CARCINOGENICITY:

Carcinogenicity Study #1

Study Title: Carcinogenicity study by dermal administration in mice
Laboratory Study Number: 15142 TCS
Sponsor Study Number: T-127/BS-530
Volume Numbers: 82 - 86
Test Facility: [redacted]
Study Date(s): 1-29-97 to 2-1-99
Date of Submission: 12-19-00
GLP Compliance/Quality Assurance: Yes
QA- Report: Yes (X) No ()
Study Type: Dermal carcinogenicity study in mice
Species/strain: CD1 mice
Number of animals per group; age at start of study: 50 mice/sex/group for oncogenicity assessment and 24 mice/sex/group for toxicokinetic assessment; 8 weeks old (males: 26.8 – 35.9 g; females: 21.5 – 29.9 g)
Animal housing: The mice were individually housed in polycarbonate cages (24.0 x 13.5 x 13.0 cm) and the floor of each cage was covered with [redacted] sawdust. Cages and sawdust were changed once a week, cage lids and racks once every four months.
Drug Lot/Batch number(s):

1) ASM 981 – Batch No. 96923
2) Ethanol, USP (vehicle)

Drug Purity / Stability / Homogeneity:

Drug purity/stability/homogeneity testing was performed by the sponsor from samples sent to the sponsor from the contract lab at various points throughout the study. All sampling points fulfilled the necessary standards for drug purity/stability/homogeneity in this study.

Doses: refer to study design table below

Study Design

ASM 981 Concentration (%)		ASM 981 Dose (mg/kg/day)	Number of Main Study Animals		Number of Toxicokinetic Animals	
Week 1-3	Week 4-end		Males	Females	Males	Females
NA	NA	Untreated Control	50	50	24	24
0	0	Vehicle Control	50	50	24	24
0.0027	0.0032	0.04	50	50	24	24
0.027	0.032	0.40	50	50	24	24
0.27[a]	0.32[b]	4.00	50	50	24	24

a – high dose stock concentration was 2.7 mg/ml in ethanol and lower dose groups were derived from

b – high dose stock concentration was 3.2 mg/ml in ethanol and lower dose groups were derived from

A 2 x 3 cm area, estimated to be at least 10% of the total body surface, was clipped with an electric clipper. The clipped zone included the dorsal retro-scapular region, on both sides of the spinal column, the back and two flanks. The animals were clipped on an as needed basis throughout the study. The test article was administered by dermal application using an adjustable volume pipette fitted with a plastic tip. No massage was performed but the tip was used to spread the formulation over the application site. The animals were not rinsed between each application and no dressing was applied to the application site. Untreated animals received no treatment but were clipped as frequently as the other animals. The volume of application of the formulations was 1.5 ml/kg/day during the first three weeks and 1.25 ml/kg/day thereafter. The total application volumes were generally lower than 50 µl in this study.

Note: Males were treated for 104 weeks and females were treated for 98 weeks. The highest percentage of ASM 981 in ethanol applied in this study was 0.32%. This is about 1/3 of the concentration that will be used clinically (1% ASM 981 cream). It would have been preferable to have the high dose set at 1% or higher, if possible.

- *Basis of Dose Selection:*

The basis for dose selection in this study was not acceptable by agency standards. Dose selection was not based on MTD or Maximum Feasible Dose. The highest dose was selected as a dose that would not produce lymphoma based on the results of the 13 week dermal mouse study,

Dose selection for the mouse dermal carcinogenicity study was made based on the results of the 13 week dermal toxicity study conducted in mice. Animals (10/sex) were treated daily with ASM 981 by dermal application of a volume of 50 µL per animal at concentrations of 3, 30, and 300 mg/mL in ethanol (0.15, 1.5, or 15 mg/animal/day; 5, 50 or 500 mg/kg/day). One group of ten animals/sex were treated with a similar volume of vehicle alone (Control group) and another

group was untreated (untreated Control). An additional 6 mice/sex were in the two control and high dose groups and maintained for a 4-week recovery period. An additional 6 mice/sex were in the vehicle control and each treated group for a satellite group to assess blood concentrations of ASM 981.

Piloerection and hunched posture were frequently observed in high dose animals. Other treatment-related signs noted in high dose animals included underactivity or overactivity, thin build, pallor, hypothermia, partially closed eyelids, abnormal respiration, and yellow perigenital staining. Two high dose males and five high dose females were killed *in extremis* during the treatment period due to the severity of these signs. The deaths were considered to be treatment-related. Low body weight gains and food conversion efficiencies were observed in high dose males. Food consumption was not affected by treatment.

Low total leukocyte counts and reduced lymphocyte numbers were noted in mid dose females and high dose animals. High eosinophil counts were apparent in high dose animals. Slightly low packed cell volumes, hemoglobin concentrations, mean cell hemoglobin, and mean cell volumes and slightly high platelet counts were observed in high dose females. Low mean cell hemoglobin was also apparent in high dose males. Plasma magnesium concentrations were low in mid and high dose animals. High urinary volumes and total sodium, potassium and chloride outputs and low urinary pH and protein concentrations were observed in high dose males. Glucose was also present in the urine of a few males in the mid and high dose groups.

ASM 981 was observed in the blood of all animals 6 and 24 hours following the last dermal application of the compound, after 13 weeks of treatment. The whole blood concentrations increased with increased dose. The concentrations were higher after 6 hours than after 24 hours. No difference was noted between male and female animals. Unfortunately adequate sampling times were not used to obtain AUC values for the various dose groups.

Numerous treatment-related histopathological findings were noted in various organs. The following findings were considered to be associated with the immunosuppressive action of the test material.

Hematopoietic tissue: Pleomorphic lymphoma was noted in mid dose animals and high dose females.

Mandibular lymph nodes: Sinus histiocytosis was noted in mid dose females and high dose animals. Pleomorphic lymphoid cell proliferation was noted in mid and high dose animals.

Mesenteric lymph nodes: Lymphocytolysis was noted in all treated groups. Pleomorphic lymphoid cell proliferation was noted in mid dose animals and high dose females.

Spleen: Lymphocytolysis was noted in mid dose males and high dose animals. Pleomorphic lymphoid cell proliferation was noted in mid dose males and high dose animals.

Thymus: Medullary atrophy was noted in low, mid and high dose animals. Cortical lymphoid hyperplasia was noted in mid dose females and high dose animals. Pleomorphic lymphoid cell proliferation was noted in one mid dose male.

The following findings were considered to be related to toxic effects of the compound.

Ovaries: Arrested follicular development was noted in mid and high dose females.

Uterus or cervix: Atrophy was noted in mid and high dose females.

Kidneys: Basophilic cortical tubules, cortical lymphocytic infiltration and chronic interstitial nephritis were noted in mid and high dose animals.

Salivary glands: Degranulation of the granular convoluted ducts was noted in high dose animals.

Pancreas: Minimal vacuolation of the islets was seen in three high dose females.

Treatment-related findings which were still apparent on completion of the reversibility period in high dose animals included slightly high eosinophil counts in males; slightly high liver weights in males and females and slightly low uterus weights in females. There was also no clear evidence of recovery from the histopathological changes in the mandibular and mesenteric lymph nodes, ovaries, and kidneys. Other findings showed evidence of complete or partial recovery during the reversibility period.

Marked general toxicity including seven deaths was noted in the high dose group. Mild nephrotoxicity and a number of effects that were probably associated with the pharmacological activity of ASM 981 were noted in the low and mid dose groups. Evidence of recovery from some of these changes was apparent during a four week reversibility period.

No clear NOAEL was identified in this study. However, it could be viewed that the effects noted in the low dose group may be attributed to the pharmacological properties associated with ASM 981. Therefore, a toxicological NOAEL of 5 mg/kg/day could be established based on the results from this study. It is stated in the study report that the highest dose for the dermal mouse carcinogenicity study was selected as 4 mg/kg/day based on the observation of pleomorphic lymphomas observed in the mid dose group (50 mg/kg/day). It would appear that the sponsor might have selected the high dose group in the dermal mouse carcinogenicity study so that pleomorphic lymphomas would not be seen in this study. This is not an appropriate criterion for selection of the high dose for a dermal mouse carcinogenicity study.

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

- *CAC Concurrence:*

No CAC concurrence was obtained for the doses selected in this study. The rationale that the sponsor used for high dose selection in the dermal mouse carcinogenicity study is not in agreement with the agency's current standard. The sponsor selected a high dose group that would probably not meet current agency guidelines.

It would have been preferable to have conducted this mouse dermal carcinogenicity study with the final marketed formulation of ASM 981 instead of with ASM 981 dissolved in ethanol. However, this mouse dermal carcinogenicity study was in progress at the time of the IND submission. The sponsor was informed shortly after the IND was submitted that the dermal carcinogenicity study would need to be conducted with the final marketed formulation of ASM 981. The sponsor conducted a second dermal carcinogenicity study in rat with the ASM 981 cream (final marketed formulation). The details and results of the second dermal carcinogenicity study in rats are presented later in this review.

- *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:* No

Study Results and Frequency of Monitoring:

- *Clinical Observations:* Each animal was observed for clinical signs once daily. Animals were palpated every two weeks from week 27 to the end of the study. The time of onset, location, size, appearance and progression of palpable masses was recorded for each animal.

No treatment related effects on clinical observations were noted in this study. No treatment related effects on the time of onset, location, size, appearance or progression of palpable masses were noted in this study.

- *Dermal Observations:* Possible signs of local irritation (erythema, edema desquamation, scabs) were recorded and graded for each animal.

No treatment related effects on local irritation were noted in this study.

