

Table 4. Skin tumors in female rats

Group	1	2	3	4	5	6	7	8	9
Treatment	Placebo gel					5% BP gel		1% CP gel	
Dose (mL/kg)	15.0	15.0	0.90	2.70	15.0	2.70	15.0	2.70	15.0
Number examined	60	60	60	60	60	60	60	60	60
Basal cell tumor [M]	0	0	0	0	0	1	0	0	0
Fibrosarcoma multiple [M]	0	0	0	0	0	0	0	0	1
Fibrosarcoma [M]	1	0	0	0	0	0	0	1	1
Fibrous histiocytoma [B]	0	0	0	0	1	0	0	0	0
Sarcoma [M]	1	1	1	0	0	0	1	0	0
Rhabdomyosaroma [M]	0	0	0	1	0	0	0	0	0
Papilloma [B]	0	0	0	0	1	0	1	0	0
Keratoacanthoma [B]	0	0	0	0	0	0	1	0	0

B - Benign; M - Malignant

**Toxicokinetics:** Toxicokinetic analysis was not performed in this study. The increased hyperkeratosis and epithelial hyperplasia noted at the treatment site in both sexes suggest that the high dose may have been an MTD.

## 2. Study Title: 2 Year Oral (Gavage) Carcinogenicity Study of an Admixture Active Gel (Benzoyl Peroxide 5% and Clindamycin Phosphate 1%) and its Components in Rats

**Key study findings:** There were no toxicologically significant differences in survival, food consumption, hematology, clinical chemistry, necropsy findings, organ weights, non-neoplastic microscopic findings. Rales and hunched posture were seen more frequently in test article-treated animals than in placebo-treated animals. Differences in body weights approached toxicological significance (i.e., decrease of approximately 10%) in Group 9 males (high-dose Clindamycin alone) and Group 5 males (high-dose Admixture Active Gel). A trend toward decreased mean body weights (between 5% to 10%) was also noted for females in Groups 4, 5, 6, 7, 8 and 9 during the latter part of the study compared to Group 1. Some commonly observed neoplasms included fibroadenomas, adenomas and adenocarcinomas in the mammary glands of females, and islet cell adenomas of the pancreas and adenomas of the pituitary in males and females. Although there were some statistically significant differences in tumor incidence noted in this study, none of them were biologically significant. Therefore, there was no evidence to suggest that oral administration of Admixture Active Gel ( ————, Benzoyl Peroxide 5% Gel, or Clindamycin Phosphate 1% Gel for up to 97 weeks caused an increased incidence of tumors in rats.

**Adequacy of the carcinogenicity study and appropriateness of the test model:** Although the combination test article is intended for dermal application in human therapeutic use, the use of the oral route in this study was to increase systemic exposure. However, use of the actual topical gel formulation for an oral gavage study is unusual. The design of this study was not optimal since the volume of administration was increased for the different dose groups. It would have been preferable to keep the volume of administration

constant and vary the concentration of each active ingredient for the different dose groups. However, the clinical clindamycin concentration and greater benzoyl peroxide concentration of the drug product were evaluated in this study, so the Exec CAC determined that the study was acceptable.

Evaluation of tumor findings: There was no evidence to suggest that oral administration of Admixture Active Gel ( \_\_\_\_\_ ), Benzoyl Peroxide 5% Gel, or Clindamycin Phosphate 1% Gel for up to 97 weeks caused an increased incidence of tumors in rats.

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**Study no.:** 92 GLA P007 S033

**Conducting laboratory and location:** \_\_\_\_\_

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**Date of study initiation:** 6-15-1993

**GLP compliance:** Yes

**QA report:** Yes (X) no ( )

**Drug, lot #, and % purity:** The test articles were received from \_\_\_\_\_ Admixture Active Gel, Lot No. 3B217B216A, 3B216E224, 3E225D229, 3E225D229, 3H430D229, 3H431K342, 3K344K342, 3M322B328, 3M322C252, 3M322C252A, 4E226E228, 4G636G634, 4H746G634, 4J625J623, 4J625J623, 4J627J623, 4K731M737, and 5B723 5B727. Benzoyl Peroxide 5% Gel, Lot No. 3B217C205A, 3C205E224, 3E225D230 3H430D230, 3H431K343, 3K344K343, 3M322M318, 3M322C253, 3M322C253A, 4E226E227, 4G636G635, 4H746G635, 4J625J624, 4J627J624, 4K731M738, 58724, and 5B728.

