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Barbara Hill, Ph.D.
Reviewing Pharmacologist

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HFD-540/DivDir/JWILKIN /S/ 2/16/00
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in OHS 6/00/00

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REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

KEY WORDS: Dermal Carcinogenicity Study, Addendum Review, DFMO

Reviewer Name: Barbara Hill
Division Name: Dermatologic and Dental Drug Products
HFD#: HFD-540
Review Completion Date: 6-7-00

JUN 12 2000

NDA number: 21-145
Note: This review is an addendum to the original review. This document contains the review of the mouse dermal carcinogenicity study only.
Serial number/date/type of submission: 000 / 9-27-99 / Original NDA Submission
Information to sponsor: Yes () No (X)

Sponsor: Westwood-Squibb Colton Holdings Partnership
100 Forest Avenue
Buffalo, NY 14213-1091
(716) 887-7680

Manufacturer for drug substance:

[redacted]

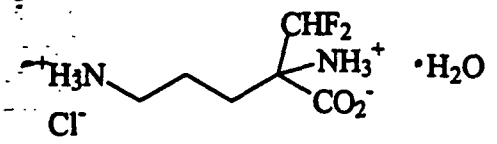
or

[redacted]

Drug:

Code Name: BMS 203522
Generic Name: eflornithine HCl 15% cream, DFMO
Trade Name: Vaniqa
Chemical Name: 2-(difluoromethyl)-DL-ornithine monohydrochloride monohydrate
CAS Registry Number: 96020-91-6
Molecular Formula/ Molecular Weight: $C_6H_{12}F_2N_2O_2 \cdot HCl \cdot H_2O$ / 236.7

Structure:



Relevant INDs/NDAs:

1) NDA 19-879 (Treatment of Trypanosoma Brucei Gambiense Sleeping Sickness, intravenous; HFD-590)
2) IND [redacted]
3) IND [redacted]
4) IND [redacted]

Drug Class: Irreversible inhibitor of ornithine decarboxylase; antineoplastic; antipneumocystis; antiprotozoal (Trypanosoma)

Indication: Hair growth in hirsute women

Clinical formulation:

The composition of the to-be-marketed cream formulation (15%) is provided in the following table:

Ingredient	% w/w	Function
Eflornithine Hydrochloride (BMS 203522)	15.0	Active
Water	[redacted]	[redacted]
Glyceryl stearate and PEG-100 stearate	[redacted]	[redacted]
Cetearyl alcohol and ceteareth-20	[redacted]	[redacted]
Mineral oil, NF	[redacted]	[redacted]
Stearyl alcohol, NF	[redacted]	[redacted]
Dimethicone	[redacted]	[redacted]
Phenoxyethanol	[redacted]	[redacted]
Methylparaben	[redacted]	[redacted]
Propylparaben	[redacted]	[redacted]

Dose:

A thin layer of cream is to be applied to the skin above the upper lip or under the chin that contains hair twice a day. Human dosing has been estimated to be 2.5 mg/kg (92.5 mg/m^2).

Route of administration: Topical dermal

Disclaimer: Note some material may be taken directly from sponsor's submission.

Introduction and drug history:

Eflornithine hydrochloride (HCl) has been used for over 15 years as an intravenous injection (Ornidyl) to treat West African (Gambian) trypanosaminasis caused by T.b. gambiense (sleeping sickness). Ornidyl was cleared for marketing for this purpose by the FDA in 1990 (NDA 19-879) and in Europe in 1991. Although not currently marketed in the United States, it is still available in countries where the disease is endemic.

Eflornithine HCl is an irreversible inhibitor of the enzyme ornithine decarboxylase (ODC). ODC is responsible for the catalysis or ornithine to putrescine. Putrescine and other polyamines (i.e., spermidine and spermine) are present in all living cells and are considered to play an important role in the regulation of cell growth and differentiation. ODC is present in the hair follicle and would be required for hair growth in this tissue. BMS-203522 is an inhibitor of ODC and is being developed as a topical product to reduce the rate of growth of unwanted facial hair in hirsute women.

Long term studies in animals have not been previously performed to evaluate the carcinogenic potential of eflornithine HCl. It was recommended to the sponsor to conduct a 2 year dermal carcinogenicity study in mice with the eflornithine HCl 15% cream and a 2 year oral rat carcinogenicity study. Executive CAC concurrence was obtained for dose selection for both the mouse dermal carcinogenicity and the rat oral carcinogenicity study protocols on 3/7/95. The sponsor's request for a waiver for conducting the rat oral carcinogenicity study was discussed during an End-of-Phase 2 meeting with the sponsor on 1/16/97. It was determined that the need for a rat oral carcinogenicity study could be waived based on the limited human percutaneous absorption (<0.5%) after topical administration. It was determined that the proposed mouse dermal carcinogenicity study would be sufficient to support the NDA.

The focus of this review is to evaluate the mouse dermal carcinogenicity study conducted with eflornithine HCl 15% cream. The rationale for conducting a review of the dermal carcinogenicity study separately is to provide the data to the Executive Carcinogenicity Assessment Committee for evaluation. The rest of the nonclinical pharmacology/toxicology studies conducted to support eflornithine HCl 15% cream will be provided in another review.

Studies reviewed within this submission:

(Note: Only one study is reviewed in this addendum review. The rest of the nonclinical pharmacology/toxicology studies are reviewed in the original review.)

1) BMS-203522 Lotion: Two-Year Dermal Carcinogenicity Study in Mice

CARCINOGENICITY:

Study Title: BMS-203522 Lotion: Two-Year Dermal Carcinogenicity Study in Mice
Study Number: 96701
Volume Numbers: 24 – 31
Test Facility: [redacted]
Study Date(s): 11/5/96 to 11/17/98
(Note: Originally I reported that the study report dates were not stated. During the Exec CAC presentation of this dermal carcinogenicity study, the Exec CAC recommended that I ask the sponsor for the study dates since this was a GLP issue. Subsequently after through scanning of the final study report, I was able to locate the study dates which are presented above.)
Date of Submission: 9-27-99
GLP Compliance/Quality Assurance: Yes
QA- Report: Yes (X) No ()
Study Type: Two year dermal carcinogenicity study in mice
Species/strain: Crl:CD-1 BR albino mice
Number of animals per group; age at start of study: 50 mice/sex/group for oncogenicity assessment and 42 mice/sex/group for toxicokinetic assessment; 7 weeks old (males: 23 – 30 g; females: 21 – 28 g)
Animal housing: The mice were individually housed in stainless steel, wire-bottom cages.
Drug Lot/Batch number(s):

1) BMS 203522-01 15% lotion; Lot numbers – 203522-M-03-A, IBR B96B011, FP 96076; 230522-M-03B, IRB B97A004, FP 97030
2) BMS 203522-01 vehicle lotion; Lot numbers – 203522-M-06-A, IBR B96F006, FP 96140)

Drug Purity / Stability / Homogeneity:

Every 6 months a 30 ml sample from the top, middle and bottom of the next test article formulation container to be used and a 30 ml sample of the control article were sent to the Sponsor for concentration and homogeneity analyses. The sponsor determined the test article formulation to be stable for the duration of the study.

Doses: refer to study design table below

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Study Design

Group	Treatment	Dose Level (µl/mouse/day)	Dose Level (mg/kg/day)	Number of Main Study Animals		Number of Toxicokinetic Animals	
				Males	Females	Males	Females
1	Untreated Control	0	0	50	50	0	0
2	Vehicle Control	0	0	50	50	0	0
3	15% BMS-203522	25	150	50	50	42	42
4	15% BMS-203522	50	300	50	50	42	42
5	15% BMS-203522	100	600	50	50	42	42

The test article formulation and vehicle control were administered by dermal application from an [redacted] pipette once daily, 7 days a week for 2 years. The test article formulation was applied to the clipped anterior dorsum up to the interscapular region of the back. The test article was applied to ~10% of the body surface (~1 x 3 cm area). The dorsal skin of each mouse was prepared for treatment by close clipping of the air with an electric clipper. The application area was clipped throughout the study period as necessary. The test article and vehicle remained on the animals for ~6 hours each day and was removed by wiping with gauze moistened with water. The untreated controls had the shaved area wiped in the same manner.

- *Basis of Dose Selection:* The highest dose for this dermal carcinogenicity study was based on the maximum feasible concentration (15%) of DFMO in the vehicle and the maximum feasible volume (100 µl) that can be applied to the mouse.

- *Relation to Clinical Use:* The intended route in humans is topical administration.

- *CAC Concurrence:* The protocol for this dermal carcinogenicity study was presented to the Executive CAC on 2/21/95. Concurrence for the dose selection and protocol were obtained on 3/7/95. A copy of the minutes from this meeting is attached to the review below as a scanned image.

- *Restriction Paradigm for Dietary Restriction Studies:* NA
- *Route of Administration:* Topical
- *Frequency of Drug Administration:* 1X/day
- *Dual Controls Employed:* No
- *Interim Sacrifices:* No
- *Satellite PK or Special Study Group(s):* refer to study design table above
- *Unscheduled Sacrifices or Deaths:* No
- *Deviations from Original Study Protocol:* NA

Study Results and Frequency of Monitoring:

- *Clinical Observations:* Detailed clinical examinations were conducted prior to study initiation and weekly during the study. This examination included pharmacological and toxicological findings as well as the occurrence, size, location and description of palpable cutaneous masses. Each mouse was observed for viability and signs of toxicity twice daily.

No treatment related clinical signs or palpable masses were noted in this study.

- *Dermal Observations:* Dermal irritation was assessed according to a modified Draize method of dermal scoring twice weekly immediately prior to dose application.

One vehicle control male animal had small scabbed areas on the treated area of the dorsum during days 197-246. No other dermal irritation was observed during the study, No treatment related dermal effects were noted in this study.

- *Mortality:* Animals were observed for viability twice daily.

No drug related mortality was noted in this study. Sporadic deaths were seen throughout the study. A high mortality rate was noted in all groups. No cause of death was stated in the final study report. The following table summarizes the early deaths that occurred during the study.

Weeks	Untreated		Vehicle		Low Dose		Mid Dose		High Dose	
	M	F	M	F	M	F	M	F	M	F
1-13	1	0	0	0	0	1	0	0	0	0
14-26	0	1	0	0	1	2	0	0	1	0
27-39	1	0	1	4	3	1	1	2	1	2
40-52	1	2	1	7	0	2	4	3	5	2
53-65	1	5	5	6	5	0	3	4	4	3
66-78	9	8	8	5	2	5	5	6	3	5
79-91	5	5	6	7	9	8	6	7	7	12
92-End	12	14	10	11	11	15	13	11	12	8
Totals	30/50	35/50	31/50	40/50	31/50	34/50	32/50	33/50	33/50	32/50

Mortality over the study period is reproduced graphically in the following two figures for males and females. These figures were scanned from the NDA submission.

Figure 1 Survival Curves – Males

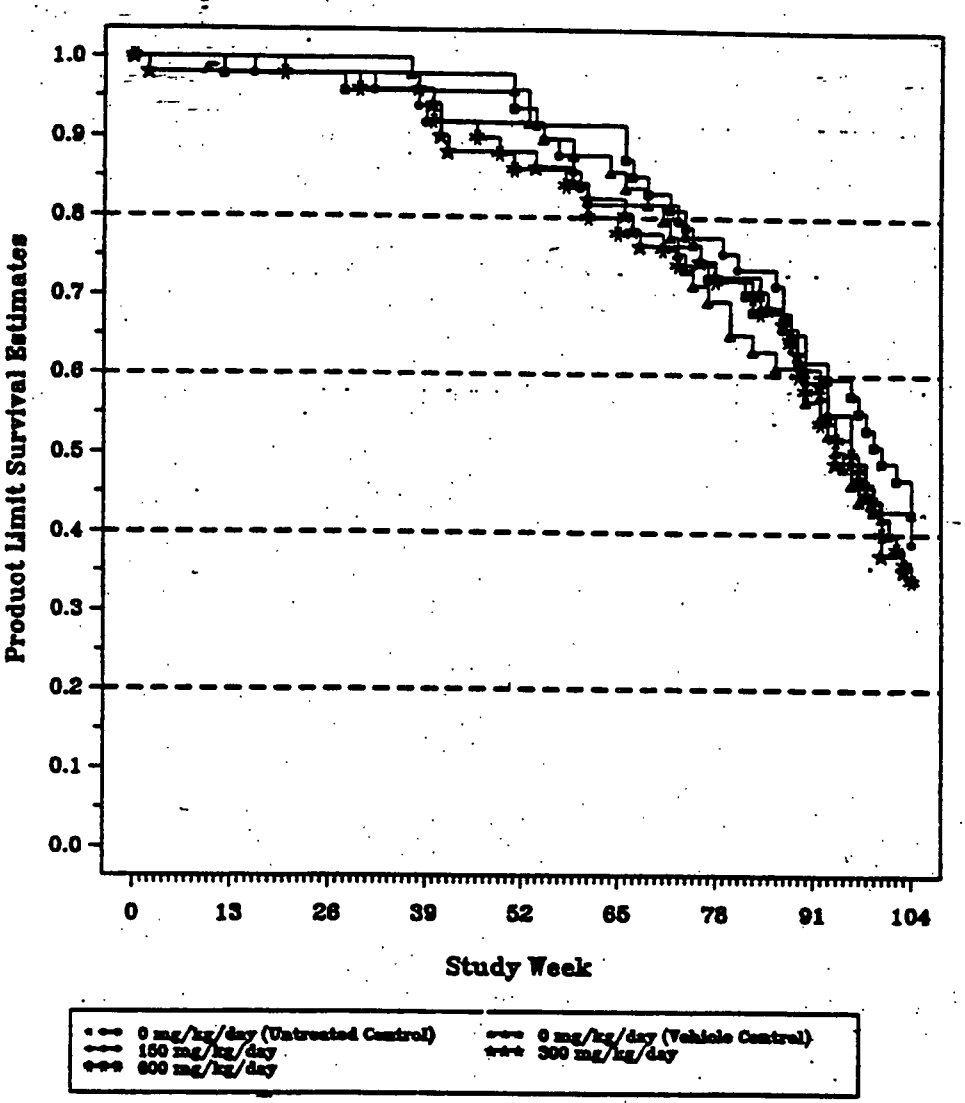

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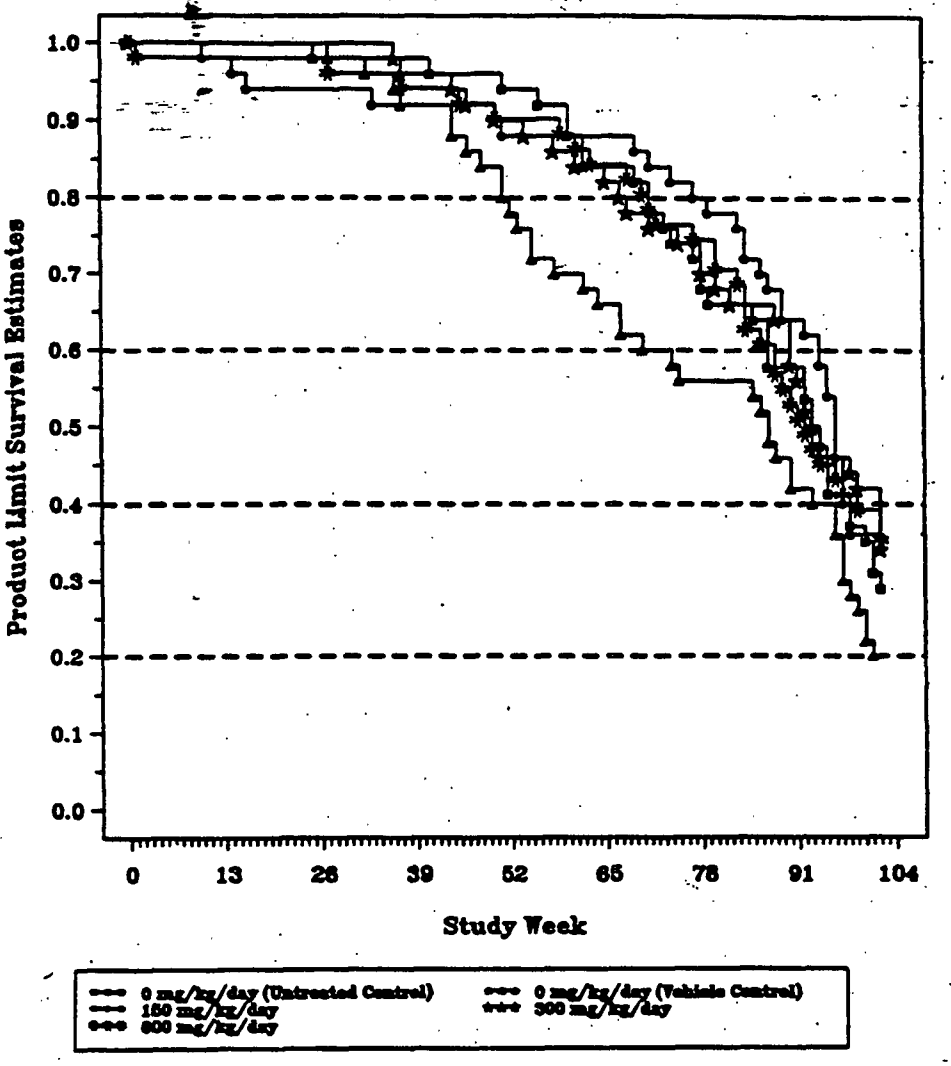
Figure 1A Survival Curves – Females



- *Body Weight:* Body weights were measured prior to initiation of test article administration and weekly thereafter.

Body weight data for males and females is presented in the two figures below scanned from the NDA. Body weights for the 3 groups of treated males were statistically significantly decreased with the untreated controls during weeks 16-30. The body weights for the treated groups were not decreased compared to the vehicle control animals. The body weight differences between the treated groups and the untreated control were not evident in the low and mid dose groups after week 30. The body weights in the high dose group males remained significantly decreased compared to the untreated controls during weeks 31 to 61.

During weeks 16-30 and 46-61, all 3 groups of treated females had body weights that were statistically significant decreased compared to the untreated control group. These differences were not evident during weeks 31-45 and after week 61. The decreases in body weight noted in this study are not considered to be treatment related.

Figure 2 **Mean Body Weight, g**
Male

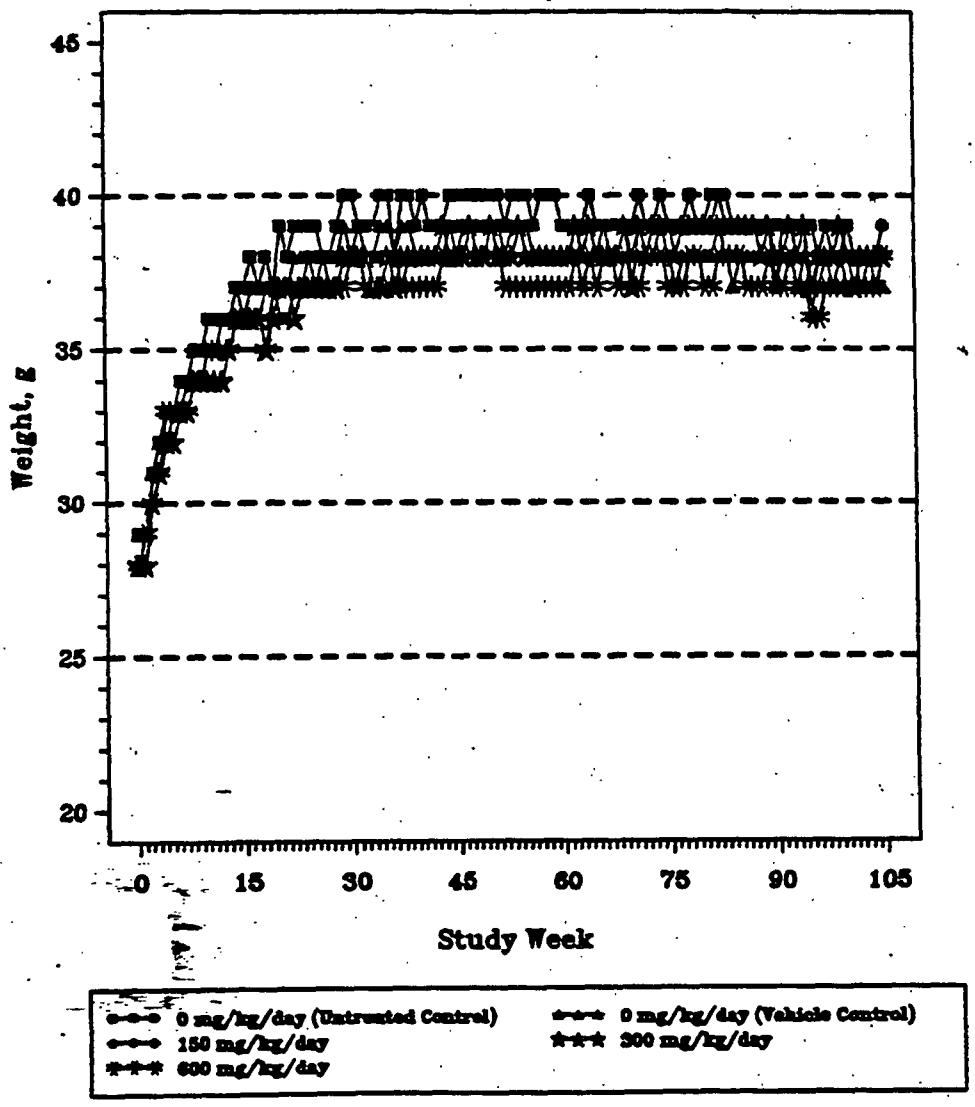
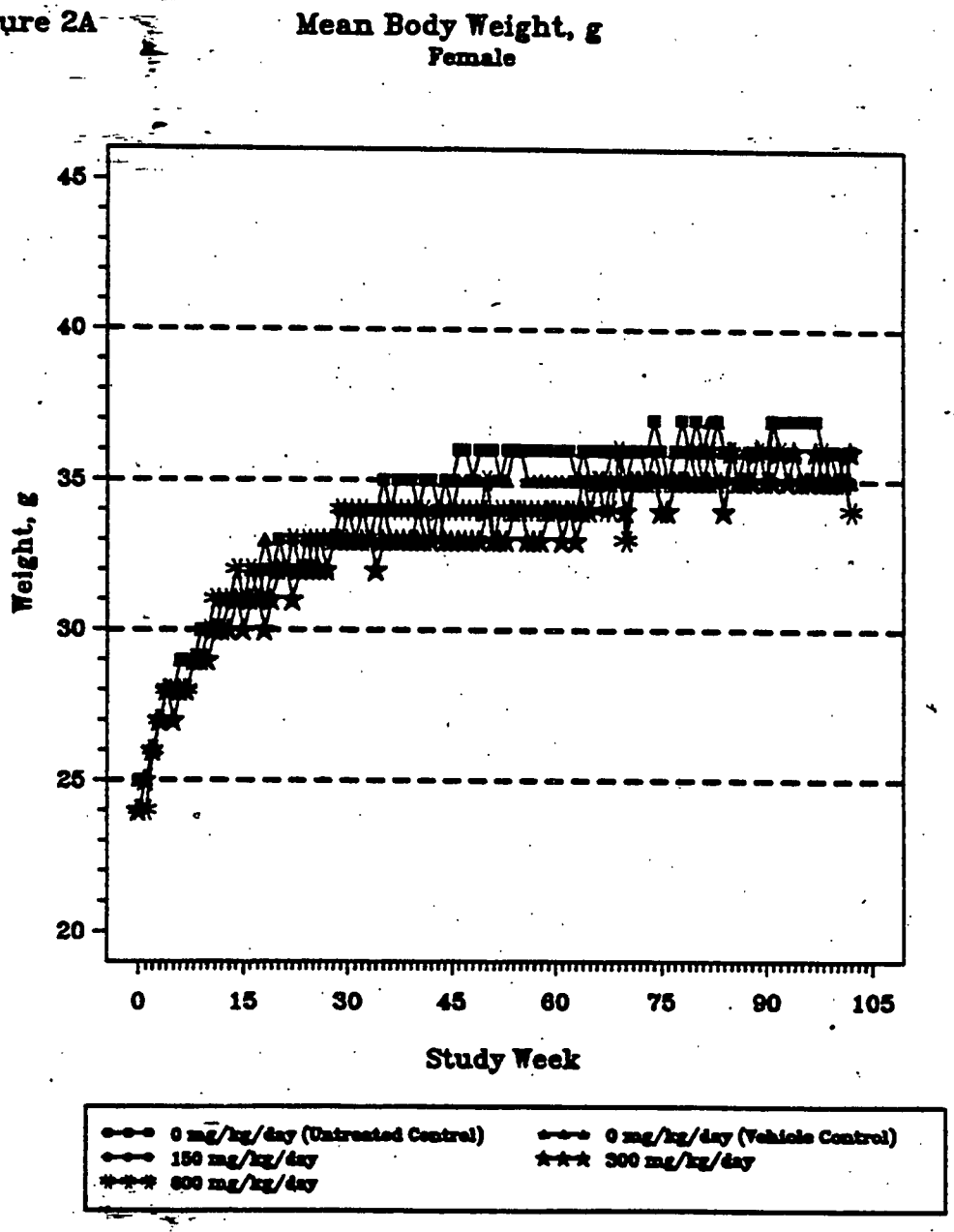


Figure 2A



- *Food Consumption:* Food consumption was measured and recorded weekly during the study.

Food consumption data for males and females are presented in the two figures below that were scanned NDA. Sporadic statistically significant differences between the control groups and the treated groups were noted throughout the study. No treatment related effects in food consumption were noted in this study.

Figure 3 Mean Food Consumption, g/animal/day
Male

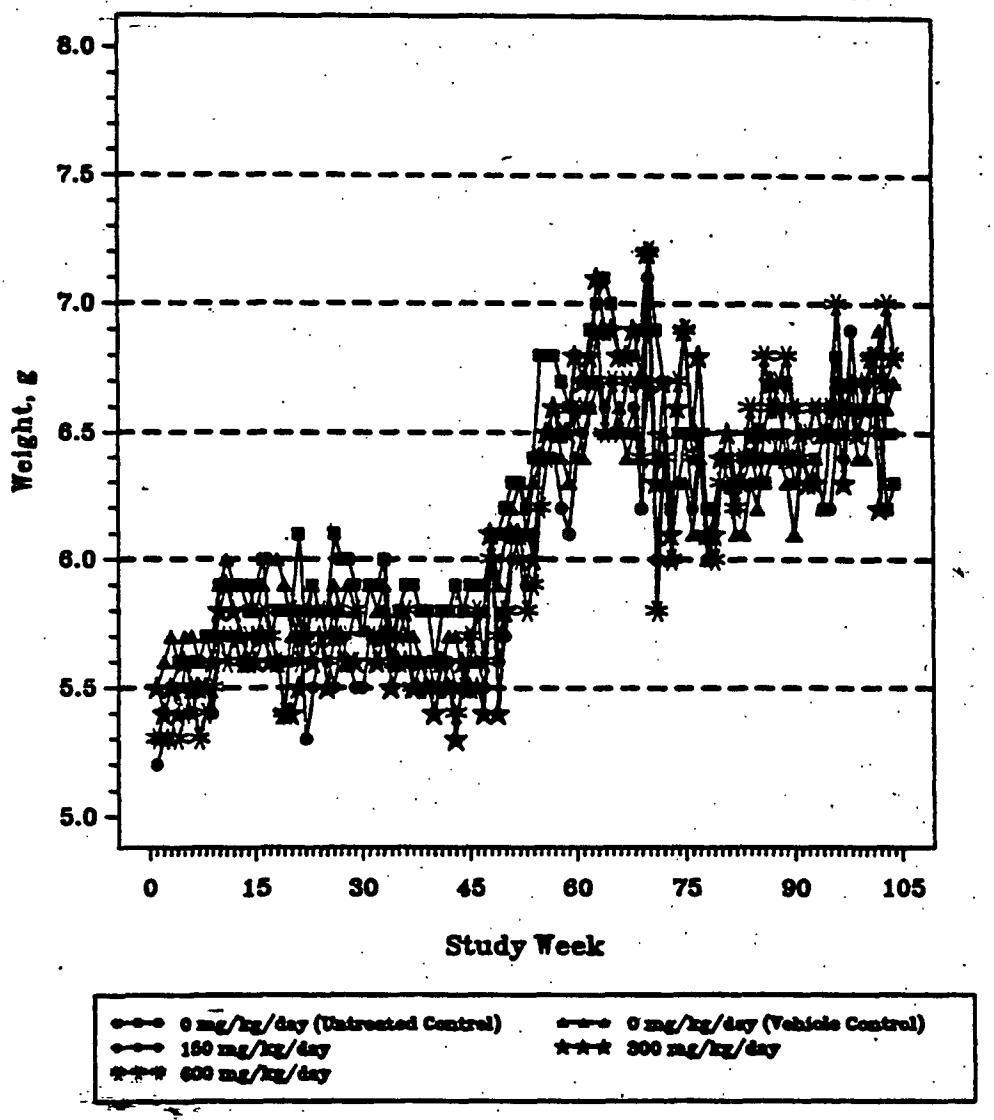


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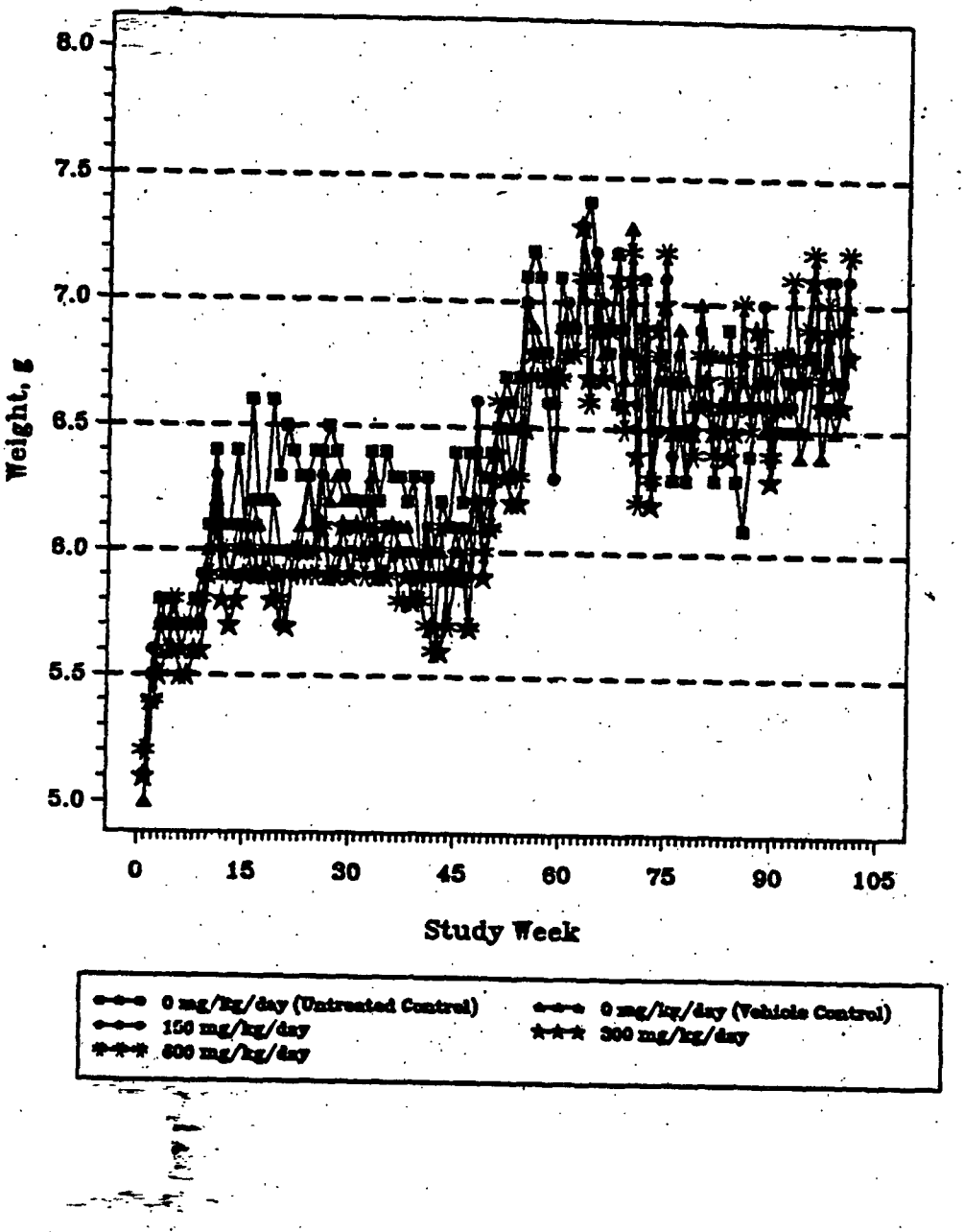
Figure 3A Mean Food Consumption, g/animal/day
Female



Gross Pathology: Performed at necropsy.

No test article related macroscopic findings were noted in treated animals compared to the untreated and/or vehicle control animals. Many mice died during the study period. The macroscopic observations in the organs and tissues examined were considered to be usual for mice of that age in the study.

- *Histopathology:* The following tissues were examined, collected for preservation at necropsy and examined histopathologically in all animals: Adrenal glands, aorta, bone with bone marrow (femur and sternum), brain (fore, mid and hind), eye including optic nerve, gallbladder, gastrointestinal tract (esophagus, stomach, duodenum, jejunum, ileum, cecum, colon and rectum), gonads (ovaries and testis with epididymis), gross lesions, hard platae, harderian gland, heart, kidneys, lacrimal gland, liver, lung, lymph nodes (mandibular, mediastrinal, and mesenteric and regional lymph node if applicable), mammary gland, nasal tissue, oral cavity, oviduct, pancreas, penis, pituitary gland, prostrate gland and seminal vesicle, salivary glands (mandibular/sublingual), sciatic nerve, skeletal muscle (thigh), skin (treated and untreated), spinal cord (cervical, thoracic, lumbar), spleen, thymus, thyroid/parathyroid glands, tissue masses, tongue, trachea, urinary bladder, uterus and cervix, vagina.

Non-Tumor findings:

Acanthosis and hyperkeratosis of the treated skin were noted in all female dose groups. Acanthosis of the treated skin was noted in all male dose groups except for the untreated control animals. The incidence and severity were relatively even across the vehicle control and treatment groups for both males and females. Therefore, the vehicle was responsible for the majority of the tissue reaction in the treated skin. The incidence, distribution and severity are provided in the following table.

	Males					Females				
	Untreat	Vehicle	Low	Mid	High	Untreat	Vehicle	Low	Mid	High
Skin, Treated										
Acanthosis, trace	0/48	5/50	3/50	5/50	2/50	2/50	16/50	12/50	17/50	22/50
Acanthosis, mild						0/50	2/50	0/50	2/50	2/50
Hyperkeratosis, trace						2/50	21/50	23/50	19/50	28/50
Hyperkeratosis, mild						0/50	1/50	0/50	0/50	3/50

No other treatment related microscopic findings were noted in this study. Additional microscopic findings noted in other organs were considered to be incidental and usual for mice of this strain and age.

Tumor findings:

Note: The sponsor's incidence of neoplastic histopathology findings is provided below in the addendum section. These tables were scanned from the tables provided in the NDA submission and include the sponsor's statistical analysis results for the neoplastic incidence levels.

No evidence of oncogenicity was noted in any organs examined from male or female mice following dermal application of the test article. The neoplastic lesion incidence rates noted in various tissues are summarized in the table below. The sponsor performed statistical analysis (Cochran Armitage Trend Test, Fisher Exact Test and Peto Test) of the data from this study. The Sponsor's biostatistical analysis showed that there were no statistically significant increase in any tumor type in the study. Steven Thomson is the assigned CDER statistical reviewer for the dermal carcinogenicity study. In Steve's biostatistical review for this study, he determined that the biostatistical analysis performed by the sponsor was adequate for the agency's purposes.

Neoplastic Lesion Incidence Table

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Tissue/ Lesion	Males					Females				
	Untreat.	Vehicle	Low	Mid	High	Untreat.	Vehicle	Low	Mid	High
Adrenal Gland, Cortex										
Adenoma	0/48	2/49	1/50	0/47	0/47					
Adrenal Gland, Medulla										
Pheochromocytoma, benign	0/46	0/49	0/49	0/46	1/45	0/50	0/50	0/49	0/50	1/49
Brain										
Meningioma, benign						0/50	0/50	1/50	0/50	0/50
Gallbladder										
Leiomyoma	0/47	1/48	0/48	0/47	0/49					
Hardian Gland										
Adenoma	1/48	1/50	3/50	6/50	3/49	4/50	0/50	1/50	1/50	1/50
Hemolympho-reticular System										
Hemangiosarcoma	4/48	1/50	1/50	2/50	1/50	2/50	2/50	0/50	1/50	1/50
Leukemia, granulocytic	0/48	0/50	0/50	1/50	0/50					
Lymphoma	1/48	2/50	3/50	0/50	2/50	3/50	8/50	7/50	5/50	8/50
Myeloma, plasma cell						0/50	0/50	1/50	0/50	0/50
Sarcoma, histiocytic	1/48	0/50	1/50	2/50	0/50	4/50	4/50	1/50	2/50	4/50
Kidney										
Adenoma, renal cell	1/48	0/50	0/50	0/50	1/50					
Large Intestine, Rectum										
Hemanigoma						0/50	0/50	1/50	0/49	0/50
Liver										
Adenoma, hepatocellular	3/48	3/50	5/50	4/50	6/50	2/49	2/50	1/50	3/50	1/50
Carcinoma, hepatocellular	2/48	0/50	4/50	5/50	0/50	0/49	1/50	0/50	0/50	0/50
Lung										
Adenoma, alveolar bronchiolar	12/48	11/50	8/50	10/50	9/50	8/50	7/50	7/50	8/50	4/50
Carcinoma, alveolar bronchiolar	3/48	0/50	3/50	1/50	3/50	2/50	1/50	2/50	3/50	3/50
Mesothelioma, benign						0/50	0/50	1/50	0/50	0/50
Mammary Gland										
Adenocarcinoma						2/50	1/50	1/48	0/49	0/48
Nasal Tissue										
Polyp	0/48	0/49	0/50	1/50	0/50					
Ovary										
Cystadenoma						0/50	1/50	4/50	1/50	2/50
Fibroma						0/50	0/50	1/50	0/50	0/50
Granulosa, cell tumor, benign						0/50	0/50	1/50	0/50	0/50
Luteoma						0/50	1/50	0/50	0/50	0/50
Sertoli cell tumor,						0/50	1/50	0/50	0/50	0/50

benign										
Teratoma						0/50	0/50	0/50	1/50	0/50
Pancreas										
Hemangioma						0/50	0/50	0/50	1/50	0/50
Pituitary										
Adenoma						1/45	1/45	2/46	2/46	1/43
Adenoma, pars intermedia	0/43	0/43	1/45	0/42	1/48	0/45	0/45	0/46	0/46	1/43
Carcinoma	1/43	0/43	0/45	0/42	0/48					
Skeletal Muscle										
Rhabdomyosarcoma	0/48	0/50	0/50	1/50	0/50					
Stomach, Nonglandular										
Carcinoma, squamous cell	0/48	0/50	0/50	1/50	0/50					
Testis										
Interstitial cell tumor, benign	0/48	1/50	1/49	1/50	0/50					
Mesothelioma, malignant	0/48	0/50	0/49	0/50	1/50					
Thymus Gland										
Thymoma, benign	0/41	0/36	1/32	0/38	0/34					
Thyroid Gland										
Adenoma, follicular	1/48	0/50	0/50	0/49	0/50	1/49	0/47	0/46	0/47	0/48
Urinary Bladder										
Mesenchymal tumor, malignant	0/47	0/50	0/49	1/50	0/50					
Uterus										
Adenoma						0/50	0/50	0/50	1/50	0/50
Hemangioma						2/50	0/50	0/50	1/50	0/50
Leiomyoma						2/50	0/50	2/50	3/50	1/50
Leiomyosarcoma						2/50	0/50	3/50	1/50	0/50
Polyp						2/50	4/50	4/50	1/50	3/50
Sarcoma, endometrial						0/50	0/50	0/50	1/50	0/50
Uterus, Cervix										
Adenocarcinoma						0/50	0/50	0/50	1/50	0/50
Fibroma						1/50	0/50	0/50	0/50	0/50
Granular cell tumor, benign						0/50	1/50	0/50	0/50	1/50
Leiomyoma						1/50	1/50	2/50	1/50	0/50
Leiomyosarcoma						2/50	0/50	0/50	0/50	1/50
Polyp						0/50	1/50	0/50	1/50	0/50

- *Toxicokinetics:* Plasma was obtained for toxicokinetic analysis in 3 animals/sex/timepoint for toxicokinetic animals on days 1 and 87. Blood samples were obtained on each of these 2 days at 1, 3, 6, 12, 18 and 24 hours after topical application of the daily dose. In addition on day 367, plasma concentrations of BMS 203522 were determined at 6 and 18 hours after topical application of the daily dose to verify exposure to the test article. Toxicokinetic analysis was performed at ——— The plasma samples were analyzed for BMS 203522 by a validated ——— method with a lower limit of quantitiation of —ng/ml.

Results from the toxicokinetic analysis showed that the systemic exposure of the mice to BMS 203522 was continuous and dose related. No difference in pharmacokinetic parameters was noted between male and female mice. No accumulation of BMS 230522 was noted over the study period. The toxicokinetic parameters are summarized in the following two tables.

Summary of Toxicokinetic Parameters
(Study Days 1 and 87 measurements)

Dose (mg/kg/day)	Study Day	C_{max} (ng/ml)		T_{max} (hr)		$AUC_{(0\text{-}24\ hr)}$ (ng·hr/ml)	
		Male	Female	Male	Female	Male	Female
150	1	15383	22007	1	1	60482	69623
	87	14941	13681	1	1	37048	37330
300	1	71825	68061	3	3	313770	282174
	87	15652	17100	1	1	52442	65924
600	1	101230	71706	1	1	442619	292739
	87	41702	55844	1	1	137254	215510

Summary of Plasma Concentrations
(Study Days 1, 87 and 367 measurements)

Dose (mg/kg/day)	Study Day	Mean Plasma Conc at 6 hr (ng/ml)		Mean Plasma Conc at 18 hr (ng/ml)	
		Male	Female	Male	Female
150	1	2248	2261	90.1	90.5
	87	1024	1137	156.2	125.2
	367	1087	2443	75.4	97.0
300	1	7522	7825	346.4	227.8
	87	1593	4171	170.7	269.9
	367	1924	1942	106.9	250.7
600	1	20008	20796	247.6	443.5
	87	6023	4925	403.8	1920
	367	2324	6122	274.1	328.6

Overall Interpretation and Evaluation:

- *Adequacy of the carcinogenicity studies and appropriateness of the test model:*

The mouse model is an appropriate model for analysis of dermal carcinogenicity. The high dose group in this study was the maximum feasible concentration for the cream formulation (15%) of DMFO and the maximum feasible volume (100 µl) was applied for each daily dose. The dose range for this dermal carcinogenicity study did receive prior Exec CAC concurrence as mentioned previously.

- *Evaluation of Tumor Findings:*

No biologically or statistically significant increase in tumors was noted for treated animals vs vehicle treated or untreated control animals.

Summary Conclusions and Recommendations:

- *Acceptability of Study(s) or Overall Testing Approach:*

This study is an acceptable mouse dermal carcinogenicity study because the design and conduct of the study was appropriate and an adequate dose range was tested in the study. The overall testing approach to use the mouse for this dermal carcinogenicity study is appropriate.

- *Major Tumor Findings:*

No biologically or statistically significant increase in tumors was noted for treated animals vs vehicle treated or untreated control animals.

- *Non-neoplastic Findings:*

Acanthosis and hyperkeratosis of the treated skin were noted in all female dose groups. Acanthosis of the treated skin was noted in all male dose groups except for the untreated control animals. The incidence and severity were relatively even across the vehicle control and treatment groups for both males and females. Therefore, the vehicle was responsible for the majority of the tissue reaction in the treated skin.

- *Recommendations for Further Analysis:*

No recommendations for further analysis at this time.

Addendum/Appendix Listing:

- *Dose-Ranging Study Report:*

No dose range study was performed for this mouse dermal carcinogenicity study. The high dose group was selected based on the maximum feasible concentration (15%) of DFMO in the cream and the maximum amount (100 µl) that can be applied to the mouse. Executive CAC concurrence was obtained for the dose range used in this mouse dermal carcinogenicity study. Refer to next section for additional details.

- *Exec CAC minutes:*

A scanned copy of the Exec CAC minutes from the 2/21/95 Exec CAC meeting to discuss the dose selection for the DMFO mouse dermal carcinogenicity study is provided below.

E L E C T R O N I C M A I L M E S S A G E

Date: 24-Feb-1995 03:04pm EST
From: Javier Avalos
AVALOSJ
Dept: HFD-540 PKLN 17B30
Tel No: 301-594-5010 FAX 301-594-6589

TO: Joseph DeGeorge (ISI 3/7/95) (DEGEORGE)
TO: Joseph F. Contrera (HFD-400) (CONTRERAJF)
TO: Glenna Fitzgerald (FITZGERALD)

CC: Abby Jacobs (JACOBSA)

Subject: Minutes of Exec. CAC disc. of DFMO protocol

Please review the text below for completeness and accuracy:

Members sitting: Joseph DeGeorge, Joseph Contrera, Glenna Fitzgerald

Background Information: Two protocols for a dermal (mice) and oral (rat) 104-week study were submitted by the Sponsor for review and comment by the Agency's CAC. The first study proposed doses of 0, 0, 25, 50, and 100 uL/mouse/day of SP-106A (15% DFMO). The high dose was selected on a maximum feasible dose volume. The second study proposed doses of 0, 0, 200, 400, 800, and 1200 mg/kg/day of DFMO. These doses were based on the results of 52-week study with doses of 0, 400, 800, and 1600 mg/kg/day. In the 52-week study, mortality was not treatment-related and body weights were significantly reduced (23-26%) in the high dose group only. In the animals treated with 800 and 1600 mg/kg/day, mild liver necrosis was significantly increased compared to control animals.

Minutes of meeting on 2/21/95:
The Exec. CAC met on 2/21/95 to discuss the proposed selected doses. Discussion included the following points:

I. For the dermal study, the confirmation of the maximum feasible volume (0.1 ml) and maximum solubility of DFMO in vehicle was the determining factor for the selection of the high dose. The maximum soluble concentration of DFMO is 15% in this vehicle and 100 uL is the maximum feasible volume administered to mice. It was the consensus of the committee that the high dose would not be changed from 100 uL of 15% DFMO.

A. Doses selected for the topical study: 0, 0, 25, 50, and 100 uL/mouse/day of SP-106A (15% DFMO).

II. It was the consensus of the committee that the high dose be lowered to enhance the survival of the animals during the 104-week study, and the low and mid doses be selected based on relative human exposure and therapeutic dosing.

Modification to the protocol:
A. Doses selected for the oral study: 0, 0, 30, 100, 300, and 900 mg/kg/day of DFMO.

The oral high dose (900 mg/kg/day) was selected based on the MTD. The low doses of the oral study were selected based on a human exposure of 150 mg/day assuming 100% bioavailability where the recommended clinical usage is a 0.5 g topical application of 2 times a day of a 15% solution. Reasonable multiples of the human exposure were calculated on a mg/m2 basis. The following assumptions were made in calculating approximate dose factors: a human body surface of 1.8 m2, a rat surface area of 325 cm2, and a rat body weight of 200 g. The human dose would then approximate 83.3 mg/m2 and the proposed rat doses would correspond to 2.2x, 7.4x, 22.2x, and 66.5x.

APPEARS THIS WAY
ON ORIGINAL

- *CAC Report:*

An Executive CAC meeting was held on May 2, 2000 to discuss the results of the dermal carcinogencity study. The minutes from this meeting are attached below. The chair for the Executive CAC, Joseph DeGeorge, signed the minutes from this meeting on May 3, 2000.

Executive CAC
May 2, 2000

Committee: Joseph DeGeorge, Ph.D., HFD-024, Chair
Joseph Contrera, Ph.D., HFD-901, Member
Al DeFelice, Ph.D., HFD-110, Alternate Member
Abby Jacobs, Ph.D., HFD-540, Team Leader
Barbara Hill, Ph.D., HFD-540, Presenting Reviewer

Author of Draft: Barbara Hill

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA # 21-145
Drug Name: Vaniqa (eflornithine HCl 15% cream; BMS-203522; DFMO)
Sponsor: Westwood-Squibb Colton Holdings Partnership

Background:

Eflornithine HCl is an irreversible inhibitor of the enzyme ornithine decarboxylase (ODC). ODC is responsible for the catalysis or ornithine to putrescine. Putrescine and other polyamines (i.e., spermidine and spermine) are present in all living cells and are considered to play an important role in the regulation of cell growth and differentiation. ODC is present in the hair follicle and would be required for hair growth in this tissue. Eflornithine HCl is an inhibitor of ODC and is being developed as a topical product to reduce the rate of growth of unwanted facial hair in hirsute women.

Mouse Carcinogenicity Study:

The following dose groups were tested in the study: untreated control, vehicle control, 150 mg/kg (25 µl of 15% BMS-203522 cream), 300 mg/kg (50 µl of 15% BMS-203522 cream) and 600 mg/kg (100 µl of 15% BMS-203522 cream). The highest dose for this dermal carcinogenicity study was based on the maximum feasible concentration (15%) of BMS-203522 in the vehicle and the maximum feasible volume (100 µl) that can be applied to the mouse. The protocol for this dermal carcinogenicity study was presented to the Executive CAC on 2/21/95. Concurrence for the dose selection and protocol were obtained on 3/7/95.

No biologically or statistically significant increase in tumors was noted for treated animals vs vehicle treated or untreated control animals. No evidence of carcinogenicity was noted for 15% BMS-203522 cream under the conditions of this mouse dermal carcinogenicity study. Therefore, 15% BMS-203522 cream was negative in the 2 year mouse dermal carcinogenicity study under the conditions used in the study.

Executive CAC Recommendations and Conclusions:

1. The committee determined that the mouse dermal carcinogenicity study was adequate and concurred that the study results were negative for carcinogenicity.
2. The committee recommended asking the sponsor for the starting and ending date for the study (a GLP question).
3. The committee recommended that human AUC values be obtained to calculate fold exposure levels for the mouse dermal carcinogenicity study.

Joseph DeGeorge, Ph.D.
Chair, Executive CAC

cc:

/Division File, HFD 540
/Abby Jacobs, HFD-540
/Barbara Hill, HFD-540
/Millie Wright, HFD-540
/ASeifried, HFD-024

Note: Originally I reported that the study report dates were not stated. During the Exec CAC presentation of this dermal carcinogenicity study, the Exec CAC recommended that I ask the sponsor for the study dates since this was a GLP issue. Subsequently after thorough scanning of the final study report, I was able to locate the study dates, which have been presented previously in this review.

Note: Human AUC values have been obtained from the Clinical Pharmacology reviewer, Taposh Ghosh, and the fold exposure levels for the dermal carcinogenicity study is discussed in the original review and related to labeling in the original review.

- *Sponsor's Incidence of Neoplastic Histopathology Findings:*

The tables presented below are scanned summary tables contained in the NDA submission. The first 5 pages are male animal data. The next 8 pages are female animal data.

Statistical Analysis of Neoplastic Lesions - Males (all groups)

Table 7

Tissue* / Lesion	0 mg/kg/day (Untreated Control)	0 mg/kg/day (Vehicle Control)	150 mg/kg/day	300 mg/kg/day	600 mg/kg/day
ADRENAL GLAND, CORTEX					
ADENOMA					
Overall Rates (a)	0/48 [0.00%]	2/49 [4.08%]	1/50 [2.00%]	0/47 [0.00%]	0/47 [0.00%]
Cochran Armitage Trend Test; P-value	0.421				
Fisher Exact Test; P-value		0.495	1.000	1.000	1.000
Peto Test; P-value	0.378				
ADRENAL GLAND, MEDULLA					
PHEOCHROMOCYTOMA, BENIGN					
Overall Rates (a)	0/48 [0.00%]	0/49 [0.00%]	0/49 [0.00%]	0/48 [0.00%]	1/45 [2.22%]
Cochran Armitage Trend Test; P-value	0.148				
Fisher Exact Test; P-value		1.000	1.000	1.000	0.496
Peto Test; P-value	0.162				
GALLBLADDER					
LEIOMYOMA					
Overall Rates (a)	0/47 [0.00%]	1/48 [2.08%]	0/48 [0.00%]	0/47 [0.00%]	0/49 [0.00%]
Cochran Armitage Trend Test; P-value	0.474				
Fisher Exact Test; P-value		1.000	1.000	1.000	1.000
Peto Test; P-value	0.482				
HARDERIAN GLAND					
ADENOMA**					
Overall Rates (a)	1/48 [2.08%]	1/50 [2.00%]	3/50 [6.00%]	6/50 [12.00%]	3/49 [6.12%]
Cochran Armitage Trend Test; P-value	0.083				
Fisher Exact Test; P-value		1.000	0.617	0.112	0.617
Peto Test; P-value	0.067				
HEMOLYMPHORETICULAR SYSTEM					
HEMANGIOSARCOMA					
Overall Rates (a)	4/48 [8.33%]	1/50 [2.00%]	1/50 [2.00%]	2/50 [4.00%]	1/50 [2.00%]
Cochran Armitage Trend Test; P-value	0.216				
Fisher Exact Test; P-value		0.200	0.200	0.431	0.200
Peto Test; P-value	0.226				

455-032 (a) - Number of tumor bearing animals / number of animals examined at site.
*Only includes tissues where at least 1 tumor was found in any group.
**Per protocol description, organs where the high dose group has a count equal to 2 or where the sum of mid-dose and high-dose is equal to 4.
All p-values are calculated using a two tail test.

Statistical Analysis of Neoplastic Lesions - Males (all groups)

Table 7 Cont.

Tissue* / Lesion	0 mg/kg/day (Untreated Control)	0 mg/kg/day (Vehicle Control)	150 mg/kg/day	300 mg/kg/day	600 mg/kg/day
HEMOLYMPHORETICULAR SYSTEM (continued)					
LEUKEMIA, GRANULOCYTIC					
Overall Rates (a)	0/48 [0.00%]	0/50 [0.00%]	0/50 [0.00%]	1/50 [2.00%]	0/50 [0.00%]
Cochran Armitage Trend Test; P-value	0.485				
Fisher Exact Test; P-value		1.000	1.000	1.000	1.000
Peto Test; P-value	0.462				
LYMPHOMA					
Overall Rates (a)	1/48 [2.08%]	2/50 [4.00%]	3/50 [6.00%]	0/50 [0.00%]	2/50 [4.00%]
Cochran Armitage Trend Test; P-value	0.974				
Fisher Exact Test; P-value		1.000	0.617	0.490	1.000
Peto Test; P-value	0.999				
SARCOMA, HISTIOCYTIC					
Overall Rates (a)	1/48 [2.08%]	0/50 [0.00%]	1/50 [2.00%]	2/50 [4.00%]	0/50 [0.00%]
Cochran Armitage Trend Test; P-value	0.962				
Fisher Exact Test; P-value		0.490	1.000	1.000	0.490
Peto Test; P-value	0.945				
KIDNEY					
ADENOMA, RENAL CELL					
Overall Rates (a)	1/48 [2.08%]	0/50 [0.00%]	0/50 [0.00%]	0/50 [0.00%]	1/50 [2.00%]
Cochran Armitage Trend Test; P-value	0.967				
Fisher Exact Test; P-value		0.490	0.490	0.490	1.000
Peto Test; P-value	1.000				
LIVER					
ADENOMA, HEPATOCELLULAR**					
Overall Rates (a)	3/48 [6.25%]	3/50 [6.00%]	5/50 [10.00%]	4/50 [8.00%]	6/50 [12.00%]
Cochran Armitage Trend Test; P-value	0.262				
Fisher Exact Test; P-value		1.000	0.715	1.000	0.487
Peto Test; P-value	0.307				

455-032 (a) - Number of tumor bearing animals / number of animals examined at site.
*Only includes tissues where at least 1 tumor was found in any group.
**Per protocol description, organs where the high dose group has a count equal to 2 or where the sum of mid-dose and high-dose is equal to 4.
All p-values are calculated using a two tail test.

Statistical Analysis of Neoplastic Lesions - Males (all groups)

Table 7 Cont.

Tissue* / Lesion	0 mg/kg/day (Untreated Control)	0 mg/kg/day (Vehicle Control)	150 mg/kg/day	300 mg/kg/day	600 mg/kg/day
LIVER (Continued)					
CARCINOMA, HEPATOCELLULAR **					
Overall Rates (a)	2/48 [4.17%]	0/50 [0.00%]	4/50 [8.00%]	5/50 [10.00%]	0/50 [0.00%]
Cochran Armitage Trend Test; P-value	0.857				
Fisher Exact Test; P-value		0.237	0.678	0.436	0.237
Peto Test; P-value	0.938				
LUNG					
ADENOMA, ALVEOLAR BRONCHIOLAR**					
Overall Rates (a)	12/48 [25.00%]	11/50 [22.00%]	8/50 [16.00%]	10/50 [20.00%]	9/50 [18.00%]
Cochran Armitage Trend Test; P-value	0.381				
Fisher Exact Test; P-value		0.813	0.321	0.632	0.466
Peto Test; P-value	0.401				
CARCINOMA, ALVEOLAR BRONCHIOLAR**					
Overall Rates (a)	3/48 [6.25%]	0/50 [0.00%]	3/50 [6.00%]	1/50 [2.00%]	3/50 [6.00%]
Cochran Armitage Trend Test; P-value	0.648				
Fisher Exact Test; P-value		0.114	1.000	0.357	1.000
Peto Test; P-value	0.782				
NASAL TISSUE C					
POLYP*					
Overall Rates (a)	0/48 [0.00%]	0/49 [0.00%]	0/50 [0.00%]	1/50 [2.00%]	0/50 [0.00%]
Cochran Armitage Trend Test; P-value	0.487				
Fisher Exact Test; P-value		1.000	1.000	1.000	1.000
Peto Test; P-value	0.369				
PITUITARY					
ADENOMA, PARS INTERMEDIA					
Overall Rates (a)	0/43 [0.00%]	0/43 [0.00%]	1/45 [2.22%]	0/42 [0.00%]	1/48 [2.08%]
Cochran Armitage Trend Test; P-value	0.340				
Fisher Exact Test; P-value		1.000	1.000	1.000	1.000
Peto Test; P-value	0.369				

455-032 (a) - Number of tumor bearing animals / number of animals examined at site.
*Only includes tissues where at least 1 tumor was found in any group.
**Per protocol description, organs where the high dose group has a count equal to 2 or where the sum of mid-dose and high-dose is equal to 4.
All p-values are calculated using a two tail test.

Statistical Analysis of Neoplastic Lesions - Males (all groups)

Table 7 Cont.

Tissue* / Lesion	0 mg/kg/day (Untreated Control)	0 mg/kg/day (Vehicle Control)	150 mg/kg/day	300 mg/kg/day	600 mg/kg/day
PITUITARY (Continued)					
CARCINOMA					
Overall Rates (a)	1/43 [2.33%]	0/43 [0.00%]	0/45 [0.00%]	0/42 [0.00%]	0/48 [0.00%]
Cochran Armitage Trend Test; P-value	0.152				
Fisher Exact Test; P-value		1.000	0.489	1.000	0.475
Peto Test; P-value	0.165				
SKELETAL MUSCLE					
RHABDOMYOSARCOMA					
Overall Rates (a)	0/48 [0.00%]	0/50 [0.00%]	0/50 [0.00%]	1/50 [2.00%]	0/50 [0.00%]
Cochran Armitage Trend Test; P-value	0.485				
Fisher Exact Test; P-value		1.000	1.000	1.000	1.000
Peto Test; P-value	0.480				
STOMACH, NONGLANDULAR					
CARCINOMA, SQUAMOUS CELL					
Overall Rates (a)	0/48 [0.00%]	0/50 [0.00%]	0/50 [0.00%]	1/50 [2.00%]	0/50 [0.00%]
Cochran Armitage Trend Test; P-value	0.485				
Fisher Exact Test; P-value		1.000	1.000	1.000	1.000
Peto Test; P-value	0.480				
TESTIS					
INTERSTITIAL CELL TUMOR, BENIGN					
Overall Rates (a)	0/48 [0.00%]	1/50 [2.00%]	1/49 [2.04%]	1/50 [2.00%]	0/50 [0.00%]
Cochran Armitage Trend Test; P-value	0.984				
Fisher Exact Test; P-value		1.000	1.000	1.000	1.000
Peto Test; P-value	1.000				
MESOTHELIOMA, MALIGNANT					
Overall Rates (a)	0/48 [0.00%]	0/50 [0.00%]	0/49 [0.00%]	0/50 [0.00%]	1/50 [2.00%]
Cochran Armitage Trend Test; P-value	0.160				
Fisher Exact Test; P-value		1.000	1.000	1.000	1.000
Peto Test; P-value	0.172				

455-032 (a) - Number of tumor bearing animals / number of animals examined at site.
*Only includes tissues where at least 1 tumor was found in any group.
All p-values are calculated using a two tail test.

Statistical Analysis of Neoplastic Lesions - Males (all groups)

Table 7 Cont.

Tissue* / Lesion	0 mg/kg/day (Untreated Control)	0 mg/kg/day (Vehicle Control)	150 mg/kg/day	300 mg/kg/day	600 mg/kg/day
THYMUS GLAND					
THYMOMA, BENIGN					
Overall Rates (a)	0/41 [0.00%]	0/36 [0.00%]	1/32 [3.13%]	0/38 [0.00%]	0/34 [0.00%]
Cochran Armitage Trend Test; P-value	0.963				
Fisher Exact Test; P-value		1.000	0.438	1.000	1.000
Peto Test; P-value	0.961				
THYROID GLAND					
ADENOMA, FOLLICULAR					
Overall Rates (a)	1/48 [2.17%]	0/50 [0.00%]	0/50 [0.00%]	0/49 [0.00%]	0/50 [0.00%]
Cochran Armitage Trend Test; P-value	0.148				
Fisher Exact Test; P-value		0.479	0.479	0.484	0.479
Peto Test; P-value	0.099				
URINARY BLADDER					
MESENCHYMAL TUMOR, MALIGNANT					
Overall Rates (a)	0/47 [0.00%]	0/50 [0.00%]	0/49 [0.00%]	1/50 [2.00%]	0/50 [0.00%]
Cochran Armitage Trend Test; P-value	0.488				
Fisher Exact Test; P-value		1.000	1.000	1.000	1.000
Peto Test; P-value	0.370				

456-032 (a) - Number of tumor bearing animals / number of animals examined at site.
*Only includes tissues where at least 1 tumor was found in any group.
All p-values are calculated using a two tail test.

Statistical Analysis of Neoplastic Lesions - Females (all groups)

Table 8

Tissue* / Lesion	0 mg/kg/day (Untreated Control)	0 mg/kg/day (Vehicle Control)	150 mg/kg/day	300 mg/kg/day	600 mg/kg/day
ADRENAL GLAND, MEDULLA					
PHEOCHROMOCYTOMA, BENIGN					
Overall Rates (a)	0/50 [0.00%]	0/50 [0.00%]	0/49 [0.00%]	0/50 [0.00%]	1/49 [2.04%]
Cochran Armitage Trend Test; P-value	0.158				
Fisher Exact Test; P-value		1.000	1.000	1.000	0.495
Peto Test; P-value	0.153				
BRAIN					
MENINGIOMA, BENIGN					
Overall Rates (a)	0/50 [0.00%]	0/50 [0.00%]	1/50 [2.00%]	0/50 [0.00%]	0/50 [0.00%]
Cochran Armitage Trend Test; P-value	1.000				
Fisher Exact Test; P-value		1.000	1.000	1.000	1.000
Peto Test; P-value	1.000				
HARDERIAN GLAND					
ADENOMA					
Overall Rates (a)	4/50 [8.00%]	0/50 [0.00%]	1/50 [2.00%]	1/50 [2.00%]	1/50 [2.00%]
Cochran Armitage Trend Test; P-value	0.176				
Fisher Exact Test; P-value		0.117	0.362	0.362	0.362
Peto Test; P-value	0.125				
HEMOLYMPHORETICULAR SYSTEM					
HEMANGIOSARCOMA					
Overall Rates (a)	2/50 [4.00%]	2/50 [4.00%]	0/50 [0.00%]	1/50 [2.00%]	1/50 [2.00%]
Cochran Armitage Trend Test; P-value	0.362				
Fisher Exact Test; P-value		1.000	0.495	1.000	1.000
Peto Test; P-value	0.317				
LYMPHOMA**					
Overall Rates (a)	3/50 [6.00%]	8/50 [16.00%]	7/50 [14.00%]	5/50 [10.00%]	8/50 [16.00%]
Cochran Armitage Trend Test; P-value	0.343				
Fisher Exact Test; P-value		0.200	0.318	0.716	0.200
Peto Test; P-value	0.457				

455-032 (a) - Number of tumor bearing animals / number of animals examined at site.
*Only includes tissues where at least 1 tumor was found in any group.
**Per protocol description, organs where the high dose group has a count equal to 2 or where the sum of mid-dose and high-dose is equal to 4.
All p-values are calculated using a two tail test.

Statistical Analysis of Neoplastic Lesions - Females (all groups)

Table 8 Cont.

Tissue* / Lesion	0 mg/kg/day (Untreated Control)	0 mg/kg/day (Vehicle Control)	150 mg/kg/day	300 mg/kg/day	600 mg/kg/day
HEMOLYMPHORETICULAR SYSTEM (Continued)					
MYELOMA, PLASMA CELL					
Overall Rates (a)	0/50 [0.00%]	0/50 [0.00%]	1/50 [2.00%]	0/50 [0.00%]	0/50 [0.00%]
Cochran Armitage Trend Test; P-value	1.000				
Fisher Exact Test; P-value		1.000	1.000	1.000	1.000
Peto Test; P-value	0.987				
SARCOMA, HISTIOCYTIC**					
Overall Rates (a)	4/50 [8.00%]	4/50 [8.00%]	1/50 [2.00%]	2/50 [4.00%]	4/50 [8.00%]
Cochran Armitage Trend Test; P-value	0.707				
Fisher Exact Test; P-value		1.000	0.362	0.678	1.000
Peto Test; P-value	0.612				
LARGE INTESTINE, RECTUM					
HEMANGIOMA					
Overall Rates (a)	0/50 [0.00%]	0/50 [0.00%]	1/50 [2.00%]	0/49 [0.00%]	0/50 [0.00%]
Cochran Armitage Trend Test; P-value	0.998				
Fisher Exact Test; P-value		1.000	1.000	1.000	1.000
Peto Test; P-value	0.857				
LIVER					
ADENOMA, HEPATOCELLULAR**					
Overall Rates (a)	2/49 [4.08%]	2/50 [4.00%]	1/50 [2.00%]	3/50 [6.00%]	1/50 [2.00%]
Cochran Armitage Trend Test; P-value	0.797				
Fisher Exact Test; P-value		1.000	0.617	1.000	0.617
Peto Test; P-value	0.772				
CARCINOMA, HEPATOCELLULAR					
Overall Rates (a)	0/49 [0.00%]	1/50 [2.00%]	0/50 [0.00%]	0/50 [0.00%]	0/50 [0.00%]
Cochran Armitage Trend Test; P-value	0.475				
Fisher Exact Test; P-value		1.000	1.000	1.000	1.000
Peto Test; P-value	0.365				

455-032 (a) - Number of tumor bearing animals / number of animals examined at site.
*Only includes tissues where at least 1 tumor was found in any group.
**Per protocol description, organs where the high dose group has a count equal to 2 or where the sum of mid-dose and high-dose is equal to 4.
All p-values are calculated using a two tail test.

Statistical Analysis of Neoplastic Lesions - Females (all groups)

Table 8 Cont.

Tissue* Lesion	0 mg/kg/day (Untreated Control)	0 mg/kg/day (Vehicle Control)	150 mg/kg/day	300 mg/kg/day	600 mg/kg/day
LUNG					
ADENOMA, ALVEOLAR BRONCHIOLAR**					
Overall Rates (a)	8/50 [16.00%]	7/50 [14.00%]	7/50 [14.00%]	8/50 [16.00%]	4/50 [8.00%]
Cochran Armitage Trend Test; P-value	0.382				
Fisher Exact Test; P-value		1.000	1.000	1.000	0.357
Peto Test; P-value	0.332				
CARCINOMA, ALVEOLAR BRONCHIOLAR**					
Overall Rates (a)	2/50 [4.00%]	1/50 [2.00%]	2/50 [4.00%]	3/50 [6.00%]	3/50 [6.00%]
Cochran Armitage Trend Test; P-value	0.384				
Fisher Exact Test; P-value		1.000	1.000	1.000	1.000
Peto Test; P-value	0.480				
MESOTHELIOMA, BENIGN					
Overall Rates (a)	0/50 [0.00%]	0/50 [0.00%]	1/50 [2.00%]	0/50 [0.00%]	0/50 [0.00%]
Cochran Armitage Trend Test; P-value	1.000				
Fisher Exact Test; P-value		1.000	1.000	1.000	1.000
Peto Test; P-value	0.910				
MAMMARY GLAND					
ADENOCARCINOMA					
Overall Rates (a)	2/50 [4.00%]	1/50 [2.00%]	1/48 [2.08%]	0/49 [0.00%]	0/48 [0.00%]
Cochran Armitage Trend Test; P-value	0.080				
Fisher Exact Test; P-value		1.000	1.000	0.496	0.496
Peto Test; P-value	0.090				
OVARY					
CYSTADENOMA					
Overall Rates (a)	0/50 [0.00%]	1/50 [2.00%]	4/50 [8.00%]	1/50 [2.00%]	2/50 [4.00%]
Cochran Armitage Trend Test; P-value	0.310				
Fisher Exact Test; P-value		1.000	0.117	1.000	0.495
Peto Test; P-value	0.296				

455-032 (a) - Number of tumor bearing animals / number of animals examined at site.
*Only includes tissues where at least 1 tumor was found in any group.
**Per protocol description, organs where the high dose group has a count equal to 2 or where the sum of mid-dose and high-dose is equal to 4.
All p-values are calculated using a two tail test.

Statistical Analysis of Neoplastic Lesions - Females (all groups)

Table 6 Cont.

Tissue* / Lesion	0 mg/kg/day (Untreated Control)	0 mg/kg/day (Vehicle Control)	150 mg/kg/day	300 mg/kg/day	600 mg/kg/day
OVARY (Continued)					
FIBROMA					
Overall Rates (a)	0/50 [0.00%]	0/50 [0.00%]	1/50 [2.00%]	0/50 [0.00%]	0/50 [0.00%]
Cochran Armitage Trend Test; P-value	1.000				
Fisher Exact Test; P-value		1.000	1.000	1.000	1.000
Peto Test; P-value	0.987				
GRANULOSA, CELL TUMOR, BENIGN					
Overall Rates (a)	0/50 [0.00%]	0/50 [0.00%]	1/50 [2.00%]	0/50 [0.00%]	0/50 [0.00%]
Cochran Armitage Trend Test; P-value	1.000				
Fisher Exact Test; P-value		1.000	1.000	1.000	1.000
Peto Test; P-value	0.987				
LUTEOMA					
Overall Rates (a)	0/50 [0.00%]	1/50 [2.00%]	0/50 [0.00%]	0/50 [0.00%]	0/50 [0.00%]
Cochran Armitage Trend Test; P-value	0.480				
Fisher Exact Test; P-value		1.000	1.000	1.000	1.000
Peto Test; P-value	0.463				
SERTOLI CELL TUMOR, BENIGN					
Overall Rates (a)	0/50 [0.00%]	1/50 [2.00%]	0/50 [0.00%]	0/50 [0.00%]	0/50 [0.00%]
Cochran Armitage Trend Test; P-value	0.480				
Fisher Exact Test; P-value		1.000	1.000	1.000	1.000
Peto Test; P-value	0.463				
TERATOMA					
Overall Rates (a)	0/50 [0.00%]	0/50 [0.00%]	0/50 [0.00%]	1/50 [2.00%]	0/50 [0.00%]
Cochran Armitage Trend Test; P-value	0.480				
Fisher Exact Test; P-value		1.000	1.000	1.000	1.000
Peto Test; P-value	0.513				

456-032 (a) - Number of tumor bearing animals / number of animals examined at site.
*Only includes tissues where at least 1 tumor was found in any group.
All p-values are calculated using a two tail test.

Statistical Analysis of Neoplastic Lesions - Females (all groups)

Table 8 Cont.

Tissue[a] / Lesion	0 mg/kg/day (Untreated Control)	0 mg/kg/day (Vehicle Control)	150 mg/kg/day	300 mg/kg/day	600 mg/kg/day
PANCREAS					
HEMANGIOMA					
Overall Rates (a)	0/50 [0.00%]	0/50 [0.00%]	0/50 [0.00%]	1/50 [2.00%]	0/50 [0.00%]
Cochran Armitage Trend Test; P-value	0.460				
Fisher Exact Test; P-value		1.000	1.000	1.000	1.000
Peto Test; P-value	0.484				
PITUITARY					
ADENOMA					
Overall Rates (a)	1/45 [2.22%]	1/45 [2.22%]	2/46 [4.35%]	2/46 [4.35%]	1/43 [2.33%]
Cochran Armitage Trend Test; P-value	0.765				
Fisher Exact Test; P-value		1.000	1.000	1.000	1.000
Peto Test; P-value	0.941				
ADENOMA, PARS INTERMEDIA					
Overall Rates (a)	0/45 [0.00%]	0/45 [0.00%]	0/46 [0.00%]	0/46 [0.00%]	1/43 [2.33%]
Cochran Armitage Trend Test; P-value	0.151				
Fisher Exact Test; P-value		1.000	1.000	1.000	0.489
Peto Test; P-value	0.156				
THYROID GLAND					
ADENOMA, FOLLICULAR					
Overall Rates (a)	1/49 [2.04%]	0/47 [0.00%]	0/46 [0.00%]	0/47 [0.00%]	0/48 [0.00%]
Cochran Armitage Trend Test; P-value	0.163				
Fisher Exact Test; P-value		1.000	1.000	1.000	1.000
Peto Test; P-value	0.125				
UTERUS					
ADENOMA					
Overall Rates (a)	0/50 [0.00%]	0/50 [0.00%]	0/50 [0.00%]	1/50 [2.00%]	0/50 [0.00%]
Cochran Armitage Trend Test; P-value	0.460				
Fisher Exact Test; P-value		1.000	1.000	1.000	1.000
Peto Test; P-value	0.528				

455-032 (a) - Number of tumor bearing animals / number of animals examined at site.
[a]Only includes tissues where at least 1 tumor was found in any group.
All p-values are calculated using a two tail test.

Statistical Analysis of Neoplastic Lesions - Females (all groups)

Table 8 Cont.

Tissue* / Lesion	0 mg/kg/day (Untreated Control)	0 mg/kg/day (Vehicle Control)	150 mg/kg/day	300 mg/kg/day	600 mg/kg/day
UTERUS (Continued)					
HEMANGIOMA					
Overall Rates (a)	2/50 [4.00%]	0/50 [0.00%]	0/50 [0.00%]	1/50 [2.00%]	0/50 [0.00%]
Cochran Armitage Trend Test; P-value	0.219				
Fisher Exact Test; P-value		0.495	0.495	1.000	0.495
Peto Test; P-value	0.200				
LEIOMYOMA**					
Overall Rates (a)	2/50 [4.00%]	0/50 [0.00%]	2/50 [4.00%]	3/50 [6.00%]	1/50 [2.00%]
Cochran Armitage Trend Test; P-value	0.600				
Fisher Exact Test; P-value		0.495	1.000	1.000	1.000
Peto Test; P-value	0.680				
LEIOMYOSARCOMA					
Overall Rates (a)	2/50 [4.00%]	0/50 [0.00%]	3/50 [6.00%]	1/50 [2.00%]	0/50 [0.00%]
Cochran Armitage Trend Test; P-value	0.382				
Fisher Exact Test; P-value		0.495	1.000	1.000	0.495
Peto Test; P-value	0.300				
POLYP**					
Overall Rates (a)	2/50 [4.00%]	4/50 [8.00%]	4/50 [8.00%]	1/50 [2.00%]	3/50 [6.00%]
Cochran Armitage Trend Test; P-value	0.846				
Fisher Exact Test; P-value		0.678	0.678	1.000	1.000
Peto Test; P-value	0.745				
SARCOMA, ENDOMETRIAL					
Overall Rates (a)	0/50 [0.00%]	0/50 [0.00%]	0/50 [0.00%]	1/50 [2.00%]	0/50 [0.00%]
Cochran Armitage Trend Test; P-value	0.480				
Fisher Exact Test; P-value		1.000	1.000	1.000	1.000
Peto Test; P-value	0.552				

455-032 (a) - Number of tumor bearing animals / number of animals examined at site.
*Only includes tissues where at least 1 tumor was found in any group.
**Per protocol description, organs where the high dose group has a count equal to 2 or where the sum of mid-dose and high-dose is equal to 4.
All p-values are calculated using a two tail test.

Statistical Analysis of Neoplastic Lesions - Females (all groups)

Table 8 Cont.

Tissue* / Lesion	0 mg/kg/day (Untreated Control)	0 mg/kg/day (Vehicle Control)	150 mg/kg/day	300 mg/kg/day	600 mg/kg/day
UTERUS, CERVIX					
ADENOCARCINOMA					
Overall Rates (a)	0/50 [0.00%]	0/50 [0.00%]	0/50 [0.00%]	1/50 [2.00%]	0/50 [0.00%]
Cochran Armitage Trend Test; P-value	0.480				
Fisher Exact Test; P-value		1.000	1.000	1.000	1.000
Peto Test; P-value	0.484				
FIBROMA					
Overall Rates (a)	1/50 [2.00%]	0/50 [0.00%]	0/50 [0.00%]	0/50 [0.00%]	0/50 [0.00%]
Cochran Armitage Trend Test; P-value	0.157				
Fisher Exact Test; P-value		1.000	1.000	1.000	1.000
Peto Test; P-value	0.147				
GRANULAR CELL TUMOR, BENIGN					
Overall Rates (a)	0/50 [0.00%]	1/50 [2.00%]	0/50 [0.00%]	0/50 [0.00%]	1/50 [2.00%]
Cochran Armitage Trend Test; P-value	0.616				
Fisher Exact Test; P-value		1.000	1.000	1.000	1.000
Peto Test; P-value	0.722				
LEIOMYOMA					
Overall Rates (a)	1/50 [2.00%]	1/50 [2.00%]	2/50 [4.00%]	1/50 [2.00%]	0/50 [0.00%]
Cochran Armitage Trend Test; P-value	0.524				
Fisher Exact Test; P-value		1.000	1.000	1.000	1.000
Peto Test; P-value	0.430				
LEIOMYOSARCOMA					
Overall Rates (a)	2/50 [4.00%]	0/50 [0.00%]	0/50 [0.00%]	0/50 [0.00%]	1/50 [2.00%]
Cochran Armitage Trend Test; P-value	0.412				
Fisher Exact Test; P-value		0.495	0.495	0.495	1.000
Peto Test; P-value	0.389				

456-032 (a) - Number of tumor bearing animals / number of animals examined at site.
*Only includes tissues where at least 1 tumor was found in any group.
All p-values are calculated using a two tail test.

Statistical Analysis of Neoplastic Lesions - Females (all groups)

Table 8 Cont.

Tissue* / Lesion	0 mg/kg/day (Untreated Control)	0 mg/kg/day (Vehicle Control)	150 mg/kg/day	300 mg/kg/day	600 mg/kg/day
UTERUS, CERVIX					
POLYP					
Overall Rates (a)	0/50 [0.00%]	1/50 [2.00%]	0/50 [0.00%]	1/50 [2.00%]	0/50 [0.00%]
Cochran Armitage Trend Test; P-value	1.000				
Fisher Exact Test; P-value		1.000	1.000	1.000	1.000
Peto Test; P-value	0.981				

455-032 (a) - Number of tumor bearing animals / number of animals examined at site.
*Only includes tissues where at least 1 tumor was found in any group.
All p-values are calculated using a two tail test.

/S/

Barbara Hill, Ph.D.
Reviewing Pharmacologist

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HFD-340
HFD-540/DIV FILES
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