GENETIC TOXICOLOGY

All genetic toxicology studies were conducted under GLP.

Background: Ten genetic toxicology studies are submitted in this NDA. However, 8 out of 10 studies were reviewed previously. SCH 32088 induced chromosomal aberration in CHO cells in one study (D-20741). However, negative results were found in other studies, including the Ames test, mouse lymphoma assay, mouse bone marrow micronucleus assay, UDS assay, and chromosomal aberration assays in CHL cells and rat bone marrow cells. In the following section, all genetic toxicology and chromosomal aberration assays are summarized.

Summary of genetic toxicology studies reviewed previously:

1. Ames Test: Two Ames tests were conducted using the test stains of TA1535, TA1538, TA97, TA 97a, TA98, TA100, TA102 and WP2uvrA. In the range finding studies, precipitate was observed at the concentration of about 500 µg/plate and cytotoxicity was not induced until 5000 µg/plate of SCH 32088. Therefore, the maximum doses used for these 2 studies were selected at 500 and 2500 µg/plate, respectively. The studies showed that SCH 32088 did not induce an increase in revertant colony counts in any test strain.

2. In vitro mouse lymphoma assay: the L5178Y $TK^{+/-}$ 3.7.2C mouse lymphoma cell line was used in this test. Cytotoxicity and solubility limits of SCH 32088 were approximately 10 and 100 µg/ml, respectively. SCH 32088 was used at the concentrations of 3.125 to 100 µg/ml. With or without S9, mutant frequencies in SCH 32088 treated cells were similar to the negative controls.

3. In vivo mouse bone marrow micronucleus assay: In a pilot study, the LD_{50} in CD-1 mice was determined at 1500 mg/kg after a 2-day intraperitoneal administration. Therefore, the CD-1 mice in the micronucleus assay were treated intraperitoneally at 0 (vehicle), 600, 900 or 1200 mg/kg for 2 days. Bone marrow cells were then taken at 24 and 48 hr after the final dose and slides were prepared for evaluation. Results of this study showed that SCH 32088 did not have significant micronucleus-inducing activity in bone marrow erythrocytes.

4. In vivo hepatocyte UDS assay: Male and female F-344 rats in the range-finding study were dosed orally with a single dose of SCH 32088 at 0 (vehicle), 312.5, 625, 1250, 2500 or 5000 mg/kg. The dose used at 5000 mg/kg reached the maximum viscosity possible of dose suspensions. After the livers were removed at 7 days postdosing, hepatocytes were prepared for cultures. The results suggested that SCH 32088 was not genotoxic to F-344 rat hepatocytes.

For all of the above studies, the results from the positive or negative controls were acceptable.

Summary of chromosomal aberration assays reviewed previously:

Since SCH 32088-induced chromosomal aberration in CHO cells was observed in one study (D-20741), all chromosomal aberration studies are summarized as the following.

5. The first chromosomal aberration assay in CHO cells (D-20741) was conducted by and reported in January 1987. In this study, chromosomal aberrations were observed when CHO cells were cultured with SCH 32088 (Batch #: 15994-109) at the concentration of 12.5 µg/ml without S9. This finding was attributed by the sponsor to a spontaneous decomposition product of SCH 32088 (9-11-epoxide). Therefore, it was suggested that the sponsor repeat a chromosomal aberration assay in CHO cells using a batch containing 9-11-epoxide, and the sponsor should also conduct 2 in vivo chromosomal aberration assays using rat bone morrow cells and mouse spermatogonia.

6. The in vivo chromosomal aberration assay in rat bone marrow cells was examined by After male and female rats were treated with SCH 32088 suspension (in 0.4% methylcellulose) at 500, 1000 and 2000 mg/kg, they were sacrificed at 6, 24 and 48 hr postdosing. Bone marrow cells were collected and prepared for examination. The study indicated that SCH 32088 did not induce chromosomal aberrations in rat bone marrow somatic cells in vivo.

7. In another study (D-23296), Chinese hamster lung (CHL) cells were treated with SCH 32088. Dose levels under metabolic activation and non-metabolic activation were 13.2 and 6.6 µg/ml, respectively. The study showed that the incidences of chromosomal aberration in SCH 32088-treated cultures were similar to those in negative control cultures.

8. **Detection of chromosome aberration in CHO cells using 2 batches of SCH 32088 and SCH 32088 degradation product (D-23579, 11/89; Vol. 110)**

The results of the repeated chromosomal aberration study in CHO cells and the in vivo chromosomal aberration assay in mouse spermatogonia are reviewed below.

This study was performed by using the following test articles:

a) SCH 32088 (Batch #: 15994-109): This batch has been previously used in another chromosomal aberration study (D-20741). It was called "SCH 32088 Original" in this study by the sponsor.

b) SCH 32088 (Batch #: 8-MMF-X-600): This batch has not been tested in any chromosomal aberration study. It was named "SCH 32088 New" by the sponsor.

c) SCH 32088 Degradation Product (SCH 32088-DP; Batch 1936-047-02) is known to be the 9,11-epoxide of SCH 32088.

The objective of this study was to determine the ability of SCH 32088 Original, SCH 32088 New, and SCH 32088-DP to induce chromosomal aberrations in CHO cells with or without S9 activation. This study was a repeat of a previous chromosomal aberration study (D-20741).

Methods: CHO cells were prepared and incubated with different test articles. Untreated and dimethyl sulfoxide (DMSO)-treated CHO cells were used as negative and solvent controls, respectively. For the positive controls, cyclophosphamide (CP; 25 and 50 µg/ml) was used with rat S9; mitomycin C (MMC; 0.5 and 1 µg/ml) was used without S9 activation.

Dose ranges for SCH 32088 were determined previously in study D-20741. A range-finding assay for SCH 32088-DP was conducted in this study. Based on the results of those studies, the dose levels of SCH 32088 Original, SCH 32088 New and SCH 32088-DP were decided as the following table:

Test article	S9 conditions	Incubation time	Dose range (µg/ml)
SCH 32088 Original	with	10 hr	25 to100
	without	10 hr	1 to 20
SCH 32088 New	with	10 hr	25 to 100
	without	10 hr	1 to 20
SCH 32088-DP	with	10 hr	100 to 601
	without	10 hr	1 to 6.01
	without	20 hr	6 to 20

After an initial chromosomal aberration study, a repeated study was conducted at the following dose ranges:

Test article	S9 conditions	Incubation time	Dose levels (µg/ml)
SCH 32088 Original	with/without	10 hr	15, 17.5, 20, 22.5, 25, 27.5 and 30
SCH 32088 Original	with/without	10 hr	
SCH 32088-DP	with/without	10 hr	15, 20, 25, 30, 40, 50, 60, 100 and 200
	without	20 hr	204, 306 and 408

Results: According to the range-finding study, toxicity of SCH 32088-DP was observed at 667 and 2000 µg/ml without S9 activation. With S9 activation, SCH 32088 at 20 to 200 µg/ml only produced slight toxicity and delayed cell cycles. Complete toxicity was observed at 100 µg/ml with S9 activation and at 10 µg/ml without S9 activation. (See table below.)

Compound: SCH-32088 Assay Number: 9106

Trial No.: I Lab Code: CY 5016

Activation	Treatment	% Cells[a]			Confluence[c] % Control
		M1	M1+	>M2	
Without	Negative Control	0	2	98	100
	Solvent Control DMSO 10 µl/ml	1	35	64	100
	Positive Control MMC 250 ng/ml	100	0	0	100
	300 ng/ml	4	37	59	100
	1.0 µg/ml	6	48	46	100
	3.0 µg/ml	1	27	72	71
	10.0 µg/ml[b]				

Trial No.: I Lab Code: CY 5016

Activation	Treatment	% Cells[a]			Confluence[c] % Control
		M1	M1+	>M2	
With	Negative Control	0	15	85	100
	Solvent Control DMSO 10 µl/ml	1	9	90	100
	Positive Control CP 20 µg/ml	5	95	0	100
	3.0 µg/ml	1	15	84	100
	10.0 µg/ml	3	15	82	100
	30.0 µg/ml	2	34	64	71
	100.0 µg/ml[b]				

[a] % cells that have completed one (M1), two (M2) or between one and two (M1+) cycles in BrdUrd.

[b] Toxic dose level.

[c] This endpoint is based upon visual observations which are made prior to the harvest of the metaphase cells. Actual cell counts are not taken and any hypertrophy of the attached cells cannot be evaluated. At the time of the confluence observation the flasks are also evaluated for the appearance of floating mitotic cells and dead cells.

In the initial study, chromosomal aberration assays were repeated twice. In the initial experiment, a positive result was found when CHO cells were cultured with SCH 32048 Original at 20 µg/ml without S9 activity. The percentage of cells with aberrations at the concentration of 15 µg/ml was about 2 times higher than the controls. (See table below.) However, negative results were

observed after CHO cells were cultured with SCH 32088 New and SCH 32088-DP.

Initial study using SCH 32088 Original: Chromosomal aberration in CHO cells under non-S9 activation				
	Cell Scored	No of aberrations per cell	% of cells with aberrations	% of cells with >1 aberration
Negative & Solvent	200	0.03	2	0.5
Positive control	25	0.36	32*	4
SCH 32088: 0.996 µg/ml	200	0.03	2.5	0
SCH 32088: 4.99 µg/ml	200	0.05	2	0.5
SCH 32088: 9.89 µg/ml	200	0.02	2	0
SCH 32088: 15 µg/ml#	200	0.06	4.5	1
SCH 32088: 20 µg/ml#	178	0.13	6.2**	2.2

* Significantly greater than the pooled negative and solvent controls, $p < 0.01$
**Significantly greater than the pooled negative and solvent controls, $p < 0.05$
Nearly toxic dose level: 100 cells not available from one of replicated culture.

In a repeated study using high concentrations of the test articles, no chromosomal aberrations were observed in the culture treated with SCH 32088-DP. Significant increases of simple chromatid and chromosome gaps and breaks were observed with SCH 32088 Original and SCH-32088 New. (See the 2 table below.) However, the percentage of cells with chromosomal aberrations did not increase with dose.

Repeated study using SCH 32088 Original: Chromosomal aberration in CHO cells under non-S9 activation				
	Cell Scored	No of aberrations per cell	% of cells with aberrations	% of cells with >1 aberrations
Negative & Solvent	200	0.02	0.5	0.5
Positive control	50	0.28	28*	0
SCH 32088: 15 µg/ml	200	0.11	6.5*	2.5
SCH 32088: 15 µg/ml@	100	0.05	5*	0
SCH 32088: 17.5 µg/ml	200	>0.35	14.5*	8*
SCH 32088: 17.5 µg/ml@	100	0.34	17*	11*
SCH 32088: 20 µg/ml	200	0.24	10*	3.5
SCH 32088: 22.5 µg/ml#				

* Significantly greater than the pooled negative and solvent controls, $p < 0.01$;
@ closed flask;
# Toxic dose level.

Repeated study using SCH 32088 New: Chromosomal aberration in CHO cells under non-S9 activation				
	Cell Scored	No of aberrations per cell	% of cells with aberrations	% of cells with >1 aberration
Negative & Solvent	200	0.02	0.5	0.5
Positive control	50	0.28	28*	0
SCH 32088: 15 µg/ml	200	0.05	3	1
SCH 32088: 17.5 µg/ml@	150	0.26	13.3*	7.3*
SCH 32088: 20 µg/ml@	150	0.07	5.3*	2
SCH 32088: 22.5 µg/ml#				

* Significantly greater than the pooled negative and solvent controls, $p < 0.01$
@ Nearly toxic dose level: 100 cells not available from one of the replication culture.
# Toxic dose level.

In summary, SCH 32088 was positive in the induction of chromosomal aberrations in CHO cells only under non-S9 condition, but not under S9 condition. However, SCH 32088-produced chromosomal aberrations were found only under toxic dose levels, and the percentages of the cells with chromosomal aberrations were displayed in a non-dose-related fashion. With or without S9 activity, SCH 32088-DP was negative for inducing chromosomal aberrations.

9. In vivo Chromosomal Aberration Assay in Spermatogonial Cells (D-23580, 11/89; Vol. 111)

This study was to determine if SCH 32088 can induce chromosomal aberrations in spermatogonia obtained from male mice. Based on the results of a range-finding study, male mice (5 males/group) were injected intraperitoneally with SCH 32088 (Lot: 8MMF-X-6003, in 0.4% methylcellulose) at 0 (vehicle), 378, 796 and 1626 mg/kg and then killed at 6, 24 and 48 hr postdosing. Positive control mice were treated with cyclophosphamide (CPA) at 40 or 80 mg/kg and killed at 24 hours postdosing.

The results of this study showed that the frequency of chromosomal aberrations was significantly increased in CPA-treated mice. However, the incidences of chromosomal aberration in the SCH 32088 treated mice were similar to the vehicle-treated control mice. In conclusion, SCH 32088 did not induce structural chromosomal aberrations in mouse spermatogonial cells.

10. Absorption, metabolism and excretion in male mice following a single intraperitoneal dose (P-5486, 5/92; Vol. 139)

This study was conducted in support of micronucleus and spermatogonial studies in mice. Male CD-1 mice (n=80/group) were injected intraperitoneally with an ^{3}H-SCH 32088 suspension (Batch 32650-49-7) at 500 or 100 mg/kg. Plasma, urine, feces and bone marrow were collected at 6, 24, 48 or 168 hr postdosing. All samples were analyzed by a scintillation spectrometer. Selected plasma samples were analyzed using a LC/MS analysis (LOQ = 50 pg/ml).

By scintillation counting, peak concentrations of ^{3}H-SCH 32088 were observed in both plasma and bone marrow at 6 hr postdosing. The concentrations of 3H-SCH 32088 in bone marrow suggested that ^{3}H-SCH 32088 and/or its metabolites may readily penetrate into the bone marrow.

Dose (mg/kg)	Mice used in each interval	Plasma Dug Levels*		Bone Marrow Drug Levels*	
		at 6 hr.	at 168 hr.	at 6 hr.	at 168 hr.
500	20	32	0	40	1
1000	20	78	1	215	6

* Data were presented as the concentration of radioactivity (µg equivalent of SCH-32088/ml)

By LC/MS analysis, ^{3}H-SCH 32088 was present in bone marrow at both 6 and 24 hr postdosing In the 1000 mg/kg group, 6-hydroxy mometasone furoate was detectable in the plasma at 6 hr postdosing, but not at 24 hr postdosing

Through the 168-hr period, radioactivity was mainly eliminated via the feces and 4.7 - 6.7% of the dosed radioactivity was found in the urine. (See table below)

Total recovery (168 hr.) of Administered Radioactivities		
Dose	500 mg/kg	1000 mg/kg
Parameter	Mean (%CV*)	Mean (%CV)
Urine	4.68 (13.74)	6.36 (19.87)
Feces	96.57 (7.18)	84.80 (31.65)
Carcass	3.41 (13.57)	14.55 (45.54)
Total Recovery	104.66 (7.29)	105.71 (22.23)

* %CV: coefficient of variation (SD/mean x 100%)

PHARMACOKINETICS

Background: A series of pharmacokinetic studies were conducted to support this NDA submission. A recent report from the Division of Scientific Investigations (DSI, HFD-340) indicated that plasma samples obtained in several pharmacokinetic (PK) studies were initially examined by using enzyme immunoassay (EIA). However, after these EIA measurements were completed, an employee of the sponsor revealed to the management that she and two other employees had deliberately falsified some data during the validation of EIA and the conduction of the studies. Related conclusions of DSI are the following:

1. "The data generated by the mometasone furoate EIA at Schering Plough are not accepted for review."

2. "The HPLC-MS data generated by Taylor Technologies, despite our confidence in their own operations, but using specimens temporarily in the custody of the three suspect individuals at Schering Plough, be not accepted for review."

3. "Any mometasone furoate study submitted to the Agency, the audit trail be traced for any biological fluid specimens stored or handled at Schering Plough between 1992 and 1995. Such studies should be referred for our audit."

Following the DSI report, all invalid PK studies have been taken out of this review.

Single Dose Pharmacokinetic Studies:

Single-dose pharmacokinetic studies were not performed under GLP.

Single-dose pharmacokinetic studies were conducted by the sponsor and reviewed in this submission. In these studies, absorption, metabolism and excretion of SCH 32088 were determined.

1. Oral bioavailability in male mice (P-6111, 5/96; Vol. 136)

Male CD-1 mice (n=9/interval) were treated with a single dose of SCH 32088 by either intravenous (IV; solution, 0.3 mg/kg) or oral (PO; suspension, 0.6 mg/kg) administration. Plasma samples were collected at 0 (pre-dose), 0.08 (for IV group only), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48 and 72 hr postdosing. SCH 32088 concentrations in the plasma were determined by using a LC-MS/MS method (LOQ = 50 pg/ml).

As demonstrated in the following table, plasma drug concentration in PO group reached the peak (Cmax =1870 pg/ml) at 0.5 hr (Tmax) postdosing. Following IV treatment, Cmax (189000 pg/ml) appeared at the first sampling timepoint (0.08 hr). After IV administration of SCH 32088, a short distribution half life ($t_{1/2}\alpha$ =0.26hr) was followed by a short elimination half life ($t_{1/2}\beta$ = 1.88 hr) in mice. Mean AUC levels for PO and IV groups were 2551 and 74603 pg.hr/ml, respectively. When AUCs were normalized by the dose administered, the absolute oral bioavailability of SCH 32088 was approximately 1.7% in mice.

Parameter	Unit	Oral Dose (0.6 mg/kg)	Intravenous Dose (0.3 mg/kg)
Cmax/C5min	pg/ml	1870	189000
Tmax	hr	0.5	0.08
t½α	hr	NC	0.26
t½β	hr	NC	1.88
AUC(0-12 hr)	pg-hr/ml	2551	74603
Absolute bioavailability (dose normalized)	%	1.7	NA

NC - Not calculated for this route
NA - Not applicable for this route

2. Pharmacokinetic study of ^{14}C-SCH 32088 in rats following a single intranasal dose (P-5352, 3/89; Vol. 134)

To determine the disposition and excretion of ^{14}C-SCH 32088, 14 male Sprague Dawley rats were treated intranasally with a single dose of ^{14}C-SCH 32088 suspension (Batch No. unknown) at 240 µg/kg. Blood samples were taken from 6 rats at 0.25, 0.5, 1, 2, 4, 6, 24, 48 and 96 postdosing. Urine and feces from 8 other rats were collected every 24 hr up to 168 hr postdosing. All samples were assayed for radioactivity content.

The results showed that plasma radioactivity levels were not higher than the background levels (≤ 1ng equiv. SCH 32088/ml) following intranasal drug administration. At 168 hr postdosing, approximately 2.4% and 93.5% administered radioactivity were recovered in urine and feces, respectively. Excretion of administered radioactivity was nearly complete within 48 hr of dosing.

3. Pharmacokinetic studies in male rats of ^{3}H-SCH 32088 following a single oral or intravenous dose of ^{3}H-SCH 32088 (P-5941, 4/96 and P-6368, 5/96; Vol. 137)

Seven groups of male Sprague Dawley rats were treated with a single PO (Batch #: 31177-133) or IV dose (Batch #: 32136-05) of ^{3}H-SCH 32088 and then sacrificed at different intervals. (See table below.) Rats in Groups 1 and 2 were used to determine the pharmacokinetics and excretion of radioactivity. Rats in Groups 3 and 4 were used to determine the metabolic profile. Rats in Group 5 were used only for the collection of blank plasma. Rats in Groups 6 and 7 (n = 1)

served as the controls. Drug-derived radioactivity was normally analyzed by a liquid scintillation spectrometer. Plasma samples from Groups 1 and 2 were also assayed by HPLC-MS/MS.

Group # (Rat #)	Dose (Route)	Blood Sampling
1 (60)	0.3 mg/kg (IV)	*
2 (56)	0.6 mg/kg (PO)	**
3 (15)	0.3 mg/kg (IV)	1, 2, 4 hr postdosing
4 (15)	0.6 mg/kg (PO)	1, 2, 4 hr postdosing
5 (10)	0	For blank samples only
6 (1)	Vehicle (IV)	1, 2, 4 hr postdosing
7 (1)	Vehicle (PO)	1, 2, 4 hr postdosing

* At 0.08, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48 and 168 hr postdosing.
** At 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48 and 168 hr postdosing.