- *Mortality:* Each animal was checked twice daily for mortality or signs of morbidity.

No treatment related effects on mortality were noted in this study. The survival rates (%) at study termination are provided in the following table.

ASM 981 dose (mg/kg/day)	Male survival rate (%)	Female survival rate (%)
Untreated	54	56
0	62	68
0.04	62	52
0.4	52	62
4.0	62	68

Note: Males were treated for 104 weeks and females were treated for 98 weeks.

- *Body Weight:* Body weights were recorded weekly.

No treatment related effect on body weight was noted in females in this study. A slight decrease in body weight was noted in mid (↓5.1%) and high dose (↓5.9%) males compared to control animals during the first 6 months of treatment. No additional treatment related effect on body weight in male animals was noted for the remainder of the study.

- *Food Consumption:* Individual food consumption was measured weekly for weeks 1-13, once every four weeks until week 78 and once every four weeks thereafter.

A slight decrease in food consumption (~↓6%) was noted in all treated animals compared to control animals.

- *Hematology:* Blood samples for hematology analyses were collected during weeks 52 and 78 of treatment.

No treatment related effects on hematology parameters were noted in this study.

- *Toxicokinetics:* Blood samples for toxicokinetic analysis were collected during weeks 13, 26 and 52. Blood samples were taken 1, 2, 4, 7 and 24 hours after application of test article. Three males and three females were sampled at each timepoint.

The mean plasma pharmacokinetic parameters of ASM 981 after dermal administration on Weeks 13, 26 and 52 in CD-1 mice are summarized in the following table.

Dose (mg/kg)	Sex	C_{max} (ng/ml) Mean			T_{max} (hr) Mean			$AUC_{0\text{-}24hr}$ (ng•h:/ml) Mean		
		Week 13	Week 26	Week 52	Week 13	Week 26	Week 52	Week 13	Week 26	Week 52
0.04	M	1.7	1.1	1.2	4	4	4	27.7	15.1	19.9
0.04	F	1.7	3.1	1.4	4	7	1	36.1	43.9	22.9
0.4	M	23.4	8.8	12.0	7	2	7	364	173	227
0.4	F	23.6	12.0	17.8	7	2	4	384	198	273
4.0	M	67.5	50.5	50.6	4	4	4	1020	852	1070
4.0	F	75.3	93.1	60.8	4	4	2	1040	1000	1090

An approximate dose proportional increase in systemic exposure (AUC) was noted between the 0.04 and 0.4 mg/kg/day dose groups. A non-dose proportional increase in systemic exposure (AUC) was noted between the 0.4 and 4.0 mg/kg/day dose group. This may indicate some level of saturation approaching the high dose group. Female animals appeared to have a slightly higher systemic exposure after dermal administration than male animals.

It is interesting to note that the AUC levels obtained in the high dose group in this dermal mouse carcinogenicity study were significantly less than the NOAEL dose for lymphoma identified in the oral mouse carcinogenicity study. The NOAEL AUC values in the oral mouse carcinogenicity study for males and females were 2204 and 5059 ng·hr/ml, respectively, after week 70 of treatment. Therefore, the NOAEL in the oral mouse carcinogenicity was about 2X – 5X greater than the AUC obtained in the high dose group in the dermal mouse carcinogenicity study. It could be anticipated that the AUC levels obtained in this dermal mouse carcinogenicity study are probably not high enough to elicit a positive lymphoma signal.

- *Gross Pathology:* Performed at necropsy.

No treatment related effects on macroscopic observations were noted in this study. Macroscopic observations that were noted in this study were typical of long term studies in mice and were of equal incidence rates for treated and control animals.

- *Histopathology:* The following tissues were examined, collected for preservation at necropsy and examined histopathologically: Adrenal glands, aorta, brain (medulla/pons cerebrum and cerebellum), cecum, colon, duodenum, epididymides, esophagus, eyes, femoral bone, gallbladder, heart, ileum, jejunum, kidneys, lacrymal glands, liver, lungs, lymph nodes (axillary, mandibular, mesenteric, tracheobronchic), mammary glands, nasal turbinates, ovaries, pancreas, pituitary gland, prostrate gland, rectum, salivary glands (sublingual and mandibular), sciatic nerve, seminal vesicles, skeletal muscle, skin (treated and untreated), spinal cord (cervical, thoracic and lumbar), spleen, sternum, stomach, testes, thymus, thyroid/parathyroid glands, tongue, trachea, urinary bladder, uterus, vagina and gross lesions.

Note: The sponsor's incidence of neoplastic histopathology findings (scanned directly from the NDA) is provided below in the addendum section. The agency's statistical reviewer, Atiar Rahman, has performed a statistical evaluation of the neoplastic findings.

No treatment related effects on nonneoplastic or neoplastic microscopic findings were noted in this study. The agency's statistical reviewer evaluated the data by multiple trends tests and multiple pairwise comparisons. Adjustment for multiple trends tests was done using the results of Lin and Rahman[1] (1998) (i.e., use p=0.025 for rare tumor type and 0.005 for common

[1] Lin KK and Rahman MA. (1998) Overall false positive rats in tests for linear trend in tumor incidence in animal carcinogenicity studies of new drugs. *Journal of Biopharmaceutical Statistics*. 8: 1 – 15.

tumor type). Adjustments for multiple pairwise comparisons was done using the results of Haseman[2] (1983) (i.e., use p=0.05 for rare tumors and p=0.01 for common tumor type).

The conclusion reached by the statistical reviewer was the following. No statistically significant dose response or increased incidence of any tumor type in the high dose group was found when compared with either control based on results of Lin and Rahman for dose-response (trend analysis) and that of Haseman for pairwise comparisons.

An Exec CAC meeting was conducted on 6-19-01 to discuss the results from all of the carcinogenicity studies conducted for ASM 981. The oral rat and oral mouse carcinogenicity studies were reviewed under the IND (IND —— . The minutes from the Exec CAC meeting are included in the addendum list of this review. The committee felt that this study was negative. However, the committee commented that the test article had obvious effects after dermal administration in mice (malignant lymphoma noted in the 13 week repeat dermal toxicity study in mice at doses ≥50 mg/kg/day). The committee recommended that this information be included in the label if the drug product is approved. The recommendations of the committee will be recommended for inclusion into the label for Elidel cream. In addition, the committee asked about the source of the metastatic carcinoma noted in the thymus of one high dose male. An informational request was sent to the sponsor on 7-10-01 to clarify the source of this metastatic carcinoma. The entire informational request is provided in the addendum list of this review.

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 sponsor selected as the high dose in the mouse dermal carcinogenicity the NOAEL established in a 13 week dermal mouse toxicity study. This dose was selected as a dose that would not elicit pleomorphic lymphoma. The criterion used by the sponsor for high dose selection for this dermal mouse carcinogenicity study was not appropriate according to current agency standards. In addition, ethanol is not an appropriate vehicle for dermal carcinogenicity studies. It is preferable to have the dermal carcinogencity study conducted with the final marketed formulation for the drug product. Therefore, the design of this dermal carcinogenicity is typically not acceptable for evaluation of dermal carcinogenicity. However, this study was reviewed to determine if any useful data could be obtained from this study. The sponsor has conducted a second dermal carcinogenicity study in rats with ASM 981 cream (final marketed formulation), which is described later in this review.

- *Evaluation of Tumor Findings:*

No treatment related neoplastic findings were noted in this study.

Summary Conclusions and Recommendations:

[2] Haseman. (1983) A re-examination of false-positive rats for carcinogenesis studies. *Fundamental and applied toxicology*. 3: 334-339.

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

The sponsor selected as the high dose in the mouse dermal carcinogenicity the NOAEL established in a 13 week dermal mouse toxicity study. This dose was selected as a dose that would not elicit pleomorphic lymphoma. The criterion used by the sponsor for high dose selection for this dermal mouse carcinogenicity study was not appropriate according to current agency standards. Therefore, the mouse dermal carcinogenicity study may be inadequate according to current agency standards.

- *Major Tumor Findings:*

No treatment related neoplastic findings were noted in this study.

- *Non-neoplastic Findings:*

No treatment related non-neoplastic findings were noted in this study.

- *Biological Significance:*

The only toxic effects noted in this study was a slight decrease of food consumption at all dose levels and a slight reduction in body weight in mid and high dose males. No treatment related neoplastic or non-neoplastic findings were noted in this study. Therefore, the NOAEL for carcinogenicity effects is 4.0 mg/kg/day under the conditions of this study. The average AUC for the NOAEL was 1080 ng·hr/ml after 52 weeks of treatment.

It is interesting to note that the AUC levels obtained in the high dose group in this dermal mouse carcinogenicity study were significantly less than the NOAEL dose for lymphoma identified in the oral mouse carcinogenicity study. The NOAEL AUC values in the oral mouse carcinogenicity study for males and females were 2204 and 5059 ng·hr/ml, respectively, after 70 weeks of treatment. The NOAEL AUC values in the oral mouse carcinogenicity were about 2X – 5X greater than the AUC obtained in the high dose group in the dermal mouse carcinogenicity study. Therefore, it is not surprising that no lymphoma was noted in this dermal mouse carcinogenicity study.

- *Potential Clinical Implications of Findings:*

The highest measured $AUC_{(0\text{-}24\ hr)}$ value measured in humans that applied 1% ASM 981 cream was 38 ng·hr/ml. This was measured in a single pediatric patient that applied 1% ASM 981 cream bid to 43.5% BSA. The multiple of human exposure will be calculated based on this highest $AUC_{(0\text{-}24\ hr)}$ value. The NOAEL identified in this study is 4 mg/kg/day (average $AUC_{(0\text{-}24\ hr)}$ = 1080 ng·hr/ml after 52 weeks of treatment). The multiple of human exposure is 28X based on the NOAEL $AUC_{(0\text{-}24\ hr)}$ levels identified in this dermal mouse carcinogenicity study.

