactose: MMAD = 3-5 Microns; GSD = 2-3

Mometasone Furoate/Lactose Ratio:
Toxicology Studies: 1:19 & 1:5.8
Clinical Formulations: 1:5.8

Delivery System: Breath actuated dry powder inhaler

b) Final Clinical Formulation:

Ingredient	200 µg/Unit Dose Inhaler		400 µg/Unit Dose Inhaler	
	µg/unit dose[1]	mg/inhaler[2]	µg/unit dose[1]	mg/inhaler[2]
Mometasone Furoate, USP (, Inhalation Grade)	200		400	
Lactose Anhydrous, NF (				
Total				

1 Unit dose is defined as a single inhalation
2 Both 200 µg and 400 µg strength inhalers have identical target fills of g of mometasone furoate:lactose anhydrose . (1:5.8)

PRE-CLINICAL STUDIES REVIEWED

Studies Submitted and Reviewed for NDA 21-067:

Pharmacology:

D-27631 An *in vitro* comparison of commonly used glucocorticoid (GC) preparations on basophil histamine release and eosinophil survival.

D-28234 Inhibition of VCAM-1 expression in human bronchial epithelial cells by glucocorticoids.

D-28024 Evaluation of the receptor binding and gene activation properties of mometasone furoate and of several comparative steroids:

D-27758 Mometasone Furoate (SCH 32088) Binding affinity and activation of both the glucocorticoid and progesterone receptors.

Toxicology/Toxicokinetics:

P-6518 Six-Month Nose-only Inhalation Study of SCH 32088:Lactose Powder Formulation (1:5.8) in Rats [ ]

P-6599 6-Month Inhalation Toxicity Study of SCH 32088:Lactose Powder Agglomerates in the Dog. [ ]

P-6600 12-Month Inhalation Toxicity Study of SCH 32088:Lactose Powder Agglomerates in the Dog. [ ] [ ]

Absorption, Distribution, Metabolism and Excretion (ADME):

P-6951 SCH 32088: Absorption, distribution, metabolism and excretion (ADME) of ^{3}H-mometasone furoate (^{3}H-SCH 32088) in mice following a single, one-hour, nose-only inhalation exposure to ^{3}H-SCH 32088:lactose powder. Kenilworth (NJ): Schering-Plough Research Institute; 1998 Oct. – Vol. 1.49

P-6952 SCH 32088: Absorption, distribution, metabolism and excretion (ADME) of ^{3}H-mometasone furoate (^{3}H-SCH 32088) in rats following a single, one-hour, nose-only inhalation exposure to ^{3}H-SCH 32088:lactose powder. Kenilworth (NJ): Schering-Plough Research Institute; 1998 Oct. – Vol. 1.50

P-6953 SCH 32088: Absorption, distribution, metabolism and excretion (ADME) of ^{3}H-mometasone furoate (^{3}H-SCH 32088) in beagle dogs following a single, one-hour, nose-only inhalation exposure to ^{3}H-SCH 32088:lactose powder. Kenilworth (NJ): Schering-Plough Research Institute; 1998 Oct. – Vol. 1.51

P-6377 SCH 32088: Identification of human liver cytochrome P-450 enzyme(s) which metabolize SCH 32088 to the 6β-OH metabolite of SCH 32088. Kenilworth (NJ): Schering-Plough Research Institute; 1997 Oct. – Vol. 1.52

Clin Doc 98279800. SCH 32088: Absorption, metabolism and excretion of ^{3}H-SCH 32088 + lactose powder administered by oral inhalation via dry powder inhaler to healthy male volunteers [Study report for protocol C97-047-01]. Kenilworth (NJ): Schering-Plough Research Institute; 1997 Sep. – Vol. 1.70

Studies Reviewed for IND 46,216 (Review #2, 12/17/98) (Attachment No.1)

P-6376 SCH 32088: In Vitro Metabolism of SCH 32088 Across Species by Liver, Lung and Intestinal Tissue Preparations. Kenilworth (NJ): Schering-Plough Research Institute; 1996 Nov. – Vol. 1.52 (Amendment No.34)

P-6121 SCH 32088: 2-week nose-only inhalation study of SCH 32088: lactose powder in rats. [ ]

P-6332 SCH 32088: 1-month nose-only inhalation toxicokinetic and comparative pilot toxicity study of SCH 32088: lactose powder formulation (1:5.8 and 1:19) in rats. [ ]

P-6230 SCH 32088: 3-month nose-only inhalation study of SCH 32088: lactose (1:19) powder in rats. [ ]

P-6078 SCH 32088: 14-day inhalation study of SCH 32088: lactose (1:19) powder in dog. [ ]

P-6333 SCH 32088: 1-month oral inhalation toxicity and toxicokinetic study of SCH 32088: lactose (1:5.8 and 1:19) powder in the dogs. [ ]

P-6231 SCH 32088: 3-month mouth-only inhalation study of SCH 32088: lactose (1:19) powder in the dog. [ ]

Studies Submitted but Not Reviewed Individually:

Validation:

P-6436 SCH 32088: Validation of the HPLC-mass spectrometric method for the determination of SCH 32088 in mouse plasma. [ ]

P-6707 SCH 32088: Validation of the HPLC-mass spectrometric method for the determination of SCH 32088 in rat plasma using beclomethasone-17-monopropionate as internal standard SCH 32088. [ ]

P-6437 SCH 32088: Validation of the HPLC-mass spectrometric method for the determination of SCH 32088 in dog plasma. [ ]

Pharmacokinetics in Human: (See the review by OCPB, DPE-II)

Clin Doc 98117801: Single-dose absolute bioavailability study [Protocol C97-046-01]
Clin Doc 98210125: Multiple-dose safety and tolerance study [Protocol C97-049-01]
Clin Doc 961665266: Multiple-dose safety and tolerance study [Protocol C95-135-01]
Clin Doc 96268229: Multiple-dose safety and tolerance study [Protocol C94-071-01]

Studies Referenced to NDA 20-762 (Nasonex)

Reproductive Toxicity Studies
Genotoxicity Studies
Carcinogenicity Studies

NOTE: The reproduction toxicity, genotoxicity and carcinogenicity have been assessed for NDA 20-762, and therefore, not reviewed here.

Table of Content

REVIEW OF STUDIES

Note: Portions of this review were excerpted directly from the sponsor's submission.

(A) Pharmacology:

The pharmacodynamic and safety pharmacology studies of mometasone furoate have been included in prior INDs (Intranasal 35932; Dry Powder Inhaler 46216; CFC Metered Dose Inhaler 32503; Mometasone Furoate Lotion 0.1% 27838) or NDA (Aqueous Nasal Spray 20-762) submissions. The most recent comprehensive description of pharmacodynamic studies of mometasone furoate is contained in the NDA 20-762, Nasonex Aqueous Nasal Spray, Section 5.A. Therefore, following four pharmacodynamic studies of mometasone furoate not previously submitted in any regulatory document are summarized here.

D-27631 **An *in vitro* comparison of commonly used glucocorticoid (GC) preparations on basophil histamine release and eosinophil survival. November 20, 1996 - Vol. 1.22**

This study was conducted to evaluate the anti-inflammatory effects of mometasone furoate and comparator steroids on basophil histamine release and eosinophil survival. Basophil-enriched cell suspensions from normal adult donors were incubated for 24 hours with mometasone furoate, fluticasone propionate, budesonide, beclomethasone dipropionate, triamcinolone acetonide or hydrocortisone acetate prior to challenge with anti-IgE antibody. Histamine release was measured using an automated fluorometric technique. For eosinophil viability, purified peripheral blood eosinophils were cultured for three days in the presence of interleukin-5 and with various concentrations of glucocorticoids.

Results:

Table 1 Concentration of Glucocorticoids Required for Inhibition of Basophil Histamine Release (HR) and Eosinophil Survival

Glucocorticoid	Basophil HR	Eosinophil Survival
Fluticasone Propionate	9×10^{-11} M*	2.5×10^{-10} M**
Mometasone Furoate	3×10^{-10} M	7×10^{-10} M
Budesonide	5.9×10^{-10} M	5.9×10^{-9} M
Beclomethasone Dipropionate	1×10^{-9} M	3×10^{-8} M
Triamcinolone Acetonide	2×10^{-9} M	1×10^{-8} M
Hydrocortisone Acetate	1.7×10^{-7} M	2.5×10^{-6} M

* Concentration for 50% inhibition of HR
** Concentration for half maximal reduction in eosinophil survival

Mometasone furoate inhibited histamine release with an IC_{50} = 0.3 nM, and fluticasone propionate with and IC_{50} = 0.09 nM, which was more potent. The rank order of potency was fluticasone propionate > mometasone furoate > budesonide> beclomethasone dipropionate > triamcinolone acetonide >> hydrocortisone acetate (Table 1). In addition, mometasone furoate reduced eosinophil survival with an IC_{50} of 0.7 nM with a concentration-dependent inhibition and with a similar rank order.

D-28234 Inhibition of VCAM-1 expression in human bronchial epithelial cells by glucocorticoids. October 20, 1997 –Vol. 1.22

In this study mometasone furoate and other steroids (fluticasone propionate, budesonide, beclomethasone dipropionate, beclomethasone 17-monopropionate, triamcinolone acetonide and hydrocortisone) were tested for their effects on TNF-α induced VCAM-1 expression on BEAS-2B cells, a human bronchial epithelium transformed cell line. BEAS-2B cells were preincubated with various concentrations of glucocorticoids for 24 hours before stimulation with TNF-α for another 24 hours.

Results:

Mometasone furoate inhibited VCAM-1 expression with an IC_{50} of 3.8 pM. The rank order of potency was mometasone furoate > fluticasone propionate >> budesonide ≥ triamcinolone acetonide > beclomethasone dipropionate ≥ beclomethasone 17-monopropionate ≥ hydrocortisone (Table 2). β-estradiol, a control steroid, had no effect.

Table 2 Effects of Mometasone Furoate and Other Glucocorticoids on TNF-α Induced VCAM-1 Expression on a Human Bronchial Epithelial Cell Line

Glucocorticoid	**IC_{50} (nM)**
Mometasone Furoate	0.0038
Fluticasone Propionate	0.0068
Budesonide	0.54
Triamcinolone Acetonide	0.8
Beclomethasone Dipropionate	8.1
Belcomethasone-17-Monopropionate	9.5
Hydrocortisone	12

D-28024 Evaluation of the receptor binding and gene activation properties of mometasone furoate and of several comparative steroids: [ ]

Two studies (D-28024 and D-27758) were conducted to determine binding affinity and gene activation potential of mometasone furoate with other glucocorticoids and progestines at the glucocorticoid and progesterone receptors. Each study also examined the relative potency of ligand-induced gene activation of the glucocorticoid and progesterone responsive elements (GRE/PRE).

In the first study, glucocorticoid receptor binding measurements were done using rat hepatic glucocorticoid receptor (rGR) isolated from liver cytosol or human glucocorticoid receptor (hGR) isolated from a human hepatoma cell line (HA22T/VGH). The competition binding studies to the rGR and hGR were performed by the evaluation of the inhibitory potency of the test compounds on the binding of ^{3}H-dexamethasone. Progesterone receptor binding studies were done using the rat uterine progesterone receptor (rPR) and the human progesterone receptor (hPR) isolated for a human breast cancer cell line, T47D. The competition binding studies to the rPR and hPR were performed by the evaluation of the inhibitory potency of the test compounds on the binding of ^{3}H-R5020 (promegesterone). Receptor binding affinity (IC_{50}) is defined as the amount of test ligand required to displace 50% of bound ^{3}H-dexamethasone or ^{3}H-progesterone *in vitro* assays. Potency is defined as the EC_{50} for GR or PR transactivation.

Results:

The Table 3 summarizes and compares the half-maximal competing concentration of each steroid tested in the hGR and hPR assays, the potency compared to corticosterone of the steroids on the hGR, and the potency compared to progesterone of the steroids on the hPR.

The comparative ability of the various steroids, when complexed to the receptor, to mediate subsequent gene activation was also evaluated in cells transiently transfected with a hormone-responsive reporter plasmid. Mometasone furoate was very potent at inducing glucocorticoid transcriptional activity (EC_{50} = 0.21 nM). Fluticasone propionate was slightly less potent (EC_{50} = 0.38 nM). The rank order of potency was mometasone furoate ≥ fluticasone propionate > budesonide ≥ triamcinolone acetonide ≥ 6-OH-mometasone furoate ≥ dexamethasone > Provera = Norgestrel > corticosterone >> progesterone activities.

Mometasone furoate was also a potent stimulator of PRE mediated transcriptional activity (EC_{50} = 0.07 nM) with activity similar to Provera (EC_{50} = 0.08 nM) and Norgestrel (EC_{50} = 0.13 nM) but more potent than progesterone (EC_{50} = 1.38 nM,). The rank order of all the test compounds was: mometasone furoate ≥ Provera ≥ Norgestrel > fluticasone propionate ≥ 6-OH-mometasone furoate > budesonide ≥ progesterone ≥ triamcinolone acetonide > dexamethasone > corticosterone.

Table 3 Summary of IC50 and Potency of Mometasone Furoate and Comparator Steroids on the Human Glucocorticoid and Progesterone Receptors

ID	hGR IC50 (nM)	GR potency	hPR+ IC50 (nM)	PR potency
Progesterone	214.52	0.44	3.35	1.00
Corticosterone	94.97	1.00	125.19	0.03
Mometasone F	10.71	8.87	4.39	0.76
6-OH-Mometasone F	8.00	11.87	4.43	0.76
Triamcinolone AC	13.38	7.10	20.68	0.16
Budesonide	8.53	11.13	19.56	0.17
Fluticasone PR	8.99	10.56	19.35	0.17
Dexamethasone	9.31	10.20		
R5020			17.00	0.20
Provera			1.55	2.16
Norgestrel			1.11	3.02

+ Normalized protein content

D-27758 Mometasone Furoate (SCH 32088) Binding affinity and activation of both the glucocorticoid and progesterone receptors.

A second study was done to profile the effects of mometasone furoate and other steroids on binding to the GR and PR and to measure ligand-induced gene activation. In this study, a transformed green monkey kidney cell line, Cos-1, devoid of endogenous GR and PR, was used instead of cell lines that endogenously expressed either the GR or PR used in study D-28024. Expression of the receptors was achieved by transient transfection with mammalian expression vectors for GR or PR.

The competition binding studies to the hGR or to the hPR were performed by the evaluation of the inhibitory potency of the test compounds on the binding of ^{3}H-dexamethasone or ^{3}H-progesterone to extracts from cells transiently expressing the GR or PR after transfection. This binding assay enabled the determination of the relative ability of a test compound to displace the radiolabeled ligand from the receptor and was expressed as relative binding affinity (RBA).

Results:

Mometasone furoate was the most potent compound in the GR binding assay (RBA = 8.1). Relative binding affinity (RBA) is the amount of test ligand needed to displace 50% of bound [^{3}H] dexamethasone relative to unlabeled dexamethasone. The rank order of potency was mometasone furoate > fluticasone propionate > 6-OH-mometasone furoate = budesonide > triamcinolone acetonide > dexamethasone. In the progesterone binding assay, mometasone furoate was the most potent competitor (RBA = 20.6) which was similar to that of Provera (RBA = 34). With the exception of dexamethasone, which was inactive, all glucocorticoids showed significant binding affinities to the PR. The rank order of potency was mometasone furoate > Provera = Norgestrel > progesterone > 6-OH-mometasone furoate > fluticasone propionate > triamcinolone acetonide = budesonide >>> dexamethasone.

Glucocorticoid or progestin-mediated gene activation studies were also done with the transiently transfected cell system used for the binding studies. Mometasone furoate was the most potent glucocorticoid (EC_{50} = 0.069 nM). The rank order of potency was mometasone furoate > fluticasone propionate > triamcinolone acetonide > 6-OH-mometasone furoate = budesonide > Provera > dexamethasone.

Mometasone furoate had an affinity for both the GR and PR and elicited a transcriptional response after binding to the respective receptors. The ratio of glucocorticoid to progesterone (GR/PR) receptor activation is similar for all the locally active glucocorticoids. Table 4 below demonstrates that mometasone furoate is in the same range of activity (EC_{50}) as the other glucocorticoids.

Table 4 Relative Activity of Steroids to Activate the Glucocorticoid (GR) and Progesterone (PR) Receptors

Compound	**Ratio of EC50 GR/PR**
Mometasone Furoate	1.2
Fluticasone Propionate	0.4
Triamcinolone Acetonide	1.0
Budesonide	2.2
6β -OH Mometasone Furoate	1.9
Provera	183

Summary of Four Pharmacology Studies:

It has been recognized that inhibition of mediator release from inflammatory cells is an important anti-inflammatory mechanism of steroids. Basophil degranulation is an early step in the cascade of mediator production which initiates the allergic response, and the importance of eosinophils to the late phase response has also been known. In addition, it has been shown that the cellular inflammmation is regulated by adhesion molecules such as VCAM-1 and ICAM-1 and their counterreceptors expressed on the surface of leukocytes and target cells such as endothelial cells, connective tissue fibroblasts and bronchial epithelial cells. VCAM-1 and ICAM-1 expression is induced by cytokines in human bronchial epithelial cells.

Two studies were conducted to analyze the anti-inflammatory effects of glucocorticoids in cell culture (ie., cytokine production, histamine release, eosinophil viability and other end-points). Mometasone furoate as well as fluticasone propionate was the most potent glucocorticoids, followed by budesonide, triamcinolone and dexamethasone for inhibiting basophil histamine release and TNF-α induced VCAM-1 expresssion on human bronchial epithelial cell line or reducing eosinophil survival in these studies.

Glucocorticoids are known to mediate their anti-inflammatory effects by binding to specific glucocorticoid receptors (GRs). Subsequently, the glucocorticoid-receptor complex, following translocation to the nucleus, regulates gene expression in either a positive or negative manner by binding to glucocorticoid responsive elements in target genes. Two studies were conducted to determine binding affinity and gene activation potential of mometasone furoate and other glucocorticoids and progestins at the glucocorticoid and progesterone receptors. Each study also examined the relative potency of ligand-induced gene activation of the glucocorticoid and progesterone responsive elements (GRE/PRE).

Mometasone furoate has a high affinity for the glucocorticoid and/or progesterone receptors and shown to be the most potent of the glucocorticoids in activating the glucocorticoid and/or progesterone receptors. However, the ratio of glucocorticoid to progesterone receptor activation demonstrates that mometasone furoate is in the same range of activity as the other glucocorticoids. The glucocorticoid to progestational functional effect ratio of mometasone furoate is 1.2 which is similar to that of triamcinolone acetonide (1.0), and budesonide (2.2), and fluticasone priopionate (0.4), other currently marketed steroids.

