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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-067

Clinical Pharmacology and Biopharmaceutics Review

Clinical Pharmacology and Biopharmaceutics Review

NDAs: 21-067	**Date of Submission:** November 14, 2003
Generic Name	Mometason Furoate (MF)
Brand Name:	**Asmanex®**
Formulations:	Multiple Dose Dry Powder (**Twisthaler™220 mcg**)
Route of Administration:	Inhalation
Indication:	Asthma/Allergic Rhinitis
Type of Submission:	NDA
Sponsor:	Schering Corporation, Kenilworth, NJ
Type of Submission:	Response to Approvable Letter
Reviewer:	Sayed (Sam) Al Habet, R.Ph., Ph.D.
Team Leader	Emmanuel Fadiran, R.Ph., Ph.D.
Date of Submission:	December 14, 2003
Date Received:	January 12, 2004
Review Date:	January 16, 2004
First Draft	January 20, 2004
DFS Draft:	February 4, 2004

Backround:

This is a response to the approvable letter dated December 4, 2000. There is no OCPB major information or issues in this submission. The revised final label has not yet been received from the sponsor.

The original NDA was submitted in November 30, 1998. Since then, there were at least 3 review cycles with three approval letters in the following sequence: September 28, 1999, February 28, 2000, and December 4, 2000.

The current submission contains mainly responses to the CMC issues that where outlined in the approval letter dated December 4, 2000. In addition, the sponsor submitted two additional clinical studies to further establish the safety and efficacy of the drug (see Medical Officer's review). No PK samples were collected in these two studies and there are no OCPB related issues.

All OCPB related issues have been resolved in the previous submissions. The original OCPB review was completed on September 22, 1999. The approvable letter dated September 28, 1999 listed all OCPB deficiencies and labeling recommendations. All OCPB deficiencies were addressed in the previous review cycle during the year 2000. In December 4, 2000 approval letter, some labeling comments were listed to be incorporated in the clinical pharmacology section of the label. These comments are not PK related, but are related to asthma management, the use of beta-2-agonist, and corticosteroid therapy.

General Comments:

- The current submission contains mainly CMC related information as a response to the approvable letter. In addition, it contains two clinical studies with no PK related information.
- The labeling comments will be made directly into the sponsor's proposed label. The label will be reviewed against the previously recommended labeling changes and the current knowledge on the drug.

RECOMMENDATION:

From the Office of Clinical Pharmacology and Biopharmaceutics perspective, no comments can be made at this time. The labeling comment will be made directly into the currently proposed label.

Reviewer

Sayed (Sam) Al Habet, R.Ph., Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaulation II

Final version signed by Emmanuel Fadiran, R.Ph., Ph.D., Team Leader----------

cc: HFD-570, HFD-870 (Al Habet, Fadiran, and Malinowski), Drug file (Biopharm File, Central Document Room).

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/s/

Sayed Al-Habet
3/4/04 02:30:11 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
3/4/04 02:38:31 PM
BIOPHARMACEUTICS
I concur

SEP 22 1999

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 21-067
Mometasone Furoate

BRAND NAME:
Asmanex 200 and 400 μg
Multiple-dose Dry Powder Inhaler

SUBMISSION DATE:
11/30/98 (Serial No. 000)
08/02/99
07/09/99 (IND 46,216 Serial No. 108)

SPONSOR: Schering

REVIEWER: Tien-Mien Chen, Ph.D.

TYPE OF SUBMISSION: Original NDA

Code: 3S

TITLE: "Review of Human Pharmacokinetics and Bioavailability Section"

I. SYNOPSIS:

Schering's NDA 20-762 for Nasonex (mometasone furoate, MF) nasal spray, 50 μg/actuation, has been previously reviewed and approved by the Agency on 10/01/97. It is indicated for the treatment of seasonal and perennial allergic rhinitis in adults and children 12 years of age and older.

Schering is also developing MF dry powder for inhalation. It is a cap-activated inhalation-driven multi-dose dry powder inhaler (MDDPI) product containing mometasone and lactose . Previously, end of phase 2 (EOP2) and pre-NDA meetings with the Agency were held on 04/04/98 and 09/14/98, respectively. Due to very low concentrations achieved (below the limit of quantitation, LOQ) and as agreed upon in the meetings with the Agency, there were only 5 pharmacokinetic (PK) studies conducted.

On 11/30/98, Schering submitted an original NDA 21-067 for Asmanex (MF) MDDPI which provides 220 μg per actuation (200 and 400 μg from the mouthpiece, respectively). It is to be indicated for the treatment of asthma as prophylactic therapy for adults and children 12 years of age and older. The recommended starting dose is 400 μg QD. It is desirable to titrate to the lowest effective dose once asthma stability is achieved. Dose reduction to 200 μg QD may be considered, increasing to 400 μg QD or 200 μg BID if more control is needed. For patients with severe asthma who may require oral corticosteroids, the starting dose is 400 μg BID. Once reduction of oral steroid dose is complete, MF dose should be titrated down to the lowest effective dose. Please see the package insert in Appendix 1 for details.

Submitted under Human Pharmacokinetic and Bioavailability (PK/Bio) section of NDA 21-067 were 5 studies. On 07/09/99, the sponsor further submitted 3 studies under

IND 46,216 (Serial No. 108). One study, No. **C97-046**, was previously submitted under IND 46,216 on 04/30/98 and reviewed on 06/25/98 by the Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE II). Therefore, 7 PK studies are reviewed here. Please see individual study reports in Appendix 2 for details. Totally, 8 PK studies which are considered pivotal were submitted to support the approval of this NDA.

Key issues addressed in the PK section (5 plus 3 PK studies submitted):

A. Basic PK Parameters [CL, $T_{1/2}$, C_{max}, T_{max}, and absolute bioavailability (F_{abs})]
B. Single-dose Dose Proportionality (100, 200, 400, and 800 μg)
C. Multiple-Dose PK
   (1). Systemic Exposures employing both 200 and 400 μg strengths
   (2). Recommended Dosing Regimens (200 and 400 μg QD and 200 and 400 μg BID)
D. *In Vivo* Metabolism
E. Related to Safety and Labeling in the package insert (PI)
   (1). Gender Differences
   (2). Drug-Drug Interaction with Ketoconazole
   (3). Hepatic Impairment (Special Population)

Overall Results:

1. **Basic PK parameters** post IV (intravenous) and DPI of single doses of 400 μg in healthy adults (12M+12F) using 200 μg/inhalation formulation (®; to-be-marketed). (The brief study description and results could be found on page 5).

   Post IV ⇒ CL: 892 ml/min and $T_{1/2}$: 4.45 hrs (no gender differences) for MF
   Post DPI ⇒ C_{max}: ≈ LOQ (50 pg/ml), T_{max}: 2.1 hrs, and F_{abs}: <1% for MF (no assessment of gender effects)

2. **Single-dose dose proportionality** (100, 200, 400, and 800 μg) in 48 male volunteers using 100 μg/inhalation formulation (exactly half that of 200 μg/inhalation, but using a pilot scale). (The brief study description and results could be found on page 6).

   As the MF doses increased from 100 to 800 μg, the number of subjects that had measurable plasma MF levels increased in a dose-related manner. The % decrease in plasma cortisol AUC_{0-24} values (as compared to placebo group) intensified as the dose increased, but the differences (-3 to –12%) were not statistically significant ($p>0.05$).

3. **Multiple-dose PK (200 μg BID and 400, 800, and 1200 μg QD for 29 days)** in 60 patients (32M+28F) using 100 μg/inhalation formulation. (The brief study description and results could be found on page 8).

For QD dosing ⇒ MF C_{max} levels increased as doses increased and steady state (SS) reached after Day 7 (some accumulation)

For 200 μg BID dosing ⇒ Not detectable (below the LOQ)

For plasma cortisol AUC_{0-24}⇒ 82%* to 107% as compared to placebo group (*; $p<0.05$ for 400 μg QD)

4. **Multiple-dose PK (400 μg BID and 800 μg BID for 28 days)** in 64 patients (46M+18F) using 200 and 400 μg/inhalation formulations®. (The brief study description and results could be found on page 9).

⇒ Plasma MF levels were detectable with some accumulation observed at SS.

⇒ For pharmacodynamic (PD) data, as compared to baseline, mean plasma cortisol AUC_{0-24} was reduced: 25%** (Day 7), 19%* (Day 14), 19%* (Day 21), and 10% (Day 28) for 400 μg BID; [* for $p<0.05$ and ** for $p<0.01$].

⇒ Post-study cosyntropin stimulation: MF 400 μg BID group (23.2 μg/dl) was not significantly different from placebo group (25.0 μg/dl).

⇒ No comparison of PK equivalency between the 2 x 200 μg and 1 x 400 μg doses was provided.

⇒ Both 200 and 400 μg strengths provided comparable dose-normalized mean C_{max} values at SS (ranging from 93 to 114 pg/ml for the 400 μg BID dosing regimen).

5. ***In Vivo* Metabolism using ^{3}H-MF DPI** in 6 healthy subjects. (The brief study description and results could be found on page 12).

⇒ Up to 7 days, about 8% and 74% of the total radioactivity were recovered in urine and feces respectively and no accumulation was found in red blood cells (RBC). MF is extensively metabolized, but its metabolic pathways and possible metabolites are not identified.

⇒ A possible metabolite, 6-β-OH MF, has been shown to have some pharmacologic activities *in vitro*, but its plasma levels were not detected (even after IV dose).

6. **Drug-drug interaction of MF 400 μg BID for 9 days** (using 200 μg formulation) and **ketoconazole 200 mg BID or placebo (Days 4 to 9)** in 24 healthy volunteers. (The brief study description and results could be found on page 15).

⇒ As compared to placebo group (on either Day 3 or 9) or ketoconazole group itself on Day 3, more and higher MF plasma levels (in the range of 211-324 pg/ml) were detected in the subjects enrolled in the ketoconazole group on Day 9.

7. **Special Population** (4 patients with mild, 4 with moderate, and 4 with severe hepatic impairment) using 200 μg formulation. (The brief study description and results could be found on page 16).

⇒ Only one or two patients had detectable MF plasma levels (in the range of 50 to 105 pg/ml) and no significant increases as compared to that in 8 volunteers (only one detectable, 78.4 pg/ml).

Finally, the validated assay method (LC/MS/MS) used previously for MF in NDA 20-762 was also employed in this NDA. However, validation report(s) of assay method(s) for plasma or urinary cortisol levels was/were not provided. Upon request, the above information was submitted on 08/03/99 for review. Both the to-be-marketed 200 and 400 μg formulations were tested in one multiple-dose PK/Bio study and the to-be-marketed 200 μg formulation was tested in several single-/multiple-dose PK/Bio studies.

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Study No.	Descriptions
I94-130:	Randomized, Single-dose, Parallel, Placebo-Controlled, 4x4 Crossover PK Study in 48 Male Volunteers..... 37
C95-135:	Randomized, Multiple-dose, Parallel, Placebo-Controlled PK Study in 60 Male and Female Asthmatic Patients..... 40
C97-049:	Randomized, Multiple-dose, Parallel, Placebo- and Positive-Controlled PK Study in 64 Male and Female Asthmatic Patients..... 43
C97-047:	Open-Label, Single-dose PK Study Using Radiolabeled ^{3}H-MF DPI in 6 Male Volunteers..... 48
I98-216:	Drug-drug Interaction Study of MF DPI and Ketoconazole in Healthy Subjects..... 50
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II. SUMMARY OF PHARMACOKINETICS, BIOEQUIVALENCE, PHARMACODYNAMICS, ETC.:

1. SINGLE-DOSE PHARMACOKINETICS:

Study No. **C97-046:**

The F_{abs} of MF DPI compared to an IV dosing was obtained from this study which had been reviewed previously by OCPB. It was a 3x3 crossover study and a single dose of 400 μg was given to 12 male and 12 female volunteers. The to-be-marketed 200 μg formulation was used.

The mean plasma profiles (IV, MF MDDPI, and MF MDI) and the study results are shown below in **Figure 1** and **Table 1**:

Figure 1. Mean plasma profiles of MF in Semilog Plot

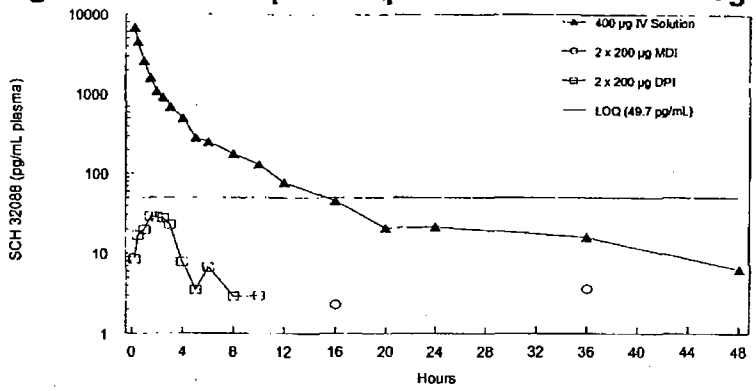


Table 1. Mean (%CV) PK Parameters of MF Following Single-Dose IV and MDDPI Administration

PK Parameters\Treatments	IV dosing (400 µg MF)	DPI (2 x200 µg MF)
C_{max} (pg/ml)	--------	49.8 (100%); n=24
T_{max} (hr)	--------	2.09 (73%), n=14
$AUC_{0-\infty}$ (pg-hr/ml)	8012[a] (24%); n=18	ND[b]
CL (ml/min)	892 (31%); n=18	ND
$T_{1/2}$ (hr)	4.45 (31%); n=18	ND

[a]. Mean (CV%).

[b]. Not detectable [only a few subjects had a value (one each) above the LOQ of 50 pg/ml].

Post IV dosing, plasma MF levels showed a two-exponential decay. Mean total clearance (CL) was estimated to be 892 ml/min. No gender differences in CL were found, i.e., 894 ml/min for male and 889 ml/min for female volunteers. Mean terminal half-life ($T_{1/2}$) was calculated to be 4.45 hr (3.83 hr for males and 5.23 hr for females) which is not different in both genders either. Mean steady-state volume of distribution (Vd_{ss}) was estimated to be 152 liters.