This multiple of human exposure probably provides an adequate safety margin for the potential concern of lymphoma formation in humans after use of 1% ASM 981 cream under maximum use conditions. Even though the high dose group was not selected according to current agency standards, it did provide for a systemic exposure level that was 28X the highest level obtained in humans under maximum use conditions. Therefore, it is unclear how much additional information would be obtained by requesting that the sponsor repeat the mouse dermal carcinogenicity study using higher doses that would elicit a positive signal for lymphoma. The NOAEL level for lymphoma formation has been established in the mouse from the oral mouse carcinogenicity study. In addition, lymphoma was noted in the 13 week dermal toxicity study in mice at the 50 mg/kg/day dose level. Therefore, it is recommended that the findings from the 13 week dermal toxicity study be included in the label to address the concern about lymphoma formation after dermal administration.

- *Recommendations for Further Analysis:*

The Exec CAC information request for this study has been sent to the sponsor.

Carcinogenicity Study #2

Study Title: 104-Week dermal carcinogenicity study in rats
Laboratory Study Number: 972052
Sponsor Study Number: T-133/BS-733
Volume Numbers: 98 - 106
Test Facility: [redacted]
Study Date(s): 3-19-98 to 3-24-00
Date of Submission: 12-19-00
GLP Compliance/Quality Assurance: Yes
QA- Report: Yes (X) No ()
Study Type: Dermal carcinogenicity study in rats
Species/strain: Wistar rats
Number of animals per group; age at start of study: 50 rats/sex/group for oncogenicity assessment and 10 rats/sex/group for toxicokinetic assessment; 6 weeks old (males: 115.4 – 178.5 g; females: 96.5 – 147.2 g)
Animal housing: Rats were individually housed in [redacted] cages with standard softwood bedding [redacted]
Bedding was [redacted]

Drug Lot/Batch number(s):

1) Vehicle cream – Batch No. Z075 1097
2) 0.2% ASM 981 cream – Batch No. Z142 1297
3) 0.6% ASM 981 cream – Batch No. Z143 1297
4) 1.0% ASM 981 cream – Batch No. Z025 0397

Drug Purity / Stability / Homogeneity:

Drug purity/stability/homogeneity testing was performed by the sponsor from samples sent to the sponsor from the contract lab at various points throughout the study. All sampling points fulfilled the necessary standards for drug purity/stability/homogeneity in this study.

Doses: refer to study design table below

Study Design

ASM 981 Dose (%)	ASM 981 Dose (mg/kg/day)	Number of Main Study Animals		Number of Toxicokinetic Animals	
		Males	Females	Males	Females
Saline Control	0	50	50	10	10
Vehicle Control	0	50	50	10	10
0.2	2	50	50	10	10
0.6	6	50	50	10	10
1.0	10	50	50	10	10

The back of each rat was shaved ~24 hours prior to the first dosing and then on a weekly basis during the course of the study. An intact skin area of ~20 cm^2 was selected from the shaved area for the administration site. Special jackets (supplier – ——— were used for each rat to fix the cover of the application site. Test article (1 gm/kg/day) was applied to the application site and spread as uniformly as possible. The application sites were covered with an insert, which was fixed to the jacket. Test article was gently washed off with lukewarm tap water after each daily 6 hour exposure period. Animals were treated with test article daily, 6 hours/day, 7 days/week for a duration of 104 weeks.

Note: It would have been preferable if the animals had been treated with test article for a 24 hour period instead of the 6 hour period. In addition, it would have been preferable if an untreated control group was used in this study instead of the saline control group.

- *Basis of Dose Selection:*

The basis for dose selection in this study was Maximum Feasible Dose. The maximum feasible concentration of ASM 981 possible in the final marketed formulation is 1%. The sponsor stated that the amount applied of the test article (1 gm/kg/day) is the maximum volume that can be applied to the rat. Therefore, the high dose in this study was the maximum feasible dose that could be applied for ASM 981 in the final to be marketed cream formulation.

Both 13 week and 26 week dermal toxicity studies have been conducted in rats. The 26 week dermal toxicity study will be summarized here for reference purposes. Wistar rats (10/sex) were administered 0%, 0.2%, 0.6% and 1% ASM 981 cream at a volume of 1 mL/kg/day. The corresponding doses were approximately 0, 2, 6, or 10 mg/kg/day. An additional ten animals per sex were in the vehicle and high dose groups and retained for a 4-week recovery period. The

cream was applied uniformly over the dorsal body area covering approximately 10 % of the total body surface. The test area was covered with gauze and Micropore ——— tape. After approximately 20 hours exposure the treated area was cleaned with soap and water and dried. A group of sham-treated animals received no test article but was massaged on the skin in a similar way to the treated groups.

No treatment related deaths were noted in this study. No treatment related skin reactions at the application site were observed throughout the treatment period. No clinical signs of systemic reaction to the treatment were observed. No treatment related effects on body weight, food consumption, ophthalmoscopy, hematology, clinical chemistry, urinalysis, organ weights, necropsy and histopathology were noted in this study. Slightly increased thickness of epidermis was present in the vehicle and high dose group animals compared to the sham control animals. This effect has been noted in other dermal toxicity studies conducted in rats and is related to vehicle and not the active moiety.

Pharmacokinetic analysis during the study demonstrated that low levels of systemic exposure (AUC) were noted in mid and high dose animals. The AUC values did not increase in a dose proportional manner. The AUC values for mid and high dose animals are provided in the following table.

ASM 981 dose (mg/kg/day)	AUC $_{(0\text{-}24\ hr)}$ (ng·hr/ml)	
	Males	Females
6	11.0	6.3
10	4.9	4.9

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

- *CAC Concurrence:* No CAC concurrence was obtained for the doses selected in this study. The sponsor used the maximum feasible dose for the ASM 981 cream for the high dose group in this dermal rat carcinogenicity study. This is an acceptable criterion for establishing the high dose group in a dermal carcinogenicity study.

- *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:* No

Study Results and Frequency of Monitoring:

- *Clinical Observations:* Each animal was observed for clinical signs once daily. Animals were palpated every week for tissue masses.

No treatment related effects on clinical observations were noted in this study. No treatment related effects on the incidence, group distribution or location of palpable masses were noted in this study.

- *Dermal Observations:* Possible signs of local irritation (erythema and edema) were performed on a weekly basis.

No treatment related effects on local irritation were noted in this study.

- *Mortality:* Each animal was checked twice daily for mortality or signs of morbidity.

No treatment related effects on mortality were noted in this study. The number of rats that died spontaneously or had to be killed in extremis are shown in the following table.

ASM 981 dose (mg/kg/day)	Deaths	
	Males	Females
0 (Saline control)	26/50	23/50
0 (Vehicle control)	20/50	18/50
2	15/50	17/50
6	20/50	18/50
10	24/50	20/50

- *Body Weight:* Body weights were recorded weekly up to week 13 and every two weeks thereafter.

No treatment related effect on body weight was noted in this study.

- *Food Consumption:* Food consumption was measured weekly up to week 13 and every two weeks thereafter.

No treatment related effect on food consumption was noted in this study.

- *Hematology:* Blood samples for hematology analyses were collected during week 103 of treatment.

No treatment related effects on hematology parameters were noted in this study.

- *Toxicokinetics:* Blood samples for toxicokinetic analyses were collected during weeks 4, 26, 52, 79 and 104. Blood samples were taken just prior to dosing and 1, 2, 4, 7

and 24 hours after application of test article. Three males and three females were sampled at each timepoint.

The mean plasma pharmacokinetic parameters of ASM 981 after dermal administration on Weeks 4, 26 and 52 in Wistar rats are summarized in the following table.

Dose (mg/kg)	Sex	C_{max} (ng/ml) Mean			T_{max} (hr) Mean			AUC_{0-24hr} (ng•hr/ml) Mean		
		Week 4	Week 26	Week 52	Week 4	Week 26	Week 52	Week 4	Week 26	Week 52
2	M	2.5	1.7	2.8	1	4	2	16.3	31.4	41.4
2	F	1.3	41.2*	3.0	4	4	7	18.1	204*	44.8
6	M	3.9	6.3	5.3	1	4	7	42.2	73.5	108
6	F	4.2	8.0	5.1	4	4	4	40.1	101	74.4
10	M	5.0	4.4	7.8	4	4	4	75.2	77.6	149
10	F	6.1	5.6	10.0	7	2	4	117	96.1	96.7

* - The study report states that the reason why these values are high is probably due to some animals ingesting the test article even though they were wearing jackets to prevent this.

The mean plasma pharmacokinetic parameters of ASM 981 after dermal administration on Weeks 79 and 104 in Wistar rats are summarized in the following table.

Dose (mg/kg)	Sex	C_{max} (ng/ml) Mean		T_{max} (hr) Mean		AUC_{0-24hr} (ng•hr/ml) Mean	
		Week 79	Week 104	Week 79	Week 104	Week 79	Week 104
2	M	2.2	3.5	4	4	40.6	57.0
2	F	2.0	3.9	7	2	32.5	51.2
6	M	6.8	7.9	7	1	113	113
6	F	6.0	6.6	1	4	90.4	99.9
10	M	7.5	10.2	1	1	101	126
10	F	6.0	12.2	4	2	89.2	124

Systemic exposure increased with increased dose but not in a dose proportional manner. No apparent difference in systemic exposure was noted between male and female animals. The systemic exposure to ASM 981 slightly increased between week 4 and week 104.