Results:

Absorption: Drug-related radioactivity was evaluated, and the mean parameters are summarized in the following table:

Phamacokinetic parameters for total radioactivity		
Parameter	IV	PO
Dose (mg/kg)	0.3	0.6
Cmax(ng eq/g)	328	5.2
Tmax(hr)	0.08*	3.0
AUC(tf; ng eq.hr/g)	748	249

* The first sampling time (0.08 hr) after IV dosing

Plasma samples were re-analyzed by LC-MS/MS (LOQ = 50 pg/ml; P-6368). Comparing the AUC values in the above table, AUC values measured by the LC-MS/MS method were much smaller than the AUC values determined by radioactivity. (See table below.)

Phamacokinetic parameters measured by LC-MS/MS		
Parameter	IV	PO
Dose(mg/kg)	0.3	0.6
Cmax(ng/g)	364	1.14
Tmax(hr)	0.08*	3.0
AUC(tf; ng.hr/ml)	192	5.23
tf (hr)	12	24
$t_{1/2}$ (hr)	1.56	4.19

* The first sampling time (0.08 hr) after IV dosing

Based on the above table, bioavailability of SCH 32088 following oral dosing was approximately 1.4% of the IV doses when plasma AUC levels were normalized for the dose administered.

Tissue distribution: The liver, lungs and gastrointestinal tissues collected from Groups 1 and 2 rats were analyzed for radioactivity. Following IV administration, radioactivity was rapidly observed in the small intestine, suggesting rapid biliary excretion of ^{3}H-SCH 32088 and/or its metabolites. The Cmax levels in the lungs and liver were detected at 0.08 hr after IV dosing.

Following PO administration, the highest concentrations of drug-derived radioactivity were found in the gastrointestinal tract. Cmax in liver or lungs was found at 6 hr after PO administration. The concentrated gastrointestinal radioactivity may be contributed by the unabsorbed drug and drug excreted into the bile.

In both IV and PO groups, drug-related radioactivity was peaked at 6 hr postdosing. (See tables below.)

Mean Percent of Administered Radioactivity in Tissues of Male Sprague Dawley Rats Following a Single Intravenous Dose of ^{3}H-SCH 32088

	Time of Sacrifice (hr)									
	0.08		1.0		6.0		12		24	
Tissue	Mean	% CV	Mean	% CV	Mean	% CV	Mean	% CV	Mean	% CV
Lungs	0.889	12	0.145	35	0.0246	20	0.0116	15	0.0085	28
Liver	13.8	24	6.55	26	5.16	25	2.81	26	2.08	26
Stomach[a]	0.779	22	1.05	74	0.0886	37	0.720	185	0.0367	41
Large Intestine[a]	0.847	4	0.798	62	61.8	12	14.7	64	1.84	41
Small Intestine[a]	18.6	20	67.5	19	12.9	67	2.32	40	0.853	61

Mean Percent of Administered Radioactivity in Tissues of Male Sprague Dawley Rats Following a Single Oral Dose of ^{3}H-SCH 32088

	Time of Sacrifice (hr)									
	0.25		1.0		6.0		12		24	
Tissue	Mean	% CV	Mean	% CV	Mean	% CV	Mean	% CV	Mean	% CV
Lungs	0	NC	0.0006	200	0.0088	12	0.0085	17	0.0013	13
Liver	0.102	62	0.169	49	0.083	20	0.615	24	0.332	41
Stomach[a]	44.14	41	29.0	65	0.110	78	0.783	188	0.0886	85
Large Intestine[a]	0.0481	138	0.0088	137	76.9	12	28.2	42	2.01	65
Small Intestine[a]	34.5	74	61.2	33	2.39	17	0.880	48	0.160	64

Results are expressed in terms of percent of administered dose and represent mean and %CV where n = 4
a Including contents
NC Not calculated
%CV Coefficients of variation expressed as a percent

Excretion: Feces and urine were collected at different intervals for up to 168 hr postdosing. Excretion of drug-derived radioactivity was rapid following both IV and oral dosing. Approximately 86% of the dose was recovered in the feces and urine within 24 hr. By 168 hr, the total radioactivity excreted from the IV and PO groups was 90% and 91%, respectively. (See table below.)

Percentage of administered radioactivity		
Samples	IV	PO
Urine	3.28	0.54
Feces	86.2	90.1
Cash Wash	0.25	0.16
Total	89.7	90.8

Metabolism: In both IV and PO groups, unchanged SCH 32088, metabolites similar in polarity to 6β-hydroxy mometasone furoate and 21-hydroxymometasone were detected in plasma (1-4 hr) by using HPLC methods. There was no unchanged SCH 32088 found in urine of IV and PO dosed rats or feces of IV dosed rats. The high-level of SCH 32088 was observed only in the feces of PO groups. However, the Sponsor did not conduct any quantitative study to determine the quantity of SCH 32088 or its metabolites in any samples.

4. Disposition of ^{3}H-SCH 32088 in rat and dog following a single IV or PO dose (P-5313, 11/88; Vol. 138)

Disposition of ^{3}H-SCH 32088 suspension (Batch #: 21120-31-20, in 0.4% methylcellulose) was evaluated in male rats (n=6/group; Dose = 1 mg/kg) and male dogs (n=4/group; Dose = 0.6 mg/kg) following a single dose IV or PO drug administration. Urine and fecal samples were collected up to 168 postdosing. Radioactivities of all samples were measured using scintillation spectrometry (LOQ ≈ 1 ng eq/ml)

In both species, parent compound and/or metabolites were eliminated mainly through the feces. However, IV-dosed radioactivity in either rats or dogs was not completely eliminated within a 168 hr period. In contrast to IV administration, PO-dosed radioactivity in rats or dogs was completely eliminated through urine and feces. (See table below.)

Recovery of Administered Radioactivity (%)

Rat	Time	0-24Hr	24-48Hr	48-72Hr	72-96Hr	96-120Hr	120-144Hr	144-168Hr	C.W*	Total	Total Recovery
IV	URINE (±SD)	0.50 (0.37)	0.56 (0.41)	0.41 (0.31)	0.26 (0.22)	0.22 (0.16)	0.16 (0.13)	0.12 (0.07)	0.22 (0.12)	2.46 (1.75)	72.31 (5.25)
	FECES (±S.D.)	5.53 (4.08)	12.16 (7.51)	11.83 (8.50)	8.35 (5.41)	5.30 (2.74	3.81 (1.91)	3.16 (1.64)	NS@	50.14 (24.9	
PO	URINE (±SD)	0.38 (0.07)	0.24 (0.25)	0.12 (0.14)	0.09 (0.10)	0.05 (0.05)	0.02 (0.02)	0.02 (0.02)	0.12 (0.08)	1.04 (0.65	113.85 (8.21)
	FECES (±SD)	92.87 (29.9)	10.96 (9.20)	6.08 (9)	3.02 (5.6)	0.71 (1.27)	0.10 (0.16)	0.10 (0.12)	NS@	113.9 (8.2	
Dog	Time	0-24Hr	24-48Hr	48-72Hr	72-96Hr	96-120Hr	120-144Hr	144-168Hr	C.W*	Total	Total Recovery
IV	URINE (±SD)	0.09 (0.02)	0.67 (0.17)	1.18 (0.05)	0.88 (0.18)	0.74 (0.12)	0.74 (0.17)	0.55 (0.10)	0.38 (0.06)	5.4 (0.52	80.92 (3.32)
	FECES (±SD)	NS@	7.30 (4.82)	25.56 (2.72)	14.64 (5.01)	9.61 (2.02)	8.04 (4.49)	7.34 (2.15)	3.04 (0.23)	75.5 (2.8	
PO	URINE (±SD)	0.31 0.14	0.12 (0.06)	0.05 (0.02)	0.02 (0.01)	0.02 (0.02)	0.01 (0.01)	0.02 (0.01)	0.11 (0.12)	0.66 (0.36	93.8 (15.4)
	FECES (±SD)	89.00 (16.8)	3.56 (2.57)	0.34 (0.17)	0.09 (0.02)	0.11 (0.16)	0.02 (0.01)	0.02 (0.01)	NS@	93.15 (15.4	

*. Cage washing fluid; @ NS: No sample

Multiple-Dose Pharmacokinetic Studies:

5. One-month nose-only inhalation pharmacokinetic studies in rats (P-6137, Vol. 143)

A one-month study was conducted to evaluate pharmacokinetic parameters in rats treated with SCH 32088 by nose-only inhalation. The concentrations of SCH 32088 in this study were 0.25, 0.5, 1 and 2 µg/L. Toxic effects of SCH 32088 were not reported in this study. The design of this study is presented in the following table:

Report # (time)	P-6137 (4/96)
Animal	SD rats
Laboratory	Battelle Pacific
Formulation	MDI
Route	Nose-only Inhalation
Duration	1- month
Daily doses on Day 1	♂: 2.6, 4.1, 10, 17µg/kg ♀: 3.7, 8.7, 14, 33 µg/kg &
Daily doses on Day 30	♂: 3.2, 6.7, 14, 24µg/kg ♀: 3.7, 8.7, 14, 33 µg/kg &
Batch #	26951-133
Blood sampling	Days 1, and 30*
Assays (LOQ= 50 pg/ml)	HPLC-APCI/MS/MS (50 pg/ml)

* 80 or 84 rat sex/time point at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 7, 9, 11, 14, 18, 23, 35 (Day 1 only) and 43 hr (Day 1 only) postdosing.

After rats inhaled SCH 32088, pharmacokinetic parameters were gender-independent. Following

either single dose (Day 1) or multiple doses (Day 30), both Cmax and AUC were generally increased almost proportionally with the dose administered. Tmax values were approximately 1 hr postdosing. (0.75 -1.5 hr; See table below.)

Parameter	Units	Target Exposure Concentration (µg/L)											
		0.25			0.50			1.0			2.0		
		M	F	M+F	M	F	M+F	M	F	M+F	M	F	M+F
Day 1													
Dose[a]	µg/kg/day	2.61	3.70	NC	4.89	8.72	NC	10.2	14.8	NC	18.7	32.8	NC
Cmax	pg/mL	595	372	339	1300	799	999	1720	1570	1660	7840	4230	5940
Tmax	hr	1.00	0.50	1.00	1.25	1.25	1.25	1.25	1.00	1.00	1.00	1.00	1.00
AUC(t)	pg*hr/mL	269	484	376	3770	3393	3496	6940	6916	6931	20363	17262	18807
t'	hr	3.00	10.0	10.0	12.0	10.0	10.0	24.0	10.0	24.0	24.0	24.0	24.0
Day 30													
Dose	µg/kg/day	3.34	5.88	NC	6.71	9.31	NC	13.6	18.1	NC	24.0	37.1	NC
Cmax	pg/mL	657	719	649	2800	1660	2800	2680	2160	2700	6840	3080	4980
Tmax	hr	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.75	1.00	1.25	1.25	1.25
AUC(t)	pg*hr/mL	2346	1983	2164	8488	3881	5184	13446	7830	10571	19488	12238	15889
t'	hr	15.0	10.0	15.0	15.0	15.0	15.0	10.0	15.0	10.0	24.0	24.0	24.0
R	-	8.27	4.10	5.70	1.87	1.24	1.46	1.89	1.29	1.83	0.956	0.715	0.845

Key: F = Female; M = Male; NC = Not calculated

a: Estimated total dose calculated from minute volume measurements and based on total deposition

6. One-month nose-only inhalation pharmacokinetic studies in mice (P-6122, Vol. 140)

A 1-month nose-only inhalation study was conducted to evaluate pharmacokinetic parameters in Swiss CD-1 mice at 0.25, 0.5, 1 and 2 µg/L of SCH 32088. After a single dose exposure, blood samples (5 mice/sex/time point) were collected at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 7, 9, 11, 14, 18, 23, 35 and 47 hr postdosing. On Day 30, blood samples (15 mice/sex/time point) were taken at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 7, 10, 14 and 23 hr postdosing. The design of this study is presented in the following table:

Report # (time)	P-6137 (7/95 - 4/96)
Animal	Swiss CD-1 mice
Laboratory	
Formulation	MDI
Route	Nose-only Inhalation
Duration	1- month
Predicted daily doses on Day 1 and Day 30	♂: 32, 64, 128, 255µg/kg ♀: 36, 71, 142, 284 µg/kg
Batch #	26951-133
Blood sampling	Days 1 and 30
Assays	HPLC-APCI/MS/MS (LOQ= 50 pg/ml)

The results showed that plasma drug concentrations were gender-independent. Following either a single exposure or a 30-day multiple-dose inhalation, plasma drug concentrations increased non-proportionally with administered doses. Except the low dose group (0.25 µg/L), plasma SCH 32088 levels were generally similar following a single dose and 30-daily doses, suggesting that the pharmacokinetics of SCH 32088 were not dependent on the treatment duration. (See table below.)

Parameter	Units	Target Exposure Concentration (µg/L)							
		0.25		0.5		1.0		2.0	
		Day 1	Day 30	Day 1	Day 30	Day 1	Day 30	Day 1	Day 30
Cmax	(pg/mL)	882	341	709	672	1910	1176	2067	3183
Tmax	(hr)	3.00	1.00	0.75	1.00	1.00	1.00	1.00	1.00
AUC(0)	(pg·hr/mL)	1171	686	1536	1440	3804	3206	6321	10281

This study displayed a dose-related systemic exposure in Swiss CD-1 mice. This mouse strain has been also used in an oncogenicity study (P-6006) conduced by . Since the predicted SCH 32088 doses in this study were similar to the predicted doses in the study P-6006, the data from this study may predict plasma drug exposure in the oncogenicity study.

7. A 28-day oral inhalation pharmacokinetic study in dogs (P-6096, Vol. 145)

Beagle dogs were treated for 28 days by oral inhalation at 20, 80 and 160 µg/kg/day. On Days 1, 15 and 28, blood samples (4 dogs/sex/group) were collected at 0.08, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hr postdosing. The design of this study is presented in the following table:

Report # (time)	P-6196 (2/95 - 3/96)
Animal	Beagle dog
Laboratory	
Formulation	MDI
Route	oral Inhalation
Duration	28-day
Predicted daily doses	20, 80 and 160µg/kg
Batch #	26951-110
Blood sampling	Days 1, 15 and 28
Assays	HPLC-APCI/MS/MS (LOQ= 50 pg/ml)

The results showed that plasma drug concentrations of 20 µg/kg/day group were under the

quantifiable levels (50 pg/ml). Pharmacokinetic parameters in the 80 and 160 µg/kg/day groups were not affected by gender or treatment duration. Following the treatment of 80 and 160 µg/kg, plasma levels of SCH 32088 were increased non-proportionally with administered doses. (See table below.)

Days of Postdosing	Pharmacokinetic Parameters	Treatment			
		80 µg/kg/day		160 µg/kg/day	
		Mean	%CV	Mean	%CV
Day 1	Cmax (pg/ml)	67.5	17	121	29
	AUC (0-24hr; pg.hr/ml)	124	48	321	81
Day 15	Cmax (pg/ml)	82	28	197	30
	AUC (0-24hr; pg.hr/ml)	418	--*	790	65
Day 28	Cmax (pg/ml)	79.2	22	143	34
	AUC (0-24hr; pg.hr/ml)	228	45	445	41

* n = 1

This study showed that plasma concentrations of SCH 32088 were under the quantifiable levels after beagle dogs were treated with 20 µg/kg/day; dose-related systemic exposures were seen in the dogs treated with 80 and 160 µg/kg/day.

8. Three-month nose-only inhalational studies in 2 species (P-5836 & P-5837; Vol. 139)

After rats and dogs were treated with SCH 32088 for 3 months by nose-only inhalation, blood and tissue samples were collected. The designs of these studies are presented in the following table:

Report # (time)	P-5836 (3/94)	P-5837(3/94)
Animal	SD rats	Beagle dogs
Laboratory		
Formulation	Dry powder	Dry powder
Route	Nose-only Inhalation	Nose-only Inhalation
Daily dose	♂: 3.4 13, 56µg/kg ♀:-4.5, 17, 74µg/kg	♂: 35, 93, 192µg/kg ♀: 57, 161, 250µg/kg
Batch #	92-MMF-DDPX-01	92-MMF-DDPX-01
Blood sampling	Weeks 1, 7 and 12*	Days 1 and 91**
Assays (LOQ)	EIA (50 pg/ml)	EIA (50 pg/ml)

* 4 rats/sex/time point at 0.25, 0.5, 1, 1.5, 2, 4 and 24 hr.
** 3 dog/sex/time point at 0.25, 1, 3, 6 and 22 hr on Days 1 and 91.

After the animals in both studies were dosed inhalationally with SCH 32088 dry powder, pharmacokinetic parameters were measured by EIA between 1992 to 1995. Based on the report from the Division of Scientific Investigations (HFD-340), the results from these pharmacokinetic studies were not acceptable. The livers and lungs in both studies were also collected at 24 hr after the final dose and were used to evaluate enzyme induction.

1. In the rat study (P-5836), SCH 32088 has almost no effect on the induction of liver and lung enzymes. The following table demonstrated the quantities of total microsomal protein, cytochrome P-450 and benzphetamine N-demethylase (BND) in the livers or lungs from the control and high dose-treated groups (56 µg/kg for the males and 74 µg/kg for the females) after a 3-month inhalational exposure. (See table below)

		Liver Enzymes (Mean±SD)		Lung Enzymes (Mean±SD)	
Treatment (Concentrations)		0 (Control)*	4 µg/L #	0 (Control)*	4 µg/L #
Liver weight (g)	♂	15.4±2.6	13.4±2.2	1.4±0.1	1.1±0.0
	♀	8.9±0.6	7.8±0.5	1.2±0.1	1.0±0.2
Total microsomal protein (mg/g tissue)	♂	31.2±1.1	31.1±3	13.6±1.6	13.5±1.2
	♀	29.9±0.9	29.8±1.5	12.4±1	12.9±2.4
Cytochrome P-450 (nmol/g liver)	♂	18.6±1	17.7±2.2		
	♀	12.5±1.3	12.4±0.3		
BND (nmol/min/g tissue)	♂	347±38	365±75	24.7±6	15.4±5.4
	♀	127±17	137±10	30.1±8.9	15.9±5.4

* n=6 sex/group/time point, treated with the vehicle.
\# n=4/sex/group/time point, treated with the drug at the concentration of 4 µg/L. This was equivalent to 56 µg/kg for the males or 74 µg/kg for the females.

2. Although liver weights in the dog study (P-5837) were increased following a 3-month SCH 32088 exposure (16 µg/L, or 192 µg/kg for the males and 250 µg/kg for the females), the concentrations of total microsomal protein, cytochrome P-450 and benzphetamine N-demethylase (BND) were not increased in the drug-treated livers or lungs. (See table below.)

		Liver Enzymes (Mean±SD)		Lung Enzymes (Mean±SD)	
Treatment (Concentrations)		0 (Control)*	16 µg/L #	0 (Control)*	16 µg/L #
Tissue weight (g)	♂	235±2.4	658±158	93.2±6.6	90±7
	♀	218±42	498±22	77.7±5.6	78±6.1
Total microsomal protein (mg/g tissue)	♂	22.1±0.9	20.4±2.1	9.0±1.1	12.3±0.6
	♀	20.6±1.1	18.9±2.2	7.2±0.1	9.9±0.3
Cytochrome P-450 (nmol/g liver)	♂	6.2±1	5.4±1	N/A	N/A
	♀	10±1.8	7.2±1.1	N/A	N/A
BND (nmol/min/g tissue)	♂	92.5±19.6	67.4±6.2	3.3±0.5	9.9±1.6
	♀	134±13	82±22	7.0±2.2	10.1±2.8

* n=3/sex/group time point, treated with the vehicle.
# n=3/sex/group interval, treated with the drug at the concentration of 16 µg/L. This was equivalent to 192 µg/kg for the males or 250 µg/kg for the females.