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Clindamycin 1% Gel, Lot No. 3C206B216A, 3B216D232, 3G218D229, 3G219D229, 3G217K342, 3K345K342, 3M321B328, 3M321B328A, 4E646C252, 4F735E228, 4G637G634, 4H745G634, 4J626J623, 4J628J623, 4K730M737, 5B725, and 5B729.

Admixture Placebo Gel, Lot No. 3C206C205A, 3C205D232, 3G218D230, 3G219D230, 3G217K343, 3K345K343, 3M321M318, 3M321M318A, 3M321M318B, 3M321M318B, 3M321C253, 4E646C253, 4F35E227, 4G637G635, 4H745G635, 4J626J624, 4J628J624, 4K730M738, 5B726, and 5B730.

Analysis for active ingredients showed that the formulations contained the expected concentrations throughout the study.

**CAC concurrence:** There is no record of CAC concurrence on the protocol. The study appears to have achieved a MTD because differences in body weights approached toxicological significance (i.e., decrease of approximately 10%) in males and females in Groups 5 (high-dose Admixture Active Gel) and 9 (high-dose Clindamycin alone).

#### Methods

Doses: 0, 0, 0.3, 0.9, and 3.0 mL/kg/day Admixture Active Gel ( \_\_\_\_\_ ), 0.9 and 3.0 mL/kg/day Benzoyl Peroxide 5% Gel; 0.9 and 3.0 mL/kg/day Clindamycin Phosphate 1% Gel.

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Group	Test Article	Applied amount of test article (mL/kg/day)	Dose active ingredient (mg/kg/day)	
			Benzoyl Peroxide	Clindamycin Phosphate
1	Placebo Gel	3.0	0	0
2	Placebo Gel	3.0	0	0
3		0.3	15	3
4		0.9	45	9
5		3.0	150	30
6	5% BP Gel	0.9	45	0
7	5% BP Gel	3.0	150	0
8	1% CP Gel	0.9	0	9
9	1% CP Gel	3.0	0	30

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Basis of dose selection (MTD, MFD, AUC etc.): The sponsor stated that the doses selected for this study were estimated to be 300 to 3000 times the maximum projected exposure of a human to the Admixture Active Gel in a lifetime exposure. Although the sponsor further stated that the doses were selected to provide a maximum dose which would not be expected to produce overt nephrotoxicity or more than a 10% body weight loss with continuous daily dosing in the rat through a lifetime, no study on this information was included within the submission.

Species/strain: Rat / SD — CD BR VAF/Plus

Number/sex/group (main study): 62/sex/group

Route, formulation, volume: Oral (gavage), once daily, 0.3, 0.9, or 3.0 mL/kg/day. The formulation tested in this study (see the next table) was not the same as the proposed clinical formulation.

Ingredient	% w/w			
	Placebo Gel	Benzoyl Peroxide 5% Gel	Clindamycin Phosphate 1% Gel	Admixture Active Gel
Clindamycin phosphate			1.000	1.000
Benzoyl peroxide				
Propylene Glycol, USP				
Carbomer — NF				
Potassium Hydroxide				
Purified water, USP				

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Frequency of dosing: The test articles and placebo were administered orally, by gavage, once daily, seven days per week for the duration of the study. Individual doses were calculated based on the most recent individual body weight data. The remaining males and females in each group were euthanized when the surviving number of animals/sex/group reached approximately 20. The study was terminated during Week 97.

It is 7 weeks before terminal sacrifice for a typical 2-year carcinogenicity study duration of 104 weeks. This may still be acceptable. However, the Agency should have been contacted prior to early termination of any dose group.