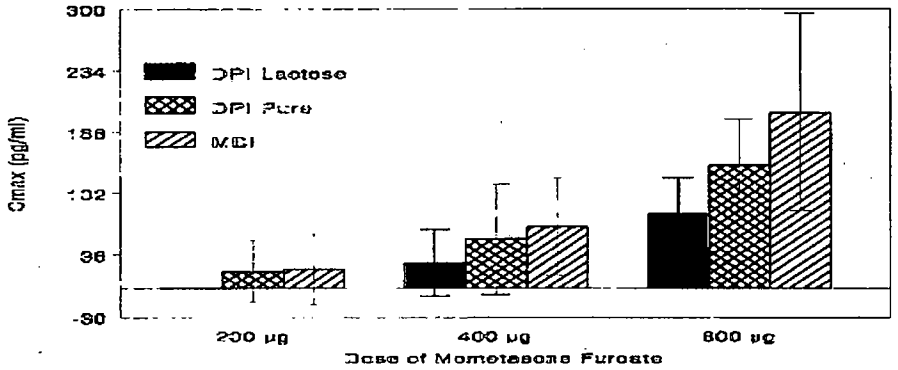
For MF DPI, **1)** the mean F_{abs} was estimated to be <1% indicating negligible systemic availability and **2)** mean peak plasma level (C_{max}) of 49.8 pg/ml was obtained at the mean time to peak (T_{max}) of 2.09 hr. Since no measurable plasma levels were obtained for MF MDI, no PK parameters are calculated.

3. DOSE PROPORTIONALITY:

Study No. **I94-130**:

Single-dose dose proportionality study was conducted at four dose levels, 100, 200, 400, and 800 μg, in 48 male volunteers. For each dose level, placebo and the following formulations were used, MF DPI (100 μg/inhalation), pure MF without lactose in DPI (100 μg/inhalation), and MF MDI suspension (50 μg/burst). This was a randomized, evaluator-blind, parallel-group, placebo-control, 4x4 crossover study. The effects of systemic exposure of MF on the HPA (hypothalamus pituitary adrenal) function were also assessed based on the 24-hr plasma cortisol AUC_{0-24} data. The mean MF C_{max} levels obtained are shown below in **Figure 2**:

Figure 2. Mean plasma MF C_{max} Values



As the MF doses increased from 100 to 800 μg, the number of subjects that had measurable plasma MF levels increased in a dose-related manner. For all the dose levels tested, different formulations were significantly different in systemic exposure ($p<0.05$). The highest was for MF MDI suspension, followed by pure MF DPI, and the lowest for MF MDDPI (with lactose). The PD effects (% decrease in plasma cortisol AUC_{0-24} compared to placebo treatment) are shown below in **Table 2**:

Table 2 Mean Plasma Cortisol AUC_{0-24} Data

Treatment	Plasma Cortisol AUC_{0-24} (μg-hr/dl)			
	MF MDDPI	Pure MF DPI	MF MDI	Placebo
100 μg (n=12)	165 (-3%)	159 (-6%)	167 (-2%)	170
200 μg (n=12)	168 (-7%)	177 (-2%)	163 (-10%)*	181
400 μg (n=12)	157 (-9%)	148 (-14%)*	150 (-13%)*	172
800 μg (n=12)	173 (-12%)	154 (-21%)*	129 (-34%)*	196

*. Statistically significant ($p<0.05$).

The % decrease in plasma cortisol AUC_{0-24} values (as compared to placebo group) intensified as the dose of each formulation increased. The above plasma cortisol data are consistent with MF systemic exposure based on PK data.

4. MULTIPLE-DOSE PHARMACOKINETICS

Study No. **C95-135**:

Multiple-dose PK of placebo, 400, 800, and 1200 μg QD plus 200 μg BID for 28 days using MF DPI (100 μg/inhalation) was investigated in this study. It was a randomized, multiple-dose, placebo-controlled, parallel-group study and 60 (28M+32F) patients completed the task. Blood samples were collected for plasma MF and cortisol levels. Twenty-four hr urine cortisol levels were also monitored. A 30-min intramuscular (IM) cosyntropin (250 μg) stimulation test was also administered to all patients on Day 29 (at the end of all treatments).

The study results show that there was essentially no measurable exposure in subjects treated with 200 μg BID or 400 μg QD and it is also true for several subjects in the 800 μg QD group. The C_{max} level was therefore considered the primary measure of exposure since many subjects had only one or two MF levels above the limit of quantitation (LOQ; 50 pg/ml). On each of the following days (Days 7, 14, 21, and 28) there was a dose-related increase in plasma C_{max} level which was statistically significant ($p<0.01$) across the QD dose groups. The steady state seemingly was reached by Day 7 for most of the dosing regimens, however, it was seemingly not reached for the 1200 μg QD dose group, since the mean plasma C_{max} levels increased with time, i.e., 123 pg/ml (Day 7), 164 pg/ml (Day 14), 201 pg/ml (Day 21), 243 pg/ml (Day 28). The reason is not known. However, it was complicated by the fact that several subjects had no measurable plasma levels on several study day(s) during the study.

Plasma cortisol AUC_{0-24} levels for all the active treatment groups compared to that for placebo group (as 100%) were calculated. The results showed that there were no dose-related or time-related changes. Overall, the mean plasma cortisol AUC_{0-24} ranged from 82 to 107%. The largest and only statistically significant ($p<0.05$) mean decrease from placebo was 18% observed for the 400 μg QD treatment group on Day 28 (**Table 3**).

Table 3 Mean (n=12) Plasma Cortisol AUC (μg·hr/dL) (Protocol No. C95-135).

Parameter	Day	Daily Dose				
		200 μg BID	400 μg QD	800 μg QD	1200 μg QD	Placebo
$AUC_{(11\ pm-11\ pm)}$	0	246	254	275	273	259
% of Placebo		95%	98%	106%	105%	
$AUC_{(11\ pm-11\ pm)}$	7	235	230	253	225	263
% of Placebo		89%	88%	96%	86%	
$AUC_{(11\ pm-11\ pm)}$	14	205	194	251	196	234
% of Placebo		88%	83%	107%	84%	
$AUC_{(11\ pm-8\ pm)}$	21	185	183	202	189	221
% of Placebo		84%	83%	91%	86%	
$AUC_{(11\ pm-11\ pm)}$	28	229	202*	253	229	245
% of Placebo		94%	82%	103%	94%	

*: $p<0.05$ compared with placebo.

For urinary free cortisol excretion, there were no significant ($p>0.10$) treatment group differences (ranged from 17 to 30 μg/24 hr at baseline and 10 to 34 μg/24 hr) during the treatment as compared to placebo group.

Finally, all the subjects had a normal plasma cortisol response (↑ by 7 to >18 μg/dl) from the baseline (at least 10 μg/dl) to a 30-min IM cosyntropin (250 μg) stimulation test on Day 29.

Study No. **C97-049**:

Multiple-dose PK of MF MDDPI 400 and 800 μg BID for 28 days was further investigated in 64 patients (46M+18F) in this study. It was a randomized, placebo-and positive-controlled, parallel study. Doses of 400 μg BID (to-be-marketed 200 μg/inhalation) and 800 μg BID (to-be-marketed 400 μg/inhalation) of MF were employed. Prednisone (2 x 5 mg tablets) QD was also given orally in the morning to one study group. Plasma levels for MF and cortisol and urinary free cortisol excretion were monitored. On Day 29, a 30-min cosyntropin stimulation test (250 μg) was also administered and plasma free cortisol levels were monitored.

The mean plasma MF PK parameters are summarized below in **Table 4** and the plasma MF profiles are in **Figures 3 and 4**:

Table 4. Mean (% CV) Plasma PK Parameters for MF

Dose (µg, BID)	Day	Cmax (pg/mL)		Tmax (hr)		AUC(tf) (pg·hr/mL)		AUC(0-12 hr) (pg·hr/mL)		Tf (hr)	
400[a]	7	87.8	(64)	1.08[b]	(32)	308	(100)	375[c]	(89)	5.77[b]	(63)
	14	106	(63)	1.69[b]	(31)	473	(95)	559[d]	(87)	6.54[b]	(38)
	21	93.5	(55)	2.46[c]	(83)	364	(81)	523[e]	(65)	6.43[c]	(42)
	28	114	(52)	2.10[d]	(84)	464	(93)	634[e]	(66)	6.67[d]	(50)
800	7	149	(69)	1.19[b]	(27)	741	(70)	819[d]	(64)	9.54[b]	(32)
	14	186	(49)	1.57[d]	(55)	977	(52)	1041	(47)	9.07[d]	(30)
	21	195	(50)	1.73[d]	(77)	1024	(64)	1073	(60)	8.83[d]	(41)
	28	194	(56)	1.64[c]	(66)	1029	(57)	1088	(53)	10.0[c]	(21)

a. Data include several subjects with plasma MF below the limit of quantitation.
b. n=13
c. n=14
d. n=15
e. n=12

Figure 3. Mean Plasma MF Profiles Post 400 µg BID

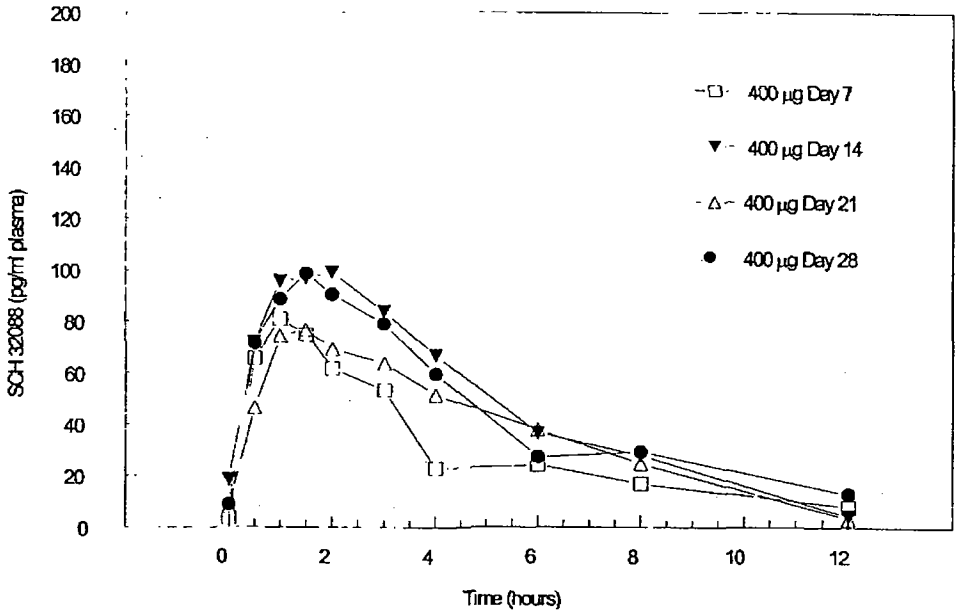
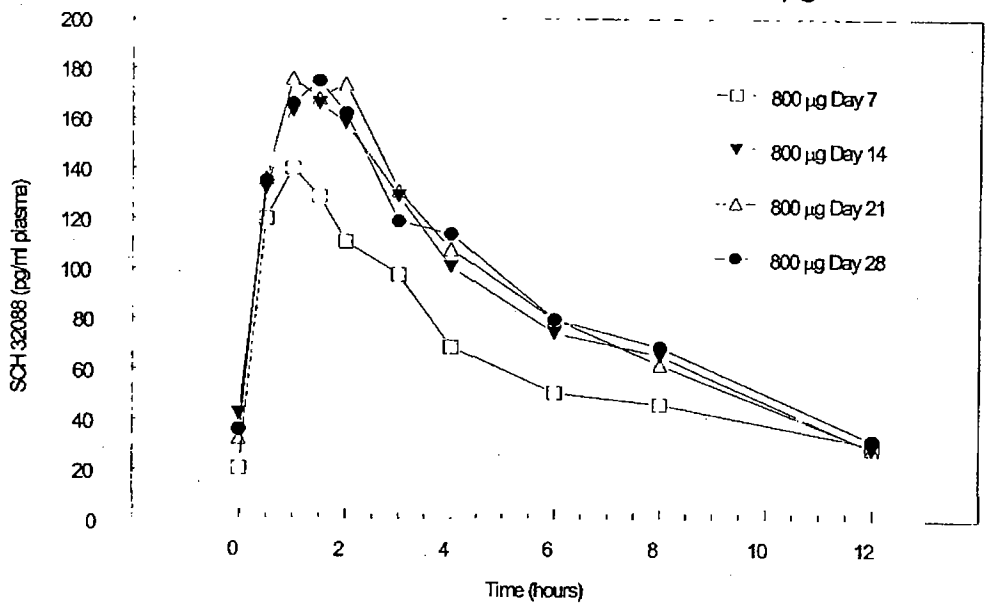


Figure 4. Mean Plasma MF Profiles Post 800 μg BID



Plasma MF levels are detectable in both 400 μg and 800 μg BID treatment groups and some accumulation at SS was observed. It is noted that for 400 μg BID dosing, plasma AUC extrapolated from the last detectable time point to 12 hrs represented 15 to 30% of AUC_{0-12} values and that for 800 μg BID, it represented only 5-10% of AUC_{0-12} values since more detectable plasma levels were obtained.

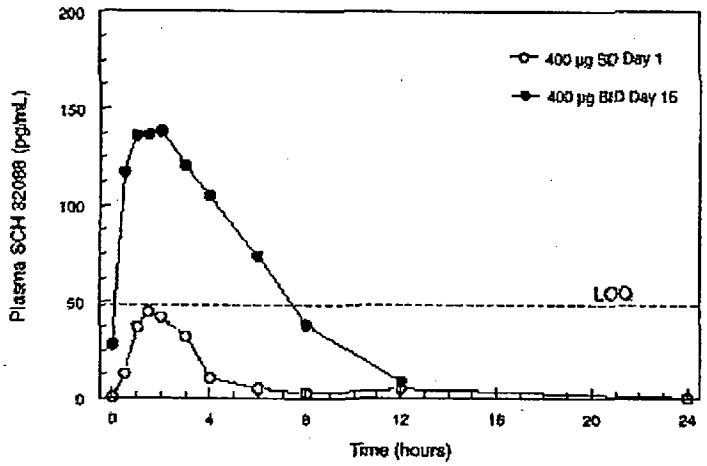
For PD data, mean plasma cortisol AUC_{0-24} was reduced by 25%** (Day 7), 19%* (Day 14), 19%* (Day 21), and 10% (Day 28) for 400 μg BID as compared to baseline and those for 800 μg BID were 40%** (Day 7), 26%** (Day 14), 25%** (Day 21), and 21* % (Day 28). The prednisone group had marked reduction in mean plasma cortisol AUC_{0-24} value, i.e., 72%** (Day 7), 65%** (Day 14), 68%** (Day 21), and 64** % (Day 28). **Note**: An asterisk (*) represents statistical significance ($p<0.05$) and two (**), represents statistical significance ($p<0.01$).