9. Three-month oral pharmacokinetic studies in 3 species (P-6104, P-6138 in Vol. 145; P-6007 in Vol. 148)

Pharmacokinetic parameters were measured after mice, rats and dogs were treated orally with a SCH 32088 suspension for 3 months. The designs of these studies are summarized in the following table:

Report # (time)	P-6140 (8/96)	P-6138 (8/96)	P-6007 (94/96)
Animal	CD-1 mice	SD rats	Beagle dogs
Laboratory			Shering-Plough
Formulation	Suspension *	Suspension *	Suspension *
Route	oral gavage	oral gavage	oral gavage
Daily dose	0, 50, 150, 450, 650 µg/kg	0, 50, 150, 450, 650 µg/kg	0, 10, 150, 650 µg/kg
Study Duration	3-month	3-month	3-month
Batch #	92-MMF-DDPX-01	92-MMF-DDPX-01	92-MMF-DDPX-01
Blood sampling	Days 28 and 90**	Days 1, 28 and 90 ***	Days 1, 43 and 91@
Assays (LOQ)	HPLC-APCI-MS/MS (50 pg/ml)	HPLC-APCI-MS/MS (50 pg/ml)	HPLC-MS/MS (50 pg/ml)

* In 0.4% methylcellulose;
** n = 61 mice/sex/interval; Blood was collected at 0 (predose) 0.5, 1, 2, 4, 6, 12 and 24 hr p.d. on Day 28, and then at 1, 2, 4 and 6 hr p.d. on Day 90.
*** n =50 rats/sex/interval: Blood was collected at 0 (predose) 0.5, 1, 2, 4, 6, 12 and 24 hr p.d. on Days 1 and 28, and then at 1, 2, 4 and 6 hr p.d. on Day 90.
@ N= 4 or 6 dogs/sex/interval; Blood was collected at 0.25, 0.5, 1, 2, 4 6, 9 (except Day 43), 12 (except Day 43) and 24 hr postdosing.

1. Plasma SCH 32088 concentrations in mice were generally increased with dose (P-6140).

Except for the 50 µg/kg group, plasma AUC(tf) levels on both Days 28 and 90 were consistently higher in females than in males. Tmax values were normally longer in the females than in males. When both AUC and Cmax values were compared between Day 28 and 90, it was found that there was no drug accumulation, and plasma SCH 32088 concentrations were not influenced by the duration of treatment. (See table below.)

		Day 28					Day 90			
Dose	Gender	C_{max}	T_{max}	tf	AUC(tf)	AUC (0-6 hr)	C_{max}	T_{max}	tf	AUC (0-6 hr)
50	M	812	2	2	381	381[a]	0[c]	-	-	0[c]
	F	171	1	4	376	376[b]	252	1	2	283[a]
	M+F	351	2	4	694	694[b]	151	1	2	165[a]
150	M	311	1	4	836	836[b]	138	1	6	515
	F	583	2	6	1789	1789	813	1	6	1479
	M+F	383	2	6	1427	1427	476	1	6	1010
450	M	655	1	6	1522	1522	594	1	6	1332
	F	1310	2	12	5781	4374	2860	1	6	4782
	M+F	888	1	12	4092	2963	1563	1	6	2838
600	M	688	1	12	2840	2190	1270	1	6	2874
	F	1490	2	12	5407	4823	1850	2	6	5373
	M+F	1054	2	12	4272	3505	1247	2	6	4204

Units: Dose, µg/kg/day; C_{max}, pg/ml; T_{max} and tf, hr; AUC, pg.hr/ml
a: tf = 2 hr
b: tf = 4 hr
c: Plasma SCH 32088 concentrations were not quantifiable

2. Plasma drug concentrations in the gavaged-rats did not vary between males and females (P-6138). Tmax values were between 1 and 2 hours. In all three sampling days, Cmax and AUC values were increased in a dose-related fashion. AUC (tf) values on Day 28 were approximately 2-fold higher than those on Day 1. However, AUC(0-6 hr) were similar on Days 28 and 90. (See table below.)

Table 4. **Mean Pharmacokinetic Parameters in Male and Female Rats Following Single- and Multiple-Dose Oral Gavage Administration of SCH 32088 as a Suspension.**

		50 µg/kg/day			150 µg/kg/day			450 µg/kg/day			600 µg/kg/day		
Parameter	Day	M	F	M+F	M	F	M+F	M	F	M+F	M	F	M+F
Cmax	1	190	219	200	433	736	572	1680	1310	1487	2010	1480	1744
	28	1000	280	699	861	1680	1280	1820	2860	2046	2430	4810	3430
	90	477	508	484	1040	1440	1158	4060	2860	2914	3010	4660	3513
Tmax	1	2	2	2	1	2	2	2	2	2	2	2	2
	28	1	2	1	1	2	2	1	2	1	1	2	2
	90	2	1	1	1	2	2	2	1	2	1	2	2
AUC(tf)	1	474	716	623	1431	3131	2370	6606	7117	6864	8421	7308	7864
	28	2137	1122	1651	3729	5436	4682	7206	16224	12281	11731	20572	16151
AUC(0-6 hr)	28	2137	864	1501½	3125	4203	3664	6886	10487	8087	7782	13476	10610
	90	1651	1562	1606	3786	4026	3822	11061	9513	11301	10076	13636	11951
tf	1	4	6	6	6	12	12	12	12	12	12	12	12
	28	6	12	12	12	12	12	12	24	24	24	24	24
	90	6	6	6	6	6	6	6	6	6	6	6	6

Units Cmax-pg/ml, Tmax-hr, AUC-pg·hr/ml, tf-hr, PK parameters were calculated with mean data, thus no estimate of variability can be

3. After dogs were dosed orally (P-6007), plasma drug concentrations on Day 1 were below the LOQ in all groups except for one 150 µg/kg male. Plasma SCH 32088 levels were also below the LOQ on Days 43 and 91 for the 10 µg/kg dose group, indicating a poor oral bioavailability in dogs. The concentrations of SCH 32088 were detected with a greater frequency at 600 µg/kg than at 150 µg/kg, suggested that the exposure in dogs was elevated with dose. Gender-related differences in plasma drug levels were not found. Both Cmax and AUC values on Day 91 were lower than those on Day 43.

Parameters in orally dosed dogs (Mean+%CV)

Parameters in orally dosed dog	Days	10 µg/kg/day		150 µg/kg/day		600 µg/kg/day	
		M	F	M	F	M	F
Cmax (pg/ml)	1	0*	0	770	0	0	0
	43	0	154	0	0	184	207
	91	0	0	70	0	43.6	48.4
AUC(0.25-24hr; pg.hr/ml	1	N/A**	N/A	22608	N/A	N/A	N/A
	43	NC#	NC	NC	NC	2363	2219
	91	NC	NC	NC	NC	347	90.2
Tmax(hr)	1	N/A	N/A	1	N/A	N/A	N/A
	43	N/A	24	N/A	N/A	0.5	0.25
	91	N/A	N/A	4	NC	9	0.5

* The mean value below the LOQ (50 pg ml) are presented as 0.
** Not applicable.
# Not calculated

Tissue Distribution:

The following studies were not conducted under GLP.

Three single-dose and one multiple-dose tissue distribution study were conducted in male rats treated by intravenous, oral or intranasal route of administration. Excretions of radioactive-labeled SCH 32088 to rat placenta and milk were also determined following a single oral dose administration. Finally, biliary excretion and enterohepatic circulation of SCH 32088 were studied in rats.

10. Tissue distribution studies in rats following a single dose administration (D-24338, D-24339 and P-5367 in Vol. 149)

Three tissue distribution studies were conducted in rats following administration of a single dose of radio-labeled SCH 32088. Radioactivity was measured. The designs of these studies are briefly summarized in the following table:

Report # (time)	D-24338 (8/90)	D-24339 (8/90)	P-5367 (3/89)
Animal	♂ SD rats	♂ SD rats	♂ SD rats
Laboratory			Schering Co.
Test Article	^{3}H-SCH 32088	^{3}H-SCH 32088	^{14}C-SCH 32088
Batch #	23650-119-9	23650-119-9	Unknown
Route	Intravenous	Oral	Intranasal
Dose level	0.12 mg/kg	0.12 mg/kg	240 µg/kg
Blood sampling	0.5, 3, 6, 24, 72, 168 hr postdosing. *	0.5, 3, 6, 24, 72, 168 hr postdosing. *	0.5, 2, 4, 24, 72, 120 hr postdosing.**
Tissue sampling	0.5, 3, 6, 24, 72, 168 hr postdosing. *	0.5, 3, 6, 24, 72, 168 hr postdosing. *	0.5, 2, 4, 24, 72, 120 hr postdosing.**
Urine & Feces	24, 48, 72, 96, 120, 144, 168 hr postdosing. *	24, 48, 72, 96, 120, 144, 168 hr postdosing. *	24, 72, 120 hr postdosing.*
Assays	Liquid Scintillation Counter	Liquid Scintillation Counter	Liquid Scintillation Counter

* n=5 rat sex/time point.
** n= 6 rats/time point.
@ Plasma samples were collected from males or females at Weeks 1, 7 and 12/13 and then pooled together.

1. After intravenous administration (D-24338), blood radioactivity was decreased throughout the study period. The highest concentrations of radioactivity were observed in the small and large intestine at 3 and 6 hr postdosing, respectively. (See table below.) It suggests that biliary excretion of SCH 32088 and/or its metabolites. At 24 hr postdosing, radioactivity recovered from feces and urine was 78% and 3% of the administered dose, respectively.

2. After oral administration (D-24339), ^{3}H-SCH 32088 was rapidly distributed throughout the body. At 24 postdosing, 91.5% and 2.9% radioactivities were recovered from feces and urine, respectively. The highest tissue concentrations of radioactivity were found in the stomach, liver, small and large intestines. A consistent secondary increase in the radioactivity at 6 hr postdosing may be due to biliary recirculation of SCH 32088 and/or its metabolites.(See table below.)

	TIME (h)											
TISSUE/ORGAN	0.5		3.0		6.0		24.0		72.0		168.0	
Stomach	37.3635	(84)	48.0144	(63)	8.6126	(97)	0.7788	(176)	0.0531	(37)	0.0168	(26)
Small Intestine	39.4191	(31)	42.3985	(41)	28.0999	(68)	1.7862	(36)	0.1301	(33)	0.0452	(44)
Large Intestine	5.0983	(299)	1.0819	(166)	56.2356	(33)	7.4188	(83)	1.0991	(110)	0.0489	(73)
Liver	7.0788	(84)	2.6257	(45)	4.3336	(14)	1.9951	(37)	0.1024	(7)	0.2499	(44)
Kidney	0.1921	(75)	0.0592	(26)	0.0842	(28)	0.0425	(14)	0.0268	(14)	0.0110	(14)
Adrenals	0.0085	(88)	0.0086	(83)	0.0012	(41)	0.0085	(65)	0.0088	(137)	0.0088	(84)
Pituitary Gland	0.0083	(91)	0.0081	(65)	0.0081	(39)	0.0089	(284)	0.0088	-	0.0088	-
Thyroid	0.0086	(85)	0.0082	(23)	0.0083	(24)	0.0081	(35)	0.0081	(17)	0.0088	-
Mesenteric Lymph	0.0057	(92)	0.0035	(36)	0.0044	(79)	0.0013	(22)	0.0086	(14)	0.0082	(18)
Pancreas	0.0188	(95)	0.0061	(38)	0.0091	(41)	0.0038	(18)	0.0084	(26)	0.0013	(22)
Lungs	0.0152	(91)	0.0164	(27)	0.0210	(28)	0.0111	(21)	0.0083	(26)	0.0043	(22)
Urinary Bladder	0.0024	(148)	0.0018	(49)	0.0012	(28)	0.0084	(36)	0.0082	(21)	0.0082	(66)
Harderian Gland	0.0083	(85)	0.0033	(44)	0.0041	(31)	0.0014	(28)	0.0084	(182)	0.0088	-
Heart	0.0256	(93)	0.0057	(27)	0.0085	(45)	0.0041	(17)	0.0025	(25)	0.0016	(33)
Spleen	0.0150	(102)	0.0066	(42)	0.0072	(45)	0.0029	(27)	0.0024	(22)	0.0018	(25)
Gland	0.2689	(77)	0.1089	(31)	0.2118	(17)	NA	-	0.1149	(11)	0.0785	(24)
Cervical Lymph	0.0028	(91)	0.0089	(49)	0.0018	(28)	0.0088	(39)	0.0082	(89)	0.0082	(191)
Prostate	0.0065	(99)	0.0038	(37)	0.0044	(35)	0.0021	(33)	0.0018	(16)	0.0013	(21)
Seminal Vesicles	0.0051	(94)	0.0085	(179)	0.0034	(29)	0.0016	(16)	0.0088	(17)	0.0085	(29)
Thymus	0.0063	(73)	0.0037	(36)	0.0039	(19)	0.0023	(65)	0.0012	(14)	0.0085	(24)
Eyes	0.0011	(67)	0.0088	(48)	0.0011	(17)	0.0012	(33)	0.0086	(22)	0.0085	(28)
Testes	0.0094	(103)	0.0101	(39)	0.0138	(7)	0.0164	(22)	0.0097	(23)	0.0057	(25)
Brain	0.0044	(79)	0.0033	(47)	0.0017	(13)	0.0038	(16)	0.0042	(22)	0.0057	(15)
Carcass	2.1165	(74)	1.1983	(77)	0.1587[a]	(32)	0.0713	(66)	0.4041	(21)	0.3845	(39)

Values represent group means (CV) where n = 5 except [a] where n = 4

[b] NA No aliquot taken

Note: Skin, fat and muscle values are not given in this table since these values are included in the carcass values

TISSUE/ORGAN	0.5		3.0		6.0		24.0		72.0		168.0	
Small Intestine	38.7775	(84)	78.1127	(34)	12.2228	(19)	2.0537	(100)	0.1188	(29)	0.0433	(36)
Liver	7.4644	(74)	7.4689	(28)	4.4162	(28)	3.0144	(4)	1.2936	(6)	0.5341	(14)
Kidney	1.2243	(64)	0.4519	(17)	0.1795	(19)	0.0918	(48)	0.0379	(15)	0.0212	(19)
Adrenal	0.0175	(64)	0.0052	(24)	0.0023	(22)	0.0086	(34)	0.0082	(25)	0.0091	(85)
Pituitary	0.0017	(73)	0.0088	(28)	0.0083	(7)	0.0089	(137)	0.0088	-	0.0088	-
Harderian Gland	0.1184	(81)	0.0535	(26)	0.0188	(28)	0.0039	(34)	0.0013	(17)	0.0088	(22)
Pancreas	0.1721	(73)	0.0484	(22)	0.0173	(31)	0.0086	(41)	0.0036	(22)	0.0021	(9)
Mesenteric Lymph Node	0.0772	(93)	0.0251	(34)	0.0085	(43)	0.0023	(126)	0.0084	(11)	0.0083	(37)
Stomach	0.4018	(65)	0.0724	(74)	0.2388	(18)	0.4389	(138)	0.0279	(81)	0.1271	(217)
Thyroid	0.0039	(89)	0.0013	(18)	0.0089	(13)	0.0084	(35)	0.0081	(61)	0.0088	(137)
Lung	0.2113	(56)	0.1217	(3)	0.0631	(16)	0.0238	(41)	0.0163	(28)	0.0178	(88)
Cervical Lymph Node	0.0093	(73)	0.0048	(22)	0.0031	(27)	0.0084	(76)	0.0082	(32)	0.0082	(46)
Large Intestine	0.7488	(89)	1.3076	(99)	88.2737	(13)	5.7272	(61)	0.1618	(34)	0.0347	(77)
Spleen	0.0064	(76)	0.0047	(18)	0.0179	(22)	0.0079	(61)	0.0032	(16)	0.0027	(37)
Heart	0.1140	(62)	0.0398	(22)	0.0165	(29)	0.0094	(37)	0.0039	(11)	0.0021	(23)
Thymus	0.0066	(83)	0.0042	(27)	0.0047	(19)	0.0045	(73)	0.0086	(61)	0.0082	(224)
Prostate	0.0540	(78)	0.0237	(24)	0.0108	(13)	0.0089	(45)	0.0084	(284)	0.0088	-
Urinary Bladder	0.0099	(73)	0.0049	(28)	0.0024	(25)	0.0089	(33)	0.0083	(8)	0.0082	(14)
Seminal Vesicle	0.0064	(77)	0.0151	(27)	0.0061	(24)	0.0026	(31)	0.0011	(42)	0.0087	(61)
Gland	0.2476	(78)	0.3599	(28)	0.2535	(14)	0.1749	(11)	0.1284	(17)	0.0838	(43)
Testis	0.1238	(81)	0.0951	(28)	0.0817	(14)	0.0245	(17)	0.0136	(25)	0.0083	(28)
Eye	0.0076	(78)	0.0041	(28)	0.0025	(18)	0.0018	(16)	0.0089	(21)	0.0085	(37)
Brain	0.0424	(76)	0.0155	(24)	0.0089	(19)	0.0088	(28)	0.0014	(224)	0.0088	-
Carcass	45.4495	(88)	19.7087	(121)	3.3498	(22)	0.1681	(137)	0.6635	(68)	0.7898	(71)

Values represent group means (CV) where n = 5

Note: Skin, fat and muscle values are not given in this table since these values are included in the carcass values

3. At 0.5 hr after rats were treated intranasally with ^{14}C-SCH 32088 (P-5367), the highest radioactivity concentrations were found in the esophagus, trachea, nasal passage and mouth. Peak concentrations of radioactivity were then observed in the stomach, small intestine and large intestine at 2, 4, and 24 hr postdosing, respectively. This finding may be due to oral ingestion of the drug. Very little radioactivity was present in the lungs and other tissues. At 24 hr postdosing, 34.4% and 2.7% of the dosed radioactivity were recovered from the feces and urine, respectively. Approximately 50% of the radioactivity was excreted from the feces (49.9%) and urine (1.9%) at 120 hr postdosing. Results from this study demonstrated that drug-related radioactivity can be extensively distributed and rapidly eliminated following intranasal administration.

11. Tissue distribution and excretion of ^{14}C-SCH 32088 in male rats following a 21-day oral administration (P-5976, 5/96; Vol. 150)

Male SD rats were dosed orally with 0.6 mg/kg of ^{14}C-SCH 32088 suspension (Batch #: 32230-70-10) for 21 consecutive days. Control rats were treated with vehicle (0.4% methylcellulose) only. The study design is presented in the following table:

Group	Activity	Dosing Day	Time (hr) After Daily Dose
1 (n=80)	Blood Collection	1 2-6 8-13 15-20 21	0.5,1,2,4,8,48,96,120 24 24 24 0.5,1,2,4,8,48,96,120
2 (n=84)	Tissue Distribution and Blood Collection	1 7 14 21	1,3,8,12,24,72,168,240 24 24 1,3,8,12,24,72,168,240
3 (n=28)	Whole Body Autoradiography	1 7 14 21	1,8,24,72,168,240 24 24 1,8,24,72,168,240
4 (n=6)	Mass Balance	2-20	24 hr collection collection at 24 hr intervals to Day 21
5 (n=1)	Tissue Control	1	ca 24 hr
6 (n=1)	Whole Body Autoradiography Control	1	ca 24 hr

After treatment, plasma, tissues and carcasses were collected at several time intervals. Radioactivity was measured using a liquid scintillation spectrometer. Plasma radioactivity was examined by an enzyme immunoassay (EIA). Profiles of 14C-SCH 32088 and its metabolites were determined by HPLC.

The concentration of radioactivity in whole blood were consistently greater than those in plasma. Following a single dose, drug-related radioactivity was not detectable in plasma or blood. However, after a 21-day oral treatment, drug-related radioactivity was quantifiable in the plasma at 24 hr postdosing and in the blood at 240 hr postdosing. Pharmacokinetic parameters are presented below:

Pharmacokinetics of ^{14}C-SCH 32088-Derived Radioactivity in Plasma of Male Albino Rats Following a Single or 21 Consecutive Daily Oral Doses of ^{14}C-SCH 32088 (0.6 mg/kg/day)

Parameter (units)	Day 21[a]
Cmax (µg eq/g)	0.006
Tmax (hr)	1.5
t½ (hr)	12.1
AUC(t) (µg eq·hr/g)	0.085
AUC(i) (µg eq·hr/g)	0.130

a Drug-derived radioactivity not detectable following single dose (Day 1)

Following a single dose administration, most of the radioactivity was observed in the gastrointestinal tract. The liver also contained significant radioactivity. At 168 hr after the single dose, radioactivity was not found in any tissue or carcass.