Satellite groups used for toxicokinetics or special groups: 18/sex/group

Age: Approximately 7 weeks old

Animal housing: Individual stainless steel wire mesh cages

Restriction paradigm for dietary restriction studies: None

Drug stability/homogeneity: Duplicate 8.00 mL samples of each test article and vehicle control formulation were obtained during study weeks 1, 13, 26, 52 and 72 for males and females, week 95 for females and week 97 for males. In addition, duplicate 8.00 mL samples of the Admixture Active Gel, the Clindamycin 1% Gel and the Admixture Placebo Gel were obtained during week 31 for males and females. Analysis for active ingredients showed that the formulations contained the expected concentrations throughout the study.

Dual controls employed: Two groups containing 62 animals per sex each were administered the Placebo Gel.

Interim sacrifices: All animals found dead or sacrificed *in extremis* were subject to gross necropsy and histological examinations.

Deviations from original study protocol: No significant changes

#### Observation Time and Results:

Mortality: Mortality and morbidity was checked twice per day. The remaining males and females in each group were euthanized when the surviving number of animals/sex/group reached approximately 20. The surviving males in Group 7 were euthanized during Week 88 and the surviving males in Group 5 were euthanized during Week 95 when the number of surviving males in these groups reached 20. The surviving males in Groups 1, 2, 3, 4, 6, 8 and 9 were euthanized during Week 97 with 23, 29, 21, 27, 21, 25, and 24 males remaining in the groups, respectively. All surviving females were euthanized during Week 95. The number of surviving females ranged from 20 in Group 2 to 28 in Group 4. Groups 1, 3, 5, 6, 7, 8 and 9 had 22, 22, 24, 27, 26, 24, and 23 females remaining, respectively.

A number of males and females from each study group were found dead or euthanized prior to study termination (unscheduled euthanasia), as shown in the next table. There were no notable differences in either sex between the Control groups and the groups receiving f ———, Benzoyl Peroxide 5% Gel, or Clindamycin Phosphate 1% Gel.

Test Article:	Admixture Placebo Gel		Admixture Active Gel			Benzoyl Peroxide 5% Gel		Clindamycin Phosphate 1% Gel	
	Group: 1	Group: 2	Group: 3	Group: 4	Group: 5	Group: 6	Group: 7	Group: 8	Group: 9
Level (cc/kg/day):	3.0	3.0	0.3	0.9	3.0	0.9	3.0	0.9	3.0
<b>Males</b>									
Found Dead	25	20	24	19	23	21	21	22	24
Unscheduled Euthanasia	14	14	17	17	19	20	21	16	14
Total	39	34	41	36	42	41	42	38	38
<b>Females</b>									
Found Dead	8	9	14	8	13	8	7	10	15
Unscheduled Euthanasia	32	33	27	26	25	27	29	28	24
Total	40	42	41	34	38	35	36	38	39

**Clinical signs:** All animals were examined for reactions to the treatment daily. A detailed clinical examination was conducted on each animal weekly. Palpable mass examination was conducted weekly.

In males, the incidence of rales appeared to be increased in a dose-related manner in the high-dose Admixture Active Gel (Group 5) and both Benzoyl Peroxide groups (Groups 6 and 7) and in both Clindamycin groups (Groups 8 and 9). However, in females, the highest incidence of rales occurred in both control groups (Groups 1 and 2). In females, the incidence of hunched posture appeared increased in the mid- and high-dose of the Admixture Active Gel and both Benzoyl Peroxide and Clindamycin groups compared to the controls. There was no dose-effect relationship. The sponsor further stated that hunched posture in males was observed at a very low incidence in all nine groups (NF, no data were found). There were no other treatment-related clinical signs.

Group	Test Article	Level (mL/kg/day)	Rales		Hunched Posture	
			Male	Female	Male	Female
1	Placebo Gel	3.0	32/6	267/23	NF	6/5
2	Placebo Gel	3.0	3/2	170/24	NF	4/3
3		0.3	6/3	135/16	NF	0/0
4		0.9	5/4	88/8	NF	29/11
5		3.0	228/33	98/16	NF	79/14
6	5% BP Gel	0.9	98/13	90/60	NF	59/13
7	5% BP Gel	3.0	273/40	107/14	NF	60/12
8	1% CP Gel	0.9	59/17	22/4	NF	50/17
9	1% CP Gel	3.0	233/34	15/7	NF	32/8

Note: Data reflect the total occurrence of each clinical finding over the number of animals exhibiting the finding.