Prednisone group also had significantly lower ($p<0.01$) post-cosyntropin stimulation mean plasma cortisol response (14.5 μg/dl) compared to the placebo group (25.0 μg/dl). The post-cosyntropin stimulation mean plasma cortisol level for MF 800 μg BID group (20.8 μg/dl) was significantly ($p<0.02$) reduced, while the MF 400 μg BID group (23.2 μg/dl) was not significantly different from placebo group. As indicated by the sponsor due to an excessive % of unevaluable points (>50%), the urinary free cortisol data were not analyzed.

Study No. **C98-290**

Single-dose of 2 x 200 μg on Day 1 and multiple-doses of MF MDDPI 2x 200 μg BID were given to 24 patients with mild to moderate asthma in this Phase-1, Open-Label study. The to-be-marketed MF 200 μg strength was used. The mean plasma MF profiles on Days 1 and 15 are shown in **Figure 5**. The study results were consistent with those obtained previously from patients or healthy subjects.

Figure 5. Mean MF Plasma Levels on Days 1 and 15



4. BIOEQUIVALENCE:

No BE study is needed since both the to-be-marketed 200 and 400 μg strengths were tested in most of the clinical trials and PK studies. No PK equivalency between the 2 x 200 μg and 1 x 400 μg was compared in any PK study. However, based on the PK results obtained from Study No. **C97-049**, both 200 and 400 μg strengths provided comparable dose-normalized mean C_{max} values at SS (ranging from 93 to 114 pg/ml for the 400 μg BID dosing regimen).

5. METABOLISM:

Study No. **C97-047:**

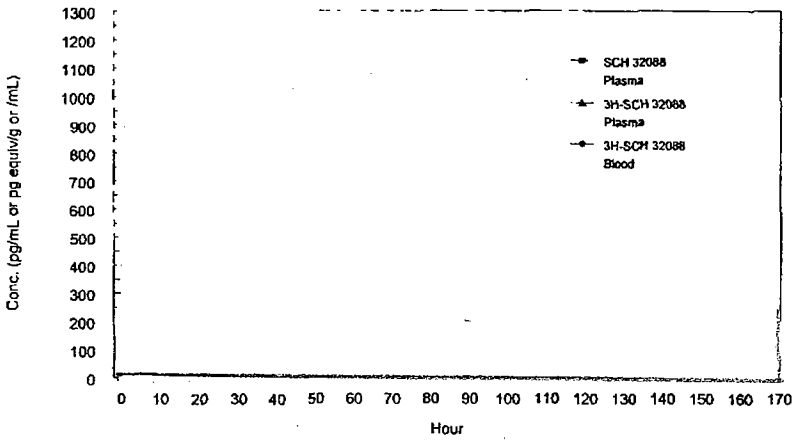
This *in vivo* metabolism study was conducted to characterize the absorption, metabolism and excretion of ^{3}H-MF following an oral inhalation to 6 healthy male subjects. A single 1-mg dose (mean: 0.97 mg) of ^{3}H-

MF (5 puffs) containing a total of 200 µCi tritium was received by each volunteer.

During the confinement at the study site, subjects' blood, urine, and feces were collected at frequent intervals over 7 days for the PK evaluations. Amount of radioactivity excreted in urine during each 24-hour period (Ae_{0-24}), and the total amount excreted during the 168-hr study period (Ae_{0-168}), were calculated. The total radioactivity in the feces was also determined. Mass balance (% recovery as the total administered radioactivity) was assessed for those recovered in urine, feces and expired air. Metabolite profiles of radioactivity in plasma, urine and feces were determined.

Profiles of radioactivity in plasma and blood and parent drug in plasma are shown in **Figure 6** below:

Figure 6. Radioactivity of ^{3}H-MF in Plasma and Blood and Parent Drug Concentration in Plasma Over A 7-day Study Period



Study results show that **1)** MF radioactivity was quantifiable in the plasma of all subjects, however, levels were limited to only one timepoint for some subjects, **2)** the ratio of radioactivity in plasma vs. blood (close to unity) indicated no or little accumulation of MF in red blood cells or no partitioning of drug-derived radioactivity into the red blood cells, and **3)** parent MF only contributed about 0.61 % of total radioactivity indicating extensive metabolism post administration via MF DPI. However, a long apparent $T_{1/2}$ for radioactivity in the body could be attributed to ^{3}H-water.

Mean radioactivity excretion data (up to 7 days) show that **1)** about 8% (ranging from 5.6 to 9.7%) was excreted in urine and 74% (ranging from

49.6 to 86.7%) in the feces. Metabolite profiles are divided into 5 regions (up to 48 hrs) as shown below in **Table 5**:

Table 5. Mean Percent of Radioactivity Recovered

Regions\Samples	Pooled Plasma (0-4 hr)	6% of Dose in Urine (0-48 hr)	40% of Dose in Feces (0-48 hr)
Very polar	6.5%	45.2%	5.5%
Polar	36.5%	22.7%	10.9%
Moderate Polar	47.5%	20.4%	13.8%
MF-like Polarity	9.3%	7.2%	65.7%
Non-Polar	0.3%	4.6%	4.0%

In the 0-48 hr fecal samples, the majority (65.7%) of the radioactivity collected was coincident with the retention time of parent drug and most likely represented the unabsorbed portion. No radioactivity was associated with parent compound in 0-48 hr urine further indicating that MF is extensively metabolized. Therefore, it is postulated that MF may undergo at least in part hydroxylation (most likely at the 6-position), hydrolysis of the furoate ester, and substitution of the C-21 chlorine.

The only identified metabolite is the 6-β-hydroxymometasone furoate (6-β-OH-MF). This metabolite has been shown *in vitro* to exhibit affinity for the human glucocorticoid receptor. As compared to the affinity of dexamethasone (as 1), MF had 8X and 6-β-OH-MF had 3X greater affinity. When potency was measured by the activation of the glucocorticoid receptor, MF had about 70X and 6-β-OH-MF had 2X more potency than dexamethasone. Reanalysis of plasma samples from Study No. **C97-046** showed no quantifiable 6-β-OH-MF plasma levels in any subjects administered MF after oral inhalation. These levels were very low and only quantifiable at levels close to the LOQ (≈70 pg/ml) even after IV administration. Finally, the plasma protein binding for MF in animals and humans was reported to be 98-99% over the range of 5-500 ng/ml, but that for 6-β-OH-MF was not provided.

6. GENDER:

It was noted from the previous OCPB review dated 09/11/97(NDA 20-762 for nasal spray MF suspension) that gender differences were reported. Females had a higher mean C_{max} (105% ↑) and a greater mean AUC (51% ↑) post oral dosing and also had a longer mean $T_{1/2}$ (115% ↑) post

IV dosing (Study No. **C95-050**). No gender differences were found post IV dosing in Study No. **I94-130**. Please see the previous Single-Dose PK Section of this review for details. Nevertheless, the reasons for the above discrepancies are not known.

7. DRUG-DRUG INTERACTION:

Study No. **I98-216**

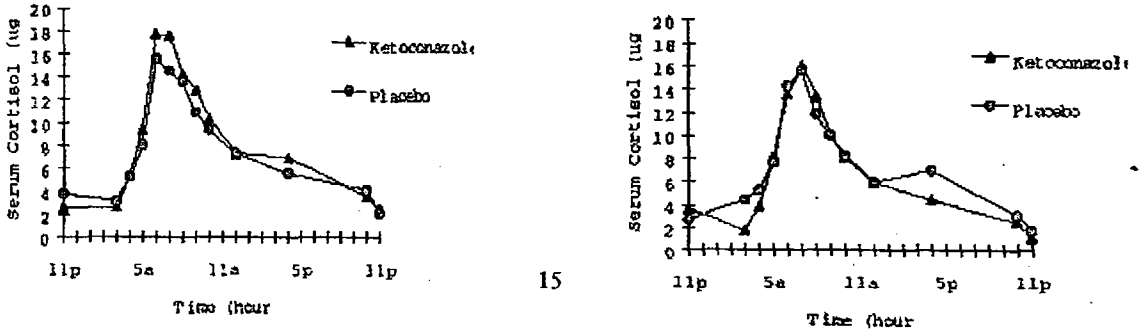
Twenty four healthy subjects received MF MDDPI 400 μg BID for 9 days and from Day 4 to Day 9, subjects also received either placebo or ketoconazole 200 mg BID. The results are shown in **Table 6** and **Figures 7A and 7B.**

Table 6. Distribution of MF C_{max} by Treatment and Day (Protocol No. I98-216)

	Ketoconazole		Placebo	
Concentration (pg/ml)	**Day 3** (n=12)	**Day 9** (n=12)	**Day 3** (n=12)	**Day 9** (n=12)
<50.1	4	4	6	6
50.1-100.1	6	2	6	0
100.2-150.2	2	2	0	6
150.3-200.3	0	0	0	0
>200.4	0	4 (211-324)	0	0

Figures 7A and 7B. Serum Cortisol Levels on Days 3 and 9

Day 3 **Day 9**



Generally, upon co-administration of ketoconazole, the number of detectable MF plasma levels increased and the serum cortisol levels decreased.

8. SPECIAL POPULATION:

Study No. **C98-291**

Single dose of MF MDDPI 400 μg was given to 8 healthy volunteers and 12 subjects with various degree of hepatic impairment (4 with mild, 4 with moderate, and 4 with severe hepatic impairment) using the to-be-marketed 200 μg strength. The study results showed that only 1 or 2 subjects in each category had detectable MF peak plasma levels (**Table 7**). An increase in number of detectable MF C_{max} was seen.

Table 7. Individual MF C_{max} and T_{max} Values Following SD of 400 μg of MF DPI to Subjects with Various Degrees of Chronic Liver Disease

Group	C_{max} (pg/ml)	T_{max} (hr)
Healthy (n=1 out of 8, detectable)	78.4	2.5
Mild (n=1 out of 4, detectable)	49.6	8.0
Moderate (n=2 out of 4, detectable)	72.6, 87.1	6, 24
Severe (n=2 out of 4, detectable)	79.3, 105	10, 8

9. PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS:

Plasma cortisol levels and/or urinary free cortisol levels were also obtained from one single-dose and two multiple-dose studies. Effects of MF DPI on adrenal suppression were studied. However, analysis of PK and pharmacodynamic (PD) relationships was not attempted.

10. FORMULATIONS, DOSAGE, AND DRUG ADMINISTRATION:

The to-be-marketed 200 and 400 μg formulations that were tested in the 2 PK/Bio study Nos. C97-046 (only the 200 μg formulation) and C97-049 (both the 200 and 400 μg formulations) and most of the clinical trials are shown below in **Table 8**.

Table 8. Composition of Asmanex (MF) DPI

Ingredient	Formulation # 3218 200 µg/Unit Dose Inhaler		Formulation # 3219 400 µg/Unit Dose Inhaler	
	µg/unit dose[1]	mg/inhale[2]	µg/unit dose[1]	mg/inhale[2]
Mometasone Furoate, USP	200		400	
Lactose Anhydrous, NF				
Total				

1. Unit dose is defined as a single inhalation.
2. Both 200 µg and 400 µg strength inhalers have identical target fills of mg of MF: lactose anhydrous agglomerates.

A not to-be-marketed formulation (# 3118) was also used in the single-dose dose-proportionality study No. **I94-130** and one multiple-dose PK study, No. **C95-135**. Formulation # 3118 [ ] lactose anhydrous, NF [ ] is exactly half that of Formulation # 3218. All the batches manufactured for PK and clinical trials were made at a batch [ ] of what a full production size batch will be. However, Formulation # 3118 was manufactured using a pilot scale [ ]

11. ASSAY:

The same validated assay method (LC/MS/MS) that was used previously for MF in NDA 20-762 and reviewed by OCPB was also employed in this NDA. As reported for study No. **C97-049**, standard curves were prepared from 50 to 5005 pg/ml (n=8) and the values of % coefficient of variation (%CV) for **1)** intra-assay precision were reported to be 2.7% to 12.7% (at 50 pg/ml) and **2)** intra-assay accuracy (% bias) were –2.1% to 2.4%. The QC samples were prepared at 149, 1653, and 3972 pg/ml (n=3) and the intra-assay precision were reported to be 6.2% to 10.5% (at 149 pg/ml) and intra-assay accuracy (% bias) were –7.4% (at 149 pg/ml) to –5.1%. The LOQ for MF in plasma was 50 pg/ml. The assay results provided are acceptable.

The validation report(s) of assay method(s) for plasma or urinary cortisol levels, however, was/were not provided. Upon request, the sponsor submitted the above assay methods and the validation reports on 08/02/99.

In Study No. **I94-130**, serum cortisol was analyzed [ ] using a standard commercially available RIA kit [ ] The following performance data provided in the kit were: **1)** Intraday Assay: %CV for 7.7, 14.6, 20.6, and 32.6 µg/dl concentrations studied being 3.5, 3.6, 2.4, and 4.5%, respectively and **2)** Interday Assay: CV % for 7.9, 15.1, 23.1, and 32.6 µg/dl concentrations studied being 5.8, 4.8, 6.4, and 7.8%, respectively. However, no assay results from the above study itself were provided.

In Study No. **I95-135**, serum cortisol was analyzed using an RIA method [ ] The following performance data provided in the kit were: **1)** Intraday Assay: CV % for 2.9, 12.1, and 47.1 µg/dl studied being 6.6, 7.7, and 8.8%, respectively and **2)** Interday Assay: CV % for 3.7, 12.1, and 36.9 µg/dl studied being 9.0, 9.8, and 8.8%, respectively. The serum cortisol assay was performed at [ ] Urine samples for free cortisol used an HPLC method (no performance data provided) and the assay was performed at [ ] However, no assay results from the above study itself (serum or urine) were provided.

In Study No. **C97-049**, serum cortisol was analyzed at [ ] using an RIA method. Standard curves of 0.5 to 64 µg/dl (n=8) and QC of 2 to 32 µg/dl (n=3) were prepared, but no assay results were provided. Urine samples for free cortisol were analyzed at [ ] using the same HPLC method as that used in Study No. **I95-135**. However, no assay results from the above study itself were provided.

Finally, the above assay methods for serum and/or urinary cortisol levels are found less satisfactory since no assay results for each study were provided. The sponsor needs to provide the missing assay results as stated above.