- *Gross Pathology:* Performed at necropsy.

No treatment related effects on macroscopic observations were noted in this study. Macroscopic observations that were noted in this study were typical of long term studies in rats and were of equal incidence rates for treated and control animals.

- *Histopathology:* The following tissues were examined, collected for preservation at necropsy and examined histopathologically: Adrenal glands, aorta, brain (medulla/pons cerebrum and cerebellum), cecum, colon, duodenum, epididymides, esophagus, eyes, femur (with bone marrow), heart, ileum, jejunum, kidneys, liver, lungs, lymph nodes (mandibular, mesenteric), mammary glands,

ovaries, pancreas, pituitary gland, prostrate gland, rectum, salivary glands (sublingual and mandibular), sciatic nerve, seminal vesicles, skeletal muscle, skin (treated and untreated), spinal cord (cervical, thoracic and lumbar), spleen, sternum (with bone marrow), stomach, testes, thymus, thyroid/parathyroid glands, tongue, trachea, urinary bladder, uterus (with cervix), vagina and gross lesions.

Non-Tumor findings:

An increased incidence of minimal to moderate epithelial hyperplasia at the application site was noted with equal incidence rates in vehicle and ASM 981 treated groups. This effect was contributed to vehicle rather than ASM 981. No other treatment related effects on non-neoplastic microscopic findings were noted in this study

Tumor findings:

Note: The sponsor's incidence of neoplastic histopathology findings (scanned directly from the NDA) is provided below in the addendum section. The agency's statistical reviewer, Atiar Rahman, has performed a statistical evaluation of the neoplastic findings.

The agency's statistical reviewer evaluated the data by pairwise comparisons of the high dose group with the two control groups, per the pharm/tox reviewer request. The rationale for this request was because there was an incomplete analysis of all the tissues in the low and mid dose groups. Therefore, it would not be accurate to perform a trend test or pairwise comparisons of the low and mid dose groups under these conditions. Adjustments for pairwise comparisons were done using the results of Haseman (1983) (i.e., use p=0.05 for rare tumors and p=0.01 for common tumor type).

The conclusion reached by the statistical reviewer was the following. A statistically significant increase in the incidence of follicular cell adenoma in the thyroid gland in the high dose group was found when compared with vehicle control ($p = 0.0357$) based on results of Haseman for pairwise comparisons. It is important to note that the follicular cell adenoma in the thyroid gland was considered a rare tumor for this statistical decision based on the incidence rate in the concurrent control group (i.e., the vehicle control group had an incidence of 0/50 and the high dose group had an incidence of 5/49). However, historical control data submitted by the sponsor per a request demonstrate that follicular cell adenoma of the thyroid gland is not a rare tumor in Wistar rats. Therefore, the increased incidence of follicular cell adenoma noted in high dose animals is not statistically significant according to adjustments based on Haseman for pairwise comparisons for a common tumor (i.e., the p value is > 0.01 for common tumors). The historical incidence rates for follicular cell adenoma in the thyroid gland are provided later in this section.

There appears to be a reduction in adenoma of the pars distalis in the pituitary gland in the high dose group compared to the two control groups. Even though the study report states that there is a statistically significant negative trend for adenoma of the pars distalis in the pituitary

gland, this is not totally accurate due to incomplete sampling in the mid and low dose groups. The incidence rates for adenoma of the pars distalis in the pituitary gland for male and female animals is provided in the following table.

Organ/ Finding	Males					Females				
	Saline	Vehicle	2 mg/kg	6 mg/kg	10 mg/kg	Saline	Vehicle	2 mg/kg	6 mg/kg	10 mg/kg
Pituitary Gland/ Adenoma-pars distalis	29/50 (58%)	17/50 (34%)	8/19 (42%)	10/26 (38%)	11/50 (22%)	42/50 (84%)	41/50 (82%)	33/42 (79%)	30/39 (77%)	34/50 (68%)

A relatively high incidence rate was noted for the following:

a) follicular cell adenoma in the thyroid gland in high dose males
b) benign leydig cell tumor in the testes in high dose males
c) malignant lymphoma in high dose females.

The incidence rates for these potential neoplastic microscopic findings are provided in the following table.

Organ/ Finding	Males					Females				
	Saline	Vehicle	2 mg/kg	6 mg/kg	10 mg/kg	Saline	Vehicle	2 mg/kg	6 mg/kg	10 mg/kg
Thyroid Gland/ Follicular cell adenoma	1/50 (2%)	0/50 (0%)	2/29 (9.1%)	3/24 (12.5%)	5/49 (10.2%)	ND[a]	ND	ND	ND	ND
Testes/ Benign Leydig Cell tumor	1/49 (2%)	1/50 (2%)	1/23 (4.3%)	0/24 (0%)	4/50 (8%)	NA	NA	NA	NA	NA
Hemolymph-oreticular system/ Malignant Lymphoma	0/50 (0%)	2/50 (4%)	0/15 (0%)	1/20 (5%)	1/50 (2%)	1/50 (2%)	2/50 (4%)	0/17 (0%)	0/18 (0%)	3/50 (6%)

a – not detected; finding was not listed in the pathology report summary table

A request was sent to the sponsor on 2/15/01 to provide the contract laboratory historical control background incidence rates in Wistar rats for the incidence of the following neoplastic lesions:

a) Testes – Benign Leydig cell tumor in male animals
b) Thyroid gland – Follicular cell adenoma in male and female animals
c) Hemolymphoreticular system – Malignant lymphoma in male and female animals
d) Pituitary gland – Adenoma/pars diatalis in male and female animals

The sponsor submitted the requested information to the NDA in a BP supplement dated 3/14/01. This submission contained the historical control data on neoplastic findings in Wistar rats from 2 year bioassays conducted by ——— between 1982 – 1996. Thirty-six studies were conducted during that time period. Only one of the studies was a dermal carcinogenicity study. The results from the control groups in the dermal carcinogenicity study did not differ from the results of the other carcinogenicity studies.

The contract lab's historical incidence rate for follicular cell adenoma of the thyroid gland in Wistar rats was the following: Males (Mean: 3.2% ± 3.2%; Range: 0 – 14.3%) and Females (Mean: 2.0% ± 1.8%; Range: 0 – 8.5%). The incidence rate of follicular cell adenoma of the thyroid gland noted in high dose males of this study was 10.2% (5/49). No follicular cell adenoma of the thyroid was noted in females in this study. The incidence rate for high dose males noted in this study is greater than the mean historical incidence rate but fell within the historical incidence rate range.

It is important to note that no potential signal from the thyroid was noted after a more thorough evaluation of the non-neoplastic lesions of the thyroid. The male incidence rates for follicular cell hypertrophy of the thyroid gland in the saline control (0/50), vehicle control (0/50), low (2/22), mid (0/24) and high (1/50) dose groups did not demonstrate any potential cause for concern in this study. In addition, the thyroid gland has not been identified as a potential target organ based on the results of the oral and dermal repeat dose toxicity studies conducted in Wistar rats up to 26 weeks in duration.

The contract lab's historical incidence rate for benign Leydig cell tumor in the testes was the following: Males (Mean: 4.4% ± 2.9%; Range: 0 – 10%). The incidence rate of benign Leydig cell tumor in the testes noted in high dose males in this study was 8% (4/50). The incidence rate for high dose males noted in this study is slightly greater than the mean historical incidence rate but fell within the historical incidence rate range.

The contract lab's historical incidence rate for malignant lymphoma was the following: Males (Mean: 3.8% ± 3.2%; Range: 0 – 12%) and Females (Mean: 3.8% ± 2.8%; Range: 0 – 10%). The incidence rate of malignant lymphoma noted in high dose males and females was 2% (1/50) and 6% (3/50), respectively. The incidence rate for high dose males noted in this study is below the mean historical incidence rate and fell within the historical incidence rate range. The incidence rate for high dose females noted in this study is within the range for the mean historical incidence rate and fell within the historical incidence rate range.

The contract lab's historical incidence rate for adenoma of the pars distalis of the pituitary gland was the following: Males (Mean: 40.5% ± 12.7%; Range: 14.3% – 71.0%) and Females (Mean: 65.5% ± 10.6%; Range: 37.1% – 83.3%). There was a reduction in adenoma of the pars distalis in the pituitary gland in the high dose group compared to the two control groups. The incidence rate for high dose males and females was 22% (11/50) and 68% (34/50), respectively. The incidence rate for high dose males noted in this study was below the mean historical incidence rate and fell within the historical incidence rate range. The incidence rate for high dose

females noted in this study is within the range for the mean historical incidence rate and fell within the historical control incidence rate range.

No rare or uncommon tumors were noted in this study. In addition, no statistically significant increase in any common tumors was detected in this study. All of the potential common neoplastic microscopic findings were within the historical control background incidence rate ranges for Wistar rats from the conducting laboratory. Therefore, it can be concluded that no significant treatment related effects on neoplastic microscopic findings were noted in this study.

