Key study findings: In this two-year dermal mouse carcinogenicity study, topical treatment of Admixture Active Gel (——— , Benzoyl Peroxide 5% Gel, or Clindamycin Phosphate 1% Gel did not cause treatment-related effects on mortality, clinical signs, body weight, food consumption, and gross pathology examinations. Only females treated with ——— (1/5) Gel or Benzoyl Peroxide 5% Gel showed slight increases in kidney weight. Focal hyperplasia of the pituitary was noted in males in all groups. The incidence of epithelial hyperplasia and hyperkeratosis at the treatment site was markedly increased in all groups treated with ——— Gel or the Benzoyl peroxide 5% Gel. The severity of the epithelial hyperplasia increased progressively with the dose of Benzoyl peroxide. The incidence of epithelial hyperplasia at the treatment site was also increased in the animals receiving 15 mL/kg/day of the Clindamycin Phosphate 1% Gel. No significant increase in tumors was seen in mice treated with the ——— Gel, Benzoyl Peroxide 5% Gel, or Clindamycin Phosphate 1% Gel. b(4)

Adequacy of the carcinogenicity study and appropriateness of the test model: The use of the topical route in mice is appropriate, since the Admixture Active Gel is intended for topical, chronic use in patients with acne. 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.

b(4)

Evaluation of tumor findings: There was no evidence to suggest that topical application of Admixture Active Gel (——— , Benzoyl Peroxide 5% Gel, or Clindamycin Phosphate 1% Gel for up to 104 weeks caused an increased incidence of tumors in mice.

Study no.: 92 GLA P007 S034
Conducting laboratory and location: ———
Date of study initiation: 6-15-1993
GLP compliance: Yes
QA report: yes (X) no ( ) b(4)
Drug, lot #, and % purity: All batches used were manufactured by ——— and shipped directly to ——— The sponsor stated that a record of the lot numbers, quantity received and date of receipt could be found in the raw data (but not provided in the study report). The study report stated that "The test articles were prepared by the Sponsor. Stability data generated by the Sponsor indicated that the dosing formulations were stable for up to 3 months."

CAC concurrence: There is no record of CAC concurrence on the protocol. The study appears to have achieved a dermal MTD based on the elevated hyperkeratosis and epithelial hyperplasia noted at the treatment site in both males and females in the high dose groups.

Methods

Doses: 0, 0, 0.9, 2.7, and 15 mL/kg/day Admixture Active Gel ('); 2.7 and 15 mL/kg/day Benzoyl Peroxide 5% Gel; 2.7 and 15 mL/kg/day Clindamycin Phosphate 1% Gel.

b(4)

Group	Test Article	Applied amount of test article (mL/kg/day)	Dose active ingredient (mg/kg/day)	
			Benzoyl Peroxide	Clindamycin Phosphate
1	Placebo gel	15.0	0	0
2	Placebo gel	15.0	0	0
3		0.90	45	9
4		2.70	135	27
5		15.0	750	150
6	5% BP gel	2.70	135	0
7	5% BP gel	15.0	750	0
8	1% CP gel	2.70	0	27
9	1% CP gel	15.0	0	150

Basis of dose selection (MTD, MFD, AUC etc.): The dose levels take into account the maximum practical dose volume to be applied to the mouse. For a mouse weighing 40 g, a dose of 15 mL/kg would require application of 0.6 mL to the approximately 5 cm^2 area used in this study. Although the sponsor also 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, no study on this information was included within the submission.

Species/strain: Mouse / CD-1

Number/sex/group (main study): 60/sex/group

Route, formulation, volume: Topical. The formulation (see the next table) was not the same as the proposed clinical formulation. Test article was applied once daily topically (see the table above) to the backs of mice from which the hair was removed by clipping once weekly. The area treated was approximately 5 cm^2, which represents approximately 10% of the total body surface area. No attempt was made to prevent ingestion of the test articles and the material was not removed at the end of the day. Occlusion was not used.

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

b(4)

Frequency of dosing: Drug was applied once daily for 103 weeks to females and 104 weeks to males.

Satellite groups used for toxicokinetics or special groups: None

Age: Approximately 6 weeks old

Animal housing: Individual polypropylene cages

Restriction paradigm for dietary restriction studies: None

Drug stability/homogeneity: Samples of each formulation were taken at the beginning of the study and at Weeks 13, 26, 52, 77, and 103. Analysis for active ingredients showed that the formulations contained the expected concentrations throughout the study.