**Body Weight:** Individual body weights were recorded for surviving animals in each group once during Weeks 1 through 13, 21, 29, 37, 45, 53, 61, 69, 77 and 85 through 97. A final body weight was recorded for each surviving animal on the day of scheduled euthanasia.

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As shown in the next two figures duplicated from the study report, there were no treatment-related effects on body weights for males in Groups 3, 4, 6, or 8. However, a trend toward decreased mean body weights (between 5% to 10%, not statistically significant) was noted for males in Groups 5 and 7 during the latter part of the study compared to control Group 1. Mean body weights for males in Group 9 were decreased throughout much of the study compared to control Group 1. The differences in mean body weight in the Group 9 males were statistically significant on Weeks 2, 45, 53, 61, and 69 when compared to group 1 (~10%). A trend toward decreased mean body weights (between 5% to 10%, not statistically significant) was also noted for females in Groups 4, 5, 6, 7, 8 and 9 during the latter part of the study compared to Group 1. In addition, mean body weights for females in Group 3 were increased throughout most of the study compared to control group 1. The increase in mean body weight was statistically significant for the Group 3 females on Week 69. Because differences in body weights approached toxicological significance (i.e., decrease of approximately 10%) in males and females in Groups 5 (high-dose Admixture Active Gel) and 9 (high-dose Clindamycin alone), a MTD appeared to be achieved in this study.