An Exec CAC meeting was conducted on 6-19-01 to discuss the results from all of the carcinogenicity studies conducted for ASM 981. The minutes from this meeting are included in the addendum list below. Incomplete histopathological analysis was performed in the low and mid dose groups in this study. The committee determined that a histopathological reanalysis of the thymus and thyroid from all low and mid dose animals is necessary to determine if the potential signal noted in these two dose groups is of potential concern or not. In addition, the committee requested a statistical reanalysis for the combined incidence for the follicular cell adenoma and follicular cell carcinoma of the thyroid. The committee inquired about the historical background incidence rate for follicular cell carcinoma of the thyroid for the strain of rat used in this study. A request was sent to the sponsor on 7-10-01 for the additional informational needs. The informational request is included in the addendum list below. A statistical reanalysis will be performed after the requested information is submitted to the agency. To date, the sponsor has not submitted a response to the informational request. A review addendum to the NDA will be made after the sponsor submits the requested information to the NDA.

Overall Interpretation and Evaluation:

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

The rat dermal carcinogenicity study is an appropriate model and this is an adequate study. The sponsor selected as the high dose in the rat dermal carcinogenicity the maximum feasible dose for the ASM 981 cream in the final to be marketed formulation. This is an acceptable criterion according to current agency standards.

- *Evaluation of Tumor Findings:*

No treatment related neoplastic findings were noted in this study.

Summary Conclusions and Recommendations:

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

The rat dermal carcinogenicity study is acceptable under current agency standards. The high dose group in this study was the maximum feasible dose for the ASM 981 cream in the final to be marketed formulation.

- *Major Tumor Findings:*

No treatment related neoplastic findings were noted in this study.

- *Non-neoplastic Findings:*

The only treatment related non-neoplastic finding noted in this study was an increased incidence of minimal to moderate epithelial hyperplasia at the application site. The incidence rate was similar in vehicle and ASM 981 treated groups. This effect was attributed to vehicle rather than ASM 981.

- *Biological Significance:*

No significant toxicity was noted in this rat dermal carcinogenicity study. Therefore, the NOAEL can be set at 10 mg/kg/day (average $AUC_{(0\text{-}24\ hr)}$ = 125 ng·hr/ml after 104 weeks of treatment).

- *Potential Clinical Implications of Findings:*

The highest measured $AUC_{(0\text{-}24\ hr)}$ value measured in humans that applied 1% ASM 981 cream was 38 ng·hr/ml. This was measured in a single pediatric patient that applied 1% ASM 981 cream bid to 43.5% BSA. The multiple of human exposure will be calculated based on this highest $AUC_{(0\text{-}24\ hr)}$ value. The NOAEL identified in this study is 10 mg/kg/day (average $AUC_{(0\text{-}24\ hr)}$ = 125 ng·hr/ml after 104 weeks of treatment). The multiple of human exposure is 3.2X based on the NOAEL $AUC_{(0\text{-}24\ hr)}$ levels identified in this dermal rat carcinogenicity study.

- *Recommendations for Further Analysis:*

The Exec CAC information request for this study has been sent to the sponsor.

Addendum/Appendix Listing:

- *CAC Report:*

An Exec CAC meeting to discuss all of the carcinogenicity studies conducted for ASM 981 (oral mouse, oral rat, dermal mouse and dermal rat) was held on 6-19-01. The minutes from that meeting are provided below.

Executive CAC
June 19, 2001

Committee: Joseph DeGeorge, Ph.D., HFD-024, Chair
Joseph Contrera, Ph.D., HFD-901, Member
Jasti Choudary, B.V.Sc,. Ph.D., HFD-180, Alternate Member
Abby Jacobs, Ph.D., HFD-540, Supervisor
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 # 21-302
Drug Name: Elidel (pimecrolimus) cream; 1% ASM 981 cream
Sponsor: Novartis Pharmaceuticals Corporation

Background:

ASM 981 is an anti-inflammatory/immunosuppressive ascomycin macrolactam derivative that is being developed for the topical treatment of moderate ——— Atopic Dermatitis. Atopic Dermatitis is primarily a pediatric indication and the duration of treatment is chronic. ASM 981 has undergone testing in a full battery of genotoxicity tests and showed no genotoxic potential. The sponsor has conducted an oral mouse carcinogenicity study, two oral rat carcinogenicity studies, a dermal mouse carcinogenicity study and a dermal rat carcinogenicity study. Exec CAC concurrence for the dose range selected in each of these studies was not obtained prior to the conduct of each study.

Mouse Oral Carcinogenicity Study:

A statistically significant increase in malignant lymphoma was noted in high dose male and female mice in the mouse oral (gavage) carcinogenicity study (refer to following table).

Incidence of Malignant Lymphoma in mice treated with ASM 981

Dose (mg/kg/day)	Males	Females
Vehicle Control 1	3/60	19/60
Vehicle Control 2	8/60	10/60
1	3/60	9/60
5	6/60	14/60
15	8/60	18/60
45	17/60	27/60

Rat Oral Carcinogenicity Studies:

Two rat oral (gavage) carcinogenicity studies were conducted for ASM 981. The doses used in the first study were 0 (Vehicle Control 1), 0 (Vehicle Control 2), 1, 5 and 25 mg/kg/day ASM 981. The doses used in the second study were 0 (Vehicle Control 1), 0 (Vehicle Control 2) and 10 mg/kg/day ASM 981. High mortality due to overt toxicity (males and females terminated after 58 weeks) was noted in high dose male and female rats in the first study. Therefore, the sponsor decided to conduct the second rat oral carcinogenicity study with a dose between the 5 and 25 mg/kg/day dose levels.

A statistically significant increase in benign thymoma was noted in 10 mg/kg/day treated male and female rats in the second rat oral carcinogenicity study. An increase in benign thymoma was noted in 5 mg/kg/day treated male rats in the first rat oral carcinogenicity study but did not reach statistical significance (the two rat oral carcinogenicity studies were not combined for statistical analysis). Therefore, the NOAEL for benign thymoma in male rats is 1 mg/kg/day and in female rats is 5 mg/kg/day. The incidence of benign thymoma for both rat oral carcinogenicity studies combined is provided in the following table.

Incidence of Benign Thymoma in rats treated with ASM 981

Study #	Dose (mg/kg/day)	Males	Females
1	Vehicle Control 1	4/60	5/58
1	Vehicle Control 2	3/60	7/60
2	Vehicle Control 1	1/60	9/60
2	Vehicle Control 2	2/60	6/60
1	1	4/60	4/59
1	5	9/60[a]	6/60
2	10	7/60[b]	17/60
1	25	1/59[c]	6/60

a – treated for 104 weeks; b – treated for 88 weeks; c – treated for 58 weeks

Mouse Dermal Carcinogenicity Study:

Doses tested in this study were 0 (untreated control), 0 (vehicle control), 0.04 (0.0032%), 0.40 (0.032%) and 4.0 (0.32%) mg/kg/day. ASM 981 was dissolved in ethanol for this mouse dermal carcinogenicity study. The highest concentration tested was 0.32% ASM 981 which is ~1/3 the concentration that will be used clinically (1% ASM 981 cream). It would have been preferable to have the highest dose be at least the 1% concentration and in the final to be marketed formulation. No signal for potential systemic or dermal carcinogenicity was noted in this study. However, the dose selection for this study was not adequate. The results of a 13 week dermal repeat dose toxicity study (ASM 981 dissolved in ethanol) demonstrated malignant lymphoma in the 50 mg/kg/day dose group. Therefore, the high dose selected for the mouse dermal carcinogenicity study was too low to have detected a possible malignant lymphoma signal.

Rat Dermal Carcinogenicity Study:

Doses tested in this study were 0 (saline control), 0 (vehicle control), 2 (0.2%), 6 (0.6%) and 10 (1.0%) mg/kg/day. The final to be marketed ASM 981 cream formulation was used in this rat dermal carcinogenicity study. The maximum feasible concentration of ASM 981 in the cream formulation (1%) was used as the high dose in this study. No apparent signal for potential systemic or dermal carcinogenicity was noted in this study. However, it is important to note that incomplete histopathological evaluation was performed for the low and mid dose groups in this study.

Executive CAC Recommendations and Conclusions:

Oral Mouse Carcinogencity Study:

1. The committee determined that a MTD was not achieved in this study.

2. The committee concurred that there was a strong signal for malignant lymphoma in this study.
3. The committee noted that hyperplastic changes were seen in the thymus at higher doses (≥ 50 mg/kg/day) in the 13 week repeat dose oral toxicity study in mice. The committee expressed concern that thymomas might have been seen at a true MTD dose in the mouse oral carcinogenicity study.
4. The committee recommended that the malignant lymphoma findings noted in this study be included in the label if the drug product is approved.
5. The committee recommended that information concerning the short latency of malignant lymphoma formation in mice after repeat oral dosing be included in the label if the drug product is approved.

Oral Rat Carcinogenicity Studies:

1. The committee determined that a MTD had been reached in this study.
2. The committee felt that this was an adequate study.
3. The committee concurred that there was a signal for benign thymoma in this study.
4. The committee commented that the finding of benign thymoma in this study does not seem irrelevant in conjunction with the hyperplastic changes noted in the thymus in the 13 week repeat dose oral toxicity study in mice.
5. The committee recommended that the benign thymoma findings noted in this study be included in the label if the drug product is approved.

Dermal Mouse Carcinogenicity Study:

1. The committee felt that this study was negative. However, the committee commented that the test article had obvious effects after dermal administration in mice (malignant lymphoma noted in the 13 week repeat dermal toxicity study in mice at doses ≥ 50 mg/kg/day). The committee recommended that this information be included in the label if the drug product is approved.
2. The committee asked about the source of the metastatic carcinoma noted in the thymus of one high dose male. A request will be sent to the sponsor to clarify the source of this metastatic tumor.