In both the rat and human GR receptor binding assays, the potencies of mometasone furoate, 6-OH-mometasone, triamcinolone acetonide, budesonide and fluticasone propionate were similar in magnitude and there were no significant differences among them within each species. Both corticosterone, the physiological corticoid present in the rat, and progesterone were significantly less effective competitors than mometasone furoate ($p < 0.05$) in both assays.

B) Asorption, Distribution, Metabolism and Excretion (ADME):

P-6951 **SCH 32088: Absorption, distribution, metabolism and excretion (ADME) of ^{3}H-mometasone furoate (^{3}H-SCH 32088) in mice following a single, one-hour, nose-only inhalation exposure to ^{3}H-SCH 32088:lactose powder. Kenilworth (NJ): Schering-Plough Research Institute; 1998 Oct. – Vol. 1.49**

Study No.: N002436A
Date of Study Initiation: 7/8/96 Report Date: 10/12/98
Laboratory: [ ]
GLP Compliance/QA Report: Yes
Formulation: ^{3}H-SCH 32088 Dry Powder/Lactose Mix 1:5.8 ratio
Batch No.: 37125-151-4 for ^{3}H-SCH 32088

Study Design:

Species/Strain	Animals	Route Regimen	Target Exposure (µg/L)
Mice/CD-1 Swiss	60 male and 10 female (10-11 weeks)	Inhalation Nose-only 1-hr exposure	2 µg /L

1. Male and Female mice (5/gr) were exposed for 1 hr to a target ^{3}H-SCH 32088 aerosol concentration of ~2 µg/L, using nose only inhalation exposure system designed by [ ]
2. During and after exposure, plasma samples were collected (at 30 and 45 min; 0, 1, 4, 12, 24, 72 and 144 hour) and assayed for radioactivity content by LSC and SCH 32088 content using a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) method (LOQ ~50 pg/ml). Pharmacokinetc parameters were calculated using these data.
3. During each exposure, pulmonary-function measurements were made to calculate estimates of the dose of ^{3}H-SCH 32088 delivered to the mice.
4. To determine the distribution and excretion patterns of the radioactivity, plasma, tissues, and excreta were collected at selected postexposure time points (at 1, 4, 12, 24, 48, 72 and 120 hour) and analyzed for total radioactivity.
5. To allow visualization of the distribution of radioactivity in exposed mice, selected animals were subjected to whole-body autoradiography (at 0, 4 and 24 hour).
6. Metabolite-profile measurements were performed on samples of plasma, lung, urine, gall bladder with bile and feces.
7. HPLC methods with MS/MS detection were validated in mouse, rat and dog plasmas for specificity, sensitivity, linearity, and accuracy and precision and all met the acceptance criteria for all validation parameters over the concentration range of ~50 to ~5000 pg/ml.

Results:

	Particle size distribution ^{3}H-SCH 32088	
	MMAD	**GSD**
Batch # 37125-151-4	3.3, 2.9 and 3.0 μm	2.0, 2.1 and 2.2
During in-life exposures	3.0 and 3.1 μm	2.3

The plasma concentrations of SCH 32088 and total radioactivity for selected timepoints and AUC(tf) from time 0 to the final measurement for male mice are compared below.

Comparison of SCH 32088 and Radioactivity (male mice)			
Time postexposure (hr)	SCH 32088 (ng/ml)	Radioactivity (ng eq/ml)	SCH 32088/Radioactivity (%)
-0.5a	2.48	2.19	113
-0.25b	3.11	4.04	77
0	2.62	3.40	77
1c	1.30	4.63	28
4	0.33	4.56	7
12	0.25	8.24	3
24	0.06	6.01	0.01
72	0	2.54	0
144	0	0.47	0
AUC(tf)d	10.7	470	2

a: 0.5 hr after the start of the 1-hr exposure
b: 0.75 hr after the start of the 1-hr exposure
c: 1 hr, the only evaluated timepoint in female mice; plasma level = 1.297 ng/ml
d: Units are ng.hr/ml for SCH 32088 and ng eq.hr/ml for radioactivity

The data for the parent drug versus those of total radioactivity indicate that SCH 32088 was rapidly and extensively metabolized upon absorption. Unchanged SCH 32088 represented 100% of the plasma radioactivity 0.5 hr after the start of exposure, but only 7% of plasma radioactivity at 4 hr postexposure. At 1 hr postexposure, unchanged drug accounted for approximately 28% and 19% of the plasma radioactivity in male and female mice, respectively, again indicating rapid metabolism of test article. The AUC(tf) for SCH 32088 accounted for only 2% of the AUC(tf) for total radioactivity.

The highest concentrations of drug-derived radioactivity (>100 ng eq/g) immediately following exposure (0 hr) were in the nasal cavity, trachea, lung, tongue, esophagus, pelt (17.3%), thyroid, small intestine and stomach (35.6%). One hr after exposure, peak concentrations of radioactivity were observed in the small intestine and its contents. Peak radioactivity concentrations were observed in large intestine contents within 4 hr and in the large intestine itself after 12 hr.

SCH 32088 was extensively metabolized to more polar compounds mainly by hydroxylation (most likely at the 6-position), hydrolysis of the furoate ester, substitution of the C21 chlorine with a hydroxy group, and possible further oxidation. No single major metabolite was detected from this study. Most of the administered dose was excreted in the feces. Summary of results is provided in the following table.

Summary of Results (P-6951)		
Findings	**Male Mice**	**Female Mice**
Mean whole body dose at the end of exposure	187 µg/kg	367 µg/kg*
Percentage of dose deposited:	GI: ~69% pelt: ~17% other tissues: ~14% lung: ~6%	
Absorption was fast: Tmax	0.75 hr	
Plasma concentration of SCH 32088 Cmax at 0.75hr: Mean concentration at the end of exposure: Mean plasma concentration at 1 hr postexposure: " at 24 hr postexposure: AUC(tf):	 3.11 ng/ml 2.62 ng/ml 1.303 ng/ml LOQ 10.7 ng.hr/ml	 1.297 ng/ml
Plasma radioactivity concentration Cmax at 12 hr postexposure: Mean plasma radioactivity conc at 1 hr: AUC(tf):	 8.24 ng eq/ml 4.63 ng eq/ml 470 ng.hr/ml	 6.92 ng eq/ml
Distribution of radioactivity was higher in the tissues than those in plasma at 1 hr postexposure. Highest in intestine, stomach, esophagus, trachea and lowest (<1 ng eq/g) in bone marrow and pituitary. Tissue distribution profile was similar in M and F, but a tissue concentration was F>M (due to higher dose in F).	Immediately following exposure, total radioactivity was 53%, 36% (GI), 17% (pelt) & 10% (respiratory tract); 5.5% in the lung at the end of exposure	
Metabolism was rapid.	100% unchanged SCH 32088 in plasma at 0.5 hr; ~28% at 1 hr & 7% at 4 hr postexposure	
Metabolites via hydroxylation, hydrolysis and further oxidation	21-OH-mometasone, mometasone, βOH-MF, 21-OH-MF, & 6-keto MF	
Excretion: Mainly in the feces as unabsorbed compound and very little (≤ 2% radioactivity) in the urine, and % dose recovered was highly variable: 67% at 0-hr but 97% at12 hr.	Total amount excreted in urine and feces: 34% (24 hr), 63% (72 hr) & 45% (144 hr)	

* Females received higher (~36% above target) exposure concentration.

Conclusion:

Following a 1-hr, nose-only inhalation exposure of mice to 2 µg ^{3}H-SCH 32088/L, administered as lactose powder mixture, a larger portion of the radioactive dose was distributed to the gastrointestinal tract than to the lung, indicating that a high percentage of the inhaled dose was swallowed. ^{3}H-SCH 32088 was rapidly absorbed, extensively distributed into tissues and rapidly eliminated. Most of the administered dose was eliminated in the feces as unabsorbed drug, and a smaller percent was eliminated in urine. [illegible]-HPLC [illegible] HPLC) profiles of drug-derived radioactivity suggested extensive metabolism of ^{3}H-SCH 32088 to several polar metabolites, and no single major metabolite was detected.

P-6952 **SCH 32088: Absorption, distribution, metabolism and excretion (ADME) of ^{3}H-mometasone furoate (^{3}H-SCH 32088) in rats following a single, one-hour, nose-only inhalation exposure to ^{3}H-SCH 32088:lactose powder. Kenilworth (NJ): Schering-Plough Research Institute; 1998 Oct. – Vol. 1.50**

Study No.: N002436A
Date of Study Initiation: 7/8/96 Report Date: 10/12/98
Laboratory: [ ]
GLP Compliance/QA Report: Yes
Formulation: ^{3}H-SCH 32088 Dry Powder/Lactose Mix 1:5.8 ratio
Batch No.: 37125-151-4 for ^{3}H-SCH 32088

Study Design:

Species/Strain	Animals	Route Regimen	Target Exposure (µg/L)
Rats/SD 5/gr	70 male and 10 female (8-10 weeks)	Inhalation Nose-only 1-hr exposure	2 µg /L

1. Male and Female rats (body weights~245g ♂ and ~237g ♀) were exposed for 1 hr to a target ^{3}H-SCH 32088 aerosol concentration of ~2 µg/L, using nose only inhalation exposure system designed by [ ]
2. During and after exposure, plasma samples were collected (at 30 and 45 min; 0, 1, 4, 12, 24, 72 and 144 hour) and assayed for radioactivity content by LSC and SCH 32088 content using a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) method (LOQ ~50 pg/ml). Pharmacokinetc parameters were calculated using these data.
3. During each exposure, pulmonary-function measurements were made to calculate estimates of the dose of ^{3}H-SCH 32088 delivered to the rats.
4. To determine the distribution and excretion patterns of the radioactivity, plasma, tissues, and excreta were collected at selected postexposure time points (at 1,4, 12, 24, 48, 72 and 120 hour) and analyzed for total radioactivity.
5. To allow visualization of the distribution of radioactivity in exposed rats, selected animals were subjected to whole-body autoradiography (at 0, 4 and 24 hour).
6. Metabolite-profile measurements were performed on samples of plasma, lung, bile and excreta samples. A limited number (4/10 animals) of bile duct-cannulated rats (10 weeks of age) were exposed for the assessment of the ^{3}H-SCH 32088 metabolite profile in bile (0-4 hr).
7. HPLC methods with MS/MS detection were validated in mouse, rat and dog plasmas for specificity, sensitivity, linearity, and accuracy and precision and all met the acceptance criteria for all validation parameters over the concentration range of ~50 to ~5000 pg/ml.

Results:

Particle size distribution ^{3}H-SCH 32088		
	MMAD	**GSD**
Batch # 37125-151-4	3.3, 2.9 and 3.0 μm	2.0, 2.1 and 2.2
During in-life exposures	2.6 to 3.5 μm	2.2 to 2.3

The plasma concentrations of SCH 32088 and total radioactivity for selected timepoints and AUC(tf) from time 0 to the final measurement for male rats are compared below.

Comparison of SCH 32088 and Radioactivity (male rats)			
Time post-exposure (hr)	SCH 32088 32088 (ng/ml)	Radioactivity (ng eq/g)	SCH 32088/Radioactivity (%)
-0.5a	1.37	1.54	89
-0.25b	1.85	2.03	91
0	2.15	2.52	85
1	1.23	1.96	63
4	0.54	1.52	36
12	0.08	1.17	7
24	0.02	0.99	2
72	0	0.80	0
144	0	0.30	0
1c	1.20	2.50	48
AUC(tf)d	8.66	115	7.5

a: 0.5 hr after the start of the 1-hr exposure
b: 0.75 hr after the start of the 1-hr exposure
c: 1 hr, the only evaluated timepoint in female mice
d: Units are ng.hr/ml for SCH 32088 and ng eq.hr/g for radioactivity

The AUC(tf) for SCH 32088 represented 7.5% of the AUC(tf) for total radioactivity, indicating that SCH 32088 was rapidly and extensively metabolized following absorption. This is further supported by the plasma concentration data, in which the unchanged drug represented 85 to 91% of the plasma radioactivity during and at the end of exposure, 63% at 1 hr post-exposure and only 7% at 12 hr post exposure. For female rats, 48% of the plasma radioactivity was associated with unchanged drug at 1 hr post-exposure.

The highest concentrations of drug-derived radioactivity (>100 ng eq/g) immediately following exposure (0 hr) were in the esophagus (2270 ng eq/g), lung (892 ng eq/g), small intestine contents (751 ng eq/g), trachea (677 ng eq/g), tongue (543 ng eq/g), stomach and contents (304 ng eq/g)), nasal cavity (133 ng eq/g), and small intestine (105 ng eq/g). One hr after exposure, peak radioactivity concentrations were observed in the lung (924 ng eq/g) and small intestine (479 ng eq/g) and its contents (2080 ng eq/g). The peak radioactivity was observed in large intestine contents within 4 hr and in the large intestine itself after 12 hr.

Most of the administered dose was excreted in the feces. Summary of results is provided in the following table.

Summary of Results (P-6952)		
Findings	**Male Rats**	**Female Rats**
Mean whole body dose of ^{3}H-SCH 32088 at the end of exposure	61.5 ± 5.8 µg/kg	70.6 ± 10.4 µg/kg*
Percentage of dose ^{3}H-SCH 32088 deposited: Total dose recovered at 144 hr was 92.6% in males.	GI: ~70% pelt: ~15% other tissues: ~8% lung: ~8%	
Absorption was fast: Tmax	0 hr timepoint at the end of 1 hr exposure	
Plasma concentration of SCH 32088 Cmax at 0 hr at the end of exposure: Mean plasma concentration at 1 hr postexposure: " at 12 hr postexposure: AUC(tf):	 2.15 ng/ml 1.23 ng/ml <4% of peak level 8.66 ng.hr/ml	 1.20 ng/ml
Plasma radioactivity concentration Cmax at 0 hr at the end of exposure: Mean plasma radioactivity concentration at 1 hr: AUC(tf):	 2.52 ng eq/g 1.96 ng eq/g 115 ng eq.hr/g	 2.50 ng eq/g
Distribution: The highest concentrations of radioactivity were found in the esophagus, large and small intestine contents, lung, and trachea; the lowest were found in the brain and pituitary. Tissue radioactivity concentrations were generally higher than those in plasma and decreased with time but detectable in most tissues at 144 hr after exposure.	Immediately following exposure, majority of radioactivity was 57%; 43% (GI), 15% (pelt), 7-12% (respiratory tract) and lowest (<1 ng eq/g) in brain and pituitary. No gender difference.	
Metabolism is extensive to numerous polar metabolites. Metabolism is by hydroxylation at the 6 position, hydrolysis of the furoate ester, substitution of the C21 chloride with OH, and further oxidation.	Most of the radioactivity is from unchanged SCH 32088 in plasma (52%), bile (65%), urine (1%), feces (39%) and lung extract (83%).	
Metabolites:	21-OH-mometasone, mometasone, βOH-MF, 21-OH-MF, & 6-keto MF	
Excretion: Mainly in the feces as unabsorbed compound and very little (≤ 2% radioactivity) in the urine.	Total amount excreted in urine and feces: 60% within 24 hr & 91.2% by 144 hr. Radioactivity was recovered in feces (89.5%), in urine (1.7%) and in bile (5%).	

* Females received higher (~15% more than males) exposure concentration.

Conclusion:

Following a 1-hr, nose-only inhalation exposure of rats to 2 µg ^{3}H-SCH 32088/L, administered as lactose powder mixture, a larger portion of the radioactive dose was found in the gastrointestinal tract than in the lung, indicating that a high percentage of the inhaled dose was swallowed. ^{3}H-SCH 32088 was rapidly absorbed, extensively distributed into tissues and rapidly eliminated. Most of the administered dose was eliminated in the feces as unabsorbed drug, and a

smaller percent was eliminated in urine. ^{3}H-SCH 32088 was extensively metabolized to numerous polar metabolites.

P-6953 **SCH 32088: Absorption, distribution, metabolism and excretion (ADME) of ^{3}H-mometasone furoate (^{3}H-SCH 32088) in beagle dogs following a single, one-hour, nose-only inhalation exposure to ^{3}H-SCH 32088:lactose powder. Kenilworth (NJ): Schering-Plough Research Institute; 1998 Oct. – Vol. 1.51**

Study No.: N002436A
Date of Study Initiation: 7/8/96 Report Date: 10/16/98
Laboratory: [redacted]
GLP Compliance/QA Report: Yes
Formulation: ^{3}H-SCH 32088 Dry Powder/Lactose Mix 1:5.8 ratio
Batch No.: 38514-54-3 for ^{3}H-SCH 32088

Study Design:

Species/Strain	Animals	Route Regimen	Target Exposure (µg/L)	Measured Exposure (µg/L)
Dogs/Beagle	6 males &	Inhalation		4.8, 5.1 & 4.9 (lst)
3/sex/gr	6 females	Mouth-only	4 µg /L	4.0, 4.5 & 5.5 (2nd)
	(10-12 mo)	30-min exposure		(21 – 38% higher)

Assignment of Dogs to Sampling Time and Sample Collection Groups

Group	Gender	Number	Samples Collected	Timepoint(s)
1	M F	3 3	Plasma*	15 min into the 30-min exposure period; ≤ 5min, and 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 120, and 168 hr postexposure
			Urine	0-4, 4-8, and 8-24 hr; daily up to 7 days postexposure
			Feces	0-8 and 8-24 hr; daily up to 7 days postexposure
2**	M F	3 3	Plasma*	15 min into the 30-min exposure period; ≤ 5min, and 0.5, 1, 2, 4, 6, 8, and 24 hr postexposure
			Bile	0-2, 2-4, 4-8, and 8-24 hr postexposure
			Urine	0.4, 4-8, and 8-24 hr postexposure
			Feces	0.8 and 8-24 hr postexposure

* A pre-exposure plasma sample was collected from all dogs within 2 hr prior to the start of exposure.
** 3/sex had the common bile duct cannulated.

1. Six male and six female dogs (body weights~10.6 kg ♂ and ~9.7 kg ♀) were exposed for 30-min to a target ^{3}H-SCH 32088 aerosol concentration of ~4 µg/L, using oral-inhalation exposure unit developed by [ ] The second group of animals (3/sex) had bile duct-cannulated for the assessment of the ^{3}H-SCH 32088 metabolite profile in bile (0-4 hr).
2. During each exposure, pulmonary-function measurements were made to calculate estimates of the dose of ^{3}H-SCH 32088 delivered to the dogs.
3. Clinical observations were made twice daily and body weight measurements were taken prior to initiation of exposure.
4. Plasma and excreta were collected from all dogs in Group 1. Plasma, excreta, and bile were collected from all dogs in Group 2.
5. During and after exposure, plasma samples were collected and assayed for radioactivity content by LSC and SCH 32088 content using a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) method (LOQ ~50 pg/ml). Pharmacokinetc parameters were calculated using these data.
6. HPLC methods with MS/MS detection were validated in mouse, rat and dog plasmas for specificity, sensitivity, linearity, and accuracy and precision and all met the acceptance criteria for all validation parameters over the concentration range of ~50 to ~5000 pg/ml.
7. $$\text{Deposited Dose (µg/kg)} = \frac{\text{SCH 32088 concentration x Total Inhaled Volume x Deposition Fraction}}{\text{Body Weight}}$$
8. Using ICRP (*International Commission on Radiological Protection, Health Physics. 1966: 12: 173-207*) model, predicted deposition to the nasopharyngeal region in dogs is approximately 50% with a particle size of ~3 µm.