**2 YEAR ORAL (GAVAGE) CARCINOGENICITY STUDY OF AN ADMIXTURE ACTIVE GEL AND ITS COMPONENTS IN RATS**

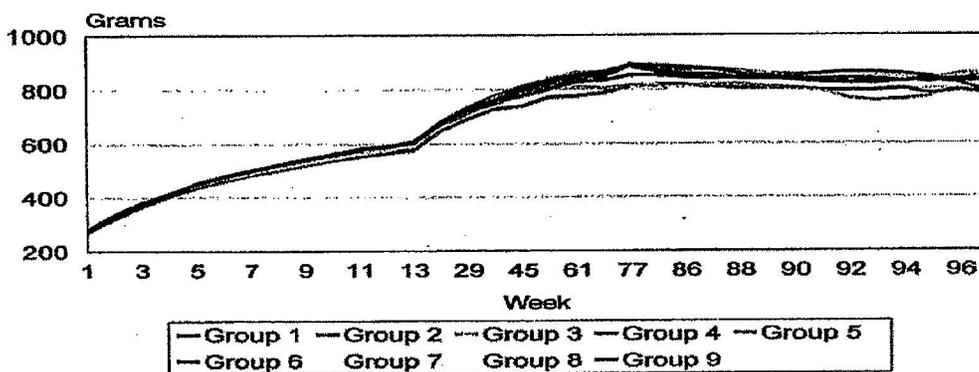


Figure 3. SUMMARY OF MEAN BODY WEIGHT DATA - MALES

**2 YEAR ORAL (GAVAGE) CARCINOGENICITY STUDY OF  
AN ADMIXTURE ACTIVE GEL AND ITS  
COMPONENTS IN RATS**

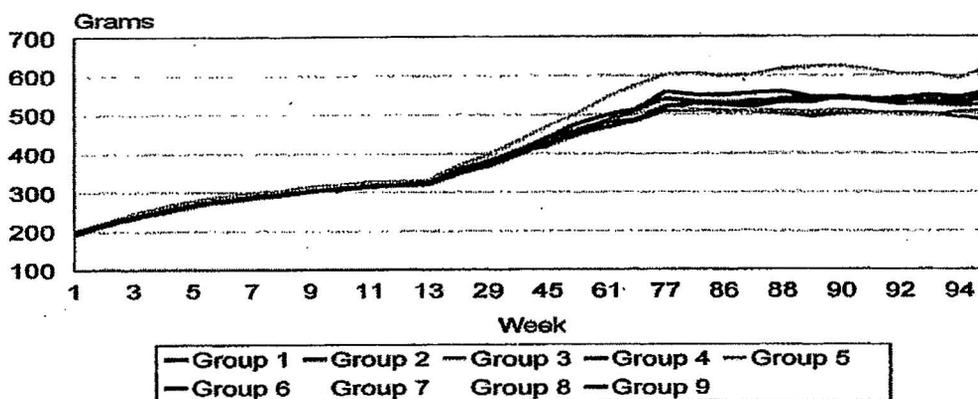


Figure 4. SUMMARY OF MEAN BODY WEIGHT DATA - FEMALES

**Food Consumption:** Individual food consumption was recorded for surviving animals during Weeks 1 to 2, 2 to 3, 3 to 4, 4 to 5, 5 to 6, 6 to 7, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 21 to 22, 29 to 30, 37 to 38, 45 to 46, 53 to 54, 61 to 62, 69 to 70, 77 to 78, 85 to 86, 86 to 87, 87 to 88, 88 to 89, 89 to 90, 90 to 91, 91 to 92, 92 to 93, 93 to 94, 94 to 95, 95 to 96, and 96 to 97. There were no treatment-related effects.

**Clinical Pathology:** Blood was collected from the first 10 males and 10 females from each group for evaluation of selected hematology and clinical chemistry parameters at Weeks 28, 54, and 80 and prior to scheduled euthanasia (Week 88, 95, or 97). The same animals were bled at each interval, when possible. There were no treatment-related effects on hematology and chemistry parameters evaluated during the study. Evaluation of clinical pathology is not recommended for a 2-year carcinogenicity study.

**Organ Weights:** There were no treatment-related effects.

**Gross Pathology:** A gross necropsy was conducted on all animals whether they died early, were sacrificed early or were sacrificed as scheduled. There were no treatment-related effects.

**Histopathology:** Microscopic examinations were performed on all tissues listed in the table from all animals in the control and high-dose groups and all animals found dead or euthanized prior to scheduled termination in the low- and mid-dose groups. In addition, the following tissues from all surviving low- and mid-dose animals were examined microscopically: adrenals, all gross lesions, brain, liver, mammary gland/skin, mesenteric lymph node, pancreas, pituitary, spleen, testes, thyroid/parathyroid, thymus, and uterus.

**Non-neoplastic:** Congestion and hemorrhage were common non-neoplastic findings in multiple organs. Other commonly observed non-neoplastic findings included vacuolar changes in the adrenal cortex of primarily males, adrenal cortical degeneration

and peliosis in primarily females, hydrocephalus and surface depression of the hypothalamus of the brain associated with large pituitary adenomas, chronic myocarditis, chronic progressive nephropathy and chronic interstitial nephritis in males and females, and pelvic mineralization of the kidneys in primarily females. There were no non-neoplastic microscopic findings in any organs or tissues examined that were considered to be test article related. The microscopic lesions observed were typical of those observed in a clinically normal population of SD — CD rats allowed to live out a normal lifespan.

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Neoplastic: Some commonly observed neoplasms in this study included fibroadenomas, adenomas and adenocarcinomas in the mammary glands of females, and islet cell adenomas of the pancreas and adenomas of the pituitary in males and females (see Tables A, B, and C). There were some statistically significant differences in tumor incidence when control groups 1 and 2 were compared to the various treated groups, according to Agency criteria (see Tables A and B, adapted from Table A.2.1. in Statistical Review by Dr. Steve Thomson). However, it seems that these differences are not biologically significant, due to either no trend with increasing dose or no difference from one of the placebo controls. Actually, there were also statistically significant differences in some tumor incidences when the control groups were compared to one another.