Dermal Rat Carcinogenicity Study:

1. The committee commented that the histopathological analysis for this study was incomplete since all the animals in the low and mid dose groups were not examined in this study. The committee did note that there may be a possible signal in the thyroid and/or thymus based on the incomplete histopathological data available for the low and mid dose groups.
2. The committee requested that the sponsor reanalyze the histopathology of the thyroid and thymus in all low and mid dose animals. In addition, the committee requested that another statistical analysis be performed after the data for the complete histopathological analysis of the thyroid and thymus in all low and mid dose animals has been submitted to the agency. A request for this histopathological re-analysis will be sent to the sponsor.
3. The committee recommended that a statistical reanalysis be performed for the combined incidence for the follicular cell adenoma and follicular cell carcinoma of the thyroid. The request for statistical reanalysis will be submitted to the biostatistical division in the agency after the complete histopathological reanalysis data has been submitted to the agency.
4. The committee requested the historical background incidence rate for follicular cell carcinoma of the thyroid for the strain of rat used in the dermal rat carcinogenicity study. This request will be sent to the sponsor.

General Comments:

[ ]

Joseph DeGeorge, Ph.D.
Chair, Executive CAC

cc:

/Division File, HFD 540
/AJacobs/Sup, HFD-540
/BHill/Pharm, HFD-540
/MWright/PM, HFD-540
/ASeifried, HFD-024

- *Informational request sent to the sponsor on 7-10-01*:

It is recommended that the following information requests be relayed to the sponsor. These information requests are based on the results of the Exec CAC meeting conducted on 6/19/01 for the carcinogenicity studies conducted for NDA 21-302.

1) It is requested that the sponsor clarify the source of the metastatic carcinoma noted in the thymus of one high dose male in the mouse dermal carcinogenicity study.

2) It is requested that the sponsor reanalyze the histopathology of the thyroid and thymus in all low and mid dose animals in the rat dermal carcinogenicity study. After this data has been submitted to the agency, then it can be better determined if the potential signal noted from the incomplete histopathological data obtained for the thyroid and thymus in low and mid dose animals is of potential concern or not.

3) It is requested that the sponsor provide the contract laboratory historical control background incidence rate in Wistar rats (from the laboratory that conducted the rat dermal carcinogenicity study) for the incidence of follicular cell carcinoma and follicular cell adenoma of the thyroid.

- *Sponsor's Incidence of Neoplastic Histopathology Findings*: The mouse dermal carcinogenicity study (T-127/BS-530) neoplastic histopathology summary table reproduced below was scanned directly from the NDA submission (Volume 8; pp. 5-175 to 5-180).

PATHOLOGY REPORT FINAL PAGE : 44
SUMMARY TABLES STUDY NO. : 15142 TCS

TEST ARTICLE : SDZ ASM 981 PATHOL. NO.: 15142 VPA
TEST SYSTEM : MOUSE, CARCINOGENICITY, DERMAL DATE : 25-OCT-99
SPONSOR : NOVARTIS PHARMA AG, BASEL

NUMBER OF ANIMALS WITH NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. +

	SEX :						MALE
	DOSE GROUP:	1	2	3	4	5	
ORGAN/FINDING	NO.ANIMALS:	50	50	50	50	50	
MESENT. LYMPH NODES	NO.EXAM.:	44	49	48	46	45	
- Hemangioma			1				
BRAIN	NO.EXAM.:	48	50	49	50	49	
- Meningioma						1	
LIVER	NO.EXAM.:	50	50	50	50	50	
- Adenoma,Hepatocell.		4	8	5	1	3	
- Adenoma,Hepatoc.2nd		1		2		1	
- Adenoma,Hepatoc.mult		1					
- Carcinoma,Hepatocel.		2	3		1		
- Hemangiosarcoma		1	1				
- Hemangioma		1					
- Carcinoma,Metastasis						1	
- Hemangiosarc.,Metast					1		
PITUITARY GLAND	NO.EXAM.:	48	49	48	50	49	
- Adenoma,P.Distalis		1	1				
- Adenoma,P.Intermed.				1			
THYROID GLANDS	NO.EXAM.:	47	50	49	47	48	
- Adenoma,Follic.Cell				1			
ADRENAL GLANDS	NO.EXAM.:	48	49	49	50	49	
- Tumor,Medullary (B)			1				
- Adenoma,Cortical			1	1		1	
SPLEEN	NO.EXAM.:	48	50	49	50	49	
- Hemangiosarcoma					1		
- Hemangioma				1			
THYMUS	NO.EXAM.:	43	43	41	43	41	
- Carcinoma,Metastasis						1	
TRACHEOBRONCHIC L.N.	NO.EXAM.:	38	29	28	28	37	
- Carcinoma,Metastasis						1	

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PATHOLOGY REPORT FINAL PAGE : 45
SUMMARY TABLES STUDY NO. : 15142 TCS

TEST ARTICLE : SDZ ASM 981 PATHOL. NO.: 15142 VPA
TEST SYSTEM : MOUSE, CARCINOGENICITY, DERMAL DATE : 25-OCT-99
SPONSOR : NOVARTIS PHARMA AG, BASEL

NUMBER OF ANIMALS WITH NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. +

	SEX :						MALE
	DOSE GROUP:	1	2	3	4	5	
ORGAN/FINDING	NO.ANIMALS:	50	50	50	50	50	
LUNGS WITH BRONCHI	NO.EXAM.:	50	50	50	50	50	
- Carcinoma,Bron.-Alv.		7	7	8	8	9	
- Adenoma,Bronchioalv.		7	12	9	8	8	
- Adenoma,Broncalv.2nd		1	1	1		2	
KIDNEYS	NO.EXAM.:	50	50	50	50	50	
- Adenoma,Tubule					1		
TESTES	NO.EXAM.:	48	50	49	50	48	
- Adenoma,Interst.Cell		3	3	3	1	3	
- Adenoma,Rete Testis						1	
- Histiocyt.Fib.Metast					1		
EPIDIDYMIDES	NO.EXAM.:	48	50	49	50	49	
- Granular Cell Tumor			1				
- Adenoma,Tubular				1			
EYES	NO.EXAM.:	48	50	49	50	49	
- Melanoma,Malignant						1	
HARDERIAN GLANDS	NO.EXAM.:	48	50	48	50	49	
- Adenoma		3	3	3	4	4	
SKIN	NO.EXAM.:	48	50	50	50	49	
- Histiocytoma,Fib.(M)					1		
RIB(S)	NO.EXAM.:			1			
- Metastasis,Carcinoma				1			
HEMOLYMPHORET. SYS.	NO.EXAM.:	6	3	3	2	6	
- Lymphoma,Malignant		6	2	3	2	5	
- Histiocytic Sarcoma			1			1	
DIAPHRAGM	NO.EXAM.:			1			
- Metastasis,Carcinoma				1			

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PATHOLOGY REPORT FINAL
SUMMARY TABLES

PAGE : 46
STUDY NO. : 15142 TCS

TEST ARTICLE : SDZ ASM 981
TEST SYSTEM : MOUSE, CARCINOGENICITY, DERMAL
SPONSOR : NOVARTIS PHARMA AG, BASEL

PATHOL. NO.: 15142 VPA
DATE : 25-OCT-99

NUMBER OF ANIMALS WITH NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. +

	SEX :						MALE
	DOSE GROUP:	1	2	3	4	5	
ORGAN/FINDING	NO.ANIMALS:	50	50	50	50	50	
THORACIC CAVITY	NO.EXAM.:	3	3	1	2	1	
- Mesothelioma				1			

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PATHOLOGY REPORT FINAL PAGE : 47
SUMMARY TABLES STUDY NO. : 15142 TCS

TEST ARTICLE : SDZ ASM 981 PATHOL. NO.: 15142 VPA
TEST SYSTEM : MOUSE, CARCINOGENICITY, DERMAL DATE : 25-OCT-99
SPONSOR : NOVARTIS PHARMA AG, BASEL

NUMBER OF ANIMALS WITH NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. +

	SEX :					FEMALE
	DOSE GROUP:	1	2	3	4	5
ORGAN/FINDING	NO.ANIMALS:	50	50	50	50	50
MAMMARY AREA	NO.EXAM.:	50	50	50	50	50
- Adenocarcinoma		2	1		2	1
MESENT. LYMPH NODES	NO.EXAM.:	46	49	48	49	50
- Hemangioma		2				
STOMACH	NO.EXAM.:	49	50	50	49	50
- Leiomyosarcoma		1				
FEMORAL BONE(+ART.)	NO.EXAM.:	49	50	50	50	50
- Lipoma			1			
LIVER	NO.EXAM.:	50	50	50	50	50
- Adenoma,Hepatocell.		1			1	1
- Carcinoma,Hepatocel.					1	1
- Hemangiosarcoma						1
- Hemangioma		1	1			
- Metast.Fibrosarcoma		1		1		
MANDIBUL. LYMPH NODE	NO.EXAM.:	45	48	48	50	49
- Metast.,Squam.C.Carc				1		
THYROID GLANDS	NO.EXAM.:	47	50	48	50	49
- Adenoma,Follic.Cell		1				
- Adenocarcinoma,Foll.					1	
ADRENAL GLANDS	NO.EXAM.:	49	50	50	50	50
- Tumor,Medullary (B)					1	
- Adenoma,Cortical					1	
OVARIES	NO.EXAM.:	49	50	50	50	50
- Thecoma,Malignant		1				
- Luteoma,Benign		1		2	2	
- Adenoma,Tubulostrom.				1		
- Carcinoma			1			