Dual controls employed: Two groups containing 60 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. Females were terminated during Week 103 due to low survival. The males were sacrificed at Week 105.

There were 446 premature deaths, distributed evenly throughout the groups (see the following table). There were no notable differences in either sex between the Control groups and the groups receiving , Benzoyl Peroxide 5% Gel, or Clindamycin Phosphate 1% Gel. b(4)

Number of Decedents Per Group

Sex	Group/Dose Level (mg.kg^{-1}.day^{-1})								
	Control		Admixture Active Gel (Clindaben)			Benzoyl Peroxide 5% Gel		Clindamycin Phosphate 1% Gel	
	1 (0)	2 (0)	3 (0.9)	4 (2.7)	5 (15.0)	6 (2.7)	7 (15.0)	8 (2.7)	9 (15.0)
Males	20/60	27/60	27/60	29/60	26/60	26/60	20/60	19/60	27/60
Females	20/60	27/60	29/60	29/60	26/60	26/60	21/60	19/60	28/60

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.

b(4)

There were no treatment-related effects. Only females treated with [redacted] Benzoyl Peroxide 5% Gel, or Clindamycin Phosphate 1% Gel showed that skin at the application site was affected by a bigger incidence of abnormal texture (either elastic or inelastic), compared to the groups receiving Admixture Active Placebo. There was no appreciable incidence of externally palpable masses at the treatment site or elsewhere.

Body Weight: Body weight was obtained for each animal weekly during the first 14 weeks and then every two weeks thereafter. There were no treatment-related effects on body weights.

Food Consumption: Food consumption was measured for each animal weekly during the first 14 weeks and then once every four weeks thereafter. There were no treatment-related effects.

Water Consumption: Water consumption was monitored by visual inspection on a weekly basis commencing one week before the start of treatment and throughout the treatment period. There were no treatment-related effects.

Organ Weights: Only females treated with [redacted] or Benzoyl Peroxide 5% Gel showed slightly increased (less than 12%) kidney weight. Clindamycin Phosphate 1% Gel showed no differences in either sex in organ weight profile compared to combined Control groups.

b(4)

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: Histopathology was conducted for all groups on the tissues listed in the table in the appendix below.

Non-neoplastic: The incidence of epithelial hyperplasia and hyperkeratosis at the treatment site was markedly increased in all groups treated with benzoyl peroxide 5%,

either in the Admixture Active Gel (———) in combination with 1% clindamycin phosphate or in those treated with Benzoyl Peroxide 5% Gel alone, compared to the Admixture Placebo Gel Control Groups 1 and 2 (see the next table). The severity of the epithelial hyperplasia increased progressively with the dose of benzoyl peroxide. In addition, an increased incidence of epithelial hyperplasia in the skin adjacent to the treated area was also noted in Groups 3, 4, 5, 6, and 7. The incidence of epithelial hyperplasia at the treatment site was also increased in the animals receiving 15 mL/kg/day of the Clindamycin Phosphate 1% Gel. b(4)

Group	Test Article	Applied amount of test article (mL/kg/day)	Epithelial hyperplasia		Hyperkeratosis	
			Males	Females	Males	Females
1	Placebo gel	15.0	3/60	5/60	1/60	0/60
2	Placebo gel	15.0	7/60	1/60	0/60	1/60
3	[redacted]	0.90	28/60	35/60	18/60	20/60
4	[redacted]	2.70	35/60	40/59	24/60	21/59
5	[redacted]	15.0	57/60	58/60	46/60	46/60
6	5% BP gel	2.70	37/60	42/60	25/60	25/60
7	5% BP gel	15.0	58/60	59/60	45/60	42/60
8	1% CP gel	2.70	5/60	5/59	0/60	2/59
9	1% CP gel	15.0	14/60	30/60	3/60	3/60

b(4)

Abscess in the ovaries were observed only in the groups treated with clindamycin phosphate, at an incidence of 4/60, 5/60, and 5/60 in ——— -treated Groups 3, 4, and 5, respectively, and 3/60 and 6/60 in Clindamycin phosphate 1% Gel-treated Groups 8 and 9, respectively. The increase in abscess in the ovaries in Group 9 was statistically significantly greater than controls (0/60 in both control groups). The sponsor stated that the increased incidence of abscess in the ovaries was likely that that clindamycin had altered the normal dermal/vaginal bacterial flora, predisposing to bacterial overgrowth and ascending infections by opportunistic bacteria. b(4)