III. COMMENTS TO THE MEDICAL OFFICER:

1. Both the to-be-marketed 200 and 400 µg strengths were tested in one of the multiple-dose PK studies. The single-dose dose-proportionality (100 to 800 µg) was investigated in the PK studies. The recommended dosing regimens (200 and 400 µg QD and 200 and 400 µg BID) were also evaluated in the PK studies. No equivalency for the PK performance between the 2x 200 µg and 1 x 400 µg MF DPI was compared in any PK

study. However, based on the PK results obtained from Study No. **C97-049** (parallel-group study), both 200 and 400 μg strengths provided comparable dose-normalized mean C_{max} values at SS (ranging from 93 to 114 pg/ml for the 400 μg BID dosing regimen). Therefore, from PK perspective, both 200 and 400 μg strengths are acceptable.

2. Systemic exposure of MF using MF MDDPI at the recommended dose was usually low, despite LOQ being 50 pg/ml.

3. Since this is a locally acting drug product, no dose adjustment can be recommended for patients with hepatic impairment or for concomitant administration of ketoconazole. However, plasma MF levels appeared to increase with severity of hepatic impairment or with co-administration of ketoconazole.

IV. RECOMMENDATION:

The human PK/Bio section of Schering's NDA 21-067 (serial No. 000) for Asmanex (MF DPI 200 and 400 μg from the mouthpiece) that was submitted on 11/30/98 and 08/02/99 and to IND 46, 216 on 07/09/99 has been reviewed by OCPB/DPE II. OCPB is of the opinion that the NDA is overall acceptable. The following General Comments (Nos. 1 and 2) and Labeling Comment as appropriate need to be conveyed to the sponsor.

V. GENERAL COMMENTS: (Nos. 1 and 2 need to be sent to the sponsor)

1. Effects of MF DPI on adrenal suppression were studied. However, analysis of PK and pharmacodynamic (PD) relationships was not attempted. It is recommended that the PK/PD relationships be analyzed in future studies.

2. The assay methods and its validation reports for plasma or urinary cortisol levels were incomplete. Upon requests, they were submitted on 08/02/99, however, the assay results are still considered less satisfactory, since no actual assay results from some individual studies were provided along with the assay methodology. It is recommended that in addition to performance data for the assay validation (copies from the commercial kits), the actual assay results obtained from the following individual studies, Nos. **I94-130, I95-135,** and **C97-049** be submitted.

VI. LABELING COMMENT:

The following is the Agency's version of PK subsection under the Clinical Pharmacology Section:

1 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

Drug-Drug Interaction: An inhaled dose of mometasone furoate 400 mcg was given to 24 healthy subjects twice daily for 9 days and ketoconazole 200 mg (as well as placebo) were given twice daily concomitantly on Days 4 to 9. Mometasone furoate plasma concentrations were <150 pcg/ml on day 3 prior to co-administration of ketoconazole or placebo. Following comcomitant administration of ketoconazole, only 4 (out of 12) subjects in ketoconazole treatment group (n=12) had peak plasma concentrations of mometasone furoate >200 pcg/ml on Day 9 (211 to 324 pcg/ml). Since mometasone furoate plasma levels appear to increase and plasma cortisol levels appear to decrease upon concomitant administration of ketoconazole, caution should be exercised.

CPB Briefing on 09/20/99: Drs. ML Chen, RS Uppoor, TM Chen, S. Al-Fayoumi, M. Wakelkamp-Barnes, and S. Suarez and Mr. Hunt

Tien-Mien Chen 09/12/99

09/12/99

Tien-Mien Chen, Ph.D.

Division of Pharmaceutical Evaluation II

RD initialed by Ramana Uppoor, Ph.D. RU 09/14/99

FT initialed by Ramana Uppoor, Ph.D. RUppoor 09/22/99

cc: NDA 21-067, IND 46,216, HFD-570 (O'Hearn, Dunn), HFD-870 (M.L. Chen, R. Uppoor, T.M. Chen), CDR (B. Murphy)

NDA 21-067 (Asmanex; Mometasone Furoate 200 and 400 μg MDDPI)

APPENDIX 1

Sponsor's Proposed Package Insert (11/30/98 Version)

13 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

NDA 21-067 (Asmanex; Mometasone Furoate 200 and 400 μg MDDPI)

APPENDIX 2

Individual Study Reports

Study No. I94-130 (Volume 1.55)

Synopsis

NAME OF COMPANY: Schering-Plough Research Institute NAME OF FINISHED PRODUCT: Mometasone Furoate Powder + Lactose Dry Powder Inhaler NAME OF ACTIVE INGREDIENT(S): Mometasone Furoate	INDIVIDUAL STUDY SYNOPSIS Page 1 of 2
Title of the Study: Single-Dose Comparative Systemic Bioactivity Study of Mometasone Furoate/Lactose (SCH 32088) Administered by a Dry Powder Inhaler	
Investigator(s): [ ]	
Study Center(s): [ ]	
Publication(s): None	
Studied Period: 18 APR to 07 JUN 1995	**Clinical Phase:** I
Objectives: To evaluate the potential for systemic exposure based on hypothalamic-pituitary-adrenal (HPA) axis function of mometasone furoate/lactose (MF/L) powder formulation doses (100 µg, 200 µg, 400 µg, and 800 µg) administered to healthy volunteers by pulmonary inhalation with a breath-actuated dry powder inhaler (DPI) compared with mometasone furoate (MF) pure powder administered by inhalation with a DPI, with MF suspension administered by inhalation with an aerosolized metered-dose inhaler (MDI), and with lactose (placebo) powder administered by inhalation with a DPI.	
Methodology: Single-dose, evaluator-blind, four-way crossover within randomized, parallel-treatment groups, placebo-controlled study. Volunteers assigned to MF dose groups: 12 received 100 µg, 12 received 200 µg, 12 received 400 µg, and 12 received 800 µg. Volunteers received each of the 4 treatments within their assigned dose group in cross-over design.	
Number of Subjects: 48 healthy male volunteers between 19 and 44 yr.	
Diagnosis and Criteria for Inclusion: Adult male volunteers within 18-45 years of age in good health based on medical history, physical examination, electrocardiogram, and routine laboratory tests (blood chemistry, hematology, and urinalysis). Screening morning plasma cortisol concentration 10-25 µg/dL, (except numbers 42 and 48 whose values were 26.0 and 28.0 µg/dL, respectively). Forced expiratory volume (FEV_1) greater than75% predicted.	
Test Product, Dose, Mode of Administration, Batch No(s).: MF/L DPI (100 µg/inhalation) batch no. 33208-118; single-dose administered by pulmonary inhalation at 2300 hours according to random code at doses of 100 µg, 200 µg, 400 µg, and 800 µg.	
Reference Therapy, Dose, Mode of Administration, Batch No(s).: MF pure powder DPI (100 µg/inhalation) batch no. 33208-116, MF MDI (50 µg/burst) batch no. 35923-016, Placebo Lactose DPI (0 µg/inhalation) batch no. 33208-093. MF treatments administered as a single-dose of either 100 µg, 200 µg, 400 µg or 800 µg. Placebo lactose administered as a single dose, number of inhalations determined by group (i.e. placebo inhalations = MF DPI inhalations). All treatments administered at 2300 hrs.	
Duration of Treatment: 4 single-doses administered at 2300 hrs with a 72 hr washout period between each dose. Duration of study confinement not more than 18 days.	
Criteria for Evaluation: 24-hour plasma cortisol AUC following each treatment.	
Statistical Methods: Analysis of Variance (ANOVA)	

NAME OF COMPANY: Schering-Plough Research Institute NAME OF FINISHED PRODUCT: Mometasone Furoate Powder + Lactose Dry Powder Inhaler NAME OF ACTIVE INGREDIENT(S): Mometasone Furoate	INDIVIDUAL STUDY SYNOPSIS Page 2 of 2

Title of the Study: Single-Dose Comparative Systemic Bioactivity Study of Mometasone Furoate/Lactose (SCH 32088) Administered by a Dry Powder Inhaler

SUMMARY - CONCLUSIONS

Results:

Clinical Pharmacology: Analyses of the results suggest that, compared with placebo, both the MF pure powder and MF/L formulations at single doses of 100 µg, 200 µg, 400 µg, and 800 µg reduced plasma cortisol $AUC_{(0\text{-}24)}$ values by 6%, 2%, 14%, and 21% and by 3%, 7%, 9%, and 12%, respectively. The changes observed with the MF/L DPI were not significantly different from placebo, whereas the effects of the MF pure powder formulation were significantly different from placebo at the 400 µg and 800 µg dose. Further analysis indicated that there was no statistically significant difference between the MF pure powder and MF/L powder formulations.

The number of subjects with quantifiable (LOQ = 50 pg/mL) plasma MF concentrations increased with dose; differences between the delivery systems were apparent at the 3 higher doses. In general, plasma concentrations were highest in subjects treated with MF MDI, and lowest with MF/L DPI. Statistical analyses conducted on the highest dose group indicated that Cmax values for the MF MDI (suspension) were higher than the corresponding values for the MF DPI; both Cmax and AUC(tf) were higher for MF DPI than for MF/L DPI.

Treatment	Parameter[a]	Plasma Mometasone Furoate							
		100 µg		200 µg		400 µg		800 µg	
		Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV
A: MF/L DPI	Cmax	0	–	0	–	27.7	127	79.9	48
	AUC(tf)	0	–	0	–	63.6	215	318	109
B: MF DPI	Cmax	6.61	346	18.0	184	52.6	112	131	38
	AUC(tf)	6.61	346	63.8	217	259	125	905	81
C: MF MDI	Cmax	0	–	20.4	181	66.7	79	189	56
	AUC(tf)	0	–	76.2	189	338	99	1363	79

a: Units: Cmax-pg/ml, AUC(tf)-pg.hr/ml.

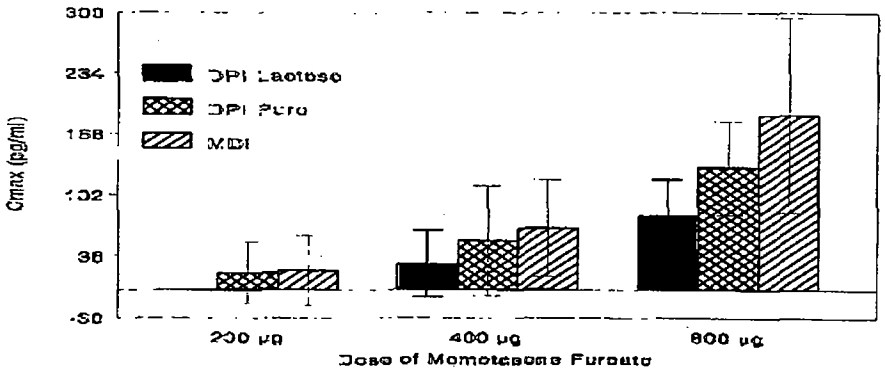
Efficacy: No efficacy evaluations were planned for this study.

Safety: 5 volunteers (10%) reported at least 1 adverse event consisting of: headache 2 (4%), dyspepsia 1 (2%), acne 1 (2%) and injection site inflammation 1 (2%). All adverse events were mild to moderate in severity. No serious adverse events were reported.

Conclusions: The administration of single-doses of MF pure powder or MF/L via DPI to healthy adult male volunteers at doses of 100 µg, 200 µg, 400 µg and 800 µg was safe and well tolerated. At increasing single doses, systemic exposure was less with MF/L than with the MF pure powder.

The mean MF C_{max} levels obtained are shown below in **Figure 1**.

Figure 1. Mean plasma MF C_{max} Values



The PD effects (% decrease in plasma cortisol AUC_{0-24} compared to placebo treatment) are shown below in **Table 1**:

Table 1. Mean Plasma Cortisol AUC_{0-24} Data

Treatment	Plasma Cortisol AUC_{0-24} (µg-hr/dl)			
	MF MDDPI	Pure MF DPI	MF MDI	Placebo
100 µg (n=12)	165 (-3%)	159 (-6%)	167 (-2%)	170
200 µg (n=12)	168 (-7%)	177 (-2%)	163 (-10%)*	181
400 µg (n=12)	157 (-9%)	148 (-14%)*	150 (-13%)*	172
800 µg (n=12)	173 (-12%)	154 (-21%)*	129 (-34%)*	196

*. Statistically significant ($p<0.05$).

As the MF doses increased from 100 to 800 µg, the number of subjects that had measurable plasma MF levels increased in a dose-related manner. The % decrease in plasma cortisol AUC_{0-24} values (as compared to placebo group) intensified as the dose increased, but the differences (-3 to –12%, **second column from left**) were <u>not</u> statistically significant ($p>0.05$).

<u>Reviewer's comments</u>:

The individual data were spot checked and the study results are found acceptable. However, for the analysis of serum cortisol levels, <u>no</u> assay results from this study were provided. Therefore, the above assay is less satisfactory and the sponsor needs to provide the missing assay data.