Results:

Particle size distribution ^{3}H-SCH 32088		
	MMAD	**GSD**
Batch # 38514-54-3	3.6 to 4.0 µm	1.9 to 2.3
During exposures: SCH 32088 Lactose	 3.8 to 4.2 µm 2.5 to 3.2 µm	 2.0 to 2.5 1.7 to 1.9

Total airway dose measured and calculated using 50% deposition factor was 20.7 to 61.2 µg SCH 32088/kg body weight with mean of 39.3 µg/kg.

The pharmacokinetic parameters for SCH 32088 and radioactivity are compared below for both intact and bile duct-cannulated dogs:

Comparison of SCH 32088 and Radioactivity (P- 6953)						
Dog Group (Gender)[a]	Material analyzed	Cmax (ng or ng eq/ml or g)	Tmax (hr post-exposure)	AUC(tf) (nq eq.hr/ml)	tf (hr)	Ratio of AUC SCH 32088: AUC ^3H
1-Intact (M)	SCH 32088	1.52	0.17	2.62	7	0.031
	^3H[b]	1.30	2.7	76.3	168	-
1-Intact (F)	SCH 32088	0.63	0.5	1.53	7	0.013[c]
	^3H	1.96	3.0	110	168	-
2-Bile-cann (M)	SCH 32088	0.58	0.17	1.89	8	0.036
	^3H	3.89	2.0	51.9	24	-
2-Bile-cann (F)	SCH 32088	1.89	-0.08[d]	3.87	8	0.093
	^3H	5.21	5.33	79.8	24	-

a: Values are mean of 3 dogs except for Intact females where n=2 for SCH 32088
b: ^3H-Total radioactivity
c: n=2
d: In 1 of 3 dogs Tmax occurred at 0.25 hr before the end of exposure

Following exposure, the radioactivity in plasma increased to peak values at about 3 hr in intact dogs and at 2-5 hr in bile duct-cannulated dogs, whereas SCH 32088 peaked at 0-0.5 hr postexposure.

The AUC(tf) for SCH 32088 represented 1-3% of the AUC(tf) for total radioactivity in intact dogs and 4-9% in the bile duct-cannulated dogs, indicating that SCH 32088 was rapidly and extensively metabolized irrespective of dog group and gender. This is further supported by the plasma concentration data as shown in the previous table, which showed that during and at the end of exposure, almost all of the radioactivity in plasma was unchanged drug, but only 4-8% of the radioactivity was unchanged drug at 8 hr postexposure.

Conclusion:

Following a 30-min, mouth-only inhalation exposure of dogs, ^3H-SCH 32088 was rapidly absorbed, most likely via the respiratory tract. The Cmax for unchanged drug in plasma occurred rapidly (0 to 0.5 hr) following exposure. The absorbed ^3H-SCH 32088 was extensively metabolized to numerous polar metabolites but no single major metabolite was detected in plasma, urine, bile, or feces. Excretion of the absorbed ^3H-SCH 32088-derived material was mostly by the biliary route. Only a small percent of the dose was eliminated in urine. A significant amount of the radioactivity in the feces was probably due to unabsorbed drug that had been swallowed.

Summary of results is provided in the following table.

Summary of Results (P-6953)		
Findings	**Male Dogs**	**Female Dogs**
Mean airway dose of ^{3}H-SCH 32088 from 30-min inhalation exposure, mouth-only	34.1 µg/kg	44.6 µg/kg
Absorption was fast: Tmax	0 – 0.5 hr postexposure (<5 min)	
Plasma concentration of SCH 32088 Mean Cmax at 0.25 hr into the 0.5 hr exposure: Mean AUC(tf):	 0.58 – 1.89 ng/ml 1.53 – 3.87 ng eq.hr/ml	
Plasma radioactivity concentration Mean Cmax at 3 hr postexposure: Mean AUC(tf):	 1.30 ng eq/g 76.3 - 110 ng eq.hr/g	1.96 ng eq.hr/g
Dogs with bile cannulae: Mean Cmax at 2 hr (M) and 5.3 hr (F) post exp.: Mean AUC(tf):	 3.89 ng eq/g 51.9 ng eq.hr/g	 5.21 ng eq/g 79.8 ng eq.hr/g
Metabolism is rapid and extensive Metabolism is via hydroxylation at the 6 position, hydrolysis of the furoate ester, substitution of the C21 chloride with OH, and further oxidation. There were numerous polar metabolites but no evidence of major metabolite in plasma, bile, urine, or feces.	Most of the radioactivity is from unchanged SCH 32088 in plasma at 0 hr (100%) but 4-8% at 8 hr postexposure. AUC(tf) for SCH 32088 accounted for 1-3% of the AUC(tf) for total radioactivity in intact dogs and 4-9% in bile duct-cannulated dogs.	
Distribution: Not measured.		
Excretion: Mainly in the feces (50 to 55% of doses) and very little (≤ 2% radioactivity) in the urine by intact animals over 0-168 hr period.	Total amount excreted in the bileduct cannulated animals over 0-24 hr was 15.8%, 2.5% in males and 17.7% and 14.7%, 2.1% and 17.5% of the dose in females into the bile, urine and feces, respectively.	

P-6377 SCH 32088: Identification of human liver cytochrome P-450 enzyme(s) which metabolize SCH 32088 to the 6β-OH metabolite of SCH 32088. Kenilworth (NJ): Schering-Plough Research Institute; 1997 Oct. – Vol. 1.52

Study No.: 96191
Date of Study Initiation: January 1996 Final Signatrue Date: 10/21/97
Laboratory: Safety Evaluation Center/Schering-Plough Research Insitute, NJ
Formulation: H-SCH 32088 Dry Powder/Lactose Mix 1:5.8 ratio
Batch No.: SCH 32088 - MMF-X-6005

Study Design:

SCH 32088 was incubated for 30 minutes with 14 human liver microsomes [ ] to determine which cytochrome P-450 enzyme(s) was responsible for its oxidative metabolism to the 6β-OH metabolite. The specific enzyme capable of this biotransformation was identified by correlation and enzyme-specific inhibition analyses and confirmed by incubation with cell-line derived human liver enzyme specific microsomes.

Results:

1. There was a high correlation between the rate of formation of 6β-OH SCH 32088 (r^2=0.50), determined in 14 human liver microsomal samples, and higher correlation with both dextromethorphan N-demethylation (r^2=0.74) and testosterone 6β-hydroxylation (r^2=0.81), both of which are catalyzed by human cytochrome P-450 3A4 (CYP3A4).

2. The formation of the 6β-OH metabolite of SCH 32088 by human liver microsomes was inhibited by approximately 50% in the presence of the selective CYP3A4 inhibitor ketoconazole. Although inhibited by 50%, the correlation between the formation of the 6β-OH metabolite and both dextromethorphan N-demethylation and testosterone 6β-hydroxylation remained high thereby confirming the primary role of CYP3A4 in the formation of 6β-OH SCH 32088.

3. Cell-line derived human CYP3A4 microsomes metabolized SCH 32088 to the 6β-OH metabolite to a comparable extent as the more active human liver microsomal samples which were shown to have high CYP3A4 activity.

Conclusion:

The results show that SCH 32088 was metabolized to the 6β-OH metabolite substantially by the CYP3A4 enzyme in human liver microsomes.

Clinical Doc 98279800. SCH 32088: Absorption, metabolism and excretion of ^{3}H-SCH 32088 + lactose powder administered by oral inhalation via dry powder inhaler to healthy male volunteers [Study report for protocol C97-047-01]. Kenilworth (NJ): Schering-Plough Research Institute; 1997 Sep. – Vol. 1.70

This is an open-label, single-dose, absorption, metabolism and excretion study in sixty healthy male subjects between the ages of 18 and 45 years. Subjects received 1-mg dose of ^{3}H-SCH 32088 + lactose powder, and blood, urine and feces were collected over 7 days for the pharmacokinetic evaluations.

Summary of Results:

Mean Mometasone Furoate Plasma and Radioactivity Results (Protocol No. C97-047)

Parameter	SCH 32088	Radioactivity
Cmax (pg/mL or pg equiv/gm)a	70.7	837
Tmax (hr)b	1.75	13
AUC(tf) (pg.hr/ml or pg equiv.hr/gm)c	279	43700

a: Maximum observed plasma concentration.
b: Time of maximum observed plasma concentration.
c: Area under the plasma concentration-time curve from time zero to time of the final quantifiable sample.

Plasma radioactivity was measurable within 2 hours of dose administration then slowly decreased. Plasma mometasone concentrations were detectable in all subjects; however, concentrations were near the LOQ of the assay. Mometasone furoate was poorly absorbed (~34%) from the gastrointestinal tract. Drug-derived radioactivity was eliminated mainly into the feces (74%) and to a lesser extent into urine (8%). Mometasone furoate is extensively metabolized at least in part via hydroxylation (most likely at the 6-position), hydrolysis of the furoate ester and substitution of the C21 chlorine with a hydroxy group. No single major metabolite was detected.

Summary of Pharmacokinetics/Toxicokinetics and ADME Studies:

The nonclinical drug metabolism and toxicokinetic studies directly supporting the DPI formulation were included in this review. Studies with ^{3}H-MF were conducted in the mouse, rat and dog (P-6951, P-6952 & P-6953) in order to characterize the pharmacokinetics, tissue distribution (mouse and rat only), metabolism and excretion of MF and drug-derived material (degredants or impurity). The exposure concentration in these studies reflected the highest exposure concentration normally utilized (2, 2, and 4 μg/L in mice, rats and dogs, respectively) in the safety evaluation studies for each species.

In vitro studies (P-6376) were performed with MF to characterize its metabolism by hepatic, pulmonary and intestinal tissues (See the Review #2 of IND 46,216), and to determine which P-450 enzyme-related isozymes were responsible for its biotransformation (P-6377). In addition, toxicokinetic data from inhalation studies with MF were obtained in rats and dogs to support the safety evaluation of the DPI formulation. Finally, the metabolism and excretion patterns of MF were also determined in humans following inhalation with the DPI formulation and IV administration (C-97-047-01). The clinical data from the study are used to compare both the exposure and disposition profile in humans to the animal data.

HPLC methods with MS/MS detection were validated in mouse, rat and dog plasmas for specificity, sensitivity, linearity, and accuracy and precision and all met the acceptance criteria for all validation parameters over the concentration range of ~50 to ~5000 pg/ml.

Pharmacokinetics (Absorptions):

The plasma profile of MF and total tritium were determined following a single inhalation exposure of an aerosolized ^{3}H-MF/lactose powder mixture to mice (P-6951), rat (P-6952) and dog (P-6953). ^{3}H-MF/L was exposed to mice, rat and dogs at the concentration of ~2 μg, ~2 μg and ~4 μg, respectively, by 1 hr, nose-only to mice and rats and 0.5 hr, mouth-only to dogs. In addition, healthy volunteers were exposed to ^{3}H-MF lactose mixture (1:5.8) as 5 puffs from a DPI delivering ~200 μ ^{3}H-MF per actuation. Aerosol disposition models were used to predict the total deposited dose in the lung from inhalation exposure in rat and dog (Table 1).

For the animal studies, Cmax of parent drug was reached either prior to or at the end of the inhalation exposure. Plasma MF concentrations then rapidly declined so that at 12 hr post-exposure, values were below or close to the LOQ of the assay. In humans, MF concentrations were limited to only one time point in 3/6 individuals and were close to the LOQ (~0.05 ng/ml). Consequently, AUC values were imprecise; the geometric mean AUC was 0.076 ng.hr/ml.

Table 1 Pharmacokinetic Parameters after Inhalation Exposure of ^{3}H-MF/Lactose Mixtures to Mice, Rats, Dogs and Humans

		Species				
		Mouse (P-6951)	Rat (P-6952)	Dog (P-6953)		Human (C-97-047-01)
Gender (Number)		M (5/time point)	M (5/time point)	M, F (3/gender)	M, F[b] (3/gender)	M (6)
Formulation MF/lactose powder (1:5.8)		Aerosol	Aerosol	Aerosol	Aerosol	DPI
Targeted Exposure Concentration (μg/L)		2	2	4	4	1 mg
Pharmacokinetic Parameters for MF						
Cmax	(ng/mL)	3.11	2.15	1.17	1.23	0.071
Tmax	(hr)[a]	0.75	1	0.85	0.55	1.75
AUC(0-∞)	(ng·hr/mL)	10.6	8.66	2.18	2.88	0.076[c]
Pharmacokinetic Parameters for ^{3}H-MF						
Cmax	(ng-eq/mL)	8.24	2.52	1.61	4.55	0.837
Tmax	(hr)[a]	13	1	2.5	3.7	13
C(24 hr)	(ng-eq/mL)	6.00	0.99	0.91	1.94	0.568

a: Time from the start of the 1 hr inhalation exposure

b: Animals were bile duct-cannulated

c: Geometric mean AUC estimated assuming an AUC of 0 for the 3 volunteers with only single plasma concentration values.

Maximum levels of radioactivity were 2.6, 1.2 and 1.4 to 3.7-fold higher than those of MF in mice, rats and dogs, respectively. For humans, total radioactivity levels were 11.8-fold greater than those for MF. Tmax for radioactivity ranged from 5 to 48 hr after dose inhalation, suggesting that tritiated material be absorbed from the gastrointestinal tract in humans. Low levels of radioactivity from urinary excretion data (Table 3) appeared to confirm these findings. Although there was some tritium exchange with body water, radioactivity levels in plasma declined at a much slower rate than for radioactivity associated with MF.

Tissue Distribution:

The distribution of tritium into tissues and organs was determined over a 6-day period following a 1 hr, nose-only inhalation exposure of an aerosolized ^{3}H-MF/lactose powder mixture (~2 µg ^{3}H-MF/lactose) to male mice and rats. At the completion of the 1hr exposure to mice, the highest amounts of radioactivity (% of the dose deposited) were associated with respiratory tract (10%), pelt (17.3%) and gastrointestinal tract (35.6%). For the rat, 11.8% of the dose was deposited in the respiratory tract, 14.5% on the pelt and 42.6% was recovered from the gastrointestinal tract. At the end of exposure 5.5% and 7.3% of total radioactivity was retained in the lungs of mice and rats, respectively.

Absorbed radioactivity was extensively distributed throughout the body and the concentrations of radioactivity were around 3 to 4 fold higher in the most tissues than measured in plasma. In the liver, the radioactivity concentrations were substantially higher than those in plasma, since MF metabolites are excreted in the bile (Table 2).

Table 2 Organ or Tissue/Plasma Ratios of Tritium Following Inhalation Exposure of ^{3}H-MF to Male Mice and Rats

Species	Organ or Tissue/Plasma Ratio							
	Mouse				Rat			
Sample Collection Time[a]	0 hr	4 hr	24 hr	72 hr	0 hr	4 hr	24 hr	72 hr
Plasma Conc. (ng-eq/mL)	3.39	4.56	6.01	2.54	2.52	1.52	0.988	0.799
Tissue								
Intestine Wall (Large)	2.4	226	81	5.9	1.0	67	41	4.3
Intestine Wall (Small)	47	52	21	3.6	42	90	16	2.2
Kidney	6.0	3.1	1.8	1.3	3.6	4.1	2.2	2
Liver	8.6	36	13	6.5	3.0	15	14	9.0
Lung	608	219	20	4.0	354	428	162	110
Lymph Node (Mesenteric)	2.5	3.8	3.6	0.54	1.5	3.1	1.2	0.59
Nasal Cavity	117	3.4	1.1	1.5	53	3.7	1.9	1.5
Trachea	752	55	2.1	1.1	269	35	14	3.8

a: Time from the end of the 1 hr inhalation exposure

Metabolism:

Metabolic pathways have been characterized *in vivo* after a single inhalation exposure of an aerosolized ^{3}H-MF/lactose powder mixture to mice and rats (1 hr, nose-only; 2 µg ^{3}H-MF/lactose), dogs (0.5 hr, mouth-only; ~4 µg ^{3}H-MF/lactose) and human volunteers administered a 1 mg dose of a ^{3}H-MF/lactose powder mixture (Table 3).

MF was found to undergo extensive metabolism to numerous metabolites, which cannot be clearly identified. However, there appear to be three metabolic pathways that can be identified across the species: 6β- hydroxylation, hydrolysis of the furoate ester and substitution of the C21 chlorine with a hydroxyl group as shown on the next page (Fig. 1).

In vitro metabolism study (P-6377) was conducted by incubations of MF with liver and lung slices and microsomes, everted intestines, and hepatocytes from mouse, rat, dog and human. When MF was incubated at low concentrations in liver slices and hepatocytes, MF was extensively metabolized in all species to numerous metabolites, one of which was confirmed to be 6β-OH-MF. In contrast, MF was metabolized primarily to 6β-OH-MF when incubated at high concentrations with liver slices. In mouse, rat and dog liver microsomes, everted intestine and human liver microsomes, MF was also metabolized primarily to 6β-OH-MF, but incubation of MF with lung microsomes and lung slices did not generate any metabolites.