Neoplastic:

1. There were no notable neoplastic findings in either sex that could be attributable to the application of Admixture Active Gel (———), Benzoyl Peroxide 5% Gel, or Clindamycin Phosphate 1% Gel. Overall, the total incidences of tumors and animals with tumors varied between groups but did not show a relationship to any of the test materials. b(4)

b(4)

TABLE 47

Dermal Carcinogenicity Study of an Admixture Active Gel (' ——
Benzoyl peroxide 5% and Clindamycin phosphate 1%) and its Components in Mice
Overall Tumour Incidence: Males and Females
In Survivors at Termination and Premature Decedent Animals Combined - Active Admixture Gel ' ——

	TUMOUR TABLE									
	MALES					FEMALES				
TREATMENT	Grp 1 0 ml/kg /day	Grp 2 0 ml/kg /day	Grp 3 0.9 ml/kg /day	Grp 4 2.7 ml/kg /day	Grp 5 15.0 ml/kg /day	Grp 1 0 ml/kg /day	Grp 2 0 ml/kg /day	Grp 3 0.9 ml/kg /day	Grp 4 2.7 ml/kg /day	Grp 5 15.0 ml/kg /day
NUMBER OF ANIMALS:	60	60	60	60	60	60	60	60	60	60
NO. OF ANIMALS WITH TUMOURS	39	34	44	30	37	41	36	30	33	33
NO. OF ANIMALS WITH SINGLE TUMOURS	26	29	30	20	21	30	26	23	20	26
NO. OF ANIMALS WITH MULTIPLE TUMOURS	13	5	14	10	16	11	10	7	13	7
NO. OF ANIMALS WITH BENIGN TUMOURS	29	17	29	18	23	18	20	15	14	19
NO. OF ANIMALS WITH MALIGNANT TUMOURS	15	19	21	16	23	30	22	22	27	19
NO. OF ANIMALS WITH METASTASISING TUMOURS	1	2		1	2	2	2	1	2	3
TOTAL NUMBER OF TUMOURS	52	39	58	44	54	54	48	38	49	40
TOTAL NUMBER OF BENIGN TUMOURS	35	19	33	24	29	20	24	15	17	20
TOTAL NUMBER OF MALIGNANT TUMOURS	17	20	25	20	25	34	24	23	32	20
TOTAL NUMBER OF METASTASISING TUMOURS	1	2		1	2	2	2	1	3	3
% ANIMALS WITH TUMOURS	65	57	73	50	62	68	60	50	55	55
% ANIMALS WITH SINGLE TUMOUR	43	48	50	33	35	50	43	38	33	43
% ANIMALS WITH MULTIPLE TUMOURS	22	8	23	17	27	18	17	12	22	12
% ANIMALS WITH BENIGN TUMOURS	48	28	48	30	38	30	33	25	23	32
% ANIMALS WITH MALIGNANT TUMOURS	25	32	35	27	38	50	37	37	45	32
% ANIMALS WITH METASTASISING TUMOURS	2	3		2	3	3	3	2	3	5

Animals with more than one tumour type are recorded as having multiple tumours.

2. 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 the next two tables, adapted from Table A.2.1. in Statistical Review by Dr. Steve Thomson). However, it appears that these differences are not biologically significant, due to either no trend with increasing dose or no difference from one of the placebo controls.

Table 1. Neoplastic findings with potentially statistically significant differences in male mice

Group	1	2	3	4	5	6	7	8	9
Treatment	Placebo Gel		Clindaben 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
Liver hepatocellular adenoma	12	6	11	11	10	15	19	9	6
Lymph node lymphoma (M)	5	3	6	3	9	6	7	4	5

M - Malignant

Table 2. Neoplastic findings with potentially statistically significant differences in female mice

Group	1	2	3	4	5	6	7	8	9
Treatment	Placebo Gel		Clindaben 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
Lung alveolar/bronchiolar adenoma	6	8	8	4	6	2	4	6	1
Mammary gland carcinoma (M)	2	2	1	0	0	0	3	2	0
Systemic hemangioma / hemangiosarcoma	1	2	3	7	2	3	4	2	1
Uterus polyp	5	7	0	6	4	7	5	3	5
Uterus stromal sarcoma	1	1	3	7	1	2	5	0	0