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Table A. Neoplastic findings with potentially statistically significant differences in male rats

Group	1	2	3	4	5	6	7	8	9
Treatment	Placebo Gel		Gel		5% BP Gel		1% CP Gel		
Dose (mL/kg/day)	15.0	15.0	0.90	2.70	15.0	2.70	15.0	2.70	15.0
Adrenal pheochromocytoma (B)	4	2	7	4	6	5	3	7	3
Kidney mesenchymal tumor	0	0	0	3	1	0	0	0	0
Lung (bronchi) histiocytic sarcoma (M)	0	0	1	0	2	1	1	2	0
Lymph node lymphoma (M)	0	0	0	3	1	0	0	0	0
Lymph node (mesenteric) histiocytic sarcoma (M)	0	0	0	0	0	0	1	2	0
Lymph node (mediastinal) histiocytic sarcoma (M)	0	0	0	0	0	0	1	2	1
Mammary gland adenocarcinoma (M)	0	0	1	2	1	0	0	3	0
Mammary gland fibroadenoma (B)	0	0	1	1	1	0	0	2	0
Mammary gland histiocytic sarcoma (M)	0	0	1	0	0	0	0	2	1
Pituitary adenoma (B)	23	25	25	22	27	30	27	30	18
Skeletal muscle histiocytic sarcoma (M)	0	0	0	0	0	0	0	2	1
Skin basal cell tumor (B)	0	0	1	2	0	2	1	1	0
Systemic histiocytic sarcoma (M)	1	0	2	0	2	1	1	4	1
Tail papilloma	0	0	0	0	0	0	0	2	0
Thyroid follicular adenoma	0	0	1	2	2	3	0	2	2

B - Benign; M - Malignant

Table B. Neoplastic findings with potentially statistically significant differences in female rats

Group	1	2	3	4	5	6	7	8	9
Treatment	Placebo Gel		Gel		5% BP Gel		1% CP Gel		
Dose (mL/kg/day)	15.0	15.0	0.90	2.70	15.0	2.70	15.0	2.70	15.0
Mammary gland adenoma (B)	3	8	7	3	3	4	4	3	4
Mammary gland fibroadenoma (B)	25	30	27	26	20	23	17	23	23
Skin fibrosarcoma (M)	0	5	0	1	0	1	1	1	2

B - Benign; M - Malignant

Table C. Some other commonly observed neoplasms

Group		1	2	3	4	5	6	7	8	9
Treatment		Placebo Gel		<del>Placebo Gel</del> Gel		5% BP Gel		1% CP Gel		
Dose (mL/kg/day)		15.0	15.0	0.90	2.70	15.0	2.70	15.0	2.70	15.0
Males	Pancreas Islet cell adenoma	3	5	1	1	3	3	0	2	3
Females	Mammary gland adenocarcinoma (M)	16	18	9	19	14	12	11	13	10
	Pancreas Islet cell adenoma	0	1	1	0	3	1	1	0	0
	Pituitary adenoma (B)	43	44	45	44	43	45	39	45	36

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B - Benign; M - Malignant

**Toxicokinetics:** Additional 18 males and 18 females were assigned to each of seven groups (see the next table) in the toxicokinetic satellite phase. Blood samples were collected from two animals/sex/group at 0.5, 1.0, and 3.0 hours following dosing during Weeks 1, 4, 26, and 52. The animals bled from the orbital plexus during Week 26 continued to be treated until Week 52. No toxicokinetics data were included within this study report.

Group	Test Article	Blood (Plasma) Collection Intervals			
		Week 1	Week 4	Week 26	Week 52
1	Admixture Placebo Gel	6M / 6F	6M / 6F	6M / 6F	6M / 6F
2	Admixture Active Gel Low Dose	6M / 6F	6M / 6F	6M / 6F	6M / 6F
3	Admixture Active Gel High Dose	6M / 6F	6M / 6F	6M / 6F	6M / 6F
4	Benzoyl Peroxide 5% Gel Middle Dose	6M / 6F	6M / 6F	6M / 6F	6M / 6F
5	Benzoyl Peroxide 5% Gel High Dose	6M / 6F	6M / 6F	6M / 6F	6M / 6F
6	Clindamycin Phosphate 1% Gel Middle Dose	6M / 6F	6M / 6F	6M / 6F	6M / 6F
7	Clindamycin Phosphate 1% Gel High Dose	6M / 6F	6M / 6F	6M / 6F	6M / 6F
Total No. of Animals at Each Interval		84	84	84	84

List of Organs and Tissues Examined:

Study	2-Year in Mice	2-Year in Rats
Adrenals	X*	X*
Aorta	X	X
Bone Marrow smear	X	X
Bone (femur)	X	X
Brain	X*	X*
Cecum	X	X
Cervix		
Colon	X	X
Duodenum	X	X
Epididymis	X	X
Esophagus	X	X
Eye	X	X

Fallopian tube		
Gall bladder		
Gross lesions	X	X
Harderian gland		
Heart	X	X
Ileum	X	X
Treatment Site	X	
Jejunum	X	X
Kidneys	X*	X*
Lachrymal gland	X	X
Larynx		
Liver	X*	X*
Lungs	X	X
Lymph nodes, mediastinal	X	X
Lymph nodes submandibular	X	X
Lymph nodes, mesenteric	X	X
Mammary Gland	X	X
Nasal cavity		
Optic nerves		X
Oral cavity (cheek)	X	X
Ovaries	X*	X*
Pancreas	X	X
Parathyroid	X	X
Peripheral nerve		X
Pharynx		
Pituitary	X	X
Prostate	X	X
Rectum	X	X
Salivary gland	X	X
Sciatic nerve	X	X
Seminal vesicles	X	X
Skeletal muscle	X	X
Skin	X	X
Spinal cord	X	X
Spleen	X	X
Sternum	X	X
Stomach	X	X
Testes	X*	X*
Thymus	X	X
Thyroid	X	X
Tongue	X	X
Trachea	X	X
Urinary bladder	X	X
Uterus	X	X
Vagina	X	X
Zymbal gland		

\* organ weight obtained

The following information on the photocarcinogenesis study was duplicated from the review by Dr. Jiaqin Yao in IND 41,733.

**3. Study title: A Photocarcinogenesis Study of An Admixture Active Gel (Benzoyl Peroxide 5% and Clindamycin Phosphate 1%) and Its Components in Albino Hairless Mice**

**Key study findings:** Treatment with Admixture Active Gel caused significant decreases in animal survival compared to the Placebo Gel-treated or untreated animals receiving 600 RBU/week. Most of the deaths were because of early sacrifice due to tumor burden. No treatment related clinical observations were noted other than the skin reactions. Greater incidences of erythema, flaking, and thickening of the skin were observed in a dose-dependent fashion in mice treated with Admixture Active Gel compared to the placebo-treated animals receiving 600 RBU/week. Edema was seen in the test article-treated animals, not in the untreated groups receiving 600 RBU/week. The severity of these skin reactions was greater in the male mice than in female mice. The skin reactions observed in Admixture Active Gel-treated mice generally did not exceed the incidence and severity of reactions observed in the untreated mice receiving 1200 RBU/week. Admixture Active Gel or Placebo Gel treatment did not produce any significant effects on body weights. The mice treated with Admixture Active Gel had a slightly increased incidence of enlarged and mottled livers.

Topical application of Admixture Active Gel was associated with apparent enhancement of photocarcinogenesis. The mice in the high UVR group developed skin tumors significantly earlier than the mice in the low UVR groups. The placebo gel appeared to cause a slight, not statistically significant enhancement of UV induced skin tumors. The tumor prevalence in mice treated with Admixture Active Gel was increased for all tumor size categories, as compared with mice treated with the placebo gel or untreated mice receiving 600 RBU/week of UV irradiation. The time to tumor onset in Admixture Active Gel-treated groups was shorter than that in the placebo gel group or the untreated group receiving 600 RBU/week. Males tended to be significantly more affected than females.

Adequacy of the carcinogenicity study and appropriateness of the test model:

Photocarcinogenesis studies conducted by \_\_\_\_\_ often use an alternating schedule of drug application and irradiation. Often the drug is applied prior to irradiation on Monday, Wednesday, and Friday and after irradiation on Tuesday and Thursday. In the current study, drug was applied after irradiation on Monday, Wednesday, and Friday and before irradiation on Tuesday and Thursday. The reason for this difference was not explained. However, the fact that an enhancement was observed suggests that the design was adequate in this case.

Evaluation of tumor findings: Only skin tumors were evaluated, which was the primary objective of this study.

**Study no.:** \_\_\_\_\_, protocol C-609-001. \_\_\_\_\_ Report No. 92 GLA P007 S035