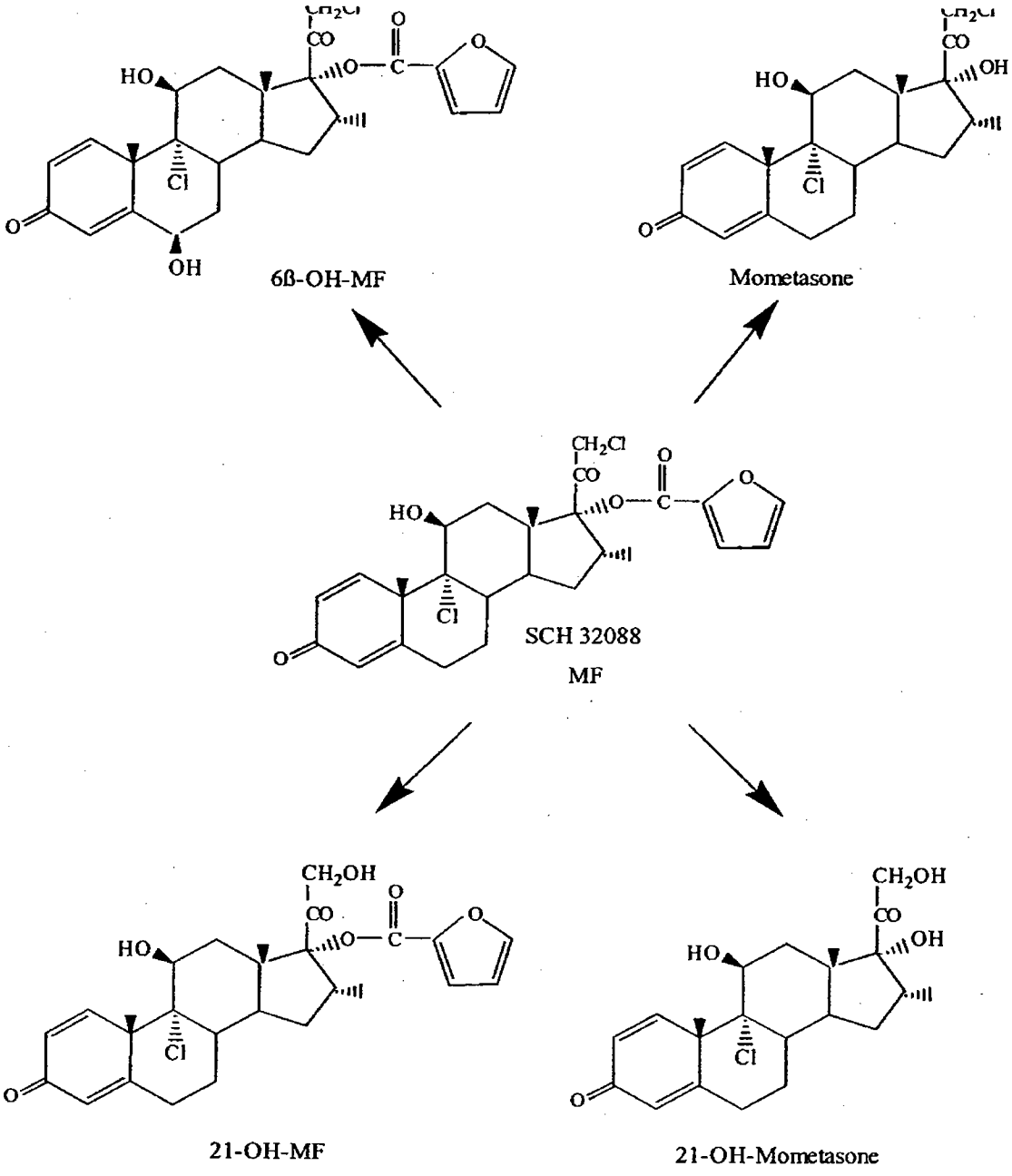
The rate of formation of 6β-OH-MF was measured in each of 14 human liver microsome samples provided in a HepatoScreen test kit and found that MF was metabolized to 6β-OH-MF exclusively by the CYP3A4 enzyme which was inhibited (~50%) in 12/14 samples by ketoconazole. This was further confirmed by incubation of MF with cell-line derived microsomes expressing only CYP3A4. In addition, it was also found that 6β-OH-MF was formed in everted mouse, rat and dog intestines, which have high amounts of CYP3A4.

Table 3 Percentage of Radioactivity Associated with the "MF-Like" Region in Selected Samples after Inhalation Exposure of ^{3}H-MF/Lactose Mixtures to Mice, Rats, Dogs and Humans

	Matrix (% radioactivity in sample associated with "MF-like" region)					
Species	Plasma (0–4 hr)[a]	Urine (0-48 hr)	Feces (0–48 hr)	Bile (0-4 hr)[a]	Lungs (0 hr)	Reference
Mouse	35	6.7[c]	41 (0 –24 hr)	5.6[b]	80	P-6951
Rat	52	4.2[c]	39	11	83	P-6952
Dog	42	2.2[c]	52	7.5 (0 –24 hr)	[d]	P-6953
Human	0[e]	0	66	[d]	[d]	C97-047

a: Pooled sample
b: Gall bladder and contents
c: Assumed to be contaminated from fur
d: Not profiled, inappropriate
e: Mass content too low to analyze

Metabolic Pathway of SCH 32088: (Fig. 1)



Excretion:

The primary route of excretion in all species was found to be fecal. Very little radioactivity was recovered in the urine; the relative percent of recovery in human urine was greater than for other species. When the data in humans was compared to that from previously conducted studies utilizing ^{3}H-MF in different formulations, it was found that ~32% of the DPI dose was systemically absorbed from gastrointestinal tract and only a small amount (~7%) seem to be deposited in the deep lung.

Excretion Pattern for Radioactivity after Inhalation Exposure of ^{3}H-MF/Lactose Mixtures to Mice, Rats, Dogs and Humans is shown in Table 4.

Table 4 Excretion Pattern for Radioactivity after Inhalation Exposure of ^{3}H-MF/Lactose Mixtures to Mice, Rats, Dogs and Humans

Species	Collection Interval (hr)	Urine (% dose)	Feces (% dose)	Total Excreta (% dose)	Bile (% dose)	Reference
Mouse[a]	0 –72 0 – 144	1.27 0.92	61.9 44.5	63.2 45.4	–[b]	P-6951
Rat	0 – 144	1.69	89.5	91.2	5.28 (0 – 4 hr)	P-6952
Dog	0 –168	1.98	51.9	53.8	15.2 (0 – 24 hr)	P-6953
Human	0 –168	7.57	73.5	81.1	–[b]	C97-047

a: Excreta was collected from two separate groups of mice
b: Bile not collected

Toxicokinetics:

Several toxicokinetic studies were conducted with MF/lactose (1:5.8) in rats and dogs, one-month to either 6-month nose-only (rats) or12-month mouth-only (dogs) inhalation studies. In addition, inhalation studies with MF/lactose (1:19) for up to 3 months and with aerosolized MF pure powder for 3-months were conducted in rats and dogs.

From the studies, Tmax normally occurred within ~5-15 minutes following the exposure period (1.25 hr for rats and 0.75 hr for dogs), demonstrating a rapid, initial absorption phase of lung-deposited MF available for transfer across the alveoli into the systemic circulation. Plasma MF concentrations were gender-independent, increased in an exposure concentration-related manner and showed no evidence of accumulation over the duration of the studies. Steady-state Cmax and AUC values are provided in table on page 55.

(C) Toxicology/Toxicokinetics:

P-6518 Six-Month Nose-only Inhalation Study of SCH 32088:Lactose Powder Formulation (1:5.8) in Rats. [ ]

Study No.: 95054
Date of Study Initiation: 3/25/96 Report Date: 1/15/98
Laboratory: [ ]
GLP Compliance/QA Report: Yes
Formulation: SCH 32088 Dry Powder/Lactose Mix 1:5.8 ratio
Batch No.: 35887-143 (35887-024 lactose)

Study Design:

Species/Strain	Animals*	Route Regimen	Groups	Target Exposure + (µg/L)	Estimated Dose# (µg/kg/day) M	F
Rats/SD	15/sex/gr (5 groups)	Inhalation nose-only 1hr/day 7days/wk for 6 month	1 (Air control)	0	0	0
			2 (Vehicle control)	0	0	0
			3 LD	0.13	5	6
			4 MD	0.50	19	22
			5 HD	2.0	76	88

* Animals: ~6 weeks of age at study start
Weight: 168.6-202.7 g (males) & 127.2-177.3 g (females)
Toxicity Study: 75/sex
Toxicokinetic Studies: 124/sex

\+ MMAD: SCH32088: 2.3-2.9 µm; lactose 2.6-3.3 µm
GSD: SCH32088: 1.5-2.0 µm; lactose 1.4-2.0 µm

Actual mean SCH 32088 exposure concentrations (within 5% of the target concentrations).
6-month TX: 0.13 ± 0.01, 0.51 ± 0.04 & 2.1 ± 0.2
3-month TK: 0.13 ± 0.01, 0.51 ± 0.04 & 2.1 ± 0.2
6-month TK: 0.13 ± 0.01, 0.50 ± 0.05 & 2.0 ± 0.2

\# Calculations for estimated initial total dose are based on values from SPRI Study Report P-6230; estimated particle size; MMAD 2.5 µ m; GSD 1.7; body weight (7 weeks of age) males 200 g, females 165 g; minute volume-males 132 mL/m, females 126 mL/min; total exposure period of 1 hr. Deposition model based on Raabe, et al. 1988.

Six-Month Nose-Only Inhalation Study in Rats with SCH 32088:Lactose Powder Formulation (1:5.8) (SN 95054)					
SCH 32088 Exposure Concentration (µg/L)	Number of Rats/Sex			SCH 32088 Predicted Daily Dose (µg /kg/day)	
	Six-Month Toxicity Study[a]	Three-Month Toxicokinetic Study[b]	Six-Month Toxicokinetic Study[a]	Males	Females
Filtered Air Control	15	10	10	0	0
Vehicle Control	15	10	10	0	0
0.13	15	10	18	5	6
0.50	15	10	18	19	22
2.0	15	10	18	76	88
a: One hour plus T90/day; 7 days/week for 6 month b: One hour plus T90/day; 7 days/week for 3 month, sacrificed following plasma collections					

Toxicokinetic Studies:

3-Month Toxicokinetic Study Design:

Plasma samples were collected from two rats/sex/group at the following post-exposure times (± 5 min): ≤ 0.25, 2, 8, 12, and 23 hr post-exposure.

6-Month Toxicokinetic Study Design:

Plasma samples were collected from four rats/sex/group in the Filtered Air and Vehicle Control groups ≤ 0.25 hr post exposure and from three rats/sex/group in these groups at 1.0 and 2 hr post-exposure times (± 5 min). Plasma samples were collected from three rats/sex/group in SCH 32088 –exposed groups at ≤ 0.25, 0.5, 1.0 1.5, 2, 4, 8, 12, 16 and 23 hr post-exposure (± 5 min).

Observations:

Clinical Observations:	Weekly (Observations twice daily.)
Ophthalmologic Examination:	Once pretest and during Exposure Week 26
Body weight:	Weekly
Food Consumption:	Monthly
Clinical Pathology:	Weeks 13 and prior to terminal sacrifice
Minute Volume Measurement:	Weeks 1, 12 and 25
Plasma SCH 32088 Concentration:	Weeks 1, 12 and 25 within 15 minutes after the end of exposure on same animals as for minute volume.
Timepoints:	≤ 0.25, 0.5, 1.0, 1.5, 2.0, 4.0, 8, 12, 16 & 23 hours post exposure
Necropsy:	Following the 6-month exposure period.
Histopathology:	For tissues collected and examined, see the histopathology table.

Results:

Mortality/Clinical Signs: No treatment-related deaths but alopecia and bulging eyes were observed which seem to be correlated to SCH 32088 exposure.

	0.50 µg/L	2.0 µg/L
Alopecia	4/12M & 4/12F	12/13M & 15/15F
Bulging eyes	5/12M & 8/15F	11/13M & 10/15F

Body Weight: The mean body weight and the mean body weight gain was lower for male rats exposed to the 0.50 µg/L SCH 32088 exposure concentration (15 and 22% respectively). At 2.0 µg/L concentration, the mean body weight for both sexes was lower (26 and 25 % for males and females, respectively), and mean body weight gain for both sexes was also less than the air control group, (39 and 49% for males and females, respectively).

Food Consumption: Adjusted food consumption (g food consumed/100 g body weight) was significantly greater than the Air control group for males and females from Week 9 onwards for the 2.0 µg/L SCH 32088 groups, and for the 0.50 µg/L groups, from Week 13 in males and from Week 21 in females. These differences were not significant when food consumption was not adjusted for body weight.

Ophthalmoscopy: No compound-related findings.

Hematology: A typical steroids effects were seen such as higher erythrocyte counts in males at concentrations ≥ 0.50 µg/L at Week 13 and lower leukocyte counts at Week 13 in 2.0 µg/L males. In addition, mean lymphocyte values were reduced in males starting at ≥ 0.5 µg/L. In females, there were significant increases in total leukocytes, segmented neutrophils, lymphocytes, and monocytes in those exposed to 0.13 and 0.5 µg/L SCH 32088 compared to air controls. At 2.0 µg/L segmented neutrophils were increased, but lymphocytes were decreased and no difference in total leukocyte count from the air controls. At terminal sacrifice, there were significant reductions in total leukocytes in males at 2.0 µg/L and in females at ≥ 0.5 µg/L due to the decrease in mean lymphocyte levels, but no effects on erythroid parameters.

Clinical Biochemistry/Urinalysis: Cholesterol values were increased at Week 13 for the 2.0 µg/L males and at Week 26 for the 2.0 µg/L males and females and the 0.50 µg/L females. In addition, serum potassium levels in females and phosphorous levels in both sexes were increased at ≥ 0.5 µg/L. At terminal sacrifice, total protein concentrations and cholesterol were significantly elevated in both sexes at 2.0 µg/L and females at 0.5 µg/L SCH 32088. There were no exposure-related effects on the urine parameters.

Corticosterone levels: In the males at Week 13, there was a significant reduction in mean corticosterone levels in the 0.5 µg/L ($p \leq 0.05$) and 2.0 µg/L ($p \leq 0.01$) SCH 32088 groups. In the females, a statistically significant reduction was evident only at 2.0 µg/L SCH 32088 ($p \leq 0.05$). At Week 26, there was a highly significant reduction ($p \leq 0.01$) in mean corticosterone

level in both sexes exposed to 2.0 µg/L SCH 32088.

Minute Volume: During Weeks 12 and 25, although the mean body weight of both male and female rats were significantly less than the Filtered air, minute volume per gram of body weight (MV/g) or pulmonary parameters were not affected by increasing concentrations of SCH 32088.

Organ Weights: There were significantly lower organ weights (absolute and/or relative) of the lung and spleen in both sexes, and thymus and ovary in females in 2.0 µg/L SCH 32088 groups.

Effects of SCH 32088 in Rats 6-Month Inhalation Toxicity Study

(n=15)	Males					Females				
Groups (µg/L)	**Air**	**Veh.**	**0.13**	**0.5**	**2.0**	**Air**	**Veh.**	**0.13**	**0.5**	**2.0**
Terminal body weight (g)	555.4	548.5	529.8	473.7*	410.9*	303.7	304.8	297.1	286.6	227.5
Body weight gain (g)	372.1	367.2	349.0	289.0	225.7	150.8	152.0	146.1	132.4	77.3
% Difference in MBWG from control	--	-1.3	-6.2	-22.3	-39.3	--	0.8	-3.1	-12.2	-48.7
Clinical Chemistry & Hematology: ***(Week 13) (n=10)***										
WBC ($x10^3/\mu L$)	14.4	14.4	14.3	11.8	6.7a	6.8	8.8	11.5a	9.7a	5.6
Seg neutrophils ($10^3/\mu L$)	1.04	1.25	1.32	1.32	0.96	0.42	0.53	1.02a	0.98a	0.83a
Lymphocytes ($x10^3/\mu L$)	13.07	12.69	12.59	10.18b	5.50a	6.30	8.17	10.21a	8.50a	4.56a
Monocytes ($x10^3/\mu L$)	0.20	0.31	0.33	0.23	0.16	0.05	0.07	0.19*	0.15*	0.13
Creatinine (mg/dL)	0.9	0.9	0.8	0.8+	0.7*	1.0	0.9	0.9	0.9	0.8*
Potassium (mmol/L)	6.2	5.8	6.6	7.0	6.7	5.8	6.0	6.2	6.7*	7.0*
Corticosterone (ng/ml)	305	380	203	110+	28.9*	497	197	314	289	63.9+
(Week 26)										
WBC ($x10^3/\mu L$)	12.4	10.5	11.6	9.7	7.2*	9.0	8.9	7.9	6.0+	4.6*
Lymphocytes ($10^3/\mu L$)	10.92	8.96	9.72	8.13	5.37*	8.07	8.14	6.92	5.39+	3.71*
Creatinine (mg/dL)	1.0	0.9+	0.9	0.9*	0.9*	1.0	0.9	1.1	1.1	1.0
Protein (g/dL)	6.7	6.8	6.9	.7.0	7.4*	7.7	7.8	8.0	8.1	8.3*
Cholesterol (mg/dL)	68	60a	77	74	104b	82	78	91	96a	111b
Corticosterone (ng/ml)	286.9	139.0	193.0	152.1	47.2*	511.2	409.9	442.8	537.5	81.2*
Organ Weights (n=15)										
Rel Heart (%bw)	0.25	0.27+	0.27+	0.29*	0.32*	0.31	0.33	0.33+	0.33+	0.41*
Rel Kidney (%bw)	0.58	0.61	0.59	0.65*	0.78*	0.63	0.64	0.68	0.68	0.83*
Lung (g)	2.01	2.01	1.91	1.81	1.67*	1.52	1.47	1.49	1.40	1.27*
Ovaries (g)						0.159	0.157	0.157	0.139	0.124*
Spleen (g)	0.70	0.76	0.71	0.67	0.51*	0.49	0.50	0.50	0.49	0.37*
Rel Testis (%bw)	0.65	0.62	0.68	0.74	0.91*					
Thymus (g)	0.306	0.346	0.294	0.249	0.243	0.249	0.253	0.190*	0.190*	0.140*
Rel Thymus (%bw)	0.056	0.063	0.056	0.052	0.057	0.082	0.083	0.064+	0.066+	0.062*

a: Variance not equal, $p \leq 0.01$ using Behrenes-Fisher t-test
b: Variance not equal, $p \leq 0.05$ using Behrenes-Fisher t-test
* ($p \leq 0.01$); + ($p \leq 0.05$)

Toxicokinetics of SCH 32088 (Appendix H, Vol. 35, P 604)

Plasma Concentrations: Plasma SCH 32088 concentrations increased in a dose related but less than proportional to the estimated total dose. There were no gender-related differences in plasma concentrations. When the target exposure concentrations increased in a 1:4:15 proportion, Cmax increased in a 1:4:10 proportion on Day 91 and 1:5:12 proportion on Day 184/185. AUC(0-24 hr) increased in a 1:5:10 proportion showing a dose related but less than proportional increases. Therefore, Cmax and AUC(0-24 hr) were similar on Day 91 and Days 184/185 indicating no accumulation over 6 months of daily exposure.

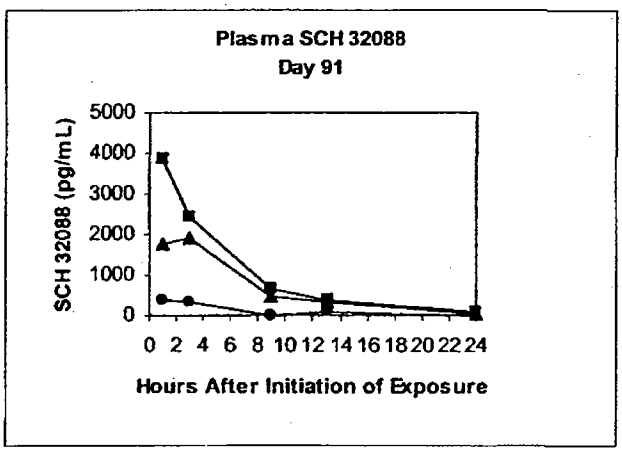
The pharmacokinetic parameters for the combined data are summarized in the following table.

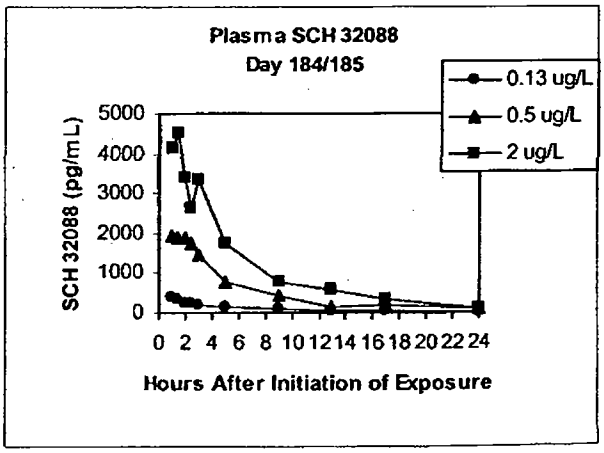
Pharmacokinetic Parameters in Rats after 3-mo and 6-mo of SCH 32088:Lactose (1:5.8) Powder (1hr/day) Exposure (sampling within 5 min post-exposure)

Target Exposure Concentration (µg/L)	Cmax (pg/ml)				AUC (0-24) (pg.hr/ml)	
	Day 91	Tmax (hr)	Day 184	Tmax (hr)	Day 91	Day 184
0.13	401	1.0	368	1.0	-	2470
0.5	1778	1.0	1943	1.0	11895	12012
2.0	3843	1.0	4499	1.5	22394	25472

Plasma SCH 32088 concentrations were determined using an LC-MS/MS assay with a limit of quantitation of 49.9 pg/mL plasma.

Plasma SCH 32088 Concentration-Time profile is provided below:





Necropsy: The gross lesions related to SCH 32088 exposure were a reduction in size of the thymus and an increased incidence of alopecia in both sexes of rats exposed to 2.0 µg/L SCH 32088.

Histopathological Findings:

Lesions observed are typical of those produced by inhaled glucocorticoids. They include:

1) Decreased globule leukocytes in tracheal epithelium in all treated groups.
2) Lymphoid depletion in the thymus of males and females exposed at ≥ 0.5 µg/L SCH 32088.
3) Lymphoid depletion and increased numbers of mast cells in the mesenteric lymph nodes of both sexes exposed at ≥ 0.5 µg/L.
4) Minimal lymphoid depletion in the bronchial-associated lymphoid tissue (BALT) in the lungs at ≥ 0.5 µ/L SCH 32088.
5) Atrophy of hair follicles in lesions noted as focal alopecia at ≥ 0.5 µg/L SCH 32088.
6) Enhanced acinar budding, lobuloalveolar development, and secretory activity in mammary glands in all treated females.
7) An increased incidence of abnormal estrous cycles (suppression of ovulation and prolongation of diestrus) in all groups of females.

Incidence summary of gross and microscopic observations in a table is provided on the following page.

Conclusion:

There were no deaths and clinical abnormalities when SCH 32088:lactose powder (1:5.8) was administered to male and female rats by nose-only inhalation for six months at exposure concentrations of 0.13, 0.50, or 2.0 µg/L. At necropsy, the mean body weight and the mean body weight gain were lower than the filtered air control group. The target tissues were lymph nodes, thymus, tracheal epithelium, hair follicles of both males and females, and mammary gland and reproductive tract of females. Glucocorticoid activity was shown as lymphoid depletion of the thymus in males and females at ≥ 0.5 µg/L SCH 32088. Progestational-like changes in combination of glucocorticoid activity were enhanced lobuloalveolar development and secretion in mammary glands of females in all SCH 32088-exposed groups. A NOAEL could not be determined due to the findings of typical glucocorticoid effects in all SCH 32088-exposed groups. Plasma SCH 32088 concentrations in rats were gender-independent, increased in an exposure concentration-related manner and were similar on Days 91 and 184/185, showing no sign of accumulation over a period of 6 months.

Incidence Summary from 6-Month Study in Rats

	Male					Female				
Groups (µg/L)	Air	Veh	0.13	0.5	2.0	Air	Veh	0.13	0.5	2.0
Findings	Controls					Controls				
Gross: (n=15)										
Abdominal Cavity:										
Excessive fluid	0	0	1	2	1	0	0	0	0	0
Eye:										
Crust	1	0	0	2	0	0	0	0	1	0
Lungs:										
Focus	0	0	0	3	1	2	1	0	0	0
Nose/Turbinate:										
Crust	0	0	1	0	2	0	0	1	0	0
Skin: Alopecia	1	0	1	5	11	0	0	1	2	13
Lesion	0	0	0	0	3	0	0	0	0	0
Thymus:										
Small	0	1	0	3	5	2	1	7	7	12
Urinary Bladder:										
Dilatation	0	0	0	2	1	0	0	0	0	0
Microscopic: (n=15)	**Increasing Severity (↓)**									
Trachea:	0	0	3	0	0	0	0	2	0	0
Decreased globule	0	0	9	0	0	0	0	6	0	0
leukocytes	0	0	3	7	3	0	0	7	3	6
	0	0	0	8	12	0	0	0	12	9
Thymus:										
Lymphoid depletion	0	0	0	2	5	0	0	0	2	12
	0	0	0	0	2	0	0	0	0	0
Mammary gland:	0	0	0	0	0	10	14	7	5	0
Acinar budding						3	1	8	9	4
						2	0	0	1	11
Ductal development	0	0	0	0	0	11	12	12	11	0
						4	3	3	4	15
Lobuloalveolar	1	3	2	3	3	4	1	3	3	5
development	12	6	4	4	9	0	1	6	5	9
	2	5	6	8	2	0	0	0	0	1
Secretory activity	0	0	0	0	0	4	4	2	4	1
						1	0	4	4	5
						0	1	3	4	8
Lungs:										
Alveoli-Macrophage aggr.	2	1	1	6	4	2	2	0	1	2
BALT-Lymphoid depletion	0	0	0	5	11	0	0	0	7	12
Mesenteric Lymph node:										
↑ mast cells	0	1	1	4	10	0	0	1	4	11
Vagina: Proestrus						5	1	2	3	13
Estrus						2	0	2	3	0
Diestrus						8	14	11	9	2
Estrous Cycle: Normal						8	9	8	9	1
Abnormal						7	6	7	6	14

P-6599 6-Month Inhalation Toxicity Study of SCH 32088:Lactose Powder Agglomerates (1:5.8) in the Dog. [ ]

Study No.: SN95055 (SP); N001368D [ ]
Date of Study Initiation: 5/01/96 Report Date: 3/16/98
Laboratory: [ ]
GLP Compliance/QA Report: Yes
Formulation: SCH 32088 Dry Powder/Lactose Mix 1:5.8 ratio
Batch Nos.: 36524-020, -024 and -025 (36524-022 and -023 lactose)

Study Design:

Species/ Animals*	Route/ Regimen	Target Aerosol Concentration Group (µg/L)	Achieved Mean Concentration (µg/L)	Estimated Total Inhaled Dose+ (µg/kg/day)		Estimated Total Deposited Dose# (µg/kg/day)	
				Males	Females	Males	Females
Dogs/	Inhalation/	1 (Air control)	BLQ	0	0	0	0
Beagle	oronasal	2 (Vehicle)	BLQ	0	0	0	0
	30 min/day	3 (0.1)	0.19	1.03	0.98	0.8	0.8
5/sex/gr	for 6	4 (0.5)	0.59	5.62	4.99	4.7	4.2
	months	5 (4.0)	4.57	41.5	37.0	33.6	30.0

* Animals: 6-8 months of age;
Weight: 6.96 to 14.78 Kg (males) & 6.62 to 11.27 Kg (females)

\+ Total Inhaled Dose (µg/kg/day) = $\frac{\text{Measured Concentration (µg/L) x Total inhaled Volume (L)}}{\text{BW (kg)}}$

\# Total Deposited Dose = Total inhaled dose x % Deposition fraction (D)

D = Total deposition fraction, according to the particle size distribution of the aerosols and published literature values for regional deposition fractions in man. (ICRP Task Group on Lung Dynamics for a tidal volume of 750 cm^3. Health Physics 1966; vol.12: pp 173-207)

Lactose means averaged 89% of the total mass of the SCH 32088:lactose 1:5.8 formulation, with the theoretical target value being 85.3%. The calculated ratio of SCH 32088:lactose based on an average of 89% lactose was 1:6.1.

Observations:

Clinical Observations:	Daily
ECG:	Pretest and Weeks 5, 13, and 25
Physical Examination:	Pretest
Ophthalmologic Examination:	Once pretest and Weeks 13 & 26
Body Weight:	Weekly
Food Consumption:	One week every other week
Clinical Pathology:	Weeks –4, -1, and 4, 12, and 26
ACTH Response test:	Week –2, and Weeks 4, 12, and 26
Respiratory Flow:	Weekly
Plasma SCH 32088 Concentration:	Days 1 and Week 26 (0, 0.25, 2, 4, 6 & 12 hrs after the exposure and prior to next day); Weeks 4 and 12 at 0.25 hours
Necropsy/Organ weight:	Week 26
Histopathology:	Week 26 on all the standard tissues (See the table)

Results:

SCH 32088:

Group Mean Total and Regional Deposited Dose of SCH 32088					
		Deposited Dose (µg/kg/day)			
Sex	**Target SCH 32088 (µg/L)**	**Oral/ Pharyngeal**	**Tracheal/ Bronchial**	**Pulmonary**	**Total**
Male	0.1	0.49	0.06	0.28	0.8
	0.5	2.79	0.35	1.53	4.7
	4.0	19.7	2.48	11.4	33.6
Female	0.1	0.46	0.05	0.26	0.8
	0.5	2.48	0.31	1.36	4.2
	4.0	17.6	2.21	10.2	30.0

Lactose:

Target SCH 32088 Aerosol Cncentration (µg/L)	Group Number	Lactose Achieved Mean Aerosol Concentration (µg/L)		Estimated Total Inhaled Dose Lactose (µg/kg/day)		Estimated Total Deposited Dose Lactose (µg/kg/day)	
		Males	Females	Males	Females	Males	Females
Air	1	0	0	0	0	0	0
Vehicle	2	23.18	23.37	187	191	152	155
0.1	3	0.88	0.62	5.8	5.5	4.8	4.6
0.5	4	3.43	3.26	32.8	29.0	28.4	25.1
4.0	5	26.47	26.24	241	213	204	180

Mortality/Clinical Signs: No deaths and no clinical abnormalities were observed. There were a variety of mild, transient clinical changes mainly of gastrointestinal distress (emesis, salivation, diarrhea, soft and/or mucoid feces) and eye discharge including control groups.

Body Weight/Food Consumption: There were small reductions (~10%) in mean body weight of males and females of SCH 32088-exposed groups relative to the air control and the vehicle group at ≥ 0.5 µg/L SCH 32088. There were no effects on food consumption.

Ophthalmoscopy: No compound-related findings.

ECG: No drug-related abnormalities were noted. There were changes in heart rate and in configuration of ST-T (more pronounced in the 4.0 µg/L group), however, the changes were inconsistent and occurred in the air and vehicle control groups as well.

Hematology/Clinical Biochemistry/Urinalysis: There were no SCH 32088 related abnormalities in hematology. Mean serum cholesterol was slightly elevated in females of the mid- and high-dose (0.5 and 4.0 µg/L groups) relative to vehicle (15%) and air control (34%) female groups and to their baseline (36%) values at pre-study. There were no changes in the urinalysis data related to SCH 32088 exposure.

ACTH Response Test (Plasma Cortisol): Exposure to SCH 32088 at 4 µg/L clearly resulted in suppression of pre- and post-ACTH cortical activity relative to controls starting from Week 4. At Weeks 12 and 26, pre- ACTH plasma cortisol levels were less than respective air and vehicle control groups in general and less than their respective pre-exposure baseline values. Post-ACTH plasma cortisol levels were lower in males than females at Week 12 and week 26.

Effects of SCH 32088 in 6-months inhalation toxicity study in dogs

	Males					**Females**				
Groups (n=5)	**Air**	**Veh.**	**0.1**	**0.5**	**4.0**	**Air**	**Veh.**	**0.1**	**0.5**	**4.0**
Final mean body weights (kg)	12.13	12.15	12.01	11.18	10.95	9.25	9.15	8.87	9.19	8.45
Organ Weights:										
Adrenal gland (g)	1.17	1.23	0.96	1.13	0.56	1.23	1.12	1.26	1.05	0.61
Relative adrenal gland	0.010	0.010	0.008	0.010	0.005	0.013	0.012	0.014	0.012	0.007
Lung (g)	102.6	102.8	102.9	95.1	96.8	74.9	76.8	73.3	83.1	73.3
Spleen (g)	68.2	71.1	71.9	87.2	60.3	66.5	49.6	50.3	51.8	48.3
Thymus (g)	10.04	10.70	8.40	10.42	10.23	7.23	8.14	10.15	7.60	6.71
Gross Pathology										
Adrenal, small	0	0	0	0	5	0	0	0	0	4
Lung, discoloration	1	1	0	0	0	0	1	0	1	1
Skin, crust	0	0	0	0	2	0	0	0	1	0
Testis, small	0	0	0	0	1					

* ($p<0.05$)

Organ Weights: Compared to the control groups, mean absolute and relative weights of adrenal gland were lower (~50%) in HD groups in both sexes. Other organs were not affected by SCH 32088 exposure.

Gross Pathological Findings: The drug-related changes were observed in the adrenal glands of the high-concentration (4.0 µg/L) group of dogs. All five male and four females in this high-dose group had small adrenal glands.

Histopathological Findings: There were changes related to SCH 32088 exposure in the adrenal glands, liver and lymph nodes of 4 µg/L exposed dogs. These changes are summarized in the following table. In general the severity increased with increasing exposure concentrations.

Histopathological Findings from 6-months Inhalation Study in Dogs

	Male					Female				
Groups (n=5/sex)	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Targeted Exposure (µg/L)	**Air**	**Veh**	**0.1**	**0.5**	**4.0**	**Air**	**Veh**	**0.1**	**0.5**	**4.0**
Organ/Finding	**Incidence Summary (Week 26)**									
Adrenal gland										
- atrophy, zona fasciculata	0	0	0	0	5	0	0	0	0	5
- atrophy, zona reticularis	0	0	0	0	5	0	0	0	0	4
- vacuolization, zona fascicul.	0	0	1	2	5	3	4	1	2	4
Liver										
- vacuolization, cytoplasmic	0	0	0	0	3	1	2	3	4	1
Heart										
- epicardial hyperplasia	0	0	2	0	0	0	0	0	0	0
- lymphocytic infiltrate	0	0	0	1	1	0	0	0	0	0
Larynx										
- lymphoid hyperplasia	2	0	1	3	0	0	1	2	2	0
Lung										
- inflammation, alveolar	3	1	0	3	0	0	0	1	0	0
- inflammation, interstitial	1	1	2	2	4	2	1	2	2	3
Lymphoid depletion										
- axillary lymph node	0	1	1	1	1	0	0	1	0	1
- msenteric lymph node	0	0	0	1	2	1	0	0	0	1
- thymus	5	5	5	5	5	5	5	5	5	5
LN-mesenteric										
- erythrophagocytosis	2	0	1	4	1	1	0	0	0	3
Prostate and Testis										
-atrophy	0	0	0	1	1					
Trachea										
- inflammation, sq.epithelium	3	3	4	3	2	2	2	4	5	4
Uterus										
- endometrial hyperplasia						3	4	3	5	3

In adrenal glands, SCH 32088 at 4 µg/L caused a thinning of the middle and inner cortical layers, zona fasciculata and zona reticularis. They were associated with atrophy, vacuolization, and a decrease in the adrenal weights.

In the liver, glycogen vacuolization was observed in some animals, 3/5 male dogs at 4 µg/L SCH 32088 which was again observed in 4/5 at 0.5 µg/L SCH 32088. This result was similar to that seen in the 14-day and 3-month studies in dogs with SCH 32088.

In addition, lymphoid depletion was seen in axillary and/or mesenteric lymph nodes at 4 µg/L SCH 32088, but no test article-related effects were observed in mammary gland, ovaries or uterus in females at the exposure levels and duration in this study. However in males, atrophy in the prostate and testis was observed.

Pharmacokinetics: **(Appendix H, Vol. 46)** Plasma SCH 32088 concentrations were generally below the assay LOQ (50 pg/mL) at the two lower exposure concentrations (0.1 and 0.5 µg/L) and quantifiable only at sporadic time points. At the 4 µg/L exposure concentrations, plasma SCH 32088 concentrations were quantifiable at most time-points, with peak concentrations (Cmax) generally observed at the first time-point after exposure termination (0.25 hr post-exposure). The concentrations declined thereafter and were quantifiable up to 2-12 hr post-exposure.

The pharmacokinetic parameters at 4 µg/L are provided in the following table.

PK Parameters at 4 µg/L SCH 32088 in 6-Month Study in Dogs

		Parameter [Mean (%CV)]			
Study Week	**Gender (n)**	**Cmax (pg/mL)**	**Tmax (hr)**	**AUC(tf) (pg.hr/mL)**	**tf* (hr)**
Day 1	M (3)	130 (9)	0.75	435 (5)	4.5
Day 1	F (2)	158 (-)	0.75	478 (17)	4.5
Day 1	M + F	144 (7)	0.75	457 (11)	4.5
Week 26	M (5)	317 (54)	0.75	865 (42)	6.0
Week 26	F (5)	355 (40)	0.75	1280 (34)	10.0
Week 26	M + F	336 (47)	0.75	1073 (38)	8.0

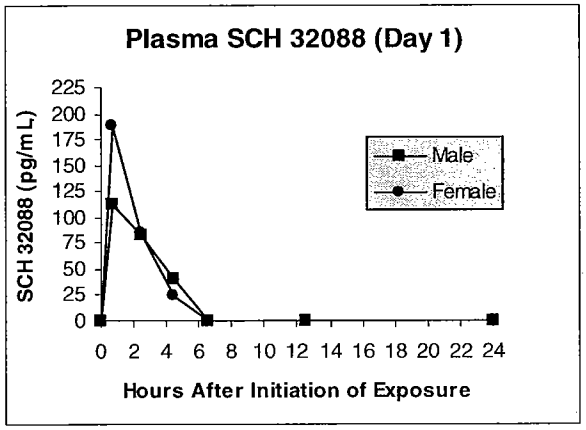
* After exposure initiation, exposure duration was 0.5 hr.

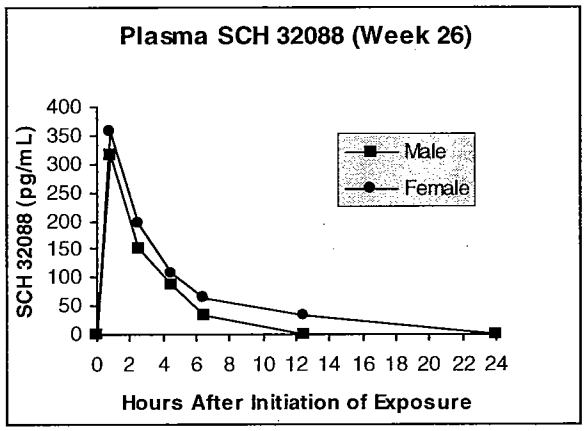
On Day 1, plasma SCH 32088 concentrations in females were higher than those in males but were similar on Week 26. Plasma SCH 32088 concentrations following multiple exposure (Week 26) were higher than those following a single exposure. There were no quantifiable plasma SCH 32088 concentrations at 24 hr post-exposure on both Day 1 and Week 26, and therefore, there was no sign of drug accumulation over 26 weeks of daily exposure.

Mean Plasma SCH 32088 Concentrations (Cmax, pg/mL) at Time 0.75 hr (Tmax) in Dogs						
Day/Week	**Males**			**Females**		
	0.1 µg/L	**0.5 µg/L**	**4 µg/L**	**0.1 µg/L**	**0.5 µg/L**	**4 µg/L**
Day 1	0	11.0*	113	16.4*	0	188
Week 4	0	42.8	298	13.9	80.7	457
Week 12	0	75.2	351	0	114	316
Week 26	0	75.0	317	0	33.6	355

* Time point at 2.5 hr after the initiation of exposure of 0.5 hr duration.

Mean plasma SCH 32088 concentrations in male and female dogs following administration of SCH 32088 (1:5.8 lactose) on Day 1 and Week 26 at the 4 µg/L exposure concentration shown below.





Conclusion: Daily administration of SCH 32088:lactose powder agglomerates (1:5.8) by mouth-only inhalation for 6 months to beagle dogs for 30 minutes per day at concentrations of 0.15, 0.59 and 4.57 µg/L in males and 0.11, 0.54, and 4.58 µg/L for females was well tolerated.

No unexpected effects were seen at any dose, and the effects observed were those of known pharmacological effects of glucocorticoids. Target organs for this inhaled SCH 32088/lactose formulation were the adrenal gland, liver, and lymph nodes. The no effect dose for glucocorticoid activity was the low-dose in this study, 0.11µg SCH 32088/L based on the minimal effects on cholesterol levels noted at 0.54 µg/L. NOAEL for progestational effects was ≥ 4.58 µg SCH 32088/L.

P-6600 **12-Month Inhalation Toxicity Study of SCH 32088:Lactose Powder Agglomerates (1:5.8) in the Dog. [ ]**

Study No.: SN95056 (SP); N001368E[ ]
Date of Study Initiation: 5/01/96 Report Date: 9/02/98
Laboratory: [ ]
GLP Compliance/QA Report: Yes
Formulation: SCH 32088 Dry Powder/Lactose Mix 1:5.8 ratio
Batch Nos.: 36524-020, -024, -025 and -079 (36524-022, -023, -040 and -067 lactose)

Study Design:

Species/ Animals*	Route/ Regimen	Target Aerosol Concentration SCH 32088 Group (µg/L)	Achieved Mean Concentration SCH 32088 (µg/L)		Achieved Mean Concentration Lactose (µg/L)		Total Mass (µg/L)	
			Males	Females	Males	Females	Males	Females
Dogs/ Beagle 5/sex/gr	Inhalation/ oronasal 30 min/day for 12 months	1 (Air control)	0	0	0	0	0	0
		2 (Vehicle)	0	0	22.72	22.90	22.25	22.65
		3 (0.1)	0.14	0.11	0.74	0.62	0.83	0.69
		4 (0.5)	0.57	0.55	3.17	3.09	3.62	3.53
		5 (4.0)	4.37	4.37	24.14	24.01	27.61	27.67

* Animals: 6-8 months of age;
Weight: 8.77 to 11.83 Kg (males) & 6.47 to 10.23 Kg (females)

Lactose means averaged 88% of the total mass of the SCH 32088:lactose 1:5.8 formulation, with the theoretical target value being 85.3%. The calculated ratio of SCH 32088:lactose based on an average of 88% lactose was 1:5.5 to 1:5.9.

Mean MMAD and GSD of SCH 32088 and Lactose				
Target SCH 32088 Concentration (µg/L)	SCH 32088		Lactose	
	MMAD (µm)	GSD	MMAD (µm)	GSD
Vehicle	--	--	3.87	1.67
0.1	3.67	1.75	4.11	1.66
0.5	3.48	1.81	4.04	1.69
4.0	3.36	1.77	3.86	1.63

Observations:

Clinical Observations:	Daily
ECG:	Pretest and Weeks 5, 13, 25, and 51
Physical Examination:	Pretest
Ophthalmologic Examination:	Once pretest and Weeks 13, 26 & 51
Body Weight:	Weekly
Food Consumption:	One week every other week

Clinical Pathology:	Weeks –4, -1, and 4, 12, 38 and 52
ACTH Response test:	Week –2, and Weeks 5, 13, 27 and 52
Respiratory Flow:	Weekly
Plasma SCH 32088 Concentration:	Days 1 and Week 52 (0, 0.25, 2, 4, 6 & 12 hrs after the exposure and prior to next day); Weeks 4 and 12 and 26 at 0.25 hours
Necropsy/Organ weight:	Week 53
Histopathology:	Week 53 on all the standard tissues (See the table)

Results:

Mean Estimated Total Inhaled Dose and Estimated Total Deposited Dose

Target SCH 32088 Aerosol Concentration (µg/L)	Estimated Total Inhaled Dose SCH 32088 (µg/kg/day)		Estimated Total Deposited Dose SCH 32088 (µg/kg/day)		Estimated Total Inhaled Dose Lactose (µg/kg/day)		Estimated Total Deposited Dose Lactose (µg/kg/day)	
	Male	Female	Males	Females	Males	Females	Males	Females
Air	0	0	0	0	0	0	0	0
Vehicle	0	0	0	0	196	169	164	141
0.1	1.04	1.07	0.96	1.00	5.6	5.81	5.17	5.36
0.5	5.23	4.68	4.37	3.91	29.6	25.9	25.6	22.4
4.0	42.3	38.9	34.7	31.9	230	214	202	188

\+ Total Inhaled Dose (µg/kg/day) = $\frac{\text{Measured Concentration (µg/L) x Total inhaled Volume (L)}}{\text{BW (kg)}}$

\# Total Deposited Dose = Total inhaled dose x % Deposition fraction (D)

D = Total deposition fraction, according to the particle size distribution of the aerosols and published literature values for regional deposition fractions in man. (ICRP Task Group on Lung Dynamics for a tidal volume of 750 cm^3. Health Physics 1966; vol.12: pp 173-207)

Group Mean Total and Regional Deposited Dose of SCH 32088

		Deposited Dose (µg/kg/day)			
Sex	Target SCH 32088 (µg/L)	Oral/ Pharyngeal	Tracheal/ Bronchial	Pulmonary	Total
Male	0.1	0.62	0.06	0.28	0.96
	0.5	2.59	0.34	1.44	4.37
	4.0	20.5	2.62	11.6	34.7
Female	0.1	0.64	0.06	0.29	1.00
	0.5	2.32	0.30	1.29	3.91
	4.0	18.8	2.41	10.7	31.9

Mortality/Clinical Signs: There were no deaths or clinical abnormalities related to SCH 32088 inhalation. There were common findings of mainly gastrointestinal distress (emesis, diarrhea, soft and/or mucoid feces) including control groups.

Body Weight/Food Consumption: There were lower mean body weight of males (10-17%) and females (<8%) of SCH 32088-exposed animals relative to the air and the vehicle control group at 4.0 µg/L SCH 32088. There were no effects on food consumption. The majority of dogs consumed ≥ 50% of the food each day.

Ophthalmoscopy: No compound-related findings.

ECG: No drug-related abnormalities were noted. There were changes in heart rate, electrical axis to QRS and in configuration of ST-T; however, the changes were inconsistent and sporadic.

Hematology/Clinical Biochemistry/Urinalysis: There were no SCH 32088 related abnormalities in hematology and serum chemistry. There were no changes in the urinalysis data related to SCH 32088 exposure.

ACTH Response Test (Plasma Cortisol): Exposure to SCH 32088 at 4 µg/L clearly resulted in suppression of pre- and post-ACTH cortical activity relative to controls throughout the study. All dogs showed similar increases in cortisol following stimulation by intravenous ACTH. By week 5 of exposures and during all subsequent weeks of measure (Weeks 13, 27 and 52) males and female dogs of the high-dose had pre-ACTH plasma cortisol levels less than their respective air and vehicle control groups and less than their respective pre-exposure baseline values. High-dose dogs showed marked suppression of post-ACTH plasma cortisol relative to baseline and air and vehicle control groups.

Necropsy:

Organ Weights: Compared to the control groups, mean absolute and relative weights of adrenal gland were lower in HD groups in both sexes. Other organs were not affected by SCH 32088 exposure.

Gross Pathological Findings: The drug-related changes were observed in the adrenal glands of the high-exposure level (4.0 µg/L) dogs of both sexes. All five females and four males in this high-dose group had small adrenal glands at necropsy. In addition, several dogs including vehicle control dog (#1215) had small thymuses and/or various lung lesions (focal discoloration or atelectasis). Other findings were focal cardiac nodules of the atrioventricular valve, spleen nodule and a nodule of strangulated mesenteric fat.

Effects of SCH 32088 in 12-months inhalation toxicity study in dogs

	Males					Females				
Groups (n=5)	**Air**	**Veh.**	**0.1**	**0.5**	**4.0**	**Air**	**Veh.**	**0.1**	**0.5**	**4.0**
Final mean body weights (kg)	12.99	12.02	12.08	12.79	11.22	9.65	9.85	9.07	9.09	8.57
Organ Weights:										
Adrenal gland (g)	1.334	1.272	1.163	1.159	0.474	1.301	1.244	1.113	1.173	0.584
Relative adrenal gland	0.010	0.011	0.010	0.009	0.004	0.014	0.013	0.012	0.013	0.007
Heart (g)	100.9	98.7	99.9	112.2	92.7	76.6	78.0	76.3	91.9	80.
Lung (g)	99.08	99.23	97.85	104.2	89.96	78.4	78.7	80.5	76.5	78.8
Prostate (g)	19.13	13.07	11.43	15.49	10.88					
Spleen (g)	75.48	84.99	86.21	72.21	67.79	55.24	72.56	56.46	45.42	65.03
Thymus (g)	9.27	11.10	10.58	13.24	10.80	8.87	8.17	6.65	8.21	9.10
Gross Pathology										
Adrenal, small	0	0	0	0	4	0	0	0	0	5
Lung, atelectasis	0	0	0	0	0	0	1	0	0	1
focus	0	0	0	1	0	0	1	1	0	1
Skin, cyst/abrasion /mass/crust	0	1	0	0	2	1	0	2	0	2
Testis, small	0	0	1	0	0					
Thymus, small	0	0	1	0	1	0	1	0	0	0

Histopathological Findings: There were changes related to SCH 32088 exposure in the adrenal glands, liver, lymphoid tissues, prostate and testes of some of the 4 µg/L exposed dogs. In addition, SCH 32088 appeared to have an effect on ovarian follicle development and estrous cycling. In general the severity increased with increasing exposure concentrations.

In adrenal glands, SCH 32088 at 4 µg/L caused a thinning of the middle and inner cortical layers, zona fasciculata and zona reticularis. They were associated with atrophy, cytoplasmic vacuolization, and a decrease in the adrenal weights. Cells of the outer cortical layer, the zona glomerulosa, also contained large cytoplasmic vaculoles ocassionally as well as in many air- and vehicle-control dogs. The morphologic appearance of the adrenal effects in this 12-month study in dogs was similar, although slightly more severe, with that observed in dogs after 6 months of exposure (SN95055).

In the liver, clear cytoplasmic (glycogen) vacuolization was observed in some animals, 5/5 male dogs at 4 µg/L SCH 32088 which was again observed in 4/5 at 0.5 µg/L SCH 32088 and vehicle control females. This result was similar to that seen in the 14-day, 3-month and 6-month studies in dogs with SCH 32088. However, no pattern of increased vacuolization was observed in the treated females in this 12-month study and considered unrelated to SCH 32088 exposure. These changes are summarized in the following table.

Histopathological Findings from 12-months Inhalation Study in Dogs

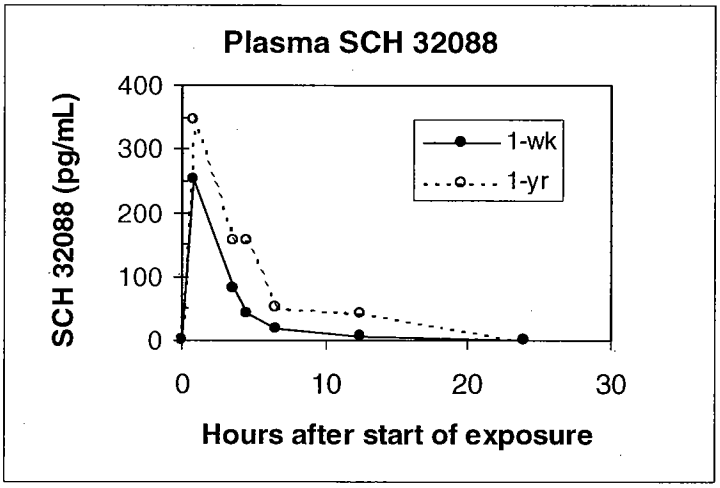
	Male					Female				
Groups (n=5/sex)	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Targeted Exposure (µg/L)	**Air**	**Veh**	**0.1**	**0.5**	**4.0**	**Air**	**Veh**	**0.1**	**0.5**	**4.0**
Organ/Finding	**Incidence Summary (Week 52)**									
Adrenal gland										
- atrophy, zona fasciculata	0	0	0	0	5	0	0	0	0	5
- atrophy, zona reticularis	0	0	0	0	5	0	0	0	0	5
- vacuolization, zona fascicul.	1	2	1	0	5	2	0	3	4	5
Bone marrow										
- icreased marrow fat	0	0	0	0	3	0	2	0	1	0
Heart										
- medial hypertrophy	2	0	1	5	0	2	1	1	1	1
- hematocyst, valve/arteritis	0	1	1	0	1	0	0	1	2	1
Kidney										
- lymphocytic infiltrate	0	1	1	0	0	0	0	1	0	1
Liver										
- vacuolization, cytoplasmic	0	0	0	4	5	2	4	0	1	3
- MN cell infiltrate	3	1	4	2	5	1	1	4	5	3
Lymphoid depletion										
- cecum/ileum	0	0	0	0	2	0	0	0	0	1
- msenteric lymph node	0	0	0	0	3	0	1	0	0	3
- thymus	5	5	5	5	5	5	5	4	5	5
Larynx										
- lymphocytic infiltrate	1	2	2	2	0	1	2	3	1	0
Lung										
- inflammation, alveolar	1	2	0	1	2	0	1	1	1	2
- inflammation, interstitial	0	0	1	2	3	2	1	2	0	3
Trachea										
- inflammation, sq.epithelium	0	3	1	4	1	3	4	3	2	4
Epididymis										
- inflammation/arteritis	0	1	2	0	0					
Prostate										
- atrophy	0	0	0	1	2					
- inflammation	0	0	0	2	3					
Testes										
- atrophy, seminiferous tubule	1	0	0	1	1					
Uterus										
- endometrial hyperplasia						2	1	3	4	1
Ovary										
- developing follicle/CL						2	0	3	4	1
- regressing corpus luteum						3	4	3	1	2
Mammary gland										
- ductal hyperplasia						0	0	1	1	0
- ductal regression/atrophy						2	1	2	1	2
- alveolar hyperplasia						2	0	0	3	0
- alveolar regression/atrophy						1	3	1	0	1

In addition, fat infiltration of the femur and lymphoid depletion in cecum, ileum and mesenteric lymph nodes and focal prostate atrophy and testicular atrophy were observed at 4.0 µg/L SCH 32088. Slight decreases in ovarian follicular development, with secondary changes on mammary development and less glandular development of uterus in the females exposed to 4.0 µg/L were considered to be a direct result of the SCH 32088 exposure, although they were not clearly discernible in 3 or 6 months studies.

In summary, adrenal glands were clearly affected at the 4.0 µg/L level. The severity of adrenal cortical atrophy was increased slightly from that seen at 6 months, to what was observed in this12- month study. The lack of response to the ACTH stimulation test at the 4.0 µg/L confirms the marked adrenal atrophy observed morphologically. Other effects seen in previous studies, such as lymphoid depletion, hepatic vacuolization, increases in fat deposited in bone marrow or other tissues, or testicular or prostatic atrophy, were also observed in the study but not clearly dose related. Slight effects on ovarian follicular development, with secondary changes on mammary development, were present in the females exposed to 4.0 µg/L. The morphologic changes in the ovaries and mammary glands are the typical glucocorticoid effects of the hypothalamic/adrenal/ovarian axis.

Pharmacokinetics: **(Appendix H, Vol. 48)** Plasma SCH 32088 concentrations were generally below the assay LOQ (50 pg/mL) at the two lower exposure concentrations (0.1 and 0.5 µg/L). At the 4 µg/L exposure concentrations, plasma SCH 32088 concentrations were generally observed at the first time-point after exposure termination (within 15 min), and values were not quantifiable beyond 4-6 hr post-exposure. Cmax was reached after termination of the 30-min exposure (Tmax=0.75 hr) and declined rapidly thereafter as shown in the graph.

Plasma SCH 32088 concentration-time profiles from 4 µg/L group (M+F) is shown below:



Mean plasma SCH 32088 concentrations following multiple exposure (Week 52) were generally 2-3-fold higher than those following a single exposure (Day 1) in this group. The AUC(tf) multiple-dose values could not be appropriately compared to the single-dose values due to appreciable differences in the tf values (5 hr vs. 10 hr). Moreover, there were no quantifiable plasma SCH 32088 concentrations at 24 hr post-exposure on both Day 1 and Week 52, which suggest that there is no evidence of drug accumulation over 52 week of daily inhalation exposure.

The pharmacokinetic parameters at 4 µg/L are provided in the following table.

PK Parameters at 4 µg/L SCH 32088 in 12-Month Study in Dogs (n=10)

		Parameter [Mean (%CV)]			
Study Week	**Gender**	**Cmax (pg/mL)**	**Tmax (hr)**	**AUC(tf) (pg.hr/mL)**	**tf* (hr)**
Day 1	M	333 (18)	0.75	844 (36)	6.90
	F	173 (46)	0.75	265 (57)	2.55
	M + F	253 (42)	0.75	555 (69)	4.73
Week 52 (Day 360)	M	348 (67)	0.75	1070 (69)	7.70
	F	342 (60)	0.75	1370 (27)	11.3
	M + F	345 (60)	0.75	1220 (47)	9.5

* After exposure initiation, exposure duration was 0.5 hr.

Overall, plasma SCH 32088 concentrations were undetectable at doses of 0.1 and 0.5 µg SCH 32088/L. At the high dose, plasma drug levels were similar in male and female dogs indicating gender-independent kinetics and increased in a exposure concentration-related manner and showed no evidence of accumulation over 52 weeks of daily inhalation.

Conclusion: Daily administration of SCH 32088:Lactose agglomerates by mouth-only administration to beagle dogs for 30 minutes per day for 12-months at concentrations of 0.14, 0.57 and 4.37 µg/L in males and 0.11, 0.55, and 4.37 µg/L for females was well tolerated.

On the basis of organ weight changes and correlated histopathologic changes, target organs were the adrenal glands, liver and reproductive organs of both sexes.

The NOAEL of exposure concentration for SCH 32088 was 0.1 µg/L as with other studies, although the sponsor determined it to be 0.5 µg/L SCH 32088 (mid-dose). The no-effect concentration for progestational activity was >4.0 µg/L SCH 32088, which was the highest concentration tested. The observed effects were those expected from known pharmacological effects of glucocorticosteroids.

Summary of Toxicology/Toxicokinetics Studies:

There were three new inhalation toxicology studies submitted for this NDA, 6-month inhalation studies in rats and dogs and 12-month study in dogs.

SCH 32088:lactose powder (1:5.8) was well-tolerated when administered by nose-only inhalation to male and female rats one hour daily for six months at exposure concentrations of 0.13, 0.50, or 2.0 μg/L SCH 32088. The target tissues for inhaled SCH 32088:lactose (1:5.8) were lymph nodes, thymus, tracheal epithelium, hair follicles of both males and females, and mammary gland and reproductive tract of females, based on organ weight changes and histopathological findings. Glucocorticoid activity was shown as lymphoid depletion of the thymus in males and females at ≥ 0.5 μg/L SCH 32088. Progestational-like changes were enhanced lobuloalveolar development and secretion in mammary glands of females in all SCH 32088-exposed groups. A NOAEL could not be determined due to the findings of typical glucocorticoid effects in all SCH 32088-exposure groups. Plasma SCH 32088 concentrations in rats were gender-independent, increased in a exposure concentration-related manner and were similar on Days 91 and 184/185, showing no sign of accumulation over a period of 6 months.

Daily administration of SCH 32088:lactose powder agglomerates (1:5.8) by mouth-only inhalation for 30 minutes per day at target concentrations of 0.1, 0.5 and 4.0 μg/L to beagle dogs for 6 months and 12 months were well tolerated. No unexpected effects were seen at any dose in 6-month study, and the effects observed were those of known pharmacological effects of glucocorticoids. Target organs for this inhaled SCH 32088/lactose formulation were the adrenal gland, liver, and lymph nodes. The no effect dose for glucocorticoid activity was the low-dose in this study, 0.1 μg SCH 32088/L based on the minimal elevation of cholesterol levels (34% vs. air control) noted at 0.5 μg/L. NOAEL for progestational effects was ≥ 4.58 μg SCH 32088/L.

In 12-months study in dogs, mean estimated total deposited doses were 0.96, 4.37 and 34.7 μg/kg/day for males and 1.0, 3.91 and 31.9 μg/kg/day for females. All dogs survived the exposure period with no signs of clinical abnormality. Lower mean body weights in high-dose males were seen throughout the study. Slight elevation of cholesterol levels observed in females at ≥ 0.5 μg/L from 6-month study was not observed in this 12-month study. Systemic changes were limited to glucocorticoid effects in high-dose dogs, and included lower mean adrenal gland weights, diminished ACTH hormone response, adrenal cortical changes (atrophy) and slight effects in females that included decreased ovarian follicular development, with no acinar or ductal development in the mammary glands. In general, the severity increased with increased exposure concentration and duration of exposure. The NOAEL for glucocorticoid effects was considered to be 0.1 μg/L SCH 32088 and >4.0 μg/L SCH 32088 for progestational activity, which was the highest concentration tested.

Plasma SCH 32088 concentrations were undetectable in exposed dogs at exposure concentrations of 0.1 and 0.5 μg SCH 32088/L in both 6-month and 12-month studies. At the high-dose (4.0 μg/L), plasma drug levels were gender-independent, increased in a exposure concentration-related manner and showed no evidence of accumulation over 52 weeks.

Histopathology Table for NDA # 21-067

Study Numbers	SN 95054	SN 95055	SN 95056				
Durations	6-mo	6-mo	12-mo				
Species	Rats	Dogs	Dogs				
Adrenals	x	x	x				
Aorta	x	x	x				
Bone Marrow smear		x	x				
Bone (femur)	x	x	x				
Brain	x	x	x				
Bronchi		x	x				
Cecum	x	x	x				
Cervix	x	x	x				
Colon	x	x	x				
Duodenum	x	x	x				
Epididymides	x	x	x				
Esophagus	x	x	x				
Eye	x	x	x				
Fallopian tube							
Gall bladder		x	x				
Haderian gland	x						
Heart	x	x	x				
Ileum	x	x	x				
Injection site							
Jejunum	x	x	x				
Kidneys	x	x	x				
Lacrymal gland		x	x				
Larynx	x	x	x				
Liver	x	x	x				
Lymph node, bronchial axillary		x	x				
Lymph nodes, cervical							
Lymph nodes, mandibular	x	x	x				
Lymph nodes, mesenteric	x	x	x				
Lungs	x	x	x				
Mammary glands	x	x	x				
Nasal cavity	x	x	x				
Optic nerves		x	x				
Ovaries	x	x	x				
Pancreas	x	x	x				
Parathyroid	x	x	x				
Peripheral nerve							
Pharynx		x	x				
Pituitary	x	x	x				
Prostate	x	x	x				
Rectum	x	x	x				
Salivary gland	x	x	x				
Sciatic nerve	x	x	x				
Seminal vesicles	x						
Skeletal muscle	x	x	x				
Skin	x	x	x				

Spinal cord	x	x	x				
Spleen	x	x	x				
Sternum							
Stomach	x	x	x				
Testes	x	x	x				
Thymus	x	x	x				
Thyroid	x	x	x				
Tongue	x	x	x				
Trachea	x	x	x				
Urinary Bladder	x	x	x				
Uterus	x	x	x				
Vagina	x	x	x				
Zymbal gland							
Tail	x						
other							

D) Overall Summary and Evaluation

Introduction:

Mometasone Furoate (MF) is a potent glucocorticoid whose nonclinical toxicity profile is related to the pharmacologic profile of a typical glucocorticoid. Nonclinical toxicology studies were conducted with this lactose-containing dry powder oral inhaler (DPI) formulation of MF (SCH 32088) in rats (2-week, 1-month, 3-month and 6-month) and dogs (2-week, 1-month, 3-month, 6-month and 12-month) and found no unexpected toxicity. In addition, nonclinical toxicology studies with other formulations have been conducted in mice, rats or dogs, such as acute, subacute, chronic and oncogenicity studies along with genetic toxicology, reproductive toxicology and local tolerance studies.

During the development of DPI formulation of MF, general toxicology studies have been completed with two different lactose-containing DPI formulations of MF (1:19 and/or 1:5.8 SCH 32088:lactose ratios) to specifically address the local and systemic toxicity of MF and lactose in this formulation. In addition, completed studies with the bulk drug or other formulations of MF (dermatological, intranasal and/or oral inhalation formulations) provide systemic toxicity, genetic toxicity, reproductive toxicity or carcinogenicity information for the active ingredient (MF). These studies have been reviewed for NDA 20-762 (NASONEX^{TM}) and are also applicable to the safety evaluation of the lactose-containing DPI formulation. Findings in the pivotal and supporting toxicology studies with the individual development formulations are linked through the use of toxicokinetic and/or ADME studies which bridge across the studies with different formulations and dose routes.

The review #2 for IND 46,216 (attachment 1) contains the review of study reports submitted for six inhalation toxicity and toxicokinetic studies (2-weeks, 1-month and 3-month duration) which were conducted in rats and dogs with SCH 32088/lactose formulation. 2-Week and 3-month studies were conducted with SCH 32088/lactose (1:19) and one-month studies with SCH 32088/lactose (1:5.8), which is the final clinical formulation. In one-month studies, two formulations were compared at high doses by adding another group of SCH 32088 1:19 formulation. Subsequently, two 6-month inhalation studies in rats and dogs and another 12-month study in dogs, which were conducted with SCH 32088/lactose (1:5.8), are reviewed within this NDA 21-067. In addition, an *in vitro* metabolism study with SCH 32088 across species (for IND 46,216) and three ADME studies in mice, rats and dogs as well as four pharmacology studies were conducted and reviewed for this NDA 21-067.

Pharmacology:

Many pharmacodynamic studies for mometasone furoate have been included in INDs [ ] 46216 &[ ] for different formulations and extensively reviewed for NDA 20-762. The current NDA 21-067 contains an overview of four additional pharmacodynamic studies of mometasone furoate not previously submitted.

Mometasone furoate (or fluticasone propionate) was the most potent glucocorticoids followed by budesonide, triamcinolone and dexamethasone for its antiinflammatory effects by: 1) inhibiting basophil histamine release, 2) inhibiting TNF-α induced VCAM-1 expression on human bronchial epithelial cell line and 3) reducing eosinophil survival. Mometasone furoate has a high affinity for the glucocorticoid (IC_{50} = 10.7 nM) and/or progesterone (IC_{50} = 4.39 nM) receptors and is the most potent of the glucocorticoids in activating the glucocorticoid and/or progesterone receptors (EC_{50} = 0.21 nM and EC_{50} = 0.07 nM, respectively). The ratio of glucocorticoid to progesterone receptor activation demonstrates that mometasone furoate is in the same range of activity as the other glucocorticoids.

Pharmacokinetics/Toxicokinetics/ADME:

The pharmacokinetics, toxicokinetics and metabolic disposition of mometasone furoate (MF, SCH 32088) were extensively studied in mice, rats, rabbits and dogs following single- and/or multiple-dose administration by different routes and formulations.

Several toxicokinetic studies were conducted with MF/lactose (1:5.8) in rats and dogs during the repeat dose toxicology studies, one-month to either 6-month nose-only (rats) or12-month mouth-only (dogs) inhalation studies. MF/lactose formulation was administered to rats via nose-only inhalation for 1 hr/day at toxicological exposure concentrations of 0.13, 0.5 and 2.0 μg/L or by mouth-only inhalation for 30 min/day to dogs at toxicological exposure concentrations of 0.1, 0.5, 1, 4 and 16 μg/L. In addition, inhalation studies with MF/lactose (1:19) for up to 3 months and with aerosolized MF pure powder for 3-months were conducted to correlate the systemic exposure achieved during the safety studies in rats and dogs with the exposure concentration or dose.

The highest concentrations were observed within 15 minutes to 30 minutes after the end of exposure. Tmax normally occurred at the first sampling time, which was within ~5-15 minutes following cessation of exposure, demonstrating a rapid, initial absorption phase of lung-deposited MF available for systemic circulation. In real time, this corresponded to ~1.25 hr (rats) and ~45 min (dogs) from the start of exposure. Plasma MF concentrations were gender-independent, increased in an exposure concentration-related manner and showed no evidence of accumulation over the duration of the studies. Steady-state Cmax and AUC values across studies are listed in the following table.

Plasma Level Data from Toxicology Studies

Species	Exposure Conc. (µg/l)	Cmax (ng/ml)					AUC(tf)* (ng.hr/ml)				
Duration of Studies		**2-Wks**	**1-Mo**	**3-Mo**	**6-Mo**	**12-Mo**	**2-Wks**	**1-Mo**	**3-Mo**	**6-Mo**	**12-Mo**
Day of Measurement		6	30	80	184		6	30	80	184	
Rats	0.13	0.313	0.220	0.323	0.368		0.82	0.772	0.975	2.47	
	0.5	1.02	1.068	1.180	1.943		4.29	4.141	4.810	12.01	
	2.0	3.23	5.195 (4.107)	4.180	4.499		11.45	19.163 (16.50)	19.80	25.47	
Day of Measurement		12	28	78	184	360	12	28	78	184	360
Dogs	1	0.30					0.835				
	4	2.031					5.10				
	16	3.885					10.70				
	0.1		-	-	-	-		-	-	-	-
	0.5		0.014	0.979	0.05	-		-	-	-	-
	4		0.318 (0.273)	0.400	0.336	0.345		0.790 (0.498)	1.060	1.073	1.220
Formulation SCH 32088/lactose mix		1:19	1:5.8 (1:19)	1:19	1:5.8	1:5.8	1:19	1.5.8 (1:19)	1:19	1:5.8	1:5.8

* tf= Time to final quantifiable sample (hrs)

Toxicokinetic and ADME/AME studies have been completed with various formulations including the lactose-containing DPI formulation. ADME/AME studies completed with various formulations have demonstrated the similarity of the metabolic profiles across all of these formulations irrespective of dose route and/or MF formulation.

Mometasone furoate is rapidly absorbed from the lungs, attaining relatively high plasma drug concentrations, and rapidly cleared via biotransformation to a large number of polar metabolic products, one of which is 6β-hydroxy-mometasone furoate (SCH 471567), and excreted into the feces via the bile, irrespective of the animal species. Mometasone furoate was found to be a weak inducer of hepatic drug metabolizing enzymes when administered orally to rats at high doses, but did not show any induction potential in either rats or dogs following daily administration of the powder formulation by inhalation.

In vitro Metabolism study showed that SCH 32088 was metabolized extensively in the liver, moderately in the GI tract, and minimally in the lung. Metabolism across species is qualitatively similar but quantitatively different. It was found that CYP3A4 enzyme plays the primary role in the metabolism of this compound.

Exposures Multiples:

Systemic exposure to mometasone furoate during toxicology studies in rats and dogs increased with increasing exposure concentrations of the powder, irrespective of the formulation used. The plasma levels from mometasone DPI (pure powder) and DPI-Mix with lactose were similar but slightly higher from the pure powder formulation in both species. When two formulations of SCH 32088/lactose mix (1:5.8 and 1:19) were compared in one-month study, the plasma levels from 1:5.8 formulation were slightly higher than those from 1:19 formulation in both rats and dogs.

The pharmacokinetics of mometasone furoate lactose mix (1:5.8) in humans has been evaluated after 400 µg BID for 28 days (C97-049-01). Based on the comparisons of systemic exposure between toxicological species and human subjects for the MF/lactose powder mixture (1:5.8), the exposure ratio in rats and dogs was ~18 and ~0.9-fold that seen in humans, respectively. However, the exposure ratio in rats and dogs increased to ~88 and ~26-fold that seen in humans, respectively for MF pure powder. The relative oral inhalation exposures of animals and humans to inhaled MF are provided in the following table.

Relative Oral Inhalation Exposures of Animals and Humans to Inhaled MF

Formulation	Species	Dose (Duration)	AUC $_{(0\text{-}24\ hr)}$ (ng.hr/mL)	Animal to Human Exposure Ratio	References (Study #)
DPI MF/lactose powder (1:5.8)	Human	400 µg BID (28 days)	1.27	1	(C97-049-01)
Aerosol MF/lactose powder (1:5.8)	Rat	2 µg/L (30-185 days)	22.4[a]	17.7	(P-6332) (P-6518)
	Dog	4 µg/L (30-365 days)	1.09[b]	0.860	(P-6333) (P-6599) (P-6600)
Aerosol MF pure powder	Rat	4 µg/L (91 days)	111	87.5	(P-5836)
	Dog	16 µg/L (91 days)	32.6	25.7	(P-5837)
MDI (CFC) Suspension	Mouse	2 µg/L (30 days)[c]	10.3	8.12	(P-6122)
	Rat	2 µg/L (30 days)[c]	15.9	12.5	(P-6137)

a: Mean of 2 studies (P-6332, P-6518)
b: Mean of 3 studies (P-6333, P-6599, P-6600)
c: Studies supporting exposure in the mouse (P-6006) and rat (P-6005) oncogenicity studies

Oncogenicity studies were conducted previously in mice (P-6006) and rats (P-6005) via inhalation with an oral metered dose inhaler formulation (MDI), which contains sorbitan triolate as a surfactant as well as a CFC propellant. For each oncogenicity study, steady-state Cmax values were similar over time but the AUC values could not be estimated. Consequently, a 1-month study was conducted in each species so that exposure based on AUC could be determined. For both the mouse and rat, Cmax on Day 30 was similar to the long-term studies suggesting that exposures in these two bridging studies could be used in support of exposures achieved in the carcinogenicity studies. The animal-to-human exposure multiples of 8 times in mice and 12 times in rats were established based on AUC comparisons in the oncogenicity studies with the MDI formulation, although doses used in rodents were lower than the clinical dose based on body surface comparisons.

The following table shows the animal-to-human exposure multiples derived from the daily doses based on body surface comparison for carcinogenicity and reproductive toxicology studies, which were conducted, with various formulations and by different routes of administration. In general, the carcinogenicity and reproductive toxicity studies in rodents were conducted with lower doses than the proposed clinical dose of 16 µg/kg/day (400 µg BID), except oral and dermal studies, when the dose per body surface is compared. However, the dose multiples to human dose increased or became comparable when the exposures by AUC values were compared.

Comparison of the Doses Used in Animals and the Clinical Dose By Dry Powder Inhaler for Labeling

Species	Daily dose (µg/kg) (Route)	Daily dose ($\mu g/m^2$)++	AUC (ng.hr/ml)	Human dose multiples by $\mu g/m^2$
Human	**16 (ih)**	**592**	**1.27**	**1 (by AUC)**
Carcinogenicity Studies				
Rats (P-6137)	67 (ih)	402	15.9	0.68 (8x by AUC)
Mouse (P-6122)	160 (ih)	480	10.3	0.82 (12x by AUC)
Subcutaneous Reproductive (Segment I and III) Studies				
Rat (P-5543)	15 (s.c.)	90	8.25+	0.15 (6.5x by AUC)
Teratology (Segment II) Studies				
Rat (D-5054)	600 (dermal)	3600	NA	6.08
(P-5543)	2.5* (s.c.)	15	1.35+	0.025 (1.1x by AUC)
Mouse (P-5478)	20* (s.c.)	60	NA	0.10
	60** (s.c.)	180	NA	0.30
	180 (s.c.)	540	NA	0.91
Rabbit (D-5066)	150 (dermal)	1850	NQ	3.04
(P-5991)	140* (oral)	1680	NQ	2.84
	700** (oral)	8400	NQ	14.2
	2800 (oral)	33600	2.28	56.7 (1.8x by AUC)

* NOAEL ** Teratogenic NA= Not Available NQ= Not Quantifiable

\+ Mean of 2 days (P-6105) – See the Table on Page 62.

++ Conversion factors (KM): human = 37; rat = 6; mouse = 3; rabbit = 12

General Toxicology:

The toxicity profile of inhalation of SCH 32088/lactose formulations in animals was typical of **dose-related corticosteroid effects.** In general, rats tolerated the mometasone furoate (SCH 32088)/lactose mix aerosol up to 2 μg/L, and dogs tolerated up to14 μg/L of SCH 32088 which correspond to estimated doses of 60 and 110 μg/kg/day, respectively. After multiple exposures, significant reductions in body weight and/or body weight gain (30-50%) were observed in rats, but less effect on body weights were noted in dogs.

Changes in clinical pathology included increased total protein, cholesterol and glucose levels in rats and decreases in plasma cortisol levels and increases in glucose levels in dogs. At very high doses (110 μg/kg/day) in 14-day study in dogs, disturbances in electrolyte balance was also noted.

Target organs were thymus and adrenal glands with reduced weights accompanied by histopathological changes of lymphoid depletion and adrenal atrophy in rats and dogs. Lymphoid depletion was also seen in various lymph nodes and gut-associated lymphoid tissues. There were minimal increased bone marrow adipose tissues in high dose groups of both rats and dogs. In addition, vacuolization of hepatocytes in the liver was observed in all treated dogs with increased hepatic glycogen at ≥ 4 μg/L. Such change in the liver was not observed in rats. Effects on reproductive organs were more pronounced in dogs with focal prostatic atrophy and testicular atrophy in the males and slight effects on uterus and ovary in females. The morphologic changes in the ovaries and mammary glands are the typical glucocorticoid effects of the hypothalamic/adrenal/ovarian axis. Enhanced lobuloalveolar development and secretion in mammary glands of female rats at the high dose level were progestational-like changes in combination with other hormones including glucocorticoid. In general, the severity of changes increased with increased exposure concentrations and duration of the exposure.

NOAELs for glucocorticoid effects was 0.1 μg/L for dogs but could not be determined in rats based on decreased tracheal globule leukocytes observed at all dose levels. NOAELs for progestational-like effects were < 0.13 μg/L for female rats and ≥ 2.0 μg/L for male rats. For dogs, there was no progestational-like effect at ≥ 4 μg/L up to 14 μg/L SCH 32088.

In general, the effects on body weights and clinical pathology appeared to be more pronounced in those rats exposed to 2.0 μg/L SCH 32088 (1:5.8) than 2.0 μg/L SCH 32088 (1:19). This finding correlates with slightly higher plasma levels observed from the 1:5.8 formulation than from the 1:19 formulation at high doses. However, the effects from both SCH 32088 (1:5.8 and 1:19) formulations were similar in dogs.

Synopsis of inhalation toxicity studies in rats and dogs with mometasone furoate/lactose (1:19 and 1:5.8) DPI formulations are provided in the next two pages.

Summary of Inhalation Studies in Rats with SCH 32088/lactose Powder

Study Duration	Animal No.	Route	Target Exposure (µg/L)	Estimated Dose (µg/kg/day)	MF/lactose Formulation
	Rats/SD	Inhalation/nose-only 1hr/day, 7 days/wk	Air, Vehicle Control, 0.13, 0.5 & 2.0 (A)	0, 0, 4, 14 & 60	
2-Weeks	16/sex/gr	same	same as (A)	0, 0, 4, 14 & 60	1:19
3-Month	25/sex/gr	same	same as (A)	0, 0, 4, 14 & 60	1:19
1-Month	16/sex/gr	same	same as (A)	0, 0, 4, 14 & 60	1:5.8
			plus HD group 2.0		1:19
6-Month	15/sex/gr	same	same as (A)	0, 0, 4, 14 & 60	1:5.8

Results:

Animals tolerated SCH 32088 exposure at concentrations of 0.13, 0.5 or 2.0 µg/L with estimated dose of 4, 14 & 60 µg/kg/day, when administered by nose-only inhalation for one hour daily up to six months. The mean body weights were generally lower (10-25%) than the controls, but the mean body weight gains were significantly lower (30-50%) in the high dose group than the controls. Based on organ weight changes and histopathology findings, the target organs for inhaled SCH 32088 (lactose formulation) were thymus, tracheal epithelium and mesenteric lymph node of both males and females, and the mammary gland and reproductive tract of females.

Glucocorticoid activity was shown as lymphoid depletion of the thymus and mesenteric lymph node of males and females at ≥ 0.5 µg/L SCH 32088. Progestational-like changes, in combination with other hormones, were noted by enhanced lobuloalveolar development and secretion in mammary glands of females at the high dose level up to 3 months but in all SCH 32088 exposed females exposed for 6 months.

In general, the effects on body weights and clinical pathology appeared to be more pronounced in those animals exposed to 2.0 µg/L SCH 32088 (1:5.8) formulation than 2.0 µg/L SCH 32088 (1:19) formulation. This finding correlates with slightly higher plasma levels observed from the 1:5.8 formulation than from the 1:19 formulation at 2.0 µg/L.

A NOAEL could not be determined due to the findings of typical glucocorticoid effects in all SCH 32088 - exposure groups. The NOAEL for progestational-like activity in females was < 0.13 µg/L SCH 32088 and was ≥ 2.0 µg/L for males.

The toxicokinetic data from the two-week through the 6-months studies for rats showed that plasma SCH 32088 concentrations in rats were gender-independent, increased in a exposure concentration-related manner and were similar on Days 91 and 184, showing no sign of accumulation over a period of 6 months.

Summary of Inhalation Studies in Dogs with SCH 32088/lactose Powder

Study Duration	Animals No.	Route	Target Exposure (µg/L)	Estimated Dose (µg/kg/day)	MF/lactose Formulation
	Dogs/Beagles	Inhalation/Oronasal 30 min/day	Air, Vehicle Control, 0.1, 0.5 & 4.0 (B)	0, 0 1.0, 4.5 & 32.5	
2-Weeks	4/sex/gr	same	0, 0, 1.0, 4.0 & 16	9.2, 32.5 & 110	1:19
3-Month	6/sex/gr	same	same as (B)	1.0, 4.5 & 32.5	1:19
1-Month	4/sex/gr	same	same as (B)	1.0, 4.5 & 32.5	1:5.8
			plus HD group 4.0		1:19
6-Month	5/sex/gr	same	same as (B)	1.0, 4.5 & 32.5	1:5.8
12-Month	5/sex/gr	same	same as (B)	1.0, 4.5 & 32.5	1:5.8

Results:

No deaths and no clinical abnormalities were observed from daily administration of SCH 32088:lactose powder agglomerates (1:19 or 1:5.8) by mouth-only inhalation to beagle dogs for 30 minutes per day. Dogs were exposed to SCH 32088/lactose at concentrations of 0.1, 0.5 up to 4 µg/L for up to 12 months or up to 14 µg/L for 14 days, which correspond to estimated dose of 1, 4.5 & 32.5 µg/kg/day or 110 µg/kg/day from 14 µg/L concentration.

Body weights were not affected up to one month but small body weight reduction (~10%) was seen after three months or longer with mild and transient gastrointestinal distress. On the basis of organ weight changes with corresponding histopathology changes, the target organs for inhaled SCH 32088/lactose formulation were adrenal glands, liver, lymphoid tissues and reproductive organs of the 4 µg/L-exposed dogs.

In adrenal glands, SCH32088 at 4 µg/L caused a thinning of the cortical layer, zona fasiculata and zona reticularis. They were associated with atrophy, cytoplasmic vacuolization (some from ≥ 0.5 µg/L), and a decrease in the adrenal weights with reduced plasma cortisol levels at 4.0 µg/L. Generally the morphologic appearance of the adrenal effects were similar in all the studies but slightly more severe as the duration of exposure increased. In addition, vacuolization of hepatocytes in the liver was observed in some treated animals with increased hepatic glycogen at ≥ 4 µg/L, but it was also observed at ≥ 0.5 µg/L SCH 32088. Lymphoid depletion was observed in gut-associated lymphoid tissues and peripheral lymph nodes as well as in thymus and spleen of dogs exposed to SCH 32088. The focal prostate atrophy and testicular atrophy were observed at 4 µg/L SCH32088 and slight decreases in ovarian follicle development with secondary changes on mammary development and less glandular development of uterus were seen after 6-month exposure. In general severity increased with increasing exposure concentrations.

The NOAELs for glucocorticoid effects was 0.1 µg (1:5.8) SCH 32088/L and for progestational-like effects was ≥ 4.0 µg SCH 32088/L (up to 14 µg/L exposure for 14 days), since no unusual effects were seen at all doses. The observed effects were those expected from known pharmacological effects of glucocorticoids.

The toxicokinetic data from the two-week through 12-months studies for dogs showed that plasma SCH 32088 concentrations were undetectable in exposed dogs at exposure concentrations of 0.1 and 0.5 µg SCH 32088/L in all the studies. At the high-dose (4.0 µg/L), plasma drug levels were gender-independent, increased in a exposure concentration-related manner and showed no evidence of accumulation over 12 months of daily inhalation exposures.

Note: Carcinogenicity, Reproductive toxicology, and Genetic toxicology of SCH 32088 was assessed for NDA 20-762 (Nasonex) which was approved on October 6, 1997. (Refer to NDA 20-762)

Carcinogenicity:

Two twenty-four month nose only inhalation oncogenicity studies in rats (P-6005) and in mice (P-6006) were conducted with MF aerosol with CFC propellant and surfactant (MMAD 2.1-3.1 μm) at chamber concentrations of 0.25, 0.5, 1.0, and 2.0 μg/L. No statistically significant increases in tumors were noted in Sprague Dawley rats in doses up to 0.68 times the clinical dose and in Swiss CD-1 mice up to 0.82 times the clinical dose on a surface area basis. However, when AUC values at each top doses were compared, these studies were conducted at 8 times and 12 times human dose multiples. (See the table on page 57.)

There was no significant dose-response relationship for any tumor types in rats or mice. It was concluded that there was no human risk of carcinogenicity associated with the therapeutic use of the DPI MF: lactose (1:5.8) formulation. The conclusion was based upon the lack of a dose-response relationship for any tumor types in these carcinogenicity studies and the low systemic exposure observed in humans at the therapeutic dose of the inhalation. These two studies have been evaluated by Executive Carcinogenicity Assessment Committee (ECAC), which determined that there was little or no risk of carcinogenic potential in humans.)

Reproductive Toxicology:

Reproduction studies were performed in rats, mice, and rabbits by oral, dermal and subcutaneous routes of administration.

The reviewer, Dr. Tom Du, stated in his review for NDA 20-762 that subcutaneous administration of SCH 32088 produced more maternal and fetal toxicity when compared with the animals treated through dermal or oral routes of administration. In rodents (s.c.), malformations and reduced survival were noted in doses lower than the clinical dose (based on body surface area comparisons). In rabbits (oral), malformations and effects on fetal growth were noted at doses well above the clinical dose. No changes in fertility were noted in an oral rat multigenerational study, although changes such as prolonged gestation and labor and reduced body weight gain were observed at doses slightly below the clinical dose (on a body surface area basis). However, when AUC values from the scanty data are compared, the exposure multiples of animals-to-humans were slightly higher than the body surface comparisons. (See the Comparison Table on page 57.)

Summary of reproductive toxicology studies conducted with mometasone furoate is provided in the following table.

Summary of Reproductive Toxicology Studies with SCH 32088

Species	Routes	Doses (µg/kg) (Reference)	Dose	Effects
Segment II Studies				
Rats	S.C.	2.5, 15 & 30 (P-5543)	2.5 µg/kg ≥ 15 µg/kg	NOAEL Maternal effects (↓ maternal & fetal body weights and delayed ossification)
	Dermal	300, 600 & 1200 (P-5054)	≥ 300 µg/kg ≥ 600 µg/kg	Maternal effects Teratogenic (↑ malformation)
	P.O.	20, 100, 200 & 600 (D-26738)	600 µg/kg	Tolerated dose
Mouse	S.C.	20, 60 & 180 (P-5578)	20 µg /kg ≥ 60 µg/kg	NOAEL Teratogenic (↓ body weight & ↑ malformations-cleft palates)
Rabbits	P.O.	140, 700 & 2800 (P-5991)	140 µg/kg 700 µg/kg	NOAEL Teratogenic (↑ resorption and malformations 6.9%)
	Dermal	150 & 300 (P-5066)	≥ 150 µg/kg	Maternal and fetal toxicity
Segment I and III Studies				
Rats	S.C.	2.5, 7.5 & 15 (P-5174 & P-5164)	No impairment of fertility up to 15 µg/kg. At 15 µg/kg: Prolonged gestation and prolonged and difficult labor, reduction in offspring, litter size and survival of rats and ↑ resorption. NOAEL: 2.5 µg/kg 7.5 µg/kg: Tolerated dose with mild glucocorticoid effects	
Separate PK Studies				
Pregnant female rats	S.C. & P.O. single dose	30 sc & 600 po (P-6084)	AUC data:	8.250 ng.hr/ml - (30 µg/kg, s.c.) 17.59 ng.hr/ml - (600 µg/kg, p.o)
Female rat: 10-day PK study	S.C. & P.O. repeat dose	2.5, 15 & 30 s.c. & p.o. (P-6105)	**Days / Dose / Routes / AUCs (ng.hr/ml)** 1 / 2.5 / p.o. / NQ s.c. / 1.25 15 / p.o. / 0.202 s.c. / 7.28 10 / 2.5 / p.o. / NQ s.c. / 1.46 15 / p.o. / 0.328 s.c. / 9.09	

NQ: Not quantifiable

Pharmacokinetic parameters were not measured from all the reproductive toxicology studies. Therefore, separate PK studies (P-6084 and P-6105) were conducted to determine the exposure (AUC) data at the comparable doses used in the reprotoxicity studies. These data are excerpted from NDA 20-762 review.

Genetic Toxicology:

A total of 10 genetic toxicology studies with SCH 32088 were conducted. MF was non-mutagenic in the mouse lymphoma assay (P-5011) and the bacteria/mammalian microsome mutagenicity assay (P-4988, P-5969), and was negative in the mouse bone marrow erythrocyte micronucleus assay (P-5050), rat bone marrow clastogenicity assay (D-23508), UDS assay in rat hepatocytes (P-6017), and mouse spermatogonial cell assay (D-23580). It was positive at cytotoxic doses for chromosome aberrations in Chinese hamster ovary (CHO) cell cultures continuously exposed (10 hrs) in the nonactivation phase but not in the presence of rat liver S9 fraction (D-20741). MF was negative for chromosomal aberrations in CHO cell cultures under metabolic activation conditions or at lower concentrations of MF (D-23296). MF was positive under non-activation conditions in this test system only at toxic dose levels (D-23579). However, chromosomal abnormalities have been observed with other glucocorticoids at high concentrations. MF Degradation Product [ ] was negative either with or without activation.

The genetic toxicology studies indicate that MF and/or metabolites are not genotoxic or clastogenic, since negative results were seen in 8 out of 10 genetic toxicology studies. The chromosomal aberrations observed at cytotoxic dose levels in the nonactivation phase of the CHO assay were not detected in three *in vivo* clastogenesis assays (mouse micronucleus, rat bone marrow cytogenetics or mouse spermatogonial cytogenetics) or in cultured mouse lymphoma or in Chinese Hamster Lung (CHL) cells.

Exipients and Impurities:

There were no lactose-related findings in any nonclinical study conducted with this dry powder oral inhaler (DPI) formulation of MF with lactose. There is also clinical experience with currently approved lactose containing inhalation products from which patients are exposed to inhaled lactose at levels of 20 to 25 mg per breath actuation, with total daily exposures of up to 200 mg of lactose. In contrast, a total daily exposure to lactose from the proposed formulation would be 4.64 mg/day based upon a maximum total daily dose of 800 µg MF. Therefore, there are no safety concerns related to the exposure levels of lactose with the mometasone lactose powder formulation.

The impurity levels in the drug substance and the final formulations have been reviewed, and appropriate modification for specification was recommended to the sponsor. (See the Chemistry Consult Review, Attachment 2)

E) Conclusion and Recommendation

Preclinical inhalation toxicity studies have been conducted with mometasone furoate in a metered dose inhaler formulation (MDI), a pure dry powder formulation and a lactose-containing dry powder formulation. Previously, preclinical safety studies have also been completed with

topical, oral (gavage), intravenous and aqueous nasal suspension formulations of mometasone furoate.

There were no unique or special toxicology findings from a lactose-containing dry powder formulation for this NDA 21-067. All findings were typical glucocorticoid class effects and were consistent with the established dose-related and duration-related systemic pharmacologic effects of glucocorticoids.

There were no special safety concerns with mometasone furoate from the pharmacokinetics and metabolic disposition in laboratory animals. Mometasone furoate is rapidly absorbed from the lungs, attaining relatively high plasma drug concentrations, and rapidly cleared via biotransformation to a large number of polar metabolic products, and excreted into the feces via the bile, irrespective of the animal species. There was no single major metabolite; however, one of the metabolites is 6β-hydroxy-mometasone furoate (SCH 471567) for which CYP 450 3A4 plays primary role in the liver.

Plasma concentrations of mometasone furoate determined during the safety evaluation and toxicokinetic studies were dose-dependent but gender independent in all animal species studied. Mometasone furoate was found to be a weak inducer of hepatic drug metabolizing enzymes when administered orally to rats at high doses, but did not show any induction potential in either rats or dogs following daily administration of the powder formulation by inhalation.

Mometasone furoate was considered not to be carcinogenic or mutagenic from previously approved NASONEX™ (NDA 20-762) Nasal Spray. However, mometasone furoate was found to be teratogenic at doses ≥ 60 μg/kg/day (s.c) in mice and 150 μg/kg/day (dermal) or 700 μg /kg/day (oral) in rabbits. Non-teratogenic subcutaneous dose levels were established at 2.5 μg/kg/day in rats and 20 μg/kg/day in mice.

Safety of mometasone furoate/lactose (1:5.8) dry powder formulation has been adequately studied. Therefore, it is recommended that Mometasone furoate/lactose (1:5.8) formulation be approved for the treatment of asthma as proposed from the preclinical standpoint.

F) Labeling Review

Following paragraphs referenced to the nonclinical studies should be revised in the Proposed Labeling as follows.

Clinical Pharmacology:

Second and third paragraphs: Same as proposed.

Carcinogenesis, Mutagenesis, Impairment of Fertility

First and second paragraphs: Same as proposed.

1 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

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cc: NDA 21-067
HFD-570/Division File
/DO'Hearn
/DToyer
/MChun
/MVogel

Attachments: 1. Review #2 for IND 46,216
2. Review for Chemistry Consult