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ON ORIGINAL

PATHOLOGY REPORT FINAL PAGE : 48
SUMMARY TABLES STUDY NO. : 15142 TCS

TEST ARTICLE : SDZ ASM 981 PATHOL. NO.: 15142 VPA
TEST SYSTEM : MOUSE, CARCINOGENICITY, DERMAL DATE : 25-OCT-99
SPONSOR : NOVARTIS PHARMA AG, BASEL

NUMBER OF ANIMALS WITH NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. +

	SEX :					FEMALE
	DOSE GROUP:	1	2	3	4	5
ORGAN/FINDING	NO.ANIMALS:	50	50	50	50	50
UTERUS	NO.EXAM.:	49	50	50	50	50
- Fibrosarcoma		6	1	1	1	1
- Fibroma						1
- Leiomyoma		1	2		2	
- Carcinoma,Adenosqu.			3			
- Hemangioma				1		
- Osteosarcoma,Metast.					1	
SPLEEN	NO.EXAM.:	49	50	50	50	50
- Metast.,Leiomyosarc.		1				
- Hemangiosarcoma						1
- Hemangioma					1	
- Osteosarcoma,Metast.					1	
LUNGS WITH BRONCHI	NO.EXAM.:	50	50	49	50	50
- Carcinoma,Bron.-Alv.		2	1	4	5	2
- Adenoma,Bronchioalv.		5	5	5	4	7
- Adenoma,Broncalv.2nd				1	1	2
- Metast.Carcinoma		1				
- Metast.Osteosarcoma					1	1
KIDNEYS	NO.EXAM.:	50	50	50	50	50
- Metast.Fibrosarcoma		1				
HARDERIAN GLANDS	NO.EXAM.:	49	50	50	49	49
- Adenoma			3		4	1
SKIN	NO.EXAM.:	49	50	50	50	50
- Carcinoma,Squam.Cell				2		
- Keratoacanthoma					1	
- Histiocytoma,Fib.(M)		1	2	1		3
HEMOLYMPHORET. SYS.	NO.EXAM.:	10	12	8	7	6
- Lymphoma,Malignant		9	10	6	6	6
- Histiocytic Sarcoma		1	2	2		
- Leukemia,Myeloid					1	

PATHOLOGY REPORT FINAL PAGE : 49
SUMMARY TABLES STUDY NO. : 15142 TCS

TEST ARTICLE : SDZ ASM 981 PATHOL. NO.: 15142 VPA
TEST SYSTEM : MOUSE, CARCINOGENICITY, DERMAL DATE : 25-OCT-99
SPONSOR : NOVARTIS PHARMA AG, BASEL

NUMBER OF ANIMALS WITH NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. +

	SEX :						FEMALE
	DOSE GROUP:	1	2	3	4	5	
ORGAN/FINDING	NO.ANIMALS:	50	50	50	50	50	
POPLITEAL LYMPH NODE	NO.EXAM.:	1	1	1	2	2	
- Metast.Carcinoma		1					
BONE	NO.EXAM.:					1	
- Osteosarcoma						1	
MESENTERY	NO.EXAM.:	1	2	2	3	1	
- Osteosarcoma,Metast.					1		
SUBCUTANEOUS TISSUE	NO.EXAM.:	9	5	11	4	9	
- Osteosarcoma				1		1	

- *Sponsor's Incidence of Neoplastic Histopathology Findings*: The rat dermal carcinogenicity study (T-133/BS-733) neoplastic histopathology summary table reproduced below was scanned directly from the NDA submission (Volume 101; pp. 5-229 to 5-234).

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PATHOLOGY REPORT — PAGE : 17/1845
SUMMARY TABLES — PROJECT: 682705

TEST ARTICLE : SDZ ASM 981 CREAM — *PATHOL. NO.*: 20025 JMA
TEST SYSTEM : RAT, 104 WEEKS, DERMAL — *DATE* : 26-OCT-00
SPONSOR : NOVARTIS PHARMA

NUMBER OF ANIMALS WITH BENIGN NEOPLASMS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. DEATHS

ORGAN/FINDING	SEX / DOSE GROUP / NO. ANIMALS	01	02	03	04	05
		50	50	50	50	50
						MALE
CEREBRUM	No.Examined	50	50	18	23	50
- Granular cell tumor		2	1	-	1	-
LUNG	No.Examined	50	50	29	29	50
- Alveolar/bronchiolar adenoma		-	-	1	1	1
DUODENUM	No.Examined	50	47	16	21	45
- Leiomyoma		-	1	-	-	-
LIVER	No.Examined	50	50	18	23	50
- Hepatocellular adenoma		-	1	-	-	1
BILE DUCT, EXTRAHEP.	No.Examined	3	2	3	3	2
- Leiomyoma		-	-	1	-	-
PANCREAS	No.Examined	50	48	15	21	50
- Islet cell adenoma		2	3	-	1	-
- Mixed acinar-islet cell adenoma		1	-	-	-	-
KIDNEYS	No.Examined	50	50	16	21	50
- Tubular cell adenoma		1	-	-	-	-
TESTES	No.Examined	49	50	23	24	50
- Benign Leydig cell tumor		1	1	1	-	4
- Hemangioma		1	-	-	1	-
PITUITARY GLAND	No.Examined	50	50	19	26	50
- Adenoma/pars distalis		29	17	8	10	11
- Adenoma/pars intermedia		2	-	-	-	--
THYROID GLAND	No.Examined	50	50	22	24	49
- C-cell adenoma		3	5	2	2	-
- Follicular cell adenoma		1	-	2	3	5
PARATHYROID GLANDS	No.Examined	49	50	21	24	46
- Adenoma		2	1	1	-	3
ADRENAL MEDULLAS	No.Examined	49	50	16	21	50
- Benign pheochromocytoma		2	-	-	-	1
- Complex pheochromocytoma		-	-	-	1	-
THYMUS	No.Examined	50	47	15	20	49
- Benign thymoma		1	-	2	3	2
MESENT. LYMPH NODE	No.Examined	50	50	21	22	50
- Hemangioma		3	8	7	3	8
SKIN/SUBCUTIS(UNSPEC)	No.Examined	50	49	23	30	50
- Basal cell adenoma		-	-	-	1	-
- Trichoepithelioma		-	-	1	-	--
- Squamous cell papilloma		1	-	1	1	--
- Keratoacanthoma		-	1	1	2	1
- Lipoma		-	-	-	1	-
- Fibroma		-	-	-	1	-
HINDFOOT/HINDFEET	No.Examined	7	21	19	12	13
- Squamous cell papilloma		-	1	-	-	-
APPLICATION SITE 1	No.Examined	50	48	15	21	50
- Basal cell adenoma		-	-	-	1	-

PATHOLOGY REPORT
SUMMARY TABLES

PAGE : 18/1845
PROJECT: 682705

TEST ARTICLE : SDZ ASM 981 CREAM
TEST SYSTEM : RAT, 104 WEEKS, DERMAL
SPONSOR : NOVARTIS PHARMA

PATHOL. NO.: 20025 JMA
DATE : 26-OCT-00

NUMBER OF ANIMALS WITH BENIGN NEOPLASMS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. DEATHS

ORGAN/FINDING	SEX / DOSE GROUP / NO. ANIMALS	01	02	03	04	05
		50	50	50	50	50
						FEMALE
CEREBRUM	No.Examined	50	50	23	30	50
- Granular cell tumor		1	1	-	1	2
CEREBELLUM	No.Examined	50	50	22	30	50
- Granular cell tumor		3	-	-	-	1
LUNG	No.Examined	50	50	21	30	50
- Alveolar/bronchiolar adenoma		1	-	-	-	-
STOMACH	No.Examined	50	50	17	19	49
- Adenoma		1	-	-	-	-
DUODENUM	No.Examined	49	49	15	19	45
- Leiomyoma		-	1	-	-	-
JEJUNUM	No.Examined	48	47	12	19	45
- Leiomyoma		-	-	-	1	-
LIVER	No.Examined	50	50	20	20	50
- Hepatocellular adenoma		-	1	1	-	1
PANCREAS	No.Examined	50	50	19	16	49
- Islet cell adenoma		-	2	-	-	-
KIDNEYS	No.Examined	50	50	18	18	50
- Tubular cell adenoma		1	-	-	-	-
OVARIES	No.Examined	50	50	22	26	50
- Benign granulosa cell tumor		2	2	2	1	2
- Benign granulosa-theca cell tumor		-	-	-	-	1
UTERUS	No.Examined	50	50	33	32	50
- Polyp/endometrial-stromal		4	4	6	7	5
- Leiomyoma		-	-	1	-	-
- Hemangioma		-	1	-	-	-
- Granular cell tumor		1	-	1	1	-
VAGINA	No.Examined	50	50	33	32	50
- Granular cell tumor		1	4	-	-	-
- Hemangioma		1	-	-	-	-
PITUITARY GLAND	No.Examined	50	50	42	39	50
- Adenoma/pars distalis		42	41	33	30	34
- Adenoma/pars intermedia		-	2	4	1	-
- Pituicytoma		-	-	-	-	1
THYROID GLAND	No.Examined	50	49	18	18	50
- C-cell adenoma		2	2	1	3	4
ADRENAL MEDULLAS	No.Examined	50	50	25	23	50
- Benign pheochromocytoma		3	-	2	-	-
SPLEEN	No.Examined	50	50	17	18	50
- Hemangioma		-	-	1	-	-
THYMUS	No.Examined	49	50	23	21	49
- Benign thymoma		4	2	7	3	2
MESENT. LYMPH NODE	No.Examined	50	49	17	19	50
- Hemangioma		2	3	1	2	5

PATHOLOGY REPORT PAGE : 19/1845
SUMMARY TABLES PROJECT: 682705

TEST ARTICLE : SDZ ASM 981 CREAM *PATHOL. NO.* : 20025 JMA
TEST SYSTEM : RAT, 104 WEEKS, DERMAL *DATE* : 26-OCT-00
SPONSOR : NOVARTIS PHARMA

NUMBER OF ANIMALS WITH BENIGN NEOPLASMS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. DEATHS

ORGAN/FINDING	SEX / DOSE GROUP / NO. ANIMALS	01	02	03	04	05	FEMALE
MAMMARY GLAND AREA	No.Examined	49	50	25	22	50	
- Fibroadenoma		7	6	4	8	3	
- Adenoma		-	1	-	-	-	
SKIN/SUBCUTIS(UNIRT)	No.Examined	50	50	22	23	49	
- Squamous cell papilloma		-	-	-	-	1	
- Keratoacanthoma		-	-	1	1	1	
- Lipoma		-	-	-	1	1	
- Benign fibrous histiocytoma		1	-	-	-	-	
- Fibroma		-	-	-	1	-	
HINDFOOT/HINDFEET	No.Examined	4	1	2	1	4	
- Hemangioma		1	-	-	-	-	
EYES	No.Examined	50	50	17	19	50	
- Uveal leiomyoma		-	-	-	1	-	
BODY CAVITIES	No.Examined	-	1	-	-	2	
- Hemangioma		-	1	-	-	-	
APPLICATION SITE 1	No.Examined	50	50	18	17	49	
- Basal cell adenoma		-	-	1	-	-	

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PATHOLOGY REPORT PAGE : 20/1845
SUMMARY TABLES -PROJECT: 682705

TEST ARTICLE : SDZ ASM 981 CREAM *PATHOL. NO.*: 20025 JMA
TEST SYSTEM : RAT, 104 WEEKS, DERMAL *DATE* : 26-OCT-00
SPONSOR : NOVARTIS PHARMA

NUMBER OF ANIMALS WITH MALIGNANT NEOPLASMS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. DEATHS

MALE

ORGAN/FINDING	SEX / DOSE GROUP / NO. ANIMALS	01	02	03	04	05
CEREBRUM	No.Examined	50	50	18	23	50
- Malignant reticulosis.		1	-	-	-	-
- Oligodendroglioma		-	-	1	-	1
- Meningeal sarcoma		1	-	-	-	1
CEREBELLUM	No.Examined	50	50	18	23	50
- Meningeal sarcoma		-	-	-	-	1
LUNG	No.Examined	50	50	29	29	50
- Squamous cell carcinoma of bronchus		-	-	-	-	1
STOMACH	No.Examined	50	50	16	24	50
- Leiomyosarcoma		-	-	-	-	1
DUODENUM	No.Examined	50	47	16	21	45
- Leiomyosarcoma		-	-	2	-	-
- Adenocarcinoma		-	-	1	-	-
JEJUNUM	No.Examined	44	43	12	16	42
- Leiomyosarcoma		-	-	-	-	1
COLON	No.Examined	49	49	14	19	47
- Adenocarcinoma		-	1	-	-	-
- Leiomyosarcoma		-	-	1	-	-
LIVER	No.Examined	50	50	18	23	50
- Hepatocellular carcinoma.		-	1	2	-	-
PANCREAS	No.Examined	50	48	15	21	50
- Islet cell carcinoma		1	-	-	-	-
KIDNEYS	No.Examined	50	50	16	21	50
- Tubular cell carcinoma		1	1	1	2	1
- Lipomatous tumor		1	-	-	-	-
THYROID GLAND	No.Examined	50	50	22	24	49
- C-cell carcinoma		1	-	-	-	-
- Follicular cell carcinoma		-	-	2	-	-
ADRENAL CORTICES	No.Examined	49	50	17	21	50
- Carcinoma.		-	-	1	-	-
ADRENAL MEDULLAS	No.Examined	49	50	16	21	50
- Malignant pheochromocytoma		1	1	-	-	1
RETICULOHISTIOCYT. SYS.	No.Examined	50	50	15	20	50
- Malignant lymphoma.		-	2	-	1	1
- Histiocytic sarcoma		-	-	-	-	1
- Malignant fibrous histiocytoma.		-	1	-	-	-
SPLEEN	No.Examined	50	50	16	20	50
- Hemangiosarcoma.		1	-	-	1	-
- Leiomyosarcoma		-	-	-	1	-
- Sarcoma (not otherwise specified).		-	-	-	-	1
LYMPH NODES	No.Examined	8	8	8	4	10
- Hemangiosarcoma.		1	-	-	-	-
HARDERIAN GLANDS	No.Examined	4	8	8	6	3
- Squamous cell carcinoma		-	-	-	1	-

PATHOLOGY REPORT — PAGE : 21/1845
SUMMARY TABLES — -PROJECT: 682705

TEST ARTICLE : SDZ ASM 981 CREAM — *PATHOL. NO.*: 20025 JMA
TEST SYSTEM : RAT, 104 WEEKS, DERMAL — *DATE* : 26-OCT-00
SPONSOR : NOVARTIS PHARMA

NUMBER OF ANIMALS WITH MALIGNANT NEOPLASMS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. DEATHS

ORGAN/FINDING	SEX / DOSE GROUP / NO. ANIMALS	01	02	03	04	05	MALE
SKIN/SUBCUTIS(UNTRT)	No.Examined	50	49	23	30	50	
- Sarcoma (not otherwise specified)		-	1	-	-	2	
- Malignant Schwannoma		-	1	-	-	-	
- Fibrosarcoma		-	-	-	1	2	
- Liposarcoma		-	-	-	-	1	
HINDFOOT/HINDFEET	No.Examined	7	21	19	12	13	
- Hemangiosarcoma		-	1	-	-	-	
EYES	No.Examined	50	50	20	24	50	
- Amelanotic melanoma		1	-	-	-	-	
BODY CAVITIES	No.Examined	3	2	2	1	-	
- Malignant Schwannoma		1	-	-	-	-	
- Malignant mesothelioma		2	2	2	-	-	
- Sarcoma (not otherwise specified)		-	-	-	1	-	
ZYMBAL'S GLANDS	No.Examined	-	-	-	1	-	
- Carcinoma		-	-	-	1	-	

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PATHOLOGY REPORT — PAGE : 22/1845
SUMMARY TABLES — PROJECT: 682705

TEST ARTICLE : SDZ ASM 981 CREAM — *PATHOL. NO.*: 20025 JMA
TEST SYSTEM : RAT, 104 WEEKS, DERMAL — *DATE* : 26-OCT-00
SPONSOR : NOVARTIS PHARMA

NUMBER OF ANIMALS WITH MALIGNANT NEOPLASMS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. DEATHS

ORGAN/FINDING	SEX / DOSE GROUP / NO. ANIMALS	01	02	03	04	05
						FEMALE
CEREBRUM	No.Examined	50	50	23	30	50
- Astrocytoma		-	-	-	-	2
HEART	No.Examined	50	50	17	18	50
- Malignant endocardial schwannoma		-	1	-	-	-
PANCREAS	No.Examined	50	50	19	16	49
- Islet cell carcinoma		-	1	-	-	-
KIDNEYS	No.Examined	50	50	18	18	50
- Tubular cell carcinoma		1	2	-	2	-
OVARIES	No.Examined	50	50	22	26	50
- Malignant granulosa cell tumor		2	-	-	2	-
- Yolk sac carcinoma		-	-	-	-	1
OVIDUCTS	No.Examined	-	-	-	-	1
- Cystadenocarcinoma		-	-	-	-	1
UTERUS	No.Examined	50	50	33	32	50
- Adenocarcinoma		3	3	2	4	2
- Leiomyosarcoma		-	-	1	-	-
- Malignant Schwannoma		1	-	-	1	2
- Stromal sarcoma		-	-	1	-	-
- Hemangiosarcoma		-	1	-	-	1
THYROID GLAND	No.Examined	50	49	18	18	50
- C-cell carcinoma		-	1	-	-	-
- Follicular cell carcinoma		1	-	-	-	1
HEMOLYMPHORET. SYS.	No.Examined	50	50	17	18	50
- Malignant lymphoma		1	2	-	-	3
SPLEEN	No.Examined	50	50	17	18	50
- Hemangiosarcoma		1	-	-	1	-
- Sarcoma (not otherwise specified)		-	-	-	-	1
PAROTID GLAND, LEFT	No.Examined	-	-	1	-	-
- Adenocarcinoma		-	-	1	-	-
MAMMARY GLAND AREA	No.Examined	49	50	25	22	50
- Adenocarcinoma		1	6	1	-	-
SKIN/SUBCUTIS(UNIRT)	No.Examined	50	50	22	23	49
- Malignant Schwannoma		1	-	-	-	-
- Fibrosarcoma		1	-	-	-	-
BODY CAVITIES	No.Examined	-	1	-	-	2
- Malignant Schwannoma		-	-	-	-	1
ZYMBAL'S GLANDS	No.Examined	-	-	1	-	-
- Carcinoma		-	-	1	-	-

Barbara Hill, Ph.D.
Reviewing Pharmacologist

cc:
NDA: 21-302 (000; Addendum)
HFD-340
HFD-540/DIV FILES
HFD-540/TOX/JACOBS
HFD-540/PHARM/HILL
HFD-540/MO/COOK
HFD-540/CHEM/PAPPAS
HFD-540/PM/WRIGHT

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PHARMACOLOGIST

Jonathan Wilkin
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