B - Benign; M - Malignant

3. Within the study report, the sponsor also described some specific tumors whose incidences occasionally showed a mild increase in some groups. None of them were biologically significant. Adenomas of the pars distalis were noted at a low incidence in most groups including controls, with the highest incidence (3/57) in the group which received 15 mL/kg/day of Admixture Active Gel (———). No increase of these tumors was seen in the groups which received similar doses of each of the components separately (Group 7 - 15 mL/kg/day Benzoyl Peroxide 5% Gel, Group 9 - 15 mL/kg/day Clindamycin Phosphate 1% Gel). b(4)

"Carcinomas of the parotid salivary gland were noted in one male that received 2.7 mL/kg/day of the Clindamycin Phosphate 1% Gel and one male that received 15 mL/kg/day of the Clindamycin Phosphate 1% Gel. A carcinoma of the parotid salivary gland was also recorded in one female that received 15 mL/kg/day of the Benzoyl Peroxide 5% Gel. "The occurrence of three tumors of the salivary gland in this study is noteworthy since these tumors are uncommon. The report states that (——— quotes a spontaneous incidence of 2/478 salivary gland tumors in female CD-1 mice between 21 and 24 months old and 0/480 in males of the same age. A database from (——— , entitled Spontaneous Neoplastic Lesions in the ——:CD-1 (ICR)BR Mouse does not list any neoplastic lesions observed in 2577 salivary glands examined from male mice in 46 different studies ——— . However, the salivary gland tumors observed in the current study can not specifically be considered an effect of clindamycin phosphate since one of the tumors occurred in an animal receiving 5% benzoyl peroxide alone. As noted above, no attempt was made to prevent ingestion of the test articles. According to published reports, salivary gland inflammation has been observed in rats treated orally with clindamycin hydrochloride and nuclear atypia of salivary gland cells has been described in rats receiving clindamycin palmitate hydrochloride in the diet. These effects have been ascribed to opportunistic infections of the salivary gland. In particular, this type of lesion has been attributed to coronavirus infections in rodents. It may be possible that the effects observed in the current study are due to the ingestion of clindamycin and benzoyl peroxide with subsequent alterations of b(4) b(4)

the bacterial flora of the mouth leading to opportunistic infections. This mechanism would not be relevant to human topical use of clindamycin phosphate."

Adenomas of the rete testis were observed in 2 males that received 2.7 mL/kg/day and in one male that received 2.7 mL/kg/day of the Clindamycin Phosphate 1% Gel. Testicular interstitial cell adenomas were noted in all control and clindamycin phosphate treated groups. "In general, it appears that tumors of the testes are not uncommon in mice from control groups of two year bioassays although, the historical database mentioned above from does not specifically list tumors of the rete testis. The study report notes that the incidence of the adenomas of the rete testis did not show any dose-response relationship to either test material. McConnell et al. (JNCI, 76:283, 1986) suggest that stromal neoplasms of the testes may be combined. If the interstitial cell and rete testis adenomas are combined then the incidence in the two control groups and the 2.7 and 15 mL/kg clindamycin phosphate groups are 2, 3, 4 and 2, respectively. Therefore, the occurrence of stromal neoplasms of the testes does not appear to be associated with clindamycin phosphate exposure." "Focal hyperplasia of the interstitial cells of the testes and the rete testis was noted in both control groups and in the animals receiving 2.7 mL/kg of the 1% clindamycin phosphate gel but not in animals receiving 15 mL/kg. This further suggests that the testicular effects are not associated with clindamycin phosphate."

b(4)

4. There was no treatment-related increase in the incidence of skin tumors (see the following two tables)

Table 3. Skin tumors in male mice

Group	1	2	3	4	5	6	7	8	9
Treatment	Placebo Gel		Clindaben 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
Number examined	60	60	60	59	60	60	60	60	60
Basal cell tumor [B]	0	0	1	0	0	0	0	0	1
Basal cell tumor [M]	0	0	1	0	0	0	1	0	0
Squamous cell carcinoma [M]	0	0	0	0	0	0	0	0	1
Fibrosarcoma [M]	0	0	0	0	0	0	1	1	0
Sarcoma [M]	1	1	0	0	0	0	1	0	0
Fibrous histiocytoma [B]	0	0	0	0	1	0	0	1	0
Fibrous histiocytoma [M]	0	0	0	0	1	0	0	1	0
Papilloma [B]	0	0	0	0	0	0	2	0	0

B - Benign; M - Malignant