Study No. C95-135 (Volume 1.60)

Synopsis

NAME OF COMPANY: Schering-Plough Research Institute **NAME OF FINISHED PRODUCT:** Mometasone Furoate Powder + Lactose Dry Powder Inhaler **NAME OF ACTIVE INGREDIENT(S):** Mometasone Furoate	**INDIVIDUAL STUDY SYNOPSIS** Page 1 of 2
Title of the Study:	SCH 32088: Multiple-Dose Safety and Tolerance Study of Mometasone + Lactose Dry Powder in Volunteers with Symptoms of Moderate Asthma (C95-135)
Investigator(s):	[illegible]
Study Center(s):	[illegible]
Publication(s):	None
Studied Period: 08 FEB 1996 to 15 MAY 1996	**Clinical Phase:** I
Objectives: To evaluate the safety and tolerance of 400 µg, 800 µg and 1200 µg of mometasone furoate (SCH 32088) plus lactose dry powder (MF/L) administered once daily and 200 µg administered twice daily for 28 consecutive days by inhalation with a breath-activated dry powder inhaler (DPI) in patients with a history of moderate asthma.	
Methodology: Multiple-dose, randomized, third-party blind, parallel group, placebo-controlled study. Volunteers assigned to MF/L groups: 12 received 400 µg qd, 12 received 200 µg bid (q12h), 12 received 800 µg qd, 12 received 1200 µg qd and 12 received 0 µg (placebo) qd. Cosyntropin stimulation test (30 min) administered on Day 29 (post-dose) to determine HPA axis function.	
Number of Subjects: 60 healthy male and female volunteers.	
Diagnosis and Criteria for Inclusion: Adult volunteers within 18-50 years of age in good health based on medical history, physical examination, electrocardiogram, and routine laboratory tests (blood chemistry, hematology, and urinalysis) with a history of moderate asthma (FEV_1 between 60% to 80% predicted) and who required asthma medication were empaneled for this study. Volunteers demonstrated reversibility of bronchospasm with a 15% improvement of FEV_1 from baseline after two inhalations (2 x 90 µg) of albuterol administered by metered-dose inhaler. Volunteers also had a screening morning (approximately 8 a.m.) plasma cortisol concentration between 10 and 25 µg/dL.	
Test Product, Dose, Mode of Administration, Batch No(s).: MF/L DPI (100 µg/inhalation) batch no. 35932-040; pulmonary inhalation at doses of 400 µg qd, 200 µg bid, 800 µg qd or 1200 µg qd.	
Reference Therapy, Dose, Mode of Administration, Batch No(s).: Placebo Lactose DPI (0 µg/inhalation) ,batch no. 35923-037; pulmonary inhalation. The number of placebo inhalations = 1200 µg MF/L inhalations (ie, 12).	
Duration of Treatment: Doses administered in the morning for all treatment groups (approximately 8 a.m.) and in the evening (approximately 8 p.m.) for 200 µg bid group. All treatments administered for 28 consecutive days.	
Criteria for Evaluation: 24-hour plasma cortisol AUC following each treatment.	
Statistical Methods: Analysis of Variance (ANOVA)	

NAME OF COMPANY: Schering-Plough Research Institute NAME OF FINISHED PRODUCT: Mometasone Furoate Powder + Lactose Dry Powder Inhaler NAME OF ACTIVE INGREDIENT(S): Mometasone Furoate	INDIVIDUAL STUDY SYNOPSIS Page 2 of 2

Title of the Study: SCH 32088: Multiple-Dose Safety and Tolerance Study of Mometasone + Lactose Dry Powder in Volunteers with Symptoms of Moderate Asthma (C95-135)

SUMMARY - CONCLUSIONS

Results:

Clinical Pharmacology: For the QD dose groups (400 µg, 800 µg and 1200 µg) on Days 14, 21 and 28, there was a significant ($p<0.01$) dose-related increase in mometasone furoate (MF) plasma concentrations; MF concentrations were significantly ($p<0.01$) greater in the 1200 µg group vs. the 400 µg and 800 µg; there was evidence of increasing MF plasma concentrations on later dosing days for the 1200 µg QD dose group. Mean maximal MF plasma concentration (Cmax) were below the LOQ for the 200 µg BID dose group and were less than twice the LOQ in the 400 µg QD dose group. There were no dose-related changes observed in mean plasma cortisol AUC values; mean cortisol AUCs ranged from 82% to 107% of the placebo treated group. There were no significant ($p>0.05$) overall treatment effects for maximal (Cmax) or 8 a.m. (C_{8AM}) plasma cortisol values. On Day 29, all subjects had a normal 30-minute plasma cortisol response to an i.m. cosyntropin (250 µg) injection. There were no treatment group differences ($p>0.10$) in urinary free cortisol concentrations.

Efficacy: No efficacy evaluations were planned for this study. However, FEV_1 and PEFR results assessed for safety purposes were generally greater for the active treatments groups than for the placebo group.

Safety: 13 subjects (22%) reported at least one adverse event (AE); headache 9 (15%), nausea 1 (2%), dry mouth 5 (8%), dry cough 1 (2%), pharyngitis 4 (7%), and rhinitis 1 (2%). All AEs were mild in severity. There were no serious and unexpected AEs.

Conclusions: The administration of multiple-doses of mometasone furoate plus lactose dry powder via dry powder inhaler (DPI) to adult males and females with moderate asthma at doses of 200 µg BID and of 400 µg, 800 µg and 1200 µg QD for 28 days was safe and well tolerated. In spite of detectable plasma concentrations of mometasone furoate at various times in some subjects, results from plasma cortisol AUC evaluations and from responses to a cosyntropin stimulation test indicated that no clinically relevant systemic exposure resulted from these dosage regimens of mometasone furoate/lactose powder administered by pulmonary inhalation with a dry powder inhaler.

Table 3 Mean (n=12) Plasma Cortisol AUC (μg·hr/dL) (Protocol No. C95-135).

Parameter	Day	Daily Dose				
		200 μg BID	400 μg QD	800 μg QD	1200 μg QD	Placebo
$AUC_{(11\ pm\text{-}11\ pm)}$	0	246	254	275	273	259
% of Placebo		95%	98%	106%	105%	
$AUC_{(11\ pm\text{-}11\ pm)}$	7	235	230	253	225	263
% of Placebo		89%	88%	96%	86%	
$AUC_{(11\ pm\text{-}11\ pm)}$	14	205	194	251	196	234
% of Placebo		88%	83%	107%	84%	
$AUC_{(11\ pm\text{-}8\ pm)}$	21	185	183	202	189	221
% of Placebo		84%	83%	91%	86%	
$AUC_{(11\ pm\text{-}11\ pm)}$	28	229	202	253	229	245
% of Placebo		94%	82%	103%	94%	

*: $p<0.05$ compared with placebo.

For QD dosing, MF C_{max} levels increased as doses increased and SS was reached after Day 7 (some accumulation). For 200 μg BID dosing, the MF plasma levels were not detectable (below the LOQ). For plasma cortisol $AUC_{0\text{-}24}$ ⇒ 82%* to 107% as compared to placebo group (*; $p<0.05$ for 400 μg QD).

Finally, all the subjects had a normal plasma cortisol response (↑ by 7 to >18 μg/dl) from the baseline (at least 10 μg/dl) to a 30-min IM cosyntropin (250 μg) stimulation test on Day 29.

Reviewer's Comments:

The individual data were spot checked and the study results are found acceptable. However, for the analysis of serum cortisol or urinary free cortisol levels, no assay results from this study were provided. Therefore, the above assay is less satisfactory and the sponsor needs to provide the missing plasma or urinary assay data.

Study No. C97-049 (Volume 1.71)
Synopsis

Title of the Study:	SCH 32088: Multiple-Dose Safety and Tolerance Study of Mometasone Furoate and Lactose Powder Administered by Dry Powder Inhaler in Subjects with Symptoms of Moderate Asthma (Protocol No. C97-049-01).	
Investigator(s):	[redacted]	
Publication(s):	None	
Studied Period:	**20 May 1997 - 4 July 1997**	**Clinical Phase: I**

Objective(s): To evaluate the potential for systemic exposure of mometasone furoate (MF) plus lactose powder administered by DPI (MF/L-DPI) at doses of either 400 µg twice-daily or 800 µg twice-daily for 29 consecutive days compared with prednisone administered orally at a dose of 10 mg once-daily in the morning and with placebo DPI in patients with mild to moderate asthma.

Methodology: Multiple-dose, randomized, third-party masked, parallel group, placebo- and positive-controlled study. Subjects assigned to groups: 16 received MF 400 µg BID, 16 received MF 800 µg BID, 16 received prednisone 10 mg QD (a.m.) and 16 received 0 µg (placebo lactose DPI) BID. Cosyntropin stimulation test (30 minute) was administered on Day 29 (post-dose) to determine HPA axis function. Twenty-four hour plasma and urine cortisol collected on Days 7, 14, 21 and 28. Plasma concentrations of SCH 32088 were determined using a validated LC/MS/MS assay with a lower limit of quantitation of 50 pg/mL. Pharmacokinetic analyses were determined from blood samples collected prior to dosing and at specified times during the 12-hour period following dosing on Study Days 7, 14, 21 and 28.

Number of Subjects: 64 male (n=46) and female (n=18) subjects.

Diagnosis and Criteria for Inclusion: Adult subjects within 18-50 years of age in good health based on medical history, physical examination, electrocardiogram and routine laboratory tests (blood chemistry, hematology and urinalysis) with a history of moderate asthma (FEV_1 between 60% to 80% predicted) and who required asthma medication were empaneled for this study. Subjects demonstrated reversibility of bronchospasm with a 15% or greater improvement of FEV_1 from Baseline after two inhalations (2 x 90 µg) of albuterol administered by metered-dose inhaler. Subjects also had a screening morning (approximately 8 a.m.) serum cortisol concentration between 10 and 25 µg/dL.

Test Product, Dose, Mode of Administration, Batch No(s): MF/L-DPI (200 µg/inhalation) 400 µg BID via pulmonary inhalation; Batch No. 36809-057, MF/L-DPI (400 µg/inhalation) 800 µg BID via pulmonary inhalation; Batch No. 36809-039.

Reference Therapy, Dose, Mode of Administration, Batch No(s): Placebo lactose DPI (0 µg/inhalation), 2 inhalations BID; Batch No. 36809-056. Prednisone (Deltasone®) 5 mg tablets; oral 10 mg QD; Batch No. 35923-037.

Duration of Treatment: Doses administered a.m. and p.m. for all DPI treatment groups (approximately 8 a.m. and 8 p.m.) and a.m. only for the prednisone group. All treatments were administered for 29 consecutive days. The p.m. treatment administration on Day 29 was omitted.

Criteria for Evaluation: Serum cortisol (HPLC assay) response to the Day 29 Cosyntropin Stimulation Test and 24-hour serum cortisol AUC on Days 7, 14, 21 and 28.

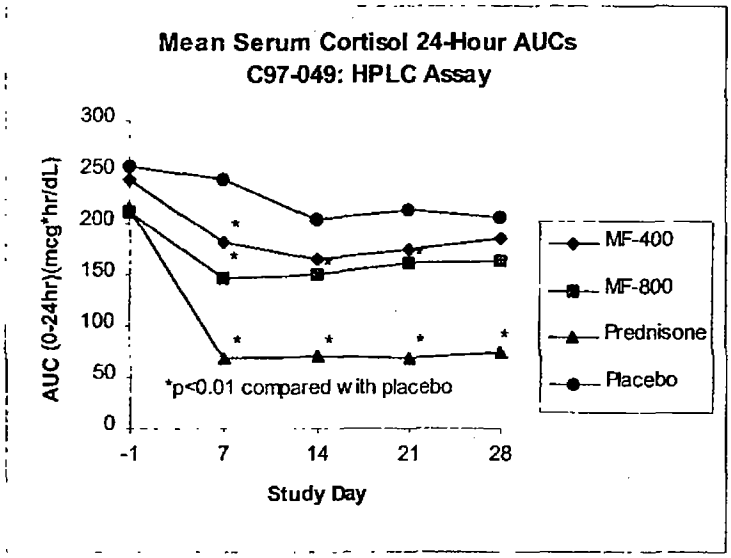
Statistical Methods: Analysis of variance (ANOVA) and analyses of covariance including Baseline as a covariate (ANCOVA).

SUMMARY-CONCLUSIONS:

RESULTS:

Clinical Pharmacology: Mean serum cortisol (HPLC assay) $AUC_{(0-24)}$ values for the MF 400 µg BID group were marginally different from the placebo group values on treatment days 14, 21 or 28 (see **Figure**). For the MF 800 µg BID treatment group, cortisol $AUC_{(0-24)}$ values were significantly ($p<0.01$) reduced compared with placebo values by 40%, 26%, 25% and 21% on study Days 7, 14, 21 and 28, respectively. The prednisone 10 mg QD group had cortisol $AUC_{(0-24)}$ values significantly reduced ($p<0.01$) from placebo by 72%, 65%, 68% and 64% on study Days 7, 14, 21 and 28, respectively, and from the MF 400 µg and 800 µg BID treatment groups. Urine samples were collected for determination of free cortisol content. However, due to an excessive percentage of unevaluable data points (>50%), the data were not analyzed.

Title of the Study: SCH 32088: Multiple-Dose Safety and Tolerance Study of Mometasone Furoate and Lactose Powder Administered by Dry Powder Inhaler in Subjects with Symptoms of Moderate Asthma (Protocol No. C97-049-01).



After 29 consecutive days of treatment and approximately 2 hours after the final study treatment, the prednisone group had significantly ($p<0.01$) lower serum cortisol concentrations than all other groups before and 30-minutes after intramuscular stimulation with cosyntropin (250 µg). Only one subject (1/16) in the prednisone group reached a post-stimulation serum cortisol concentration of >18 µg/dL compared with 15/16 in the placebo group, 14/16 in the MF DPI 800 µg per day group, and 11/16 in the MF DPI 1600 µg per day group.

Mean (%CV) pharmacokinetic parameters at the 400 µg and 800 µg twice daily doses are summarized in the table below. Following the 400 µg SCH 32088 twice daily dose, plasma concentrations of SCH 32088 were not quantifiable in one to three subjects on Days 7, 14, 21 and 28. In those subjects whom SCH 32088 was quantifiable, the concentrations were low, and the mean maximal concentration (Cmax) did not exceed 114 pg/mL. Following the SCH 32088 800 µg twice daily dose, plasma concentrations were not quantifiable in at least one patient on each sampling day. Mean SCH 32088 concentrations in this dose group, however, were higher than those in the 400 µg twice daily dose group. The mean maximal Cmax in the 800 µg BID dose group was 195 pg/mL.

Title of the Study: SCH 32088: Multiple-Dose Safety and Tolerance Study of Mometasone Furoate and Lactose Powder Administered by Dry Powder Inhaler in Subjects with Symptoms of Moderate Asthma (Protocol No. C97-049-01).

Mean (%CV) Pharmacokinetic Parameters of SCH 32088 Following Multiple-Dose Pulmonary Administration of SCH 32088 and Lactose Powder by DPI to Patients with Moderate Asthma (n=16/treatment group).

Dose (µg, BID)	Day	Cmax (pg/mL)	(hr)	Tmax	(pg·hr/mL)	AUC(tf)	(hr)	tf	
400[a]	7	87.8	(64)	1.08[b]	(32)	308	(100)	5.77[b]	(63)
	14	106	(63)	1.69[b]	(31)	473	(95)	6.54[b]	(38)
	21	93.5	(55)	2.46[c]	(83)	364	(81)	6.43[c]	(42)
	28	114	(52)	2.10[d]	(84)	464	(93)	6.67[d]	(50)
800	7	149	(69)	1.19[b]	(27)	741	(70)	9.54[b]	(32)
	14	186	(49)	1.57[d]	(55)	977	(52)	9.07[d]	(30)
	21	195	(50)	1.73[d]	(77)	1024	(64)	8.83[d]	(41)
	28	194	(56)	1.64[c]	(66)	1029	(57)	10.0[c]	(21)

a: Data include several subjects with plasma SCH 32088 below the limit of quantitation (50 pg/mL).
b: n=13
c: n=14
d: n=15
e: n=12

Safety: Nineteen (19) patients (30%) reported at least one adverse event; dry throat 11 (17%), headache 10 (16%), pharyngitis 1 (2%), abdominal pain 1 (2%), diarrhea 1 (2%), and nausea 2 (3%). Adverse events were mild to moderate in severity. No serious nor unexpected adverse events were reported. No subject discontinued treatment nor participation in this study due to adverse events. The follow-up physical examination and vital signs for all patients were within the ranges seen in adult male and female asthma patients. At follow-up, all ECG changes from Baseline (screening) were deemed by the Investigator to be normal or not clinically significant. There were no clinically relevant changes in clinical laboratory safety test results reported for any patient.