At 24 hr following 7 or 14 consecutive doses, radioactivities in tissues were greater than that at 24 hr following a single daily dose. This suggests that the concentrations of tissue radioactivity were increased with the length of the exposure period. (See table below.)

Ratio Analysis of Mean Concentrations (C24hr) of Radioactivity in Tissues of Male Albino Rats Following a Single or Multiple Oral Doses of ^{14}C-SCH 32088 (0.6 mg/kg/day)

Tissue	µg equivalents/g			Ratio		
	Day 1	Day 7	Day 14	Day 7:1	Day 14:1	Day 14:7
Carcass						
Skin						
Plasma						
Blood						
Eyes						
Bone Mar.						
Brain						
Epidid. Fat						
Peri. Fat						
Subcut. Fat						
Brown Fat						
Skel. Musc.						
Heart						
Lungs						
Spleen						
Liver	0.013					
Kidney						
Stomach						
Stom. Cont	0.001[a]					
Lge Intest						
LI. Cont						
Small Int						
S.I. Cont						
Hypophysis						
Thyroid						
Thymus						
Saliv. Glan						
Testes						
Harder. Gl.						
Pancreas						
Adrenals						
Bladder	0.005[a]					
Cerv. Lymp						
Mes. Lymp						
Epididymis						
Prostate						
Semin. Ves.						

C24hr Concentration measured 24 hours after dose

a Two samples below the limit of detection; 0 used in calculation of mean

b One sample below the limit of detection; 0 used in calculation of mean

NC Could not be obtained from existing data

ND All samples below the limit of detection (< 2 x background)

After 21 consecutive oral doses, the highest concentration was present in the gastrointestinal tract. In comparison with a single dose, Cmax and AUC values for liver and kidneys were increased following 21 consecutive doses. Except for the liver, kidney and gastrointestinal tract, the concentrations of radioactivity were also elevated in other tissues following 21-day treatment, including skin, bone, lungs, spleen and pancreas. The terminal phase half-life of the drug-derived radioactivity in plasma, estimated after 21 days of dosing, was approximately 12 hr. (See the tables below.)

Cmax, Tmax and Ratio Analysis of Maximum Mean Concentrations (Cmax) of Radioactivity in Tissues of Male Albino Rats Following a Single Dose or 21 Consecutive Daily Oral Doses of ^{14}C-SCH 32088 (0.6 mg/kg/day)

	Day 1		Day 21		Ratio
Tissue	Cmax µg equiv/g	Tmax hr	Cmax µg equiv/g	Tmax hr	Cmax Day 21:1
Carcass	0.026[a]	12	0.007[b]	24	0.3
Skin	ND	NC	0.015[a]	24	NC
Plasma	ND	NC	0.006	24	NC
Blood	ND	NC	0.021	24	NC
Eyes	0.001[a]	6	ND	NC	NC
Bone Mar.	ND	NC	0.004[b]	24	NC
Brain	ND	NC	ND	NC	NC
Epidid. Fat	ND	NC	ND	NC	NC
Perit. Fat	ND	NC	ND	NC	NC
Subcut. Fat	ND	NC	ND	NC	NC
Brown Fat	ND	NC	ND	NC	NC
Skel. Musc.	ND	NC	ND	NC	NC
Heart	0.006[a]	12	0.004[b]	24	0.7
Lungs	ND	NC	0.012	24	NC
Spleen	ND	NC	0.008	24	NC
Liver	0.056	6	0.225	24	4.0
Kidney	0.009	6	0.036	24	4.0
Stomach	2.83	1	1.20	1	0.4
Stom. Cont.	2.73	1	2.20	1	0.8
Lge Intest	0.232	6	0.355	6	1.5
LI. Cont	3.09	6	4.48	6	1.5
Small Int	1.09	3	2.31	1	2.1
S.I. Cont	3.89	3	3.54	1	1.0
Hypophysis	ND	NC	ND	NC	NC
Thyroid	ND	NC	ND	NC	NC
Thymus	ND	NC	ND	NC	NC
Sallv. Glan	ND	NC	0.005[b]	24	NC
Testes	ND	NC	ND	NC	NC
Harder. Gl.	ND	NC	ND	NC	NC
Pancreas	ND	NC	0.010	24	NC
Adrenals	0.025[a]	24	ND	NC	NC
Bladder	0.006[a]	24	0.002[b]	24	0.3
Cerv. Lymph	ND	NC	0.019[a]	24	NC
Mes. Lymph	0.019	6	0.033	24	1.7
Epididymis	ND	NC	ND	NC	NC
Prostate	ND	NC	ND	NC	NC
Semin. Ves.	ND	NC	ND	NC	NC

ND All samples below the limit of detection (< 2 x background)
NC Could not be obtained from existing data
[a] Two samples below the limit of detection; 0 used in calculation of mean
[b] One sample below the limit of detection; 0 used in calculation of mean

Area Under the Tissue Concentration vs Time Curves, Ratio Analysis and Estimated Half-Life of Radioactivity in Tissues of Male Albino Rats Following a Single Oral Dose for 21 Consecutive Doses of ^{14}C-SCH 32088 (0.6 mg/kg/day)

Tissue	Day 1 AUC(tf) µg equiv·hr/g	Day 1 Half-Life Hr	Day 21 AUC(tf) µg equiv·hr/g	Day 21 Half-Life Hr	Ratio AUC(tf) Day 21:1
Carcass	0.053	NC	0.089	NC	1.7
Skin	NC	NC	0.474	NC	NC
Plasma	NC	NC	0.095	12.1	NC
Blood	NC	NC	3.82	NC	NC
Eyes	0.002	NC	NC	NC	NC
Bone Mar.	NC	NC	0.016	NC	NC
Brain	NC	NC	NC	NC	NC
Epidid. Fat	NC	NC	NC	NC	NC
Perit. Fat	NC	NC	NC	NC	NC
Subcut. Fat	NC	NC	NC	NC	NC
Brown Fat	NC	NC	NC	NC	NC
Skel. Musc.	NC	NC	NC	NC	NC
Heart	0.018	NC	0.004	NC	0.2
Lungs	NC	NC	0.999	68.5	NC
Spleen	NC	NC	0.546	NC	NC
Liver	1.55	7.5	16.2	7.5	10.5
Kidney	0.073	7.5	3.95	7.5	54.1
Stomach	5.82	7.5	5.58	7.5	1.0
Stom. Cont.	6.17	7.5	9.54	7.5	1.5
Lge Intest	3.06	7.5	10.2	7.5	3.3
L.I. Cont	39.2	7.5	58.5	7.5	1.5
Small Int	5.94	7.5	10.3	7.5	1.7
S.I. Cont	17.4	7.5	16.8	7.5	1.0
Hypophysis	NC	NC	NC	NC	NC
Thyroid	NC	NC	NC	NC	NC
Thymus	NC	NC	NC	NC	NC
Saliv. Glan	NC	NC	0.005	NC	NC
Testes	NC	NC	NC	NC	NC
Harder. Gl.	NC	NC	NC	NC	NC
Pancreas	NC	NC	0.410	NC	NC
Adrenals	0.896	NC	NC	NC	NC
Bladder	0.048	NC	0.003	NC	0.1
Cerv.Lymph	NC	NC	0.010	NC	NC
Mes. Lymph	0.116	NC	2.12	NC	18.3
Epididymis	NC	NC	NC	NC	NC
Prostate	NC	NC	NC	NC	NC
Semin. Ves.	NC	NC	NC	NC	NC

NC Could not be obtained from existing data

HPLC profiles showed that the metabolism of SCH 32088 in rats was qualitatively similar after either single or multiple oral doses. Unchanged SCH 32088 and moderately polar metabolites similar in retention to 6β-hydroxymometasone furoate and 21-hydroxymometasone were detected in the plasma collected on Days 1 and 21. Due to the small sample quantity, SCH 32088 and metabolites were not studied quantitatively.

Radioactivity was detectable in urine until 22 days postdosing. However, radioactivity was measurable in feces until 26 days postdosing. (See table below.) Most of the drug-related radioactivity was recovered in the feces (89.3%) and less than 0.4% of the dose was recovered in

urine. At the end of the study, total recovered dose was approximately 90% of administered dose. (See table below.)

Mean Daily Recovery (%) of Radioactivity in Excreta of Male Albino Rats Following Once Daily Oral Administration of ^{14}C-SCH 32088 (0.6 mg/kg/day) for 21 Consecutive Days

	Percent of Administered Dose			
	Urine		Feces	
Study Day	Mean	%CV	Mean	%CV
2	0.01	89	3.37	2
3	0.01	22	3.38	8
4	0.01	28	3.63	4
5	0.01	21	3.64	6
6	0.01	27	4.05	7
7	0.01	37	4.04	6
8	0.01	36	3.97	4
9	0.01	18	3.81	2
10	0.02	21	4.15	9
11	0.02	25	4.17	3
12	0.02	16	4.40	5
13	0.02	28	4.74	4
14	0.02	27	4.05	13
15	0.02	30	4.53	2
16	0.01	27	4.21	8
17	0.02	36	4.80	6
18	0.02	33	4.30	8
19	0.02	31	4.89	2
20	0.02	30	4.87	4
21	0.02	24	5.02	3
22	0.02	29	5.18	2
23	0	27	0.24	34
24	0	NC	0.02	32
25	0	NC	0.01	16
26	0	NC	0.01	39
27	0	NC	0	NC
28	0	NC	0	NC
29	0	NC	0	NC
30	0	NC	0	NC
31	0	NC	0	NC

Results are expressed as a percentage of the total dose administered during the 21 consecutive days of dosing
Results represent mean and %CV where n = 6
%CV Coefficient of variation expressed as a percent
NC Not calculated

12. Distribution and excretion of ^{14}C-SCH 32088 into rat placenta following a single oral dose (P-6000, 5/96; Vol. 151)

Femals SD rats (n=2 or 3/interval) on Day 18 pregnancy were treated orally with a single dose of ^{14}C-SCH 32088 suspension (Batch #: 32230-97-30) at 0.6 mg/kg. Blood and tissue samples were collected at 0, 1, 4, 12, 24 and 48 hr postdosing. Urine, feces and cage wash fluid were collected only from the rats sacrificed at 48 hr postdosing. Radioactivities were determined by using Liquid Scintillation Spectrometry. (LOQ = 0.18 ng eq/g)

Plasma radioactivity in dams was detectable until 24 hr postdosing, but not at 48 hr postdosing. PK parameters in dams are presented in the following table:

Parameters	Values
Cmax (ng eq/g)	4.27
Tmax (hr)	4
AUC (0-24hr;ng/eq.hr/ml	63.8.1

In tissues, most of the radioactivity was found in the gastrointestinal tract and its contents. Lower levels of radioactivity were observed in the liver, uterus and kidneys. Radioactivity concentrations in the placenta, ovaries and amnions were just above the LOQ, indicating that SCH 32088 and/or its metabolites are able to cross the placenta. (See table below)

Tissues	Mean Concentration ng eq/g (%CV)[a]									
	Time (hr)									
	1		4		12		24		48	
Liver	9.76	(42)	36.8	(4)	24.4	(53)	20.7	(53)	10.8	(20)
Lg. Intestine	16.7	(122)	3.62	(83)	80.3	(72)	6.72	(32)	1.34	(20)
Lg. Int. Contents	1.37	–[b]	85.6	(158)	1790	(36)	46.3	(37)	61.5	(102)
Sm. Intestine	522	(99)	282	(61)	24.3	(68)	14.4	(42)	0.880	(8)
Sm. Int. Contents	7230	(9)	3360	(36)	161	(122)	86.7	(82)	3.40	(8)
Stomach	891	(58)	384	(52)	4.21	(119)	8.23	(131)	0.153	(87)
Stomach Contents	7420	(80)	8290	(36)	79.3	(132)[c]	382	(165)	ND	–
Cecum	9.83	(91)	85.2	(126)	36.4	(48)	3.65	(37)	2.72	(41)
Cecum Contents	28.1	(96)	3340	(79)	1410	(32)	89.0	(70)	37.5	(46)
Urinary Bladder	1.01	(173)	6.68	(36)	4.15	(64)	0.626	(173)	ND	–
Kidneys	1.10	(46)	3.11	(10)	1.48	(52)	1.64	(66)	0.786	(20)
Lungs	ND	–	0.737	(23)	0.442	(87)	46.0	(173)	2.61	(173)
Heart	ND	–	0.228	(173)	0.176	(173)	ND	–	ND	–
Brain	ND	–	ND	–	ND	–	ND	–	ND	–
Mammary Glands	0.071	(173)	1.20	(18)	0.669	(46)	0.168	(87)	ND	–
Uterus	1.48	(158)	1.43	(13)	1.33	(52)	0.817	(20)	0.150	(87)
Placentas	0.877	(110)	1.73	(37)	1.86	(66)	0.636	(34)	0.244	(13)
Amnions	4.09	(173)	1.89	(82)	2.01	(84)	2.25	(46)	1.16	(46)
Amniotic Fluid	ND	–	ND	–	ND	–	ND	–	ND	–
Ovaries	1.97	(25)	4.89	(4)	3.22	(46)	1.55	(40)	ND	–
Blood	1.22	(41)	3.42	(6)	3.37	(47)	2.86	(82)	1.89	(13)
Plasma	1.10	(40)	4.27	(7)	3.05	(50)	1.27	(33)	ND	–

a. Means based on n=3
b. Mean calculated on n=1, due to failed duplicate test
c. Mean and %CV calculated on n=2, due to failed duplicate test
ND = Samples below the limit of quantitation (<2 X background)
– Not calculated

Radioactivity was also detectable in fetal liver, brain, lungs, blood and body. Radioactivity in the fetal liver was decreased over time. Compared with the dams, radioactivity in fetal liver was lower. However, radioactivity in fetal brain and lungs was higher than the levels in the dams.

Table 7. Mean Concentration of Radioactivity in Tissues of Fetal Rats Following a Single Oral Dose of ^{14}C-SCH 32088 to 18-Day Pregnant Rats.

Tissue	Concentration (ng eq/g) (%CV)									
	1 hr		4 hr		12 hr		24 hr		48 hr	
Liver	0.741	(173)	1.83	(6)	1.23	(87)	0.405	(129)	0.044	(173)
Heart	ND		ND		ND		ND		ND	
Kidney	ND		ND		ND		ND		ND	
Brain	ND		ND		1.032	(173)	ND		ND	
Blood	ND		ND		ND		0.414	(173)	ND	
Lung	ND		ND		0.282	(173)	0.142	(173)	ND	
Carcass	0.613	(173)	ND		0.379	(173)	ND		ND	

ND = Samples below the limit of quantitation (< 2x background, ~ 0.02 ng eq/g)

In the dams, most of the administered radioactivity was excreted in the feces (75.9%). Only a small portion of dosed radioactivity was recovered in the urine (1.7%).

13. Excretion of ^{14}C-SCH 32088 in rat milk following a single oral dose administration (P-6010, 5/96; Vol. 151)

Lactating rats (n=3/interval; Mean bodyweight= 396g) at 14-day post-partum were treated orally with 0.6 mg/kg of ^{14}C-SCH 32088 suspension (Batch No. 32230-97-30). Plasma and milk samples from the dams were collected at 0, 0.5, 1, 4, 24, and 72 hr postdosing. Blood and plasma samples were also obtained at each time-point from 6 pups/dam selected at random from individual litters. Radioactivity was measured by using a liquid scintillation analyzer. Metabolite profiles of SCH 32088 were analyzed using HPLC.

Plasma radioactivity was observed in the dam for up to 24 hr postdosing, but no radioactivity was detected in the plasma of the pups. Radioactivity was detected in the milk of 1/3 rats at 0.5 and 1 hr postdosing, but in all 3 rats at 4 hr postdosing. Pharmacokinetic analysis of plasma and milk radioactivity is presented in the following table:

Parameter		Mean Plasma Radioactivity	Mean Milk Radioactivity
Cmax	ng equiv/ml	3.2	2.5
Tmax	hr	4	4
AUC(0-12 hr)	ng equiv·hr/ml	31.5	14.8
AUC(tf)	ng equiv·hr/ml	47.3	4.85
tf	hr	24	4

Based upon the average daily milk consumption (2 ml/pup) and the maximum milk concentration observed (2.5 ng eq/ml), daily drug exposure to each pup can be calculated as the following:

$$\frac{2.5 \text{ ng eq/ml} \times 2 \text{ml/pup}}{0.6 \text{ mg/kg} \times 0.396 \text{ kg}} \times 100\% = 0.002\%$$

Based on the above calculation, the daily dose for each pup would be approximately 0.002% of the daily dose administered to the dam. If a pup at birth was 6 g, the daily dose would be 4.75 ng eq/per pup (0.00792 mg/kg). Therefore, only 1.3% of the administered SCH 32088 was given to each pup.

14. Biliary excretion and enterohepatic circulation in rats following a single oral dose administration of ^{14}C-SCH 32088 (P-6009, 6/95; Vol. 151)

Two groups of fasted and bile-duct-cannulated male SD rats (n=4/group) were used in this study. To test biliary excretion, rats in Group 1 (donors) were treated PO with a single dose of ^{14}C-SCH 32088 suspension (Batch # 32230-97-30). To assess enterohepatic circulation, rats (recipients) in Group 2 were treated intraduodenally (ID) with the bile collected from Group 1 rats. The study design is presented in a table below.

Group	Treatments	Route	Dose
Donor Recipient	^{14}C-SCH 32088 0-24 hr pooled donor bile	PO ID	0.6 mg/kg 4.5 ml/rat

After treatment, bile was collected at 0-2, 2-4, 4-6, 6-8, 8-24 and 24-48 hr, and urine and feces were collected up to 48 hr postdosing. Gastrointestinal tissues and contents, and carcasses were pooled at 48 hr postdosing. Radioactivities in all samples were assayed by liquid scintillation counter. Metabolites of SCH 32088 in the bile and fecal samples were analyzed using both liquid scintillation counter and HPLC.

As demonstrated in the following table, approximately 14% of the oral-dosed ^{14}C-SCH 32088 was excreted through the bile. About 27% of the absorbed dose was reabsorbed and underwent enterohepatic circulation. In both groups, drug-related radioactivity was mainly eliminated through the feces. Approximately 0.5 and 3% of radioactivity were excreted in the urine of donor and recipient groups, respectively.

Excretion of radioactivity: % of Dosed ^{14}C-SCH 32088 (Mean(%CV)

Samples	Donor Group	Recipient Group
Bile	13.68 (37)	27.11 (7)
Urine	0.48 (43)	3.12 (34)
Feces	60.71 (29)	56.09 (7)
GI Tract	8.13 (121)	9 (66)
Carcass	1.65 (124)	0 (0)
Total	84.65 (6)	95.32 (10)

SCH 32088 was found in fecal samples of the donors, but not in the recipient group. In the bile samples collected from the donor and recipient groups, radioactivity was present in several peaks, including those coincident with standards for 21-hydroxy mometasone, 6β-hydroxy mometasone furoate and mometasone. However, SCH 32088 was not observed in any bile sample, suggesting that absorbed SCH 32088 was completely metabolized.

Protein Binding and in vitro Drug Metabolism:

These studies were not conducted under GLP.

15. In vitro protein binding of SCH 32088 in rat, mouse, rabbit, dog and human plasma (P-6004, 7/95; Vol. 149)

Drug-free plasma samples from rat, mouse, rabbit, dog and human were spiked with ^{3}H-SCH 32088 (Batch # 30329-46-10) at therapeutically relevant concentrations of 5 to 500 ng/ml plasma. After the spiked plasma samples were prepared, liquid scintillation radiometry (LOQ = 250 ng/ml) was used to determine the extent of protein binding. The means of plasma protein binding of ^{3}H-SCH 32088 in each species are shown in the following table:

SCH 232088 (ng/ml)	Rat		Mouse		Rabbit		Dog		Human (Frozen)		Human (Fresh)	
	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV
500	99.0	0.10	99.4	0.03	98.4	0.11	99.6	0.04	99.1	0.07	99.5	0.06
250	98.9	0.07	99.5	0.05	98.4	0.02	99.6	0.02	99.0	0.36	99.3	0.05
100	98.9	0.11	99.5	0.04	98.4	0.20	99.6	0.01	99.2	0.12	99.3	0.02
25	98.7	0.11	99.2	0.09	98.2	0.21	99.6	0.07	99.0	0.04	99.2	0.06
5	BQL	-	BQL	-	97.2	0.28	BQL	-	BQL	-	BQL	-

* BQL - Below quantifiable limits

Several reference compounds (chloramphenicol, lidocaine, warfarin and indomethacin) were

utilized as positive controls for system validation; the values obtained were within the ranges previously reported for each compound.

In summary of the above finding, ^{3}H-SCH 32088 was highly bound to rat (98.9%), mouse (99.4%), rabbit (98.3%), dog (99.6%) and human (99.1%) plasma proteins. There was no significant difference for the protein binding potentials at 100 to 500 ng/ml.

16. In vitro metabolism in pulmonary and hepatic tissues (P-5642, 8/92; Vol. 152)

To determine SCH 32088 metabolisms in rat or mouse pulmonary and hepatic tissues, ^{3}H-SCH 32088 (Batch #: 23650-49-7) was incubated in vitro with the supernatant of lung and liver fractions. After culture, the supernatant was analyzed using HPLC-LC/MS. Each incubation was divided into three groups. Group I represented the live protein, 30 min incubations which were analyzed to identify metabolic products. Groups II (Live protein + 0 min incubation) and III (denatured protein + 30 min incubation) were used as controls. Only the peaks in Group I (but not in other groups) were identified as the metabolites. If a metabolic product appeared in all groups, it was considered an artifact.

Results showed that no metabolism of ^{3}H-SCH 32088 was found in rat or mouse lung S9 incubations. Since SCH 32088-9, 11-epoxide was found in all mouse incubation groups, it was considered to be an artifact. (See table below.)

LUNG S9 METABOLIC PROFILE

(Mean (%CV) percent of total peak area)

Incubation	Epoxide*	SCH 32088
Rat Lung		
Ia**	–	99.02 (1.7)
Ib	–	100
IIa	–	100
IIb	–	100
IIIa	–	100
IIIb	–	100
Mouse Lung		
Ia	2.5 (12)	97.5 (0.3)
Ib	1.2 (21)	98.8 (0.3)
IIa	2.9 (75)	97.1 (2)
IIb	1.1 (25)	98.9 (0.3)
IIIa	2.8 (4)	97.2 (0.1)
IIIb	1.2 (3)	98.8 (0)

Epoxide*: SCH 32088-9,11-epoxide

**: 0.05 mM substrate concentration

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In rat liver S9 incubation, SCH 32088 was extensively metabolized. Approximately 40% of SCH 32088 (0.05mM substrate) was converted to 6-hydroxy SCH 32088. Mometasone and two unknown metabolites (UK1 and UK2) were also detected. In mouse liver, 6-hydroxylation, ester hydrolysis and metabolism to an unidentified product were observed. (See table below)

LIVER S9 METABOLIC PROFILE

(Mean (%CV) percent of total peak area)

Incubation	6-OH*	UK1	Mometasone	Epoxide	UK2	SCH 32088
Rat Liver						
Ia**	38.5 (3)	0.8 (24)	0.7 (42)	1.9 (20)	2.1 (16)	55.9 (3)
Ib	5.1 (4)	0.3 (15)	0.3 (9)	0.7 (6)	0.3 (18)	93.5 (0.3)
IIa	–	–	–	0.7 (12)	–	99.3 (0.1)
IIb	–	–	–	0.5 (4)	–	99.5 (0.02)
IIIa	–	–	–	2.2 (8)	–	97.8 (0.2)
IIIb	–	–	–	0.9 (15)	–	99.1 (0.1)
Mouse Liver						
Ia	3.2 (9)	1.0 (31)	0.8 (5)	1.9 (2)	–	93.0 (0.6)
Ib	1.4 (17)	0.3 (26)	0.5 (12)	1.5 (18)	–	96.2 (0.4)
IIa	–	–	–	2.6 (76)	–	97.4 (2)
IIb	–	–	–	1.3 (12)	–	98.7 (0.2)
IIIa	–	–	–	2.7 (23)	–	97.3 (0.6)
IIIb	–	–	–	1.2 (5)	–	98.8 (0.1)

6-OH*: 6β-Hydroxy Mometasone Furoate
UK1: unknown 1
Epoxide: SCH 32088-9,11-epoxide
UK2: unknown 2
a**: 0.05 mM substrate concentration
b: 0.50 mM substrate concentration
I: live protein, 30 min incubation
It: live protein, 0 min incubation
III: denatured protein, 30 min incubation

The above results showed that SCH 32088 in rats or mice was extensively metabolized by liver S9, but not by lung S9 system in vitro. This result can be attributed to low concentrations of metabolic enzymes in the lungs in comparison with the livers.

17. Other studies

1) The following studies were briefly summarized in the following table:

Study	Report No./ Labs.	Animals/sex/ group (Batch #)	Method	SCH32088 Daily dose	AUC (pg.hr/ml) ♂/♀
Rat: 14-day nose-only inhalation (dry powder/ lactose)		16 (25887-023)	HPLC*	♂: 4.9 µg/kg ♀: 4.5, µg/kg	824**
				♂: 17 µg/kg ♀: 16 µg/kg	4293**
Young rat: 1-mon oral study	P-6045/Schering, Lafayette, NJ	16 (93-MMF-DDPX-01)	HPLC*	♂ & ♀: 0.5 µg/kg	AUC (Day 1) 133/162; AUC (Day 30) ND/ND@
				♂ & ♀: 5 µg/kg	AUC (Day1) 125/356; AUC (Day 30) ND@/16
Young dog: 1-mon oral study	P-6008 /Schering, Lafayette	5 (92-MMF-DDPX-01)	HPLC	♂ & ♀:0.15, µg/kg	(Day 26) ND/ND@
				♂ & ♀: 0.6 µg/kg	(Day 26) 1034/1849
Dog: 3-wk oral study	P- 6045/ Schering	4 ♂ only (93-MMF-DDPX-01)	HPLC*	600 µg/kg	Plasma SCH 32088 was below the LOQ

*LOQ = 10 to 50 pg/ml; **: Only mean AUC from both males and females were provided.
@ND: Plasma SCH32088 was either not detectable or below LOQ
#. In this study, the dogs in the low-dose group were treated inhalationally at 20 µg/kg. plasma drug concentration in this group was below the quantifiable level.

2) The following studies were conducted by Schering-Plough between 1992 and 1995. Pharmacokinetic parameters in these studies were measured by using the unacceptable EIA technique.

Study	Report No./ Labs.	Method	Conclusion
Rat: 3-mon nose-only inhalation (powder)	P-5836/ & Schering	EIA	Invalid study
Rat: 3-mon nose-only inhalation (MDI)	P-5737/ & Schering	EIA	Invalid study
Rat: 3-mon nose-only inhalation (MDI)	P-5738/ & Schering	EIA	Invalid study
Beagle Dog: 14-day mouth-only inhalation (dry powder/ lactose)	P-6078/ & Schering	EIA	Invalid study
Beagle Dog: 3-month mouth-only inhalation (dry powder/ lactose)	P-5837/ & Schering	EIA	Invalid study
Mouse: 1-mon nose-only inhalation (MDI)	P-5739/ & Schering	EIA	Invalid study
Mouse: 1-mon oral study	P-5967/ Schering, Lafayette	EIA	Invalid study
Beagle Dog: 4-wk oral inhalation (powder)	P-5994 & Schering	EIA	Invalid study
Single IP dose in mice	P-5486/Schering	EIA	Invalid study
Single PO and IV dose study in mice	P-5494/Schering	EIA	Invalid study
Single dose inhalation in mice	D-26298/Schering	EIA	Invalid study
Single PO and SC dose study in dog	P-6001/Schering	EIA	Invalid study
Single dose PO and IV study in dog	P-6001/Schering	EIA	Invalid study

CARCINOGENICITY STUDIES

1. Two-year nose-only inhalation carcinogenicity study in rats (Report #: P-6005; Study #: 88050; 5/96; Vol. 119)

2. Two-year nose-only inhalation carcinogenicity study in mice (P-6006; Study #: 88051; 5/96; Vol. 119)

Laboratory: GLP: Yes

Study Date: July 30, 1992- May 15, 1996

Inhalational carcinogenicity studies in rat and mouse were previously reviewed. The dose levels selected in rats were based on the MTD obtained from 3- and 6-month inhalational toxicology studies. When mice were treated inhalationally with SCH 32088 for 3 months, mortality was present in the 0.5 and 4.0 μg/L groups, but steroid-like toxicities were only found in the 4.0 μg/L group. The designs of both rat and mouse carcinogenicity studies were previously accepted by the agency. The dose levels used for the studies are present in the following 2 tables:

Dose Levels used in Rats		
Concentration of SCH 32088	Predicted Daily Dose (μg/kg/day)	Predicted Daily Dose(μg/m² body surface #)
0 (Filtered Air)	0	0
0 (Vehicle *)	0	0
0.25 (±0.03) μg/L	9	53.1
0.5 (±0.05) μg/L	17	100.3
1.0 (±0.1) μg/L	34	200.6
2.0 (±0.2) μg/L	67	395.3

A conversion factor of 5.9 was used to convert mg/kg to mg/m².

Dose Levels used in Mice		
Concentration of SCH 32088	Predicted Daily Dose (μg/kg/day) for ♂/♀	Predicted Daily Dose (μg/m² body surface #) for ♂/♀
0 (Filtered Air)	0/0	0/0
0 (Vehicle)	0/0	0/0
0.25 (±0.03) μg/L	26/20	78/60
0.5 (±0.05) μg/L	51/40	153/120
1.0 (±0.1) μg/L	102/80	306/240
2.0 (±0.2) μg/L	204/160	612/480

A conversion factor of 3.0 was used to convert mg/kg to mg/m².

In these studies, both rats and mice were exposed to aerosolized SCH 32088. Survival rates in both species were acceptable. The death rates were not tumor-related. The causes of death were mainly attributed to the non-neoplastic changes.

Most clinical abnormalities (including clinical signs, reduced bodyweight and food consumption, hematological changes) were more severe in the high dose-treated animals, but less obvious in the 0.25 and 0.5 μg/L groups. Dose-related necropsy findings were mainly present in the skin and eyes. These abnormalities were possibly related to direct drug exposure. Pancreatic islet cell and mammary gland hyperplasia, and enlarged pituitary glands were dose-dependent in rats. However, these findings were not observed in mice, suggesting that mice may be less sensitive to SCH 32088.

Due to falsification of EIA results and sample preparation, plasma concentrations of SCH 32088 may not be reliable. However, the data obtained from the exposure chamber filters showed that the concentrations of SCH 32088 on the filters increased with dose. In contrast, SCH 32088 was not present on the filters used for control groups.

Dose-related tumors were noted in the mammary gland and pancreas in rats, and in the urinary bladder and lymphoid tissues in mice. The incidence of mammary gland adenoma in rats and malignant lymphoma in mice were seen within the Sponsor's and Charles River's historical control ranges. Based on the available literatures, benign mesenchymal tumor of mouse urinary bladders is also referred to as a leiomyosarcoma which is a unique tumor type for CD-1 or related mouse strains (Chandra M and Firth CH. Toxicol Pathol. 19: 164-76, 1991). This tumor type is not found in B6C3F1 mice, rats, domestic animals or humans. This neoplastic lesion was also reviewed by Dr. Leopold Koss, MD, Chairman of Dept. of Pathology, the University Hospital for the Albert Einstein College of Medicine. He stated that the morphology of this tumor type was not seen to any human urinary bladder. Therefore, urinary bladder tumor seen in mice was not considered to be relevant to human cancer risk.

The occurrence of pancreatic mixed islet cell tumors was not dose-related. When the incidence of this tumor type was combined with other pancreatic islet cell tumors, the combined incidences were present within the historical control ranges.

In a previous clinical study (C95-050-01), both Cmax and AUC were not quantifiable following intranasal administration at 400 μg/kg/day. In this NDA submission, the proposed clinical dose of SCH 32088 nasal suspension is 200 μg/day, which is equivalent to 4 μg/kg/day on the basis of body weight or 125 $\mu g/m^2$/day on the basis of body surface areas. Since the human AUC values are not available, the exposure rates of 2 carcinogenicity studies are compared with the proposed clinical dose based on the body weight and body surface area. (See table below.)

Species/Duration	Study #	Predicted dose		Safety Margin	
		µg/kg/day	µg/m ^{2}	µg/kg/day	µg/m ^{2}
Rats/2-year	P-6005	9-67	54 -402	2.3-16.8	0.4 -3.2
Mice/19-month	P-6006	20 -160	60-480	5 -40	0.5 -4

As shown in the above table, the dose levels used in rat and mouse carcinogenicity studies were up to 3- and 4-times the maximum recommended daily intranasal dose in adults (125 $\mu g/m^2$/day) on a $\mu g/m^2$ basis, respectively.

In summary, the appearance of most dose-related tumor types were found within the available historical control ranges. However, the historical control values used in this evaluation were not generated by the testing laboratory. Variability of historical ranges among the different testing laboratories should be considered. The highest incidences of most tumor types in the studies were higher than the average values of the historical controls. However, based on the body weight and body surface areas, exposure rates in both carcinogenicity studies were much higher than the proposed human clinical dose. Therefore, SCH 32088 presents a very limited cancer risk to humans.

In conclusion, based on the available data and results, SCH 32088 has none or a very limited cancer risk to human. (See attachments A and B.)

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SUMMARY AND EVALUATION

Summary and Evaluation of Pharmacology Studies

NASONEXTH (SCH 32088 or Mometasone furoate) is a potent corticosteroid. Inhalation administration of SCH 32088 can inhibit allergen-induced pulmonary eosinophil infiltration and Th cell accumulation in allergic mouse and guinea pig models. In comparison with some corticosteroid, SCH 32088 has more potency in the inhibition of cytokine releases and leukotriene productions. Anti-inflammatory activities of SCH 32088 in animals were also observed in the treatment of RPAR, and acute and chronic dermal inflammation.

Side-effects of SCH 32088 were also evaluated by the sponsor. When SCH 32088 was compared with betamethasone valerate, SCH 32088 had less potency for suppressing the HPA axis, but had greater potency for the induction of thymolysis and skin atrophy. SCH 32088 also had significant effects on female sexual maturation, and had some antiuterotrophic activity. However, SCH 32088 had no androgenic, antiandrogenic and estrogenic activity. SCH 32088 affects neither biliary secretion nor gastric acid and pepsin secretion. SCH 32088 showed mineralocorticoid activity in rats. Although SCH 32088 had no effects on the central nervous, cardiovascular, respiratory systems in the experimental animals, it did increase urine volume, creatinine release and decrease ICG (an indicator of hepatic function). Oral administration of SCH 32088 did not significantly reduce the concentration of circulating lymphocytes. Following subcutaneous injection, apparent hepatic glycogen accumulation was not seen in rats dosed up to 60 mg/kg, but was observed in mice treated at 200 mg/kg.

Finally, when all effects of SCH 32088 in different pharmacology studies were compared, the potencies of topically used SCH 32088 on the skin are much higher than systemically dosed SCH 32088.

Summary and Evaluation of Acute Toxicity Studies

Acute inhalation toxicity studies were evaluated in mice (3.16 mg/L), rats (3.31 and 5 mg/L) and dogs (♂: 139.5 μg/L; ♀: 121.5 μg/L). After treatment, bodyweight reduction was observed in rodents, and food consumption was slightly decreased in dogs. After sacrifice, small spleens were found in rats; discoloration of lung, liver, kidney and skin were seen in both rodent species. Death was only seen in the mice (♂: 1/5; ♀: 1/5) exposed for 4 hours to SCH 32088 at a concentration of 3.16 mg/L.

Acute oral and subcutaneous toxicity studies were conduced in rats and mice administered at 20, 200 and 2000 mg/kg. Following a single oral dose treatment at 2000 mg/kg, SCH 32088 was well tolerated by mice and rats; a target organ of toxicity was not identified. When the animals were treated subcutaneously, lethal doses for the rats and mice were 2000 and 200 mg/kg, respectively. Target organs of toxicities were the injection site, abdominal viscera, gastrointestinal tract and kidney.

Based on the results of the acute toxicity studies, subcutaneous administration of SCH 32088 produced much higher systemic toxicity when compared with orally administered SCH 32088. This finding may be attributed to poor oral bioavailability of SCH 32088.

Summary and Evaluation of Intranasal Toxicity Studies

Summary of Intranasal Toxicity Studies:

The intranasal irritation potential was determined by using SCH 32088 nasal suspension at the concentration of 0.05% or 1%. Intranasal administration either at 400 μg/kg/day for 3 days or at 180 μg/kg/day for 1-month did not produce nasal irritation in dogs.

Intranasal toxicity studies were conducted in rats and dogs treated with SCH 32088 nasal suspension for 6 months or 1 year. The objective of these studies was to investigate the potential systemic and nasal toxicities following intranasal administration of SCH 32088.

In a 6-month intranasal toxicity study, Sprague-Dawley rats were dosed intranasally with SCH 32088 at 0.017, 0.05, 0.15 or 0.6 mg/kg/day. The formulation of SCH 32088 used in this study was the same as the proposed final clinical formulation. Alopecia was found mainly in the 0.6 mg/kg rats, but was also seen in the 0.05 and 0.15 mg/kg groups. Nasal irritation was not reported in any group. Constant bodyweight reductions were only present in the 0.6 mg/kg group. Plasma cholesterol levels were statistically increased in the 0.15 (24-53%) and 0.6 mg/kg (16-31%) males. Skin hypotrichosis was only seen in the 0.6 mg/kg group. No pathological alteration was found in other organs. Therefore, the NOAEL dose was established as 0.05 mg/kg/day for the rats. SCH 32088 at 0.15 mg/kg/day was considered as a tolerated dose with mild glucocorticoid effects. At 30 days postdosing, AUC levels of the 0.05 and 0.15 mg/kg/day groups were 322 and 772 pg/hr/ml, respectively. No target organ of systemic toxicity was identified in this study.

Beagle dogs were also treated for 6 months by intranasal administration of SCH 32088 at

0.0075, 0.015, 0.045 and 0.15 mg/kg/day. The formulation of SCH 32088 used in this study was the same as the proposed final clinical formulation. No dose-related clinical sign or nasal irritation was reported in any group. Decreased eosinophil count and increased plasma cholesterol were only found in the 0.15 mg/kg group. Plasma cortisol levels in the 0.15 mg/day group were generally lower than the vehicle-treated controls. After animals were treated for 26 weeks, serum cortisol concentration in the 0.045 mg/kg group was also decreased. In comparison with the control values, ACTH response was normal in the 0.045 mg/day group, but was lower in the 0.15 mg/kg group. No dose-related pathological changes were observed in the nasal cavity or other organs. In conclusion, target organs of systemic toxicity were not identified in this study. The NOEL dose was 0.015 mg/kg/day in dogs. The intranasal dose of 0.045 mg/kg/day can be considered a tolerated dose with mild glucocorticoid effects. For the animals treated with SCH 32088 at 0.015 and 0.045 mg/kg/day, plasma drug concentrations were below the quantifiable levels.

In a 1-year intranasal toxicity study, dogs received intranasal doses of 0.1, 0.2, 0.6 or 2.0 mg/day. (Doses for the male dogs: 0.0075, 0.015, 0.045 and 0.15 mg/kg/day, respectively; doses for the female dogs: 0.0089, 0.018, 0.054 and 0.179 mg/kg/day, respectively.) The formulation of SCH 32088 used in this study was the same as the proposed final clinical formulation. Alopecia was found in 6 high-dose animals (2 mg/day: ♂ = 3/5, ♀ = 3/5), but also seen in the 0.2 mg/day group (♂ = 1/5, ♀ = 1/5). No other dose-related clinical signs or nasal irritations were seen. Significant reductions (>20%) in the leukocyte and lymphocyte counts were noted only in the 2 mg/day group. Two 0.06 mg/day males had undetectable pre-ACTH values and normal post-ACTH cortisol responses. Adrenal cortex atrophy was found in one of them. The association between the reduction of ACTH output and morphological alterations of the adrenal cortex indicated that adrenocortical insufficiency could be induced in dogs treated with SCH 32088 at 0.6 mg/day. Both basal and post-ACTH cortisol responses were significantly decreased in the 2 mg/day dogs. Small adrenal glands and low adrenal weights were observed only in the 2 mg/day males and females. Pathological changes in the thymus, skin and adrenal glands were mainly found in the 2 mg/day dogs, but also in some 0.6 mg/day dogs. Absences of lymphoid aggregates were mainly seen in the 0.6 and 2 mg/kg dogs. This morphological change was considered a corticosteroid-related effect. Based on the results of this study, the NOAEL dose was 0.1 mg/day. Intranasal administration at 0.2 mg/day can be considered a tolerated dose with mild glucocorticoid effects. AUC levels of 0.1 and 0.2 mg/kg/day groups were not quantifiable. Although adrenal cortex atrophy and undetectable pre-ACTH values were found in one 0.6 mg/day male, average cortisol levels were comparable between the 0.6 mg/day and control groups. Therefore, if close clinical monitoring is available, dose levels between 0.2 and 0.6 mg/day can be also acceptable.

In summary, following a 12-month intranasal administration, target organ toxicities in dogs were in the thymus, skin and adrenal glands. All intranasal irritation and intranasal toxicity studies are summarized in the following table.

Summary of Relevant Intranasal Studies			
Study Name	**Report No. (#/sex/group)**	**Daily dose (μg/kg)**	**Observation**
Dog: 1-week Nasal Irritation study	P-5995 (3)	♂: 47, 93, 187 ♀: 61, 122, 244	NOEL: ♂: 187; ♀ 244 μg/kg Target organ: not determined AUC data: None
Dog: 1-month Nasal Irritation study	P-5336 (3)	♂: 180, 360 ♀: 220, 440	NOEL: ♂: 180; ♀: 220 μg/kg Target organ: not determined AUC data: None
Dog: 1-month Nasal Irritation study	P-5474 (3)	♂: 210, 430 ♀: 250, 510	NOEL: ♂: 210; ♀: 250 μg/kg Target organ: not determined AUC data: None
Rat: 6-month intranasal toxicity study	D-6117 (25)	17, 50, 150, 600	NOAEL: 50 μg/kg; Tolerated dose: 150 μg/kg Target organ: not determined AUC data (Day 30): 322 pg.hr/ml (50 μg/kg group) 772 pg.hr/ml (150 μg/kg group)
Dog: 6-month intranasal toxicity study	D-6118 (5)	7.5, 15, 45, 150	NOEL: 15 μg/kg; Tolerated dose: 45 μg/kg Target organ: not determined AUC data (Day 180): unquantifiable (15 and 45 μg/kg groups)
Dog: 1-year intranasal toxicity study	D-6116 (5)	♂: 7.5, 15, 45, 150 ♀: 8.9, 18, 54, 179	NOAEL: 7.5/8.9 μg/kg; Tolerated dose: 15/18 μg/kg Target organ: not determined AUC data (Day 363): unquantifiable (7.5/8.9 and 15/18 μg/kg groups)

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Evaluation of Intranasal Toxicity Studies:

In this NDA submission, the proposed human daily dose of SCH 32088 is 200 μg/day. When the NOEL or NOAEL dose levels obtained from dog intranasal irritation studies were compared with the proposed human dose by using nasal surface area, the intranasal doses in dogs were approximately 7- to 15-times higher than the proposed human dose. (See table below.) Therefore, results from the dog intranasal irritation studies provide a safety margin for the proposed human intranasal dose.

Comparison of intranasal doses between dog and human

Animal (Duration)	NOEL* or NOAEL@ dose in dog (μg/kg) ♂/♀	Daily dose (μg/animal) ♂/♀	Daily dose(μg/cm² of nasal surface area)* ♂/♀	Human dose (μg/cm² of nasal surface area)**	Margin of Safety
Dog (3-day)	400*/ 520*	4280/4264	19.4/19.3	1.25	15
Dog (7-day)	187*/ 244*	2001/2001	9.05/9.05	1.25	7
Dog (1-mon)	180*/ 220*	1998/2002	9.04/9.05	1.25	7
Dog (1-mon)	210@/ 250@	1974/175	8.93/8.93	1.25	7

* NOEL dose level
@ NOAEL dose level
* Nasal surface areas (cm^2): Man = 160; Dog = 221; Rat =14 (Acta Pharm. Nord. 2, 1990)
** Human dose is calculated based on the proposed clinical dose (200 μg/person/day)

In pharmacokinetic studies from intranasal toxicity studies, AUC in the dog was below the quantifiable level (BQL) following treatment up to 45 μg/kg/day. AUC levels were detectable in the rats treated at 50 μg/kg/day (NOAEL dose) or 150 μg/kg/day (a tolerated dose with mild glucocorticoid effects). In a previous clinical study (C95-050-01), both Cmax and AUC were not quantifiable in humans following the intranasal administration at 400 μg/kg/day. In the NDA submission, the proposed clinical dose of SCH 32088 nasal suspension is 200 μg/day or 4 μg/kg/day.

In the 6-month and 1-year intranasal toxicity studies, the formulation of SCH 32088 used in animals was the same as the proposed human clinical formulation. When dose levels used in animals were compared with the proposed human dose, the NOEL or NOAEL doses obtained from animals were approximately 2- to 12-times greater based on bodyweight and 1.2- to 2.4-times greater based on body surface area; the tolerated doses obtained from animals were approximately 4- to 38-times greater based on bodyweight and 2.4- to 7-times greater based on body surface area.

Species (Duration)	Preclinical data				Margin of Safety	
	Dose levels	Daily dose (µg/kg bodyweight)	Daily Dose (µg/m² body surface area)*	AUC(tf) (pg/hr/ml)	µg/kg bodyweight**	µg/m² body surface area**
Rat (6 mon)	NOAEL	50	300	137 - 322	12	2.4
	Tolerated dose	150	900	487 - 772	38	7
Dog (6 mon)	NOEL	15	300	BQL	4	2.4
	Tolerated dose	45	900	BQL	11	7
Dog (12 mon)	NOAEL	7.5	150	BQL	2	1.2
	Tolerated dose	15	300	BQL	4	2.4

* Body surface area: Rat = 0.025 m² ; Dog= 0.4 m²; Human = 1.6 m²

** 50 kg bodyweight/person was used for the calculation; Daily dose: 4 µg/kg bodyweight or 125 µg/m² body surface areas

In conclusion, tolerated doses from rat and dog intranasal studies were greater than the proposed clinical dose of SCH 32088. Therefore, the preclinical data from intranasal studies support the proposed intranasal dose in humans.

Summary and Evaluation of Inhalation Toxicology Studies

Summary of Inhalation Toxicology Studies:

In a 26-week oral inhalation study (P-5591), dogs were treated with SCH 32088 at 21 (low-dose), 37 (mid-dose) and 74 (high-dose) µg/kg/day. After treatment, dose-related death and clinical signs were not noted. Statistically decreased bodyweight and food consumption were observed in the high-dose group. Total leukocyte counts were comparable among the groups. However, leukocyte differentiation was not performed in this study. Therefore, the suppression of lymphocyte or other leukocytes could not be evaluated. Blood cortisol levels in the test groups were generally lower, but was only statistically reduced in the high-dose males. This finding was associated with the decreased adrenal weight in the high-dose males (48%↓). Morphologically, adrenal cortex atrophy was observed in 2/4 mid-dose males, 3/4 high-dose males, and 4/4 high-dose females. This study suggested that the inhalation dose of 21 µg/kg/day in dogs is the tolerated dose with mild glucocorticoid effects. The target organ of toxicity was adrenal glands, based on pathological observation.

In another 26-week inhalation study, rats were treated inhalationally at 50, 93 or 214 µg/kg/day for the males, and at 55, 102 or 234 µg/kg/day for the females. The animals had dose-related alopecia (8%, 75%, 83% and 97% of rats in the control to high-dose group) and scabbing of the muzzle, neck and other skin regions (5%, 50%, 61% and 57% of the rats in the control to high-dose group). Between Weeks 12 to 26, 16 animals were sacrificed following observation of

progressive respiratory abnormalities (wheezing, gasping and labored breathing), and the frequency increased with dose level (1, 4 and 11 rats in the low-, mid- and high-dose group, respectively). Decreased bodyweight and food consumption were also induced by the treatment. Hematological examination revealed dose-related increases in neutrophils and decreases in lymphocyte and total leukocyte counts. Organ weight reductions were observed in the spleen, thymus, uterus and adrenal glands. Atrophy was found in the adrenal, spleen, thymus and lymph nodes at all dose levels. A dose-related secondary lesion in several animals was a pulmonary fungal infection. This infection may be attributed to SCH 32088-induced immunosuppression. Subtle perturbations of the estrous cycle and enhanced mammary gland lobuloalveolar development were reported in all dosed groups. Based on the above results, a NOEL or a tolerated dose with mild glucocorticoid effects was not established for low-dose animals (50 µg/kg/day for the males or 55 µg/kg/day for the females). Major target organs of toxicity were liver, spleen, lungs, thymus, heart, kidney, uterus and thyroid, adrenal and mammary glands.

In a 3-month inhalation dog study, animals were exposed to SCH 32088 aerosols at 44, 79 or 158 µg/kg/day. After the treatment, there were no dose-related deaths, clinical signs, body weight decreases and food consumption changes. Significant reductions in leukocyte counts were found in the mid- and high dose females. Serum cortisol levels in all test groups were generally lower than the control group, particularly in the mid- and high-dose groups. Liver weights were increased in a dose-related manner. The histopathology evaluation showed that liver glycogen accumulation was found in all high-dose dogs and about 50% of the mid-dose and low-dose dogs. Dose related changes in the zona glomerulosa of adrenal glands was also observed. In this study, target organs of systemic toxicity were the liver, thymus and adrenal gland. The NOEL was not established.

In a 3-month inhalation rat study (conducted by), rats received inhalation doses at 48, 102 or 273 µg/kg/day. Treatment-related alopecia and changes in body weight and food consumption were seen in all test groups in a dose dependent manner. Dose-related significant decreases in leukocyte and lymphocyte counts were present in the mid- and high-dose groups. Increases in plasma cholesterol, glucose and reduction in cortisol were observed in the mid-dose and high dose group. Reduced spleen, adrenal, thymus weights in the mid- and high-dose groups were associated with morphological alterations. Therefore, the inhalation dose at 48 µg/kg was considered as the NOAEL in rats. Target organs of systemic toxicity were defined in thymus, spleen and adrenal glands.

Another 3-month inhalation rat study was performed by . Rats in this study were treated at the concentrations of 0.25, 0.5, 1, 2 or 4 µg/L. The target doses were 8, 17, 18, 34, 67 or 134 µg/kg/day for the males, and were 8, 18, 37, 73 or 146 µg/kg/day for the females. Dose-related clinical signs were not found in any group. Body weights were reduced statistically in the 1, 2 and 4 µg/L groups. Decreased liver, spleen and lung weights were mainly present in the two high-dose groups. Microscopic examination demonstrated that treatment-related tracheal globule cell decrease occurred in 100% of the test animals, but not in any of the control rats. Uterine granulocytic leukocytes were also decreased in

a dose-related manner. Based on the results of this study, a NOEL dose was not established.

In a 2-week inhalation study (D-22607), dogs were exposed to SCH 32088 aerosols at 80 (low-dose), 240 (mid-dose) and 800 (high-dose) µg/kg/day. The results showed that SCH 32088 did not affect mortality, clinical signs, body weight change, food consumption and parameters of clinical pathology. Plasma cortisol levels were not measured in this study. Histopathological changes in the liver, adrenal cortex, mammary gland, lymph nodes and thymus were observed in the mid- and high-dose group. Since no other obvious abnormalities were seen in the low-dose group, except adrenal atrophy (♂: 1/3; ♀: 1/3), the inhalation dose at 80 µg/kg/day in dogs was considered a tolerated dose with mild glucocorticoid effects. Target organs of toxicity were the liver, adrenal, lymph nodes, mammary glands and thymus.

In another 2-week inhalation study (D-22680), rats were treated at 80, 240 and 800 µg/kg/day, respectively. Achieved daily doses were 0, 68, 239 and 636 µg/kg/day for male rats and 0, 76, 268 and 710 µg/kg/day for female rats. Treatment-related changes were mainly found in the mid- and high-dose groups, including reduced body weight and food consumption, decreased leukocyte and lymphocyte counts, decreased GPT, GOT and alkaline phosphatase levels. Spleen, adrenal and thymus weights were reduced in the mid- and high-dose groups. Obvious atrophy was seen in the adrenal and thymus of the mid- and high-dose groups, but also seen in one low-dose female. Since adrenal atrophy was only seen in one low-dose animal (1/20), 68 µg/kg for the male rats and 76 µg/kg for the female rats can be considered a tolerated dose with mild glucocorticoid effects. Target organs of systemic toxicity were the thymus, spleen and adrenal glands.

Pharmacokinetic parameters were not measured in the above inhalation studies. In an inhalation pharmacokinetic study, when beagle dogs were treated by 28-day oral inhalation (P-6096), plasma concentrations of SCH 32088 were under the quantifiable levels in the 20 µg/kg group, and the AUC level in the 80 µg/kg group was 228 pg/hr/ml on Day 28. In a 1-month pharmacokinetic study, inhalation doses were up to 24 µg/kg/day for male rats and up to 33 µg/kg/day for female rats. The AUC value in the high dose rats (♂: 24 µg/kg or ♀: 33 µg/kg) was 15898 pg.hr/ml. However, the highest inhalation doses in this rat PK study were lower than tolerated doses given to the rats in the inhalation studies. All inhalation toxicity studies are summarized in the following table:

Summary of relevant Inhalation Toxicity Studies			
Study Name	**Report No.(#/sex/group)**	**Daily dose (μg/kg)**	**Observation**
Dog: 26-week inhalation study	P-5591 (4)	21, 37, 74	NOEL dose: not established Tolerated dose: 21 μg/kg Target organ: adrenal AUC data: None
Rat: 26-week inhalation study	P-5598 (20)	♂: 50, 93, 214 ♀: 55, 102, 234	NOEL dose: not established Tolerated dose: ♂: 50 μg/kg; ♀: 55 μg/kg Target organ: liver, spleen, lungs, thymus, heart, kidney, uterus, thyroid, adrenal, mammary gland AUC data: None
Dog: 3-month inhalation study	D-22796 (4)	44, 79, 158	NOEL or tolerated dose: not established Target organ: liver, thymus, adrenal AUC data: None
Rat: 3-month inhalation study	D-22797 (15)	48, 102, 273	NOEL dose: not established NOAEL dose: 48 μg/kg. Target organ: adrenal, spleen, thymus AUC data: None
Rat: 3-month study	P-5736 (10)	♂: 8, 17, 34, 67, 134 ♀: 8, 18, 37, 73, 146	NOEL or tolerated dose: not established Target organ: trachea, spleen, lungs, uterus AUC data: None
Dog: 2-week inhalation study	D-22607 (3)	80, 240, 800	NOEL dose: not established Tolerated dose: 80 μg/kg Target organ: liver, lymph nodes, thymus, adrenal AUC data: None
Rat: 2-week inhalation study	D-22680 (10)	♂: 68, 239, 636 ♀: 76, 268, 710	NOEL dose: not established Tolerated dose: ♂: 68 μg/kg; ♀:76 μg/kg Target organ: liver, spleen, thymus, adrenal AUC data: None
Rat: 1-month inhalation PK study	P-6137 (80 or 84)	♂: 3.2, 6.7, 14, 24μg/kg ♀: 3.7, 8.7, 14, 33 μg/kg	NOEL or Tolerated dose: not determined Target organ: not determined AUC data (Day 30): 2164 pg.hr/ml (3.2/3.7 μg/kg group); 15898 pg.hr/ml (24/33 μg/kg group)
Dog: 1-month inhalation PK study	P-6096 (4)	20, 80, 160μg/kg	NOEL or Tolerated dose: not determined Target organ: not determined AUC data (Day 28): Not quantifiable (20 μg/kg group); 445 pg.hr/ml (160 μg/kg group)

Evaluation of Inhalation toxicology studies:

In the 6-month and 3-month inhalation toxicity studies, systemic toxicities in dogs were produced following treatment of 34 μg/kg. The NOEL or NOAEL dose level was not established in these studies. A tolerated inhalation dose with mild glucocorticoid effects was 21 μg/kg in dogs. However, the dose level at 80 μg/kg was tolerated by dogs in a 2-week inhalation study. The studies indicated that systemic toxic effects of SCH 32088 increased with the dose and the duration of treatment. Target organs of toxicity in dogs were mainly the liver, thymus and adrenal glands. For this NDA submission, the proposed human daily dose is 200 μg/day, which is equal to a daily dose of 4 μg/kg bodyweight or 125 $\mu g/m^2$ body surface area. Based on the available pharmacokinetic data, the plasma drug concentration was below the quantifiable level (50 pg/ml) when dogs were treated inhalationally at 20 μg/kg/day for 28 days (P-6096). An undetectable plasma drug level was also observed in humans treated with an intranasal dose of SCH 32088 of 400 μg/day (C95-050-01). To further evaluate the data from the 6-month dog inhalation study, a tolerated inhalation dose is compared with the proposed human intranasal dose on the basis of bodyweight or body surface area. As demonstrated in the following table, a tolerated inhalation dose with mild glucocorticoid effects was 3.4- to 5-time higher in dogs than the proposed human intranasal dose.

Tolerated dose in dogs		Margin of safety *	
μg/kg bodyweight**	$\mu g/m^2$ body surface area***	μg/kg	$\mu g/m^2$ body surface area
21	420	5	3.4

* 50 kg bodyweight person was used for the calculation; Daily dose: 4 μg/kg body weight or 125 $\mu g/m^2$ body surface areas
**. Based on mean bodyweight = 10 kg
*** Body surface area: Rat = 0.025 m^2 ; Dog= 0.4 m^2; Human = 1.6 m^2

In a 2-week rat study, the inhalation dose at 68 μg/kg/day was established as a tolerated dose with mild glucocorticoid effects. A 6-month inhalation study showed that systemic toxicities can be induced in rats at 50 - 55 μg/kg/day. Major target organs of toxicity in the 6-month study were the liver, spleen, lungs, thymus, heart, kidney, uterus and thyroid, adrenal and mammary glands. Two 3-month inhalation toxicity studies were conduced in rats by 2 different laboratories. In one 3-month inhalation toxicity study (D-22797), the NOAEL dose in rats was defined as 48 μg/kg/day and toxic effects were noticed at 102 μg/kg/day. In another study (P-5736), decreased tracheal globule cells were found in all test animals, although systemic toxicity was not obvious in the rats at 34 μg/kg. Since decreased tracheal globule cells were not confirmed in adult rats by other short- or long-term toxicity studies, the importance of this observation is not clear.

The NOAEL dose (48 μg/kg) from one 3-month inhalation study (approximately 288 $\mu g/m^2$ on a body surface basis) is compared to the proposed clinical dose. As shown in the table below, the

NOAEL dose obtained from the rats was 2.3- to 12-times higher than the proposed human intranasal dose.

NOAEL dose in rat		Margin of safety *	
µg/kg bodyweight**	µg/m² body surface area***	µg/kg	µg/m² body surface area
48	288	12	2.3

* 50 kg bodyweight person was used for the calculation; Daily dose: 4 µg/kg body weight or 125 µg/m² body surface areas
**. Based on mean bodyweight = 0.2 kg
*** Body surface area: Rat = 0.0313 m²; Dog= 0.4 m²; Human = 1.6 m²

As demonstrated by the above inhalation studies, tolerated inhalation doses with mild glucocorticoid effects were much higher than the proposed human intranasal dose. Therefore, the data from preclinical inhalation studies is sufficient to support the proposed clinical intranasal dose.

Summary and Evaluation of Pediatric Studies

In a 1-month inhalation study, 2-week-old pediatric rats were exposed to SCH 32088 powder at the concentrations of 0.01, 0.05, 0.25 or 1 µg/L. No treatment-related deaths or clinical signs were observed in any group. Statistically significant decreased bodyweight and hematological changes were present in the 1 µg/L group. In comparison with the controls, serum corticosterone levels were statistically higher in the treated males, but not the treated females. Major pathological alterations were decreased tracheal globule cells, nasal goblet cell hyperplasia and increased bone marrow adipose cells. Alveolar histiocytic infiltration and enhanced mammary gland development were observed in all dosed male and female groups, respectively. Based on the results of this study, a NOEL was not established in the females. Although pulmonary alveolar histiocytic infiltration was found in 1/24 treated males, a tolerated dose with mild glucocorticoid effects was 0.2 µg/kg/day for the male rats. Major target organs of toxicity were trachea, nasal cavity, bone marrow, mammary gland and lungs on the basis of pathological findings.

In another inhalation study, 6-week-old dogs were treated for 7 weeks at the concentration of 0.04, 0.2 and 1 µg/L. There were no drug-related death and clinical signs after the treatment. Significant reduction in bodyweight gains was present in the high-dose group during the treatment, but was fully recovered after a 9-week recovery period. Elevated serum potassium, GGT, ALT and ALP were observed in the high-dose animals. The high-dose dogs had a low pre-ACTH value and a normal post-ACTH value, suggesting the normal response of adrenal cortices to ACTH. The PK study showed that plasma drug levels was not quantifiable in the low-dose group, and was detectable in the mid-dose group only in the Week 5. For the high-dose group, Cmax and AUC levels in Week 5 were higher than in Week 1, which suggests

drug accumulation. Organ weight changes in the lungs, epididymis, thyroid, spleen and thymus were observed in all drug-treated groups, particularly in the high-dose group. Decreased adrenal weight was only found in the high-dose group. After a 9-week recovery period, epididymis weight remained decreased, however, the weights of other organs were similar between the high-dose and control groups. Morphologically, pulmonary hemorrhage, alveolar edema as well as acute cellular infiltration were present as primary pathological changes in all groups, including the control group. These acute structural changes may be attributed to the mechanical damage produced by an improperly used exposure mask. There were no dose-related pathological findings in other organs. Based on the results of this study, oral inhalation at 0.2 μg/L can be accepted as a tolerable dose for pediatric dogs. The inhalation dose at the concentration of 0.2 μg/L was equal to 7.1 μg/kg/day for male dogs or 7.3 μg/kg/day for the female dogs.

Based on the above inhalation toxicology studies in pediatric animals, a tolerated dose with mild glucocorticoid effects was not established in rats, but was defined as 7.1-7.3 μg/kg/day in dogs. Currently, SCH 32088 is not indicated for a pediatric population.

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Summary and Evaluation of Reproductive Toxicology Studies

Segment II studies were conducted in rats, rabbits and mice by oral, topical and subcutaneous routes of administration.

In a pilot oral Segment II study, a tolerated oral dose with mild glucocorticoid effects was greater than 600 μg/kg/day in pregnant rats. However, a subcutaneous Segment II rat study demonstrated that reduced fetal and maternal body weights and delayed ossification were seen at 15 and 30 μg/kg. In this rat subcutaneous study, the NOEL dose was at 2.5 μg/kg/day for both dams and fetuses.

In an oral Segment II study, the incidences of malformations in the rabbits were 2.3%, 4.8% and 6.9% in the control, 140 μg/kg/day and 700 μg/kg/day groups, respectively. Conjoined twin, extra sternebra and fused ribs were observed in the 140 μg/kg/day rabbits. An oral dose at 700 μg/kg/day increased the incidences of resorption and malformations, including cleft palate and/or head malformations (consisting of hydrocephaly or domed head). A dose level at 2800 μg/kg/day caused pregnancy failure in most rabbits. The malformation rate in the 140 μg/kg/day group was considered to be comparable to the control value (2.3%). Since the daily oral dose at 140 μg/kg did not produce significant toxic effects to either the dams or their offsprings, it was accepted as a NOAEL.

In a subcutaneous Segment II mouse study, SCH 32088 at 60 or 180 μg/kg/day caused body weight loss and an increased incidence of cleft palate. The NOEL in mice was 20 μg/kg/day for both the dams and the offsprings

When SCH 32088 at 300, 600 and 1200 μg/kg was used dermally (topical) in a rat Segment II study, fetal growth suppression and delayed ossification occurred in all treated groups. However, umbilical hernia and cleft palate were observed in the 600 and 1200 μg/kg rats.

After rabbits in a dermal Segment II study were treated topically at 150 and 300 μg/kg, maternal and fetal toxicities were induced in rabbits. Observed malformations in the animals were gallbladder agenesis, umbilical hernia and flexed front paws.

Segment I and III studies were conducted in rats treated with a subcutaneous dose at 2.5, 7.5 or 15 μg/kg. Impairment of fertility in rat was not produced by subcutaneous dose up to 15 μg/kg/day. Prolonged gestation, and prolonged and difficult labor were produced by the subcutaneous dose at 15 μg/kg. The treatment at 15 μg/kg also caused significant reductions in the offspring delivered, litter size and survival rats, as well as increase resorption. In both Segment I and III studies, a subcutaneous dose at 2.5 μg/kg was the NOEL, and at 7.5 μg/kg was considered as a tolerated dose with mild glucocorticoid effects.

All reproductive toxicology studies and related PK studies are summarized in the following table:

Summary of Reproductive Toxicity Studies			
Study Name	**Report**	**Daily dose (μg/kg)**	**Observation**
Rabbit: oral segment II study	P-5991	140, 700, 2800	NOAEL: Not established Tolerated dose: 140 μg/kg AUC data: 2282 pg.hr/ml in the 2800 μg/kg group, but not quantifiable in the 140 and 700 μg/kg groups
Rat: subcutaneous segment II study	P-5543	2.5, 15, 30	NOEL: 2.5 μg/kg AUC data: None
Mouse: subcutaneous segment II study	P-5478	20, 60, 180	NOEL: 20 μg/kg AUC data: None
Rat: dermal segment II study	D-5054	300, 600, 1200	NOAEL: Not established AUC data: None
Rabbit: dermal segment II study	D-5066	150, 300	NOAEL: Not established AUC data: None
Rat: subcutaneous segment I study	D-5174	2.5, 7.5, 15	NOAEL: 2.5 μg/kg Tolerated dose: 7.5 μg/kg AUC data: None
Rat: subcutaneous segment III study	D-5164	2.5, 7.5, 15	NOAEL: 2.5 μg/kg Tolerated dose: 7.5 μg/kg AUC data: None
Pregnant female rat: single dose PK study	P-6084	Subcutaneous: 30 Oral: 600	NOAEL or Tolerated dose: Not determined AUC data: 8250 pg.hr/ml after subcutaneous treatment; 17595 pg.hr/ml after oral treatment
Female rat: 10-day PK study	P-6105	Subcutaneous: 2.5, 15, 30 Oral: 2.5, 15, 30	NOAEL or Tolerated dose: Not determined AUC data: On Day 1 1. PO group: Not quantifiable in the 2.5 μg/kg group; 202 pg.hr/ml in the 15 μg/kg group 2. SC group: 1248 pg.hr/ml in the 2.5 μg/kg group; 7282 pg.hr/ml in the 15 μg/kg group On Day 10: 1. PO group: Not quantifiable in the 2.5 μg/kg group; 328 pg.hr/ml in the 15 μg/kg group 2. SC group: 1457 pg.hr/ml in the 2.5 μg/kg group; 9090 pg.hr/ml in the 15 μg/kg group

In this NDA submission, pharmacokinetic parameters in pregnant rats (single dose), pregnant rabbits (14 daily doses) and female rats (10 daily doses) were determined after the exposure to

SCH 32088. In a single dose study, oral bioavailability in pregnant rats was only 11%. AUC levels were not detectable in pregnant rabbits dosed orally for 14 days at 140 μg/kg/day (NOAEL). In subcutaneous Segment I, II and III studies, NOEL doses were 2.5 μg/kg in rats. However, pharmacokinetic parameters in rats were not examined in these subcutaneous reproductive toxicology studies. AUC levels in rats were determined by another pharmacokinetic study. After female rats were treated subcutaneously at 2.5 μg/kg, AUC values were greater than the AUC levels in the rats treated intranasally at 50 (NOEL; Study #: P-6117) or 150 μg/kg (a tolerated dose with mild glucocorticoid effects; Study #: P-6117). AUC and NOEL (or a tolerated dose with mild glucocorticoid effects) obtained from different studies are compared in the following table:

	Rat (intranasal toxicity study; P-6117)		Rat (Subcutaneous PK study & Seg. I, II, III)		Rabbit (Oral Seg. II study)
	Day 1	Day 30	Day 1	Day 10	Day 14
NOEL (μg/kg/day)	50	50	2.5	2.5	N/A
AUCtf (pg/hr/ml)	137	322	1248	1457	NO**
Tolerated dose* or NOAEL dose*** (μg/kg/day)	150*	150*	N/A	N/A	140***
AUCtf (pg/hr/ml)	487	772	N/A	N/A	N/A

* Tolerated dose with mild glucocorticoid effects
** Not quantifiable
*** NOAEL dose

The results from the above studies suggest that reproductive toxicities may not be produced in rats when they are treated intranasally at the NOEL dose and a tolerated dose with mild glucocorticoid effects. The intranasal NOEL dose (50 μg/kg) in female rats was approximately 12-times greater than the proposed human intranasal dose (4 μg/kg).

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Summary and Evaluation of Genetic Toxicology Studies

Ten genetic toxicology studies were conducted by the sponsor, negative results were found in 8 of the studies. Chromosomal aberration in CHO cells was observed in 2 studies. Both studies showed that SCH 32088, but not its degradation product, may induce chromosomal aberration in CHO cells. However, SCH 32088 produced chromosomal aberration in CHO cells under toxic dose levels, and the incidence of the aberration were not dose-related. Chromosomal aberration results were negative in CHL cells in vitro, spermatogonial cells in vivo and rat bone marrow cells in vivo.

SUMMARY OF GENETIC TOXICOLOGY STUDIES

Study	Dose levels	Finding
Ames	31.25 to 500 μg/plate	Negative
Ames	100 to 2500 μg/plate	Negative
In vitro mouse lymphoma assay	3.125 to 100 μg/ml	Negative
In vitro chromosomal aberration in CHO cells	No-S9: 5 to 20 μg/ml S9: 25 to 100 μg/ml	No-S9: Positive for chromosomal aberration at 12.5 μg/ml
In vitro chromosomal aberration in CHO cells using SCH 32088 or its degradation product	No-S9: 1 to 22.5 μg/ml S9: 25 to 100 μg/ml	No-S9: Positive for chromosomal aberration at 15 μg/ml
In vitro chromosomal aberration in CHL	1.65 - 13.2 μg/ml	Negative
In vivo mouse bone marrow micronucleus	600 to 1200 mg/kg	Negative
In vivo chromosomal aberration in spermatogonial cells	378 to 1626 mg/kg	Negative
In vivo chromosomal aberration in rat bone marrow cells	378 to 1626 mg/kg	Negative
In vivo hepatocyte UDS assay	1250 to 5000 mg/kg	Negative

Based on the above results, SCH 32088 induced mutagenic changes were only found in CHO cells with no-S9 activity, but not in other studies.

Summary and Evaluation of Phamacokinetic (PK) Studies

Summary of single dose PK studies:

In the single-dose studies, most of the administered dose was generally eliminated through the feces regardless of the animal species or route of administration. In PO-dosed animals, drug excreted through the feces (>90%) was generally greater than those in IV-dosed animals (50-86.2%). The data are summarized in the following table:

Study No.	Species/Route of administration	Period for excretion	Excretion: % of administered-dose	
			in Feces (%)	in Urine (%)
P-5352	rat/PO	168 hr	93.5	2.4
P-5941	rat/PO	168 hr	90.1	0.5
P-5313	rat/PO	168 hr	114*	1
P-5313	dog/PO	168 hr	93	0.7
P-5941	rat/IV	168 hr	86.2	3.3
P-5313	rat/IV	168 hr	50	2.5
P-5313	dog/IV	168 hr	76	5.4
Mean			86	2.3

* Based on the recovery of radioactivity in fecal samples.

Tissue distribution studies indicated that drug concentrations in the gastrointestinal tract were higher than those in other tissues regardless of intravenous (P-5941) or oral (P-5941) routes of administration. Elevated drug concentrations in the feces may be due to either biliary secretion of the drug or unabsorbed drug in the gastrointestinal tract.

As summarized in the following table, plasma drug concentrations in IV-dosed groups were higher than those in PO-dosed groups. It was found that oral bioavailability was 1.7% in mice (P-6111) and 1.4 % in rats (P-6368). It suggests that oral bioavailability of SCH 32088 was very poor.

Study No.	Species/Route	Dose (μg/kg)	Cmax (ng/ml)	Tmax (hr)	AUC	
					Duration	ng.hr/ml
P-6111	mouse/PO	600	1.87	0.5	0-12hr	2.55
P-5941	rat/PO	600	1.14	3	0-tf	5.23
P-6111	mouse/IV	300	189	0.08	0-12 hr	74.6
P-5941	rat/IV	300	364	0.08	0-tf	192

After either IV or PO administration, the major metabolites were mometasone, 6β-hydroxymometasone furoate, 21-hydroxymometasone and 21-hydroxymometasone furoate (P-5941; P-6368). However, the metabolites were not determined quantitatively in any study.

Summary of multiple-dose PK studies:

In the 6-month rat and 1-year dog intranasal studies (P-6117; P-6118; P-6116), plasma drug concentrations were not detectable when the animals were dosed at 45 μg/kg or less. In both species, plasma Cmax and AUC values increased with dose, although gender or treatment duration had no effect on PK values. Drug accumulation and enzyme induction were not found in all intranasal studies.

SCH 32088 at 2.6 to 33 μg/kg was also given to rats by nose-only inhalation for a month (P-6137). Drug absorption following inhalational administration was greater than intranasal administration. After rats were treated inhalationally, plasma drug concentrations increased with dose, although gender or treatment duration had no effect on PK values. This finding was similar to the intranasal study. Following 3 months of inhalation administration, the concentrations of liver and lung enzymes were not increased in rats (P-6836) or dogs (P-6837). It suggests that SCH 32088 did not induce enzymes in the liver and lung tissues.

Following 3 months of oral administration at 10 to 650 μg/kg, gender-dependent pharmacokinetic changes were found in mice, but not in rats and dogs. Plasma AUC levels in mice were higher in females than in males. This finding was different from the results of mouse intranasal and inhalation studies. It may be due to absorption rate or metabolism differences between male and female mice. In these oral PK studies, plasma drug levels in dogs and rats were increased in a dose-related fashion. In rats, AUC(tf)s on Day 1 were almost doubled on Day 28, while AUC(0-6 hr) values on Day 28 were similar to those on Day 90. For dogs, SCH 32088 was not well-absorbed in the 150 μg/kg group, which suggests that oral bioavailability was poor in the dog.

Summary of Tissue Distribution:

In single-dose studies, male rats were treated by oral, intranasal and intravenous routes of administration. SCH 32088 was predominantly present in the gastrointestinal tract regardless of the route of administration. In the intranasal study, the highest drug concentrations were seen in the esophagus, trachea, nasal passage and mouth, but not in the lungs. Drug concentrations in the liver and kidneys were also higher than most tissues. Biliary recirculation of SCH 32088 and/or its metabolites was only observed in orally dosed rats.

In a 21-day oral study, tissue drug concentrations in male rats were progressively increased, and were mainly present in the gastrointestinal tract, liver and kidney. However, SCH 32088 did not accumulate in tissues. Drug-related radioactivity was not detectable on Day 23 in urine and on Day 27 in feces. In both single- and multiple-dose tissue distribution studies, SCH 32088 and/or its metabolites were predominantly eliminated through the feces.

Using pregnant and lactating rats, it was found that SCH 32088 and/or its metabolites are not only able to cross the placenta, but also are secreted into milk. Finally, biliary excretion and enterohepatic circulation were determined in bile-duct-cannulated rats. Approximately 14% of oral-dosed drug was excreted through the bile. About 27% of the absorbed dose in these rats was reabsorbed and underwent enterohepatic circulation.

Summary of Protein Binding and in vitro Drug Metabolism:

The in vitro protein binding potential of ^{3}H-SCH 32088 was tested using the plasma samples collected from rat, mouse, rabbit, dog and human. Results showed that ^{3}H-SCH 32088 was highly bound to rat (98.9%), mouse (99.4%), rabbit (98.3%), dog (99.6%) and human (99.1%) plasma proteins. Within the dose range from 100 to 500 ng/ml, there was no significant change in protein binding activity of ^{3}H-SCH 32088. Based on the results of this study, the fractions of unbound drug in rat, dog and human plasma were 1.1%, 0.4% and 0.9%, respectively. Free drug in human plasma was approximately 2-times higher than that in dog plasma, but was slightly lower than that in rat plasma.

In vitro metabolism of SCH 32088 was examined using pulmonary and hepatic tissues from rats and mice. It showed that SCH 32088 was extensively metabolized by hepatic enzymes, but not by pulmonary enzymes. In rat liver incubation, approximately 40% of parent compound was converted to 6-hydroxy SCH 32088. Mometasone and two other unknown metabolites (UK1 and UK2) were also detected. In mouse liver incubation, 6-hydroxylation, ester hydrolysis and metabolism to an unidentified product were found. The lack of the metabolism in the lung might be due to the low concentration of metabolic enzymes in the lungs. The results of this in vitro metabolism study agreed generally with the metabolic profile obtained from single dose pharmacokinetic studies.

OVERALL SUMMARY AND EVALUATION

NASONEXTH is the nasal spray formulation of Mometasone furoate monohydrate (SCH 32088), a potent corticosteroid. Inhalation administration of SCH 32088 inhibits allergen-induced pulmonary eosinophil infiltration and Th cell accumulation in allergic mouse and guinea pig models. Anti-inflammatory activities of SCH 32088 were also observed in the treatment of acute and chronic dermal inflammation in animals.

Compared to betamethasone valerate, SCH 32088 had less potency in suppressing HPA axis, but more potency in inducing thymolysis and skin atrophy. SCH 32088 had no mineralocorticoid, androgenic, antiandrogenic and estrogenic activities. SCH 32088 did not increase the secretions of bile, gastric acid and pepsin. SCH 32088 showed on effect on the central nervous, cardiovascular, respiratory systems of the experimental animals. It can increase urine volume, creatinine release and accumulation of hepatic glycogen. SCH 32088 possesses some antiuterotrophic activity and also may accelerate sexual maturation in the females.

Single subcutaneous doses at 200 mg/kg and 2000 mg/kg may be lethal in dogs and rats, respectively. However, single oral doses at up to 2000 mg/kg did not cause any death in rats and dogs. This suggests that subcutaneous administration of SCH 32088 is more toxic than oral administration.

Toxicity of SCH 32088 was evaluated in rats and dogs by the intranasal and inhalation routes of administration. Testing duration lasted up to one year. Like other corticosteroids, major target organs of toxicity of SCH 32088 were the liver, thymus, lymph tissues, lungs, skin, spleen, mammary and adrenal glands. Changes included increases in liver weight, atrophy of the thymus and adrenal glands, and suppression of the HPA axis. Following a 6-month inhalation, the tolerated dose with mild glucocorticoid effects in dogs was 21 μg/kg/day, which was approximately 5 and 3.4 times of the proposed human intranasal dose on a bodyweight or body surface area basis, respectively. In a 3-month rat study (P-5737), SCH 32088 at as low as 8 μg/kg/day decreased tracheal globule cells in all animals tested. However, this pathological abnormality was absent in another 3-month study at dose levels up to 48 μg/kg/day, the NOAEL of the study (D-22797). The dose level of 48 μg/kg/day was approximately 12 and 2.3 times the proposed human intranasal dose on a bodyweight or body surface area basis, respectively.

Inhalation toxicity studies of SCH 32088 showed that juvenile animals are more sensitive to the drug than adults. A one-month juvenile rat study produced toxicity in the trachea, nasal cavity, bone marrow, mammary glands and lungs. Based on the results of this study, a NOEL was not established in the females. Although pulmonary alveolar histiocytic infiltration was found in 1/24 treated males, a tolerated dose with mild glucocorticoid effects was defined at 0.2 μg/kg in male rats, but not in female rats. In contrast with the rats, SCH 32088 was more

tolerable to pediatric dogs. A tolerated inhalation dose with mild glucocorticoid effects in young dogs was defined at 7.2 μg/kg/day. Currently, SCH 32088 is only for adults and adolescents 12 years of age or older.

The intranasal administration of 0.05 or 1% of SCH 32088 suspension for up to 1 year did not induce nasal irritation in dogs. These dogs received up to 180 to 520 μg/kg/day of SCH 32088, which were approximately 7 to 15 times higher than the proposed human daily dose on the basis of nasal surface area. After 6 months intranasal administration, systemic toxicity was generally not noted. Two 6-month intranasal toxicity studies failed to identify target organs of toxicity in both rat and dogs on the basis of pathological observations. Acceptable tolerated doses in the 6-month studies were 150 μg/kg/day and 45 μg/kg/day for rats and dogs, respectively. A 1-year intranasal dog study showed mild effects in thymus, skin and adrenal gland. A tolerated daily dose with mild glucocorticoid effects was defined as 15 μg/kg body weight or 300 $\mu g/m^2$ body surface area. This is approximately 4- and 2.4-times the proposed human dose on the bodyweight basis and body surface area basis, respectively. Therefore, the preclinical data from intranasal toxicity studies are sufficient to support the proposed human intranasal dose of SCH 32088.

Reproductive toxicity was evaluated by oral, dermal and subcutaneous routes of administration. Subcutaneous administered SCH 32088 produced more maternal and fetal toxicity when compared with the animals treated through dermal or oral routes of administration. In a rabbit oral Segment II study, NOAELs for both dams and offspring were 140 μg/kg/day, which produced unquantifiable AUC levels. In subcutaneous Segment I, II and III rat studies, NOEL doses were 2.5 μg/kg/day. Following a subcutaneous dose at 2.5 μg/kg/day, AUC values in the female rats were greater than the AUC levels in the rats treated with intranasal doses at 50 (NOEL) or 150 μg/kg/day (tolerated dose with mild glucocorticoid effects). When the AUC and NOEL levels from different studies are compared, reproductive toxicity is not produced in animals treated intranasally at the NOEL dose or tolerated doses with mild glucocorticoid effects.

Ten genetic toxicology studies were conducted by the sponsor. Negative results were reported in 8 out of 10 studies, including Ames test, mouse lymphoma assay, mouse bone marrow micronucleus assay, UDS assay, assays of chromosomal aberration in CHL cells and chromosomal aberration in rat bone marrow cells. Chromosomal aberration in CHO cells was reproducibly observed in 2 studies under non-S9 condition. However, SCH 32088 produced chromosomal aberration in CHO cells at cytotoxic dose levels, and incidences of the aberration were not dose-related. Chromosomal aberration was not seen on CHL cells in vitro, spermatogonial cells in vivo and rat bone marrow cells in vivo.

Two inhalation carcinogenicity studies in rat and mouse have been reviewed previously. The results of these studies demonstrated that SCH 32088 has none or a very limited cancer risk to humans.

Oral bioavailability of SCH 32088 was very poor in all test species, including mice, rats and dogs. Pharmacokinetic studies showed that plasma drug levels were undetectable in the rats and dogs treated by intranasal doses for up to 45 μg/kg. When dog or rat was treated inhalationally or intranasally (dose > 45 μg/kg), plasma AUC values were increased with dose, although gender or treatment duration had no effect on AUC values. In vitro studies demonstrated that SCH 32088 was not an inducer of hepatic or lung enzymes. More than 80% of administered dose was generally eliminated through the feces regardless of the animal species or route of administration. Drug accumulation and enzyme induction were not found in any intranasal or inhalation study. After intranasal dosing, the highest drug levels were distributed in the esophagus, trachea, nasal passage and mouth, but not in the lungs. The in vitro protein binding studies showed that SCH 32088 was highly bound to human and animal plasma proteins. The binding rate of human plasma protein (99.1%) was between that of rats (98.9%) and dogs (99.6%). The fractions of unbound drug in rat, dog and human plasma were 1.1%, 0.4% and 0.9%, respectively. This suggested that under a similar plasma drug concentration, the levels of free drug in humans and rats may be approximately 2-times higher than that in dog plasma. Therefore, rats might be more sensitive to the systemic exposure of SCH 32088 when compared with the dog model. The in vitro metabolism studies demonstrated that SCH 32088 was extensively metabolized by hepatic enzymes, but not by pulmonary enzymes. Results of PK studies indicate that intranasally dosed SCH 32088 may be predominantly concentrated in the nasal cavity and upper-airways. Due to poor bioavailability or low pulmonary concentration of SCH 32088, an tolerated intranasal dose may not be able to produce significant systemic effects.

Finally, the formulation of SCH 32088 used in three pivotal preclinical intranasal toxicity studies (6-month in rats, 6-month and 1-year in dogs) was the same as that proposed for the marketed product.

In summary, NASONEXTH is a potent anti-allergic and anti-inflammatory drug. It has greater local pharmacological activities when compared with systemic activities. After a single intranasal dose, the highest drug levels were seen in the esophagus, trachea, nasal passage and mouth, but not in the lungs. Plasma drug concentrations in animals increased with dose, but were not affected by gender or treatment duration. SCH 32088 is eliminated mainly through the feces. Experimental data from intranasal and inhalation studies show that the tolerated doses with mild glucocorticoid effects were much higher in animals than the proposed human dose. Reproductive toxicities may not be induced in animals treated intranasally at a tolerated dose with mild glucocorticoid effects. Negative results were seen in 8 out of 10 genetic toxicology studies. Although SCH 32088 produced chromosomal aberrations in CHO cells at cytotoxic concentrations, this finding may not be drug-related. Results from two 2-year carcinogenicity studies showed that NASONEX has none or a very limited cancer risk to human. Therefore, preclinical data is sufficient to support the proposed human clinical use.

RECOMMENDATION

NASONEXTH nasal spray is indicated for the prophylaxis and treatment of symptoms of seasonal allergic rhinitis and the treatment of symptoms of perennial rhinitis, in adults and adolescents 12 years of age and older. The efficacy and safety of NASONEXTH are supported by the data obtained from preclinical studies. Therefore, this product is recommended to be approved.

LABELING REVIEW

Three sections were revised from the label proposed by the sponsor, including 1) Clinical Pharmacology, 2) Carcinogenesis, Mutagenesis, Impairment of Fertility, and 3) Pregnancy.

Clinical Pharmacology: When inhibitory activity to the synthesis/release of cytokines was compared (P-5558), the potency of mometasone furoate (IC_{50} = 0.1 nM) to IL-1 was approximately 8-times higher than betamethasone valerate (IC_{50} = 0.82 nM). Therefore, the lowest inhibitory activity of mometasone furoate to cytokine production should be 8-times, but not 10-times higher than other tested steroid.

Only one study showed that in an ovalbumin sensitized and challenged mice, mometasone furoate at ≥ 13 μg/kg may reduce the numbers of eosinophils into the brochoalveolar lavage fluid, and the peribronchial and bronchiolar regions of the lung tissues. Eosinophil infiltration in the lungs is one of the important pathological alterations in asthmatic patients. In order to describe the animal model and site of eosinophil infiltrations in the study, a minor revision was made in the second paragraph of clinical pharmacology.

Carcinogenesis, Mutagenesis, Impairment of Fertility: To give a clear picture, tumor findings in the carcinogenicity studies were revised. The incidence of urinary bladder mesenchymal tumors in mice was increased with administered doses. However, no statistically significant tumors were observed in mice and rats.

Although human plasma drug concentrations were not quantifiable with the maximum recommended human daily intranasal dose (4 μg/kg), the dose levels used in the rat and mouse carcinogenicity studies were compared with the maximum recommended daily intranasal dose in adults on a body surface area basis (μg/m^2). The dose levels used in rat and mouse carcinogenicity studies were up to 3- and 4-times the maximum recommended daily intranasal dose in adults (125 μg/m^2/day) on a μg/m^2 basis, respectively.

The maximum subcutaneous dose of mometasone furoate was administered at 15 μg/kg/day in rat reproductive toxicology studies (Segment I and III). Based on the available data, impairment of fertility was not seen at ≤ 15 μg/kg/day. Prolonged gestation, prolonged and difficult labor, reduced offspring survival and body weight gain were observed following the

treatment at 15 μg/kg. The daily dose at 15 μg/kg in rats was compared with the maximum recommended daily intranasal dose in adults on a $\mu g/m^2$ basis.

The doses used in animals and the maximum recommended daily intranasal dose in adults are compared in the following table:

Comparison of the doses used in animals and the dose used in human*					
Carcinogenicity Studies					
	μg/kg	67	N/A	N/A	N/A
Rat	$\mu g/m^2$ **	402	N/A	N/A	N/A
	A/H ratio#	3.2	N/A	N/A	N/A
	μg/kg	20	40	80	160
Mouse	$\mu g/m^2$ **	60	120	240	480
	A/H ratio#	0.48	0.96	1.92	3.84
Subcutaneous Reproductive (Segment I and III) Studies					
	μg/kg	15	N/A	N/A	N/A
rat	$\mu g/m^2$ **	90	N/A	N/A	N/A
	A/H ratio#	0.72	N/A	N/A	N/A

* Maximum recommended daily intranasal dose in adults = 4 μg/kg or 125 $\mu g/m^2$ (Bodyweight = 50kg; Surface area = $1.6m^2$).

** Conversion factor: rat = 6; mouse = 3; rabbit = 12.

\# The ratio of the doses used in animal (A) and the maximum recommended daily intranasal dose in human adults (H).

Pregnancy: As shown in a table below, mometasone furoate in teratology (Segment II) studies was given to several species by using various routes of administration.

Routes	Oral	Dermal (topical)	Subcutaneous
Species	Rabbit	Rat & Rabbit	Rat & Mice

Since human plasma drug concentration was not quantifiable (<50 pg/ml) following intranasal exposure, the dose levels used in the animal teratology studies were compared to the maximum recommended daily intranasal dose in adults (125 $\mu g/m^2$/day) on a $\mu g/m^2$ basis.

Mometasone furoate at 60 and 150 μg/kg/day was teratogenic for mouse and rabbits, respectively. Non-teratogenic subcutaneous dose levels were established at 2.5 μg/kg in rats and 20 μg/kg in mice.

In an oral teratology study, rabbits were treated with placebo and mometasone furoate at 140, 700 and 2800 μg/kg. The incidences of malformations were 2.3%, 4.8% and 6.9% for the rabbits dosed at 0 (placebo), 140 and 700 μg/kg, respectively. In the 2800 μg/kg group, there were too few fetuses (n=4) to evaluate because of a high pregnancy failure rate. At 700 μg/kg, there were increased incidences of resorptions and malformations, including cleft palate and/or head malformations (consisting of hydrocephaly or domed head). In the 140

μg/kg group, conjoined twin, extra sternebra and fused ribs were observed.

The doses used in animals and the maximum recommended daily intranasal dose in adults are compared in the following table:

Comparison of the doses used in animals and the dose used in human*					
Teratology (Segment II) Studies					
	μg/kg	2.5	600	N/A	N/A
Rat	$\mu g/m^2$ **	15	3600	N/A	N/A
	A/H ratio#	0.12	28.8	N/A	N/A
	μg/kg	20	60	180	N/A
Mouse	$\mu g/m^2$ **	60	180	540	N/A
	A/H ratio#	0.48	1.44	4.32	N/A
	μg/kg	140	150	700	2800
Rabbit	$\mu g/m^2$ **	1680	1800	8400	33600
	A/H ratio#	13.4	14.4	67.2	268.8

* Maximum recommended daily intranasal dose in adults = 4 μg/kg or 125 $\mu g/m^2$ (Bodyweight = 50kg; Surface area = $1.6m^2$).

** Conversion factor: rat = 6; mouse = 3; rabbit = 12.

The ratio of the doses used in animal (A) and the maximum recommended daily intranasal dose in human adults (H).

The following is the proposed revised preclinical labeling

Proposed Revised Labeling:

CLINICAL PHARMACOLOGY

NASONEX Nasal Spray, is a glucocorticosteroid demonstrating anti-inflammatory properties. The precise mechanism of glucocorticosteroid action on allergic and nonallergic rhinitis is not known. On a concentration basis (nM of IC_{50}), mometasone furoate in cell culture was shown to be at least 8 times more potent than several other steroids (beclomethasone dipropionate, betamethasone, hydrocortisone, and dexamethasone) at inhibiting the synthesis/release of IL-1, IL-6 and TNFα. Mometasone furoate (0.12 nM) in cell culture was also at least ten times more potent than BDP and betamethasone dipropionate at inhibiting IL-5 production. In cultured human blood CD4+ T-cells, mometasone furoate was a potent inhibitor of the production of IL-4 and IL-5 (0.27 nM). Also, in mixed leukocytes from atopic patients, mometasone furoate inhibited the release of leukotrienes.

In an allergic mouse model, inhaled mometasone furoate (at 13 μg/kg) inhibited

allergen-induced eosinophil infiltration into brochoalveolar lavage fluid, and the peribronchial and bronchiolar regions of the lung tissues. Additionally, mometasone furoate reduced the number of lymphocytes, and the levels of messenger RNA for the proallergic cytokines IL-4 and IL-5.

In two clinical studies utilizing nasal antigen challenge, NASONEX Nasal Spray has shown anti-inflammatory activity in both the early- and late- phase allergic responses. This has been demonstrated by decreases (vs placebo) in histamine and eosinophil activity, and reductions (vs baseline) in eosinophils, neutrophils, and epithelial cell adhesion proteins.

The effect on nasal mucosa was examined following twelve months of treatment with NASONEX Nasal Spray. There was no evidence of atrophy or other adverse effects on nasal mucosa. The epithelial mucosa integrity improved, and there was a marked reduction in inflammatory cells.

In patients with seasonal allergic rhinitis, NASONEX Nasal Spray demonstrated a clinically significant onset of action (at least moderate improvement in nasal symptoms) within 12 hours after the first dose. Maximum benefit is usually reached in several days.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No statistically significant tumors were observed when mometasone furoate was evaluated in Sprague Dawley rats at inhalation doses up to 67 μg/kg (approximately 3 times the maximum recommended daily intranasal dose in adults on a $\mu g/m^2$ basis). In a 19-month inhalation study in Swiss CD-1 mice, no statistically significant tumors were noted. A dose-related increased in mouse urinary bladder mesenchymal tumors was noted at 20, 40, 80 and 160 μg/kg (approximately 1/2, 1, 2 and 4 times the maximum recommended daily intranasal dose in adults on a $\mu g/m^2$ basis).

At cytotoxic doses, mometasone furoate produced an increase in simple chromosome aberrations in vitro in Chinese hamster ovary-cell cultures in the nonactivation phase, but not in the presence of rat liver S9 fraction. Mometasone furoate was nonmutagenic in a mouse-lymphoma assay, a Salmonella/E-coli/mammalian microsome mutation assay, a Chinese hamster lung cell (CHL) chromosomal-aberrations assay, an in vivo in the mouse bone-marrow erythrocyte-micronucleus assay, a rat bone-marrow clastogenicity assay, and the mouse male germ-cell clastogenicity assay. Mometasone furoate also did not induce unscheduled DNA synthesis in vivo in rat hepatocytes.

In rat subcutaneous reproductive toxicity studies, mometasone furoate caused prolonged gestation, prolonged and difficult labor, reduced offspring survival and body weight gain following treatment at 15 μg/kg (approximately 1/2 of the maximum recommended daily intranasal dose in adults on a $\mu g/m^2$ basis). Impairment of fertility in rats was not produced by subcutaneous doses up to 15 μg/kg.

Pregnancy: Teratogenic Effects: Pregnancy Category C: Mometasone furoate was

teratogenic in mice. It caused cleft palate and reduced offspring survival in mice at subcutaneous doses of 60 and 180 μg/kg, respectively (approximately 1 and 4 times the maximum recommended daily intranasal dose in adults on a μg/m^2 basis, respectively). Non-teratogenic dose level in mice was established at a subcutaneous dose of 20 μg/kg (approximately 1/2 of the maximum recommended daily intranasal dose in adults on a μg/m^2 basis).

In rabbits, mometasone furoate was teratogenic and caused gallbladder agenesis and flexed front paws at a topical dermal dose of 150 μg/kg (approximately 14 times the maximum recommended daily intranasal dose in adults on a μg/m^2 basis).

In rats, mometasone furoate produced umbilical hernia, cleft palate and delayed ossification at a topical dermal dose of 600 μg/kg(approximately 30 times the maximum recommended daily intranasal dose in adults on a μg/m^2 basis). Non-teratogenic dose level in rats was established at a subcutaneous dose of 2.5 μg/kg (approximately 1/10 of the maximum recommended daily intranasal dose in adults on a μg/m^2 basis).

In these teratogenicity studies, there were also reductions in maternal body weight gains, effects on fetal growth (lower fetal body weights and/or delayed ossification) in mice (subcutaneous, 60 μg/kg), rabbits (dermal, 150 μg/kg) and rats (dermal, 600 μg/kg).

In an oral teratology study in rabbits, incidences of malformations were 2.3%, 4.8% and 6.9% for the rabbits dosed at 0 (placebo), 140 and 700 μg/kg, respectively. Conjoined twin, extra sternebra and fused ribs were observed in the rabbits at the dose level of 140 μg/kg (approximately 15 times the maximum recommended daily intranasal dose in adults on a μg/m^2 basis). An oral dose of 700 μg/kg increased the incidences of resorptions and malformations, including cleft palate and/or head malformations (consisting of hydrocephaly or domed head; approximately 70 times the maximum recommended daily intranasal dose in adults on a μg/m^2 basis). At 2800 μg/kg, pregnancy failure was observed in most rabbits (approximately 270 times the maximum recommended daily intranasal dose in adults on a μg/m^2 basis).

There are no adequate and well controlled studies in pregnant women. NASONEX Nasal Spray should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Proposed Labeling Editing:

The shaded areas are the proposed addition of the sponsor's proposed labeling. The strike out is the proposed deletion.

CLINICAL PHARMACOLOGY

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---------- a Chinese hamster lung cell (CHL) chromosomal-aberrations assay, ~~or~~ an in vivo in the mouse bone-marrow erythrocyte-micronucleus assay, ~~in the~~ a rat bone-marrow clastogenicity assay, and the mouse male germ-cell clastogenicity assay. Mometasone furoate also did not induce unscheduled DNA synthesis in vivo in rat hepatocytes.

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Pregnancy: Teratogenic Effects: Pregnancy Category C: Mometasone furoate was teratogenic in mice. It caused cleft palate and reduced offspring survival in mice at subcutaneous doses of 60 and 180 μg/kg, respectively (approximately 1.5 and 4 times the maximum recommended daily intranasal dose in adults on a μg/m^2 basis, respectively). Non-teratogenic dose level in mice was established at a subcutaneous dose of 20 μg/kg,

approximately 1/2 of the maximum recommended daily intranasal dose in adults on a $\mu g/m^2$ basis.

In rabbits, mometasone furoate was teratogenic and caused gallbladder agenesis and flexed front paws at a topical dermal dose of 150 $\mu g/kg$, approximately 14 times the maximum recommended daily intranasal dose in adults on a $\mu g/m^2$ basis.

In rats, mometasone furoate produced umbilical hernia, cleft palate and delayed ossification at a topical dermal dose of 600 $\mu g/kg$, approximately 30 times the maximum recommended daily intranasal dose in adults on a $\mu g/m^2$ basis. Non-teratogenic dose level in rats was established at a subcutaneous dose of 2.5 $\mu g/kg$, approximately 1/10 of the maximum recommended daily intranasal dose in adults on a $\mu g/m^2$ basis.

In these teratogenicity studies, there were also reductions in maternal body weight gains, effects on fetal growth (lower fetal body weights and/or delayed ossification) in mice (subcutaneous, 60 $\mu g/kg$), rabbits (dermal, 150 $\mu g/kg$) and rats (dermal, 600 $\mu g/kg$).

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Tao Tom Du, Ph.D.

Pharmacologist/Toxicologist

Original NDA
c.c. /Division File
/T. Tom Du
/Dr. Alexandra Worobec
/Dr. Hilary Sheevers
/Dr. Martin Himmel
/Dr. Graig Bertha
/Ms. D. Toyer

I concur, although final labeling comments will be addressed in the future with the sponsor.

Hilary Sheevers
8/21/97

1st draft: 3/5/97
2nd draft: 4/30/97
3rd draft: 6/16/97
4th draft: 6/30/97
5th draft: 8/7/97