CONCLUSIONS:

- The administration of multiple-doses of MF/L via a DPI to adult male and female patients with mild to moderate asthma at MF doses of 400 µg and 800 µg twice daily for 29 days was well-tolerated.
- MF plasma concentrations were detectable in both the 400 µg BID and 800 µg BID dosage regimens and were lower following the 400 µg BID dose.
- Mean serum cortisol $AUC_{(0-24)}$ values across the treatment periods decreased with the placebo group having the highest values, followed by the MF 400 µg BID group, the MF 800 µg BID group, and the prednisone 10 mg daily group. Prednisone values were significantly lower than both of the MF treatment groups.
- The post-cosyntropin stimulation mean serum cortisol concentration for the MF 400-µg BID group was similar to placebo, while the MF 800 µg BID and prednisone 10 mg daily groups were significantly reduced. Only one of 16 patients in the prednisone group reached a post-stimulation serum cortisol concentration >18 µg/dL compared with 15/16 in placebo, 14/16 in MF 400 µg BID, and 11/16 in 800 µg BID groups.
- The systemic exposure effects from both MF dose regimens were remarkably less than those observed with oral prednisone at a daily dose as low as 10 mg.

The mean plasma MF PK parameters are summarized below in **Table 1** and the plasma MF profiles are in **Figures 1 and 2**:

Table 1. Mean (% CV) Plasma PK Parameters for MF

Dose (µg, BID)	Day	Cmax (pg/mL)		Tmax (hr)		AUC(tf) (pg·hr/mL)		AUC(0-12 hr) (pg·hr/mL)		Tf (hr)	
400[a]	7	87.8	(64)	1.08[b]	(32)	308	(100)	375[c]	(89)	5.77[b]	(63)
	14	106	(63)	1.69[b]	(31)	473	(95)	559[d]	(87)	6.54[b]	(38)
	21	93.5	(55)	2.46[c]	(83)	364	(81)	523[e]	(65)	6.43[c]	(42)
	28	114	(52)	2.10[d]	(84)	464	(93)	634[e]	(66)	6.67[d]	(50)
800	7	149	(69)	1.19[b]	(27)	741	(70)	819[d]	(64)	9.54[b]	(32)
	14	186	(49)	1.57[d]	(55)	977	(52)	1041	(47)	9.07[d]	(30)
	21	195	(50)	1.73[d]	(77)	1024	(64)	1073	(60)	8.83[d]	(41)
	28	194	(56)	1.64[c]	(66)	1029	(57)	1088	(53)	10.0[c]	(21)

a. Data include several subjects with plasma MF below the limit of quantitation.
b. n=13
c. n=14
d. n=15
e. n=12

Figure 1. Mean Plasma MF Profiles Post 400 µg BID

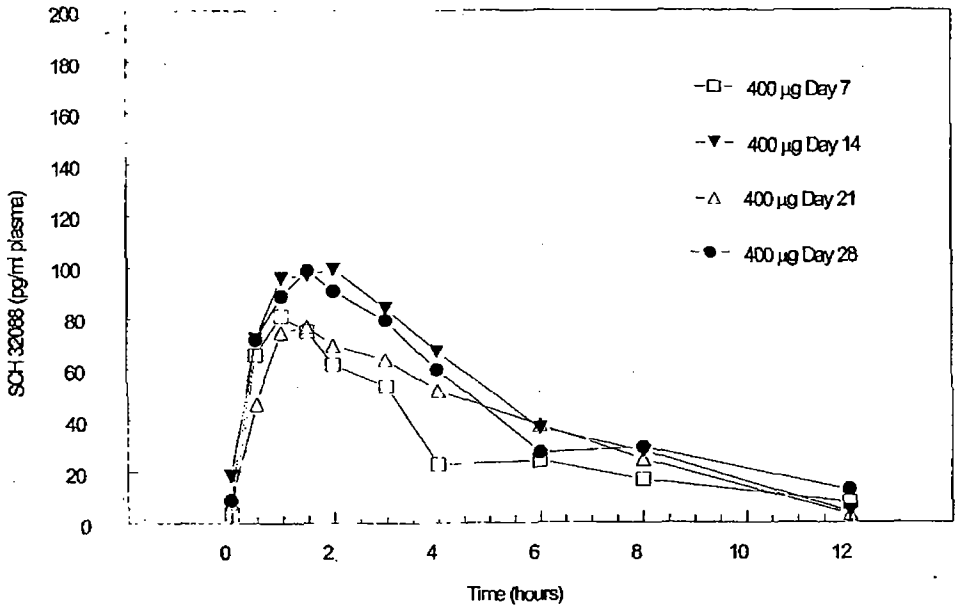
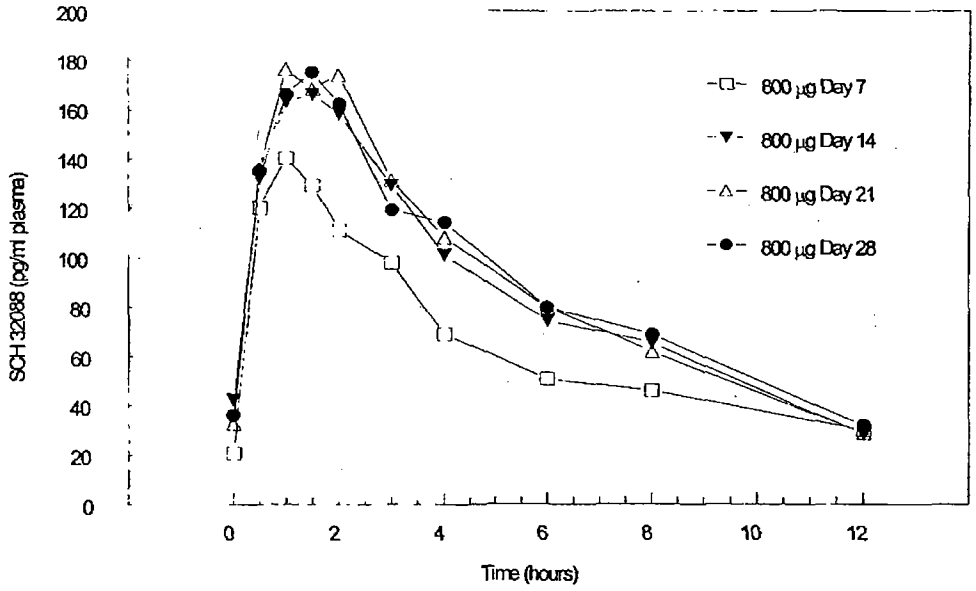


Figure 2. Mean Plasma MF Profiles Post 800 μg BID



Plasma MF levels were detectable with some accumulation observed at SS. For PD data, as compared to baseline, mean plasma cortisol AUC_{0-24} was reduced: 25%** (Day 7), 19%* (Day 14), 19%* (Day 21), and 10% (Day 28) for 400 μg BID; [* for $p<0.05$ and ** for $p<0.01$]. Post-study cosyntropin stimulation: MF 400 μg BID group (23.2 μg/dl) was not significantly different from placebo group (25.0 μg/dl)

No comparison of PK equivalency between the 2 x 200 μg and 1 x 400 μg doses was provided. Both 200 and 400 μg strengths provided comparable dose-normalized mean C_{max} values at SS (ranging from 93 to 114 pg/ml for the 400 μg BID dosing regimen).

Reviewer's Comments:

The individual data were spot checked and the study results are found acceptable. However, for the analysis of serum cortisol or urinary free cortisol levels, no assay results from this study were provided. Therefore, the above assay is less satisfactory and the sponsor needs to provide the missing plasma or urinary assay data.

Study No. C97-047 (Volume 1.70)
Synopsis

Title of the Study: SCH 32088: Absorption, Metabolism and Excretion of ^{3}H-SCH 32088 + Lactose Dry Powder Administered by Oral Inhalation Via Dry Powder Inhaler to Healthy Male Volunteers (Protocol C97-047-01)

Investigator(s): [ ]

Publication(s): None

Studied Period: July 24, 1997 – August 15, 1997 | **Clinical Phase:** I

Objective(s): To characterize the absorption, metabolism and excretion of ^{3}H-Mometasone furoate (^{3}H-SCH 32088) following administration by oral inhalation to healthy volunteers via dry powder (DPI) containing ^{3}H-mometasone furoate powder and lactose

Methodology: Open label single dose design

Number of Subjects: Six adult male volunteers were enrolled and completed in this study.

Diagnosis and Criteria for Inclusion: Adult, non-smoking, male volunteers between the ages of 18 and 45 years, in good health based upon medical history, physical exam, electrocardiogram, urine screen for drugs and laboratory safety tests.

Test Product, Dose, Mode of Administration, Batch No(s): ^{3}H-SCH 32088, 1 mg, oral inhalation via DPI

Reference Therapy, Dose, Mode of Administration, Batch No(s): N/A

Duration of Treatment: One single dose treatment period. Subjects were confined from 12 hours pre-dose to 168 hr post-dose.

Criteria for Evaluation: Pharmacokinetic parameters [Cmax, Tmax, AUC, Ae(day), Ae(total)], reported adverse events, chemistry panel, CBC, urinalysis, and ECG.

Statistical Methods: Descriptive statistics (mean, standard deviation and %coefficient of variation)

SUMMARY-CONCLUSIONS:

RESULTS:

Clinical Pharmacology:

The mean pharmacokinetic parameters for SCH 32088 (mometasone furoate) in plasma and total ^{3}H in plasma and blood following a single oral inhalation dose of 1 mg SCH 32088 were as follows:

Parameter	Plasma SCH 32088	(%CV)	Plasma ^{3}H	(%CV)	Whole Blood ^{3}H	(%CV)
Cmax	70.5 pg/Ml	(36)	837 pg equiv/gm	(28)	644 pg equiv/mL	(31)
Tmax	1.75 hr	(39)	13.0 hr	(133)	12.7 hr	(138)
AUC(tf)	279 pg·hr/mL	(116)	43700 pg equiv·hr/gm	(54)	49700 pg equiv·hr/mL	(30)
tf	4.17 hr	(80)	88.0 hr	(56)	136 hr	(27)

Mean cumulative excretion of radioactivity (0-168 hr) was 8% in urine and 74% in feces. Administered radioactivity recovered on gauze pads used to collect exhaled drug-derived radioactivity ranged from 0-14% of the dose. SCH 32088 was extensively metabolized at least in part via hydroxylation, most likely at the 6-position, hydrolysis of the furoate ester and substitution of the C21 chlorine with a hydroxy group. The polar nature of the remaining radioactivity indicated that further oxidation had also occurred. There was no evidence of the formation of a major metabolite.

Efficacy: Not evaluated

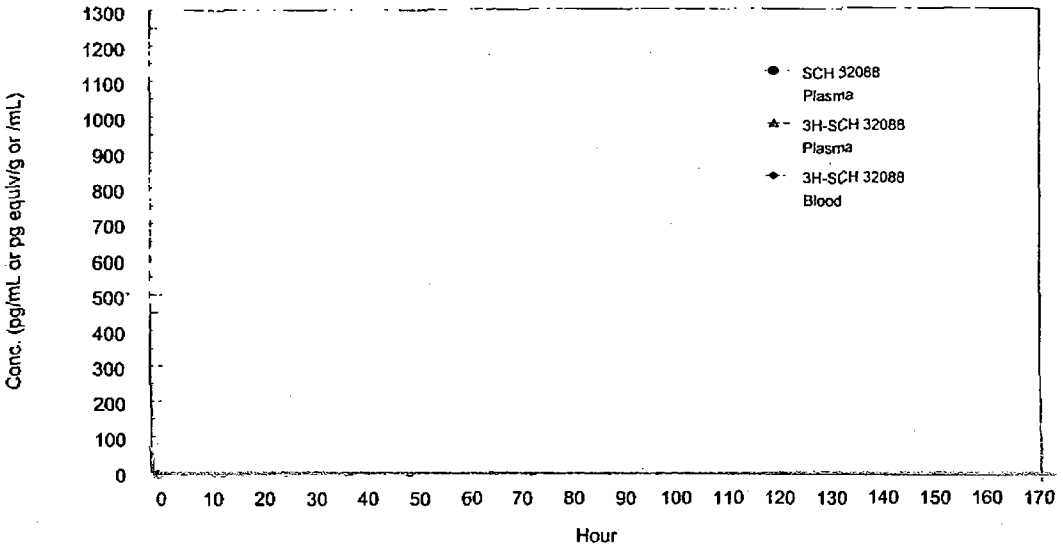
Safety: Mometasone furoate (1mg) administered as a dry powder and lactose combination labeled with tritium (200 µCi) was safe and well-tolerated when orally inhaled via a dry powder inhaler.

CONCLUSIONS:

- A single dose of ^{3}H-SCH 32088 (~200µCi) was safe and well tolerated following administration via a dry powder inhaler.
- SCH 32088 was absorbed, extensively metabolized and excreted mainly in the feces following oral inhalation as a powder.

Profiles of radioactivity in plasma and blood and parent drug in plasma are shown in **Figure 1** below:

Figure 1. Radioactivity of ^{3}H-MF in Plasma and Blood and Parent Drug Concentration in Plasma Over A 7-day Study Period



Up to 7 days, about 8% and 74% of the total radioactivity were recovered in urine and feces respectively and no accumulation was found in RBC. MF is extensively metabolized, but its metabolic pathways and possible metabolites are not identified.

Reviewer's Comments:

The individual data were spot checked and the study results are found acceptable.

Study No. I98-216 (IND 46,216, Volume 5of 5)
Synopsis

Title of the Study: SCH 32088: Drug Interaction Study of Mometasone Furoate/Lactose Dry Powder and Ketoconazole in Healthy Subjects.		
Investigator(s): [ ]		
Publication(s): None.		
Studied Period: July 15, 1998 - August 15, 1998.		Clinical Phase: I
Objective(s): The objective of this study was to evaluate the effects of co-administration of mometasone furoate + lactose dry powder administered by DPI (MF/L-DPI) and ketoconazole on the pharmacokinetics of mometasone furoate in healthy subjects.		
Methodology: Randomized, open-label, parallel-group, multiple-dose, placebo-controlled study. Twenty-four subjects received MF/L-DPI 400 µg BID (8 a.m. and 8 p.m.) on Days 1-9. In addition, subjects were randomized to receive either Treatment A (ketoconazole 200 mg po BID on Days 4-9) or Treatment B (placebo tablet po BID on Days 4-9). Blood and 24 hour urine/serum cortisol samples were collected at pre-specified times for pharmacokinetic/pharmacodynamic and safety evaluation. ECG's and vital signs were obtained at pre-specified times for safety evaluation. Volunteers were continuously observed and questioned throughout the study for the possible occurrence of adverse events. Plasma samples were assayed for mometasone furoate and 6-β-OH mometasone furoate content using a validated high performance liquid chromatography-tandem mass spectrometry (HPLC- — MS/MS), with a limit of quantitation of 50.1 pg/mL and 46.6 pg/mL, respectively.		
Number of Subjects: Twenty-four healthy subjects.		
Diagnosis and Criteria for Inclusion: Adult male or female subjects between 18-50 years of age inclusive, in good health based on medical history, physical examination, electrocardiogram, and routine laboratory tests (blood chemistry, hematology, and urinalysis) and having a BMI between 19-27 were empaneled for this study.		
Test Product, Dose, Mode of Administration, Batch No(s): MF/L - DPI (200 µg/inhalation), 400 µg BID via pulmonary inhalation, Batch No. 37660-038. Ketoconazole 200 mg, oral, Lot No. 97129/180 Exp. Date 08-2002 (commercial product).		
Reference Therapy, Dose, Mode of Administration, Batch No(s): MF/L - DPI lactose (200 µg/inhalation), 400 µg BID via pulmonary inhalation, Batch No. 37660-038. Placebo tablets, oral, Batch No. 52123-048.		
Duration of Treatment: All subjects received MF/L-DPI 400 µg BID (8 a.m. and 8 p.m.) throughout the study. In addition, subjects were randomized to receive either Treatment A (ketoconazole 200 mg po BID, 7 a.m. and 7 p.m. on Days 4-9) or Treatment B (placebo, 7 a.m. and 7 p.m. on Days 4-9).		
Criteria for Evaluation: Blood samples for determination of plasma mometasone furoate and 6-β-OH mometasone furoate pharmacokinetic parameters (AUC and Cmax) were collected over 12 hours following the 8 a.m. dose on Days 3 and 9. Blood and urine samples were collected over a 24 hour period starting at 11 p.m. on Day 3 and Day 9 for determination of serum cortisol and urine free cortisol content, respectively.		
Statistical Methods: The effect of treatment on the change from Baseline (Day 3) to Day 9 plasma mometasone furoate Cmax and AUC, serum cortisol Cmax and AUC, and urine cortisol excretion were to be evaluated using a one-way ANOVA model. Summary statistics were also to be provided for the derived pharmacokinetic parameters and the responses at each sample time.		
SUMMARY-CONCLUSIONS: **RESULTS:** The study was conducted as planned. **Safety:** Blood pressure, pulse rate, respiratory rate, oral body temperature and electrocardiogram evaluations showed no consistent changes of clinical relevance and remained within the range observed for healthy subjects. Overall, 4 of 24 (17%) subjects reported treatment-emergent adverse events. All reported adverse events were mild in severity except one which was reported as moderate. No subject discontinued participation in the study due to adverse events and no intervention was required to treat any adverse event.		

Title of the Study: SCH 32088: Drug Interaction Study of Mometasone Furoate/Lactose Dry Powder and Ketoconazole in Healthy Subjects.

Clinical Pharmacology: In the presence or absence of ketoconazole/placebo, plasma concentrations of mometasone furoate were quantifiable only in 14 out of 24 subjects. All of the mometasone furoate plasma concentrations on Day 3 (prior to ketoconazole/placebo coadministration) were less than two times the assay limit of quantitation (LOQ). On Day 9, mometasone furoate concentrations were generally higher (2 to 4 times the LOQ) than Day 3, with higher concentrations observed in the group receiving concomitant ketoconazole. None of the subjects had quantifiable 6-β-OH mometasone furoate concentrations. The results of this study indicate that ketoconazole caused a mean 2-fold increase in the plasma concentrations of mometasone furoate with no effect on 6-β-OH metabolite. However, due to the large variability (CV ~100%) associated with the very low concentrations of mometasone furoate, statistical significance could not be demonstrated. The change (Day 9-Day 3) mean serum cortisol AUC(0-24) values were statistically significant between the two treatment groups with the ketoconazole groups having lower values. The analysis of urine cortisol levels did not reveal any statistically significant differences between the two treatment groups.

CONCLUSIONS:

- MF/L-DPI administered with either ketoconazole or placebo was safe and well tolerated.
- In subjects who received concomitant MF/L-DPI and ketoconazole, MF Cmax and AUC values were ~2-fold higher than in subjects who received MF/L-DPI and placebo.
- Co-administration of ketoconazole with MF/L-DPI caused small but statistically significant decrease in serum cortisol AUC, however, these changes are unlikely to be of clinical significance.

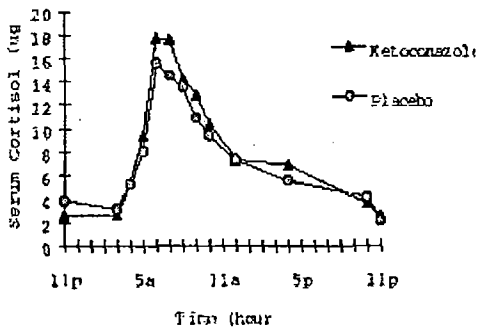
The results are shown in **Table 1** and **Figures 1A and 1B**.

Table 1. Distribution of MF C_{max} by Treatment and Day (Protocol No. I98-216)

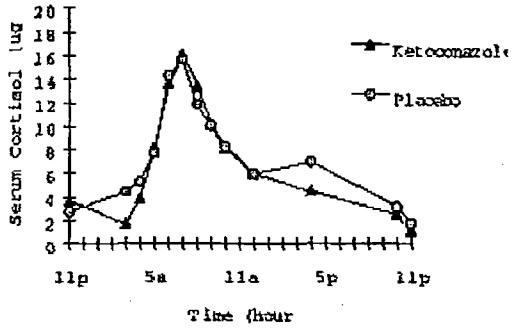
	Ketoconazole		Placebo	
Concentration (pg/ml)	**Day 3** (n=12)	**Day 9** (n=12)	**Day 3** (n=12)	**Day 9** (n=12)
<50.1	4	4	6	6
50.1-100.1	6	2	6	0
100.2-150.2	2	2	0	6
150.3-200.3	0	0	0	0
>200.4	0	4 (211-324)	0	0

Figures 1A and 1B. Serum Cortisol levels on Days 3 and 9

Day 3



Day 9



As compared to placebo group (on either Day 3 or 9) or ketoconazole group itself on Day 3, more and higher MF plasma levels (in the range of 211-324 pg/ml) were detected in the subjects enrolled in the ketoconazole group on Day 9. Generally, upon co-administration of ketoconazole, the number of detectable MF plasma levels increased and the serum cortisol levels decreased.

Reviewer's Comments:

The individual data were spot checked and the study results are found acceptable.

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Study No. C98-290 (IND 46,216, Volume 1 of 5)

Synopsis

Title of Study:	SCH 32088: Single/Multiple Dose Pharmacokinetic Study of Mometasone Furoate/Lactose Dry Powder Inhaler in Subjects with Mild to Moderate Asthma (Protocol C98-290)
Investigator(s):	[ ]
Publication(s):	None
Studied Period:	03 AUG 1998 – 26 AUG 1998 **Clinical Phase:** I

Objective(s): To determine the pharmacokinetic profile of mometasone furoate (MF) and 6-β-OH MF in subjects with mild to moderate asthma following administration of MF-DPI as a single 400 µg dose and 400 µg twice daily for 14 days.

Methodology: Open-label, single/multiple-dose, single-center study in adult subjects (males or females) with mild to moderate asthma. Following administration of MF-DPI as a single 400 µg dose and 400 µg twice daily for 14 days blood samples were collected at pre-specified times for pharmacokinetic and safety evaluations. Vital signs were obtained at pre-specified times for safety evaluation. Volunteers were continuously observed and questioned throughout the confinement periods for the possible occurrence of adverse events. Plasma samples were assayed for MF and its metabolite 6β-OH MF using a validated HPLC – MS/MS assay (LOQ=48.5 and 47.4 pg/mL, respectively).

Number of Subjects: Twenty-four.

Diagnosis and Criteria for Inclusion: Adult male or female subjects between 18-50 years of age inclusive with mild to moderate asthma (FEV_1 of 60% to 80% predicted) who were in good health based on medical history, physical examination, electrocardiogram and routine laboratory tests (blood chemistry, hematology, and urinalysis) were empaneled for this study.

Test Product, Dose, Mode of Administration, Batch No(s): MF–DPI (200 µg/inhalation), 400 µg via oral inhalation, Batch No. 38101-047.

Duration of Treatment: MF 400 µg administered as a single dose, followed by multiple doses twice daily on Days 2-15.

Reference Therapy, Dose, Mode of Administration, Batch No(s): None.

Criteria for Evaluation: Blood samples were collected for determination of plasma MF and 6β-OH MF pharmacokinetic parameters (AUC, Cmax and Tmax).

Statistical Methods: Summary statistics were calculated for the concentration data at each sampling time and the derived pharmacokinetic parameters. No statistical comparisons were made.

SUMMARY - CONCLUSIONS:

RESULTS: The study was conducted as planned.

Clinical Pharmacology: The mean (%CV) pharmacokinetic parameters for MF at the 400 µg single dose and 400 µg BID for 14 days are summarized in the table below.

Mean (%CV) Pharmacokinetic Parameters of MF Following Single and Multiple-Dose Pulmonary Administration of MF-DPI to Patients with Mild to Moderate Asthma.

MF Dose	Day	Cmin[a] (pg/mL)	Cmax[a] (pg/mL)	Tmax (hr)	AUC(tf)[a] (pg·hr/mL)	tf (hr)	AUC (0-12hr)[a] (pg·hr/mL)
400µg SD (n=24)	1	-[d]	53.6 (79)	2.26 (114)[b]	128 (135)	2.9 (115)	152 (129)
400 µg BID(n=24)	12	23.1 (148)	-[d]	-[d]	-[d]	-[d]	-[d]
	13	16.4 (181)	-[d]	-[d]	-[d]	-[d]	-[d]
	14	20.4 (146)	-[d]	-[d]	-[d]	-[d]	-[d]
	15	27.6 (127)	151 (57)	1.63 (43)[c]	-[d]	-[d]	864 (68)

a: Data include several subjects with plasma MF below the limit of quantitation.

b: n=17.

c: n=23.

d: Not applicable.

Title of Study:	SCH 32088: Single/Multiple Dose Pharmacokinetic Study of Mometasone Furoate/Lactose Dry Powder Inhaler in Subjects with Mild to Moderate Asthma (Protocol C98-290)

Plasma 6β-OH MF concentrations were not detectable in any subjects following either 400 µg single or multiple-dose administration of MF-DPI.

Following single and multiple dose administration of MF 400 µg plasma concentrations of MF were low, and the mean Cmax was 53.6 pg/mL on Day 1 (400 µg single dose) and 151 pg/mL on Day 15 (400 µg BID). On Day 1 MF concentrations were not quantifiable in 7 of the 24 subjects. On Day 15 MF concentrations were quantifiable in all subjects except Subject No. 9. In those subjects in whom MF was quantifiable, the levels were generally low and close to the LOQ. The Cmin samples obtained on Days 12, 13 and 14 had mean (%CV) plasma MF concentrations of 23.1 (148%), 16.4 (181%) and 20.4 (146%) pg/mL, respectively. These mean concentrations are very low and include several values below the LOQ (reported as zero).

Due to the large variability in plasma MF at these low concentrations, the derived pharmacokinetic parameters also showed large variability. Comparative analyses on pharmacokinetic parameters (AUC, Cmax) to evaluate accumulation were not done because AUC(I) could not be calculated and Cmax values were either below or close to the LOQ for the single dose administration.

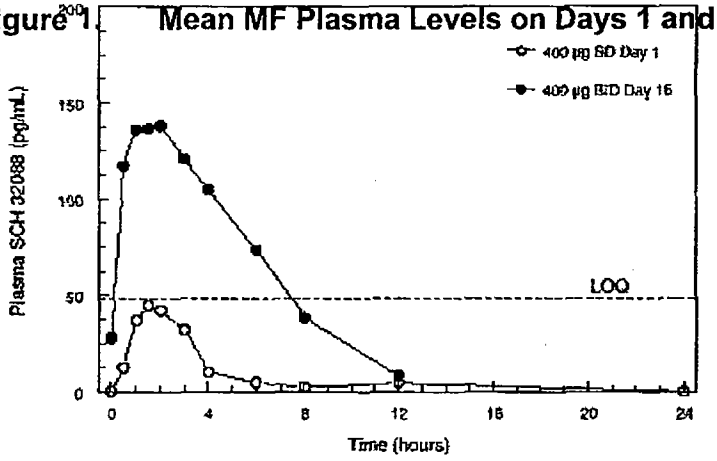
Safety: Blood pressure, pulse rate, respiratory rate, oral body temperature and electrocardiogram evaluations showed no consistent changes of clinical relevance and remained within the range observed for the population. Overall, 19 of 24 (79%) subjects reported treatment-emergent adverse events. The most frequently reported adverse event was headache. All reported adverse events were mild to moderate in severity except for one subject who reported a severe headache. Eight subjects required additional therapy with acetaminophen 1000 mg p.o. pm for adverse events. No subject discontinued participation in the study due to adverse events and no intervention was required to treat any adverse event.

CONCLUSIONS:

- MF-DPI administered to subjects with mild to moderate asthma was safe and well tolerated.
- At the MF 400 µg single dose, plasma MF concentrations were not quantifiable in several subjects, and were low in others; the mean Cmax did not exceed 53.6 pg/mL.
- At the MF 400 µg BID multiple-dose of plasma MF concentrations were quantifiable in most subjects, and the mean Cmax did not exceed 151 pg/mL.
- 6β-OH MF was not detectable in plasma following both the 400 µg single and 400 µg multiple-dose (BID) administration of MF-DPI.

The study results were consistent with those obtained previously from patients or healthy subjects.

Figure 1 Mean MF Plasma Levels on Days 1 and 15



Reviewer's Comments:

The individual data were spot checked and the study results are found acceptable.

Study No. C98-291 (IND 46,216, Volume 3 of 5)
Synopsis

Title of Study:	SCH 32088: Single-Dose Pharmacokinetics In Subjects With Various Degrees of Chronic Liver Disease (Protocol C98-291)	
Investigator(s):	[ ]	
Publication(s):	None	
Studied Period:	8 OCT 1998 to 26 OCT 1998	**Clinical Phase:** I

Objective(s): The primary objective of this single-dose study was to compare the pharmacokinetics of mometasone furoate (MF) and its metabolite 6-β-OH MF, if detectable, following administration of mometasone furoate plus lactose dry powder administered by oral inhalation via DPI (MF-DPI) in subjects with normal liver function to subjects with various degrees of stable chronic liver disease.
The secondary objective of this study was to determine the safety and tolerability of single-doses of MF-DPI in patients with chronic liver disease based on safety laboratory tests and reported adverse events.

Methodology: Open-label, single-dose, parallel-group, single-center study in adult subjects (males or females) with either normal liver function (n=8) or with stable chronic liver disease (n=12) were selected for this study; subjects with hepatic impairment were assigned to one of three liver function groups according to the score by Pugh's Modification of Child's Classification of Severity of Liver Disease. Following single-dose administration of MF-DPI 400 µg blood samples were collected at pre-specified times for pharmacokinetic and safety evaluations. Vital signs were obtained at pre-specified times for safety evaluation. Volunteers were continuously observed and questioned throughout the confinement periods for the possible occurrence of adverse events. Plasma samples were assayed for MF and its metabolite 6β-OH mometasone furoate using a validated HPLC — MS/MS assay (LOQ=48.5 and 47.4 pg/mL, respectively).

Number of Subjects: Twenty subjects (8 healthy and 12 with chronic liver disease)

Diagnosis and Criteria for Inclusion: Adult male or female subjects between 18-65 years of age inclusive with stable chronic liver impairment and healthy volunteers with no evidence of hepatic impairment who were in good health based on medical history, physical examination, electrocardiogram and routine laboratory tests (blood chemistry, hematology, and urinalysis) were empaneled for this study.

Test Product, Dose, Mode of Administration, Batch No(s): MF – DPI (200 µg/inhalation), 400 µg via oral inhalation, Batch No. 38101-047.

Duration of Treatment: MF-DPI 400 µg administered as a single dose.

Reference Therapy, Dose, Mode of Administration, Batch No(s): None.

Criteria for Evaluation: Blood samples for determination of MF and 6β-OH MF pharmacokinetic parameters (AUC, Cmax, Tmax, K, CL/F, Vd/F, t1/2) were collected over 72 hours following study drug administration.

Statistical Methods: Summary statistics were calculated for the concentration data at each sampling time and the derived pharmacokinetic parameters. Due to the non-quantifiable plasma MF concentrations in the majority of subjects no statistical comparisons were made.

SUMMARY - CONCLUSIONS:

RESULTS: The study was conducted as planned.

Clinical Pharmacology: Plasma MF concentrations were not quantifiable in the majority of subjects (14 out of 20 subjects). In healthy subjects, plasma MF concentrations were not quantifiable in 7 out of the 8 subjects over the entire 72 hour sampling interval. Similarly, in subjects with mild hepatic impairment plasma MF concentrations were not quantifiable in 3 out of the 4 subjects. In subjects with moderate and severe hepatic impairment 2 out of 4 subjects in each group had quantifiable plasma MF concentrations. In those subjects in whom MF was quantifiable (6 out of 20 subjects), plasma levels were generally low (≤2.2 the LOQ; see Table below)

Title of Study: SCH 32088: Single-Dose Pharmacokinetics In Subjects With Various Degrees of Chronic Liver Disease (Protocol C98-291)

Mean (%CV) Pharmacokinetic Parameters of MF Following Single Dose Pulmonary Administration of 400 µg MF-DPI to Subjects with Various Degrees of Chronic Liver Disease are shown in the table below.

Group	Cmax (pg/mL)	Tmax (hr)	AUC(tf) (pg·hr/mL)
Mild[a]	12.4 (200)	8 –[e]	24.8 (200)
Moderate[b]	39.9 (116)	15 (85)	635 (117)
Severe[c]	46.1 (118)	9 (16)	258 (161)
Healthy[d]	9.80 (283)	2.5 –[e]	45.5 (283)

Data include several subjects with plasma SCH 32088 below the limit of quantitation (see text).

a: n=4 (only 1 out of 4 subjects showed detectable levels).

b: n=4 (only 2 out of 4 subjects showed detectable levels).

c: n=4 (only 2 out of 4 subjects showed detectable levels).

d: n=8 (only 1 out of 8 subjects showed detectable levels).

e: Plasma levels were quantifiable in only one subject; therefore, CV could not be calculated.

Due to the low plasma MF concentrations and inherent large variability in MF the derived pharmacokinetic parameters [Cmax and AUC (tf)] also showed high variability. Subjects with hepatic dysfunction had plasma MF concentrations similar to those observed for healthy subjects. Furthermore, the MF plasma concentrations observed in those subjects with hepatic dysfunction were similar to those reported in other studies using the same dose from a DPI device in healthy subjects. Plasma concentrations of 6β-OH MF, the metabolite of MF, were not quantifiable in any subject.

Safety: Blood pressure, pulse rate, respiratory rate, oral body temperature and electrocardiogram evaluations showed no consistent changes of clinical relevance and remained within the range observed for the population. Overall, 4 of 20 (20%) subjects reported treatment-emergent adverse events. All reported adverse events were mild in severity except for two reported by one subject which were characterized as moderate and severe. Subject 6, a 62 year old male with a 5 year history of mild alcoholic cirrhosis received a single 400 µg dose of MF-DPI on Study Day 1. Aside from liver function test results consistent with cirrhosis, the patients screening laboratory tests were within normal limits 11 days prior to treatment administration. Three days following study drug administration, the patient's hemoglobin and hematocrit had decreased significantly to 8.4 g/dL and 23.5%, respectively. Repeat tests 5 days later revealed a further decrease to a hemoglobin of 6.3 g/dL and hematocrit 18.6% and a rectal exam revealed hemoccult stool. The patient revealed he had felt constipated around study Day 1 and noted a dark stool the week after he had received the study medication. He also gave a history of dizziness over the two days preceding the retest. The subject was hospitalized at this time and received 4 units of packed red cells. An endoscopy and colonoscopy were essentially negative and although there was no bleeding it was felt there may have been a small variceal bleed. The subject was discharged four days later and was feeling well. Pharmacokinetic analysis revealed that this subject did not have any quantifiable plasma MF concentrations over the sampling duration. The Investigator considered all adverse events to be unlikely related to treatment administration. No subject discontinued participation in the study due to adverse events and three subjects required to additional treatment.

CONCLUSIONS:

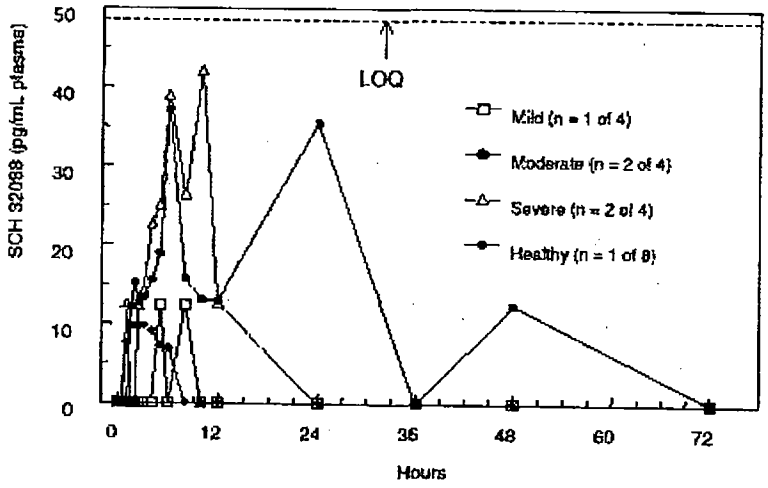
- MF-DPI administered as a single dose of 400 µg to subjects with various degrees of hepatic dysfunction was safe and tolerated.
- Plasma MF concentrations were not quantifiable in fourteen subjects and barely quantifiable in the remaining six subjects. The highest Cmax value observed (105 pg/mL) was only 2.2-fold greater than the LOQ.
- Cmax and AUC(tf) values were similar in subjects with liver impairment compared to healthy subjects.
- Plasma 6β-OH mometasone furoate levels were not quantifiable in any subject.

The study results showed that only 1 or 2 subjects in each category had detectable MF peak plasma levels (**Table 1**). An increase in number of detectable MF C_{max} was seen.

Table 1. Individual MF C_{max} and T_{max} Values Following SD of 400 µg of MF DPI to Subjects with Various Degrees of Chronic Liver Disease

Group	C_{max} (pg/ml)	T_{max} (hr)
Healthy (n=1 out of 8, detectable)	78.4	2.5
Mild (n=1 out of 4, detectable)	49.6	8.0
Moderate (n=2 out of 4, detectable)	72.6, 87.1	6, 24
Severe (n=2 out of 4, detectable)	79.3, 105	10, 8

Figure 1. MF mean plasma profiles.



Reviewer's Comments:

The individual data were spot checked and the study results are found acceptable.

Div File

JAN 7 1999

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
DIVISION OF PHARMACEUTICAL EVALUATION II

Date: January 07, 1999

To: Project Manager, Denise Toyer, Pharm.D. (HFD-570)
Director, Mei-Ling Chen, Ph.D. (HFD-870)
Deputy Director, John Hunt (HFD-870)

Through: Team Leader, Ramana Uppoor Ph.D. (HFD-870) 01/07/99

From: Tien-Mien Chen, Ph.D. (HFD-870) Tien-Mien Chen 1/7/99

RE: Filing Meeting for NDA 21-067 (Mometasone Furoate Dry Powder Inhaler)

SYNOPSIS:

Schering's NDA 20-762 for Nasonex (mometasone furoate, MF) nasal spray, 50 µg/actuation, has been reviewed previously and approved by the Agency on 10/01/97. It is indicated for the treatment of seasonal and perennial allergic rhinitis in adults and children 12 years of age and older.

On 11/30/98, Schering submitted an original NDA 21-067 for MF, a cap-activated inhalation-driven multi-dose dry powder inhaler (DPI) product which provides 220 and — µg per actuation (200 and 400 µg from the mouthpiece, respectively). It is to be indicated for the treatment of asthma as prophylactic therapy for adults and children 12 years of age and older. The recommended starting dose is 400 µg QD. It is desirable to titrate to the lowest effective dose once asthma stability is achieved. Dose reduction to 200 µg QD may be considered, increasing to 400 µg QD or 200 µg BID if more control is needed. For patients with severe asthma who may require oral corticosteroid, the starting dose is 400 µg BID. Once reduction of oral steroid dose is complete, MF dose should be titrated down to the lowest effective dose. Please see the package insert in Attachment 1 for details.

Prior to the submission of NDA 21-067 for MF DPI, the end of phase 2 (EPO2) and pre-NDA meetings with the Agency were held on 04/04/98 and 09/14/98, respectively. Due to assay sensitivity and as agreed upon in the meetings, there were only 5 pharmacokinetic studies submitted under Human Pharmacokinetics (PK) and Bioavailability (Bio) section of NDA 21-067. These PK/Bio studies are considered to be

pivotal which cover single-dose mass balance (using ^{3}H preparation of this compound), single-dose absolute bioavailability for DPI (compared with an intravenous preparation), single-dose dose proportionality for DPI (100, 200, 400, and 800 µg), multiple-dose safety and tolerance for DPI (400; 800, and 1200 µg QD and 200 µg BID), and multiple-dose (400 and 800 µg BID) using DPI. The single-dose studies were conducted in healthy volunteers, while multiple dose studies were in asthmatic patients. Plasma cortisol levels and/or urinary free cortisol levels were also obtained from one single-dose and two multiple-dose studies. However, analysis of PK and pharmacodynamic relationships was not attempted.

The to-be-marketed 200 and 400 µg formulations were tested in some PK/Bio studies. Upon the Agency's request in a meeting, one of the single-dose studies was submitted under IND 46,216 on 08/17/98 and has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE II). The study was found acceptable with a comment sent to the sponsor to verify if there were any major metabolites. In the *in vivo* mass balance study, radioactivities that did not correspond to parent compound were only classified into 5 regions, e.g., very polar, polar, moderate polar, non-polar, etc. Identification of possible metabolite(s) was attempted, but no major metabolite(s) was/were identified. Neither the *in vivo* metabolic pathways of MF nor the *in vitro* study for pharmacologic activities of metabolite(s) have been provided. The validated assay method (LC/MS/MS) used previously for MF in NDA 20-762 was also employed in this NDA, however, validation report(s) of assay method(s) for plasma or urinary cortisol levels was/were not provided. The package insert for this product is not annotated. Finally, this NDA was submitted in hardcopy as well as in electronic format.

RECOMMENDATION:

The Schering's NDA 21-067 for MF DPI, 200 and 400 µg/actuation, has been briefly reviewed for filing purposes. OCPB is of the opinion that the NDA with limited PK data submitted is acceptable for filing. The sponsor should respond adequately to the following OCPB comments which need to be conveyed to the sponsor ASAP.

COMMENTS: (Need to be sent to the sponsor)

1. The package insert (PI) for this NDA is not annotated. Therefore, it is recommended that the PI be annotated and submitted to the Agency for review as soon as possible.

2. The validation report(s) of the assay method(s) used for plasma and urinary cortisol levels was/were not provided in the Item 6. Therefore, it is recommended that validation report(s) be submitted for review.

3. It is recommended that the following information be submitted to Item 6 for review,**1)** protein binding, **2)** *in vivo* metabolic pathway(s) of mometasone and the possible metabolites, if available, **3)** data to support statement in the PI "In vitro studies have confirmed the primary role of CYP3A4 in the metabolism of this compound , and **4)** *in vitro* tests for pharmacologic activities of metabolite(s).

cc: HFD-870 (T.M. Chen, R. Uppoor, J. Hunt, M.L. Chen), CDR (B. Murphy).

NDA 21-067
(Mometasone Furoate DPI 200 and 400 µg/actuation)

ATTACHMENT 1

Package Insert

13 Page(s) Withheld

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

____ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling