

**Table 12. Potentially Statistically Significant Results in Male Rats**

Organ/tumor	Incidence/p-values									
	Ctrl1	Ctrl2	C1BP3	C1BP4	C1BP5	BP6	BP7	C18	C19	
	pboth	pCvs3	pCvs4	pCvs5	pBP	pCvs6	pCvs7	pC1	pCvs8	pCvs9
<b>KIDNEY</b>										
Mesenchymal Tumor	0	0	0	3	1	0	0	0	0	
	.139	.	.049	.297	.	.	.	.	.	.
<b>LUNG (BRONCHI)</b>										
HISTIOCYTIC SARCOMA [M]	0	0	1	0	2	1	1	2	0	
	.047	.316	.	.094	.127	.212	.278	.497	.050	.
<b>LYMPH NODE</b>										
LYMPHOMA [M]	0	0	0	3	1	0	0	0	0	
	.139	.	.049	.297	.	.	.	.	.	.
<b>LYMPH NODE (MESENTERIC)</b>										
HISTIOCYTIC SARCOMA [M]	0	0	0	0	0	0	1	2	0	
	.	.	.	.	.238	.	.278	.497	.050	.
<b>LYMPH NODE - MEDIASTINAL</b>										
HISTIOCYTIC SARCOMA [M]	0	0	0	0	0	0	1	2	1	
	.	.	.	.	.238	.	.278	.241	.050	.366
<b>MAMMARY GLAND</b>										
Adenoma/Fibroadenoma/-carcinoma	0	0	1	2	1	0	0	3	0	
	.160	.316	.128	.297	.	.	.	.355	.013	.
FIBROADENOMA [B]	0	0	1	1	1	0	0	2	0	
	.146	.316	.350	.297	.	.	.	.497	.050	.
HISTIOCYTIC SARCOMA [M]	0	0	1	0	0	0	0	2	1	
	.629	.316	.	.	.	.	.	.241	.050	.366
<b>SKELETAL MUSCLE (GROSS LESION)</b>										
HISTIOCYTIC SARCOMA [M]	0	0	0	0	0	0	0	2	1	
	.	.	.	.	.	.	.	.241	.050	.366
<b>Skin</b>										
BASAL CELL TUMOR, BENIGN	0	0	1	2	0	2	1	1	0	
	.584	.316	.128	.	.146	.050	.278	.702	.212	.
<b>Systemic</b>										
HISTIOCYTIC SARCOMA [M]	1	0	2	0	2	1	1	4	1	
	.165	.242	.675	.219	.283	.374	.473	.479	.014	.592
<b>TAIL (GROSS LESION)</b>										
PAPILLOMA	0	0	0	0	0	0	0	2	0	
	.	.	.	.	.	.	.	.497	.050	.
<b>THYROID</b>										
ADENOMA, FOLLICULAR	0	0	1	2	2	3	0	2	2	
	.052	.316	.128	.094	.512	.013	.	.105	.050	.139

### 3.2.2. Study 11484: Dermal Carcinogenicity Study of an Admixture Gel (\_\_\_\_\_ - Benzoyl Peroxide 5% and Clindamycin Phosphate 1%) and Its Components in Mice.

b(4)

MOUSE STUDY DURATION: Males: to Week 104.

Females: to Week 103.

DOSING STARTING DATE: June 29, 1993.

TERMINATION OF STUDY: June 20 to July 4, 1995.

b(4)

STUDY ENDING DATE (Final Report dated): June 7, 2006.

MOUSE STRAIN: \_\_\_\_\_ (UK) — CD-1® (ICR)BR Mice.

ROUTE: Daily Dermal Application.

Rats were randomized to the nine treatment groups per gender, numbered by the Sponsor as groups 1-9, with groups 1 and 2 denoting a vehicle control (15 ml/kg/day), group 3 with 5%

benzoyl peroxide and 1% clindamycin in a dose of 0.9 ml/kg/day, group 4 with 5% benzoyl peroxide and 1% clindamycin in a dose of 2.7 ml/kg/day, group 5 with 5% benzoyl peroxide and 1% clindamycin in a dose of 15 ml/kg/day, group 6 with 5% benzoyl peroxide in a dose of 2.7 ml/kg/day, group 7 with 5% benzoyl peroxide in a dose of 15 ml/kg/day, group 8 with 1% clindamycin in a dose of 2.7 ml/kg/day, and group 9 with 1% clindamycin in a dose of 15 ml/kg/day. For reports these were labeled as Cntrl1, Cntrl2, CIBP3, CIBP4, CIBP5, BP6, BP7, C18, and C19, respectively. Test materials were applied daily.

The Sponsor reports that: “The doses selected for this study were calculated to be in vast excess over the maximum projected exposure of a human to the active ingredients on a lifetime exposure. In addition 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 though its lifetime. The dose levels also take into account the maximum practical dose volume to be applied in the mouse.” (page 25 of report)

Dose were applied as follows: “The fur on the backs of the animals were clipped using Ostler Golden A5 clippers at least once weekly over an area approximately 10% of the total body surface area. This represented an area of approximately 5 sq cm (2.0 cm wide and 2.5 cm long). The test materials were applied . . . directly to the centre of the shaved area using a 1 ml plastic syringe and then spread with the end of that syringe until an even coverage of the shaved area had been achieved. The volume of dosing suspension to be administered to each animal as recorded at the time of the last body weight determination.

“No attempt was made to prevent oral ingestion nor to remove any excess material at the end of the day. Occlusion was not used.

“The vehicle was applied to the Control animals (Control groups 1 and 2) at a dose volume equivalent to the high dose volume applied to the test groups.” (page 26 of report)

During the study animals were housed individually. Water was available ad libitum. The Sponsor states that detailed physical examinations were made on all animals each week. Body weights were recorded weekly for the first 14 weeks, beginning approximately one week before initiation of dosing, and every two weeks thereafter. Food consumption was assessed every four weeks.

### 3.2.2.1 Sponsor's Results and Conclusions

This section will present a summary of the Sponsor's analysis on survivability and tumorigenicity in mice.

#### Survival analysis:

The Sponsor summarizes the following mortality:

b(4)

**Table 13: Sponsor's Summary Mortality Counts**

Number of Decedents Per Group

Sex	Group/Dose Level (mg.kg <sup>-1</sup> .day <sup>-1</sup> )								
	Control		Admixture Active Gel (Clindabene)			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

Females terminated during Week 103 due to low survival

“There were no notable differences in either sex between the Control groups and the groups receiving Admixture Active Gel ( ——— ), Benzoyl peroxide 5% Gel or Clindamycin phosphate 1% Gel. All deaths were judged to be incidental to treatment and due to causes typical for mice of this age and strain at Inveresk.” (page 14 of report)

b(4)

In males these values differ slightly from those in the FDA analysis derived from the submitted data sets summarized in tables 14 below. In females differences are more notable, with the FDA estimates of mortality uniformly higher than those reflected in the table above. Presumably this is from slightly different definitions of terminal survival.

**Tumorigenicity analysis:**

According to the Sponsor: “There were no notable neoplastic findings in either sex that could be attributable to the application of Admixture Active Gel ( ——— ), Benzoyl peroxide 5% or Clindamycin phosphate 1% Gel. The findings seen were considered to be typical for mice of this age and strain in a study of this type and duration.

b(4)

“Overall the total incidences of tumours and animals with tumours varied between groups but did not show a relationship to any of the test materials. Incidences of specific tumours occasionally showed a mild increase in some groups; these are discussed below.

“Males  
Pituitary

Adenomas of the pars distalis were recorded at a low incidence in most groups including controls, with the highest incidence (3/57) in the group which received 15 ml.kg<sup>-1</sup> 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<sup>-1</sup> Benzoyl peroxide 5%

b(4)

NDA 50819 ——— Gel

b(4)

Dow Pharmaceuticals, Inc.

Gel, Group 9 - 15 ml.kg<sup>-1</sup> Clindamycin 1% Gel). Focal hyperplasia was noted in all groups with the highest incidence and severity in Control Group 1.

“Parotid Salivary Glands

Carcinomas were recorded in one male which received 2.7 ml.kg<sup>-1</sup>.day<sup>-1</sup> Clindamycin phosphate 1% Gel and one male which received 15 ml.kg<sup>-1</sup>.day<sup>-1</sup> Clindamycin phosphate 1% Gel. The parotid salivary glands were not examined in all animals in this study.” (pages 46-47 of report)

Note that pages 31-32 of the report list the organs that had histopathological analysis.

“Testes

Rene testis adenomas were recorded in 2/60 males from the group receiving 2.7 ml.kg<sup>-1</sup>.day<sup>-1</sup> Admixture Active Gel ( ——— and 1/60 males from the group receiving 2.7 ml.kg<sup>-1</sup>.day<sup>-1</sup> Clindamycin phosphate 1% Gel. As this incidence showed no dose-relationship to either test material this pattern of incidence was considered coincidental and will not be discussed further.

b(4)

“Females

Parotid Salivary Glands

A carcinoma was recorded in one female from Group 7 (15 ml.kg<sup>-1</sup>.day<sup>-1</sup> of Benzoyl peroxide 5% Gel).”

(pages 46-47 of report)

**3.2.2.2 FDA Reviewer's Results**

This section will present the current Agency findings on survival and tumorigenicity in male and female mice.

**Survival analysis:**

Again, Kaplan-Meier plots comparing survival among treatment groups in both studies are given in Appendix 1, along with more details of the analysis. The following tables (Table 14 for male mice, Table 15 for female mice) summarize the mortality results for the dose groups. The data in the tables were grouped for each specified time period, and present the number of deaths during the time interval over the number at risk at the beginning of the interval. The percentage cited is the percent survived to the end of the interval.

**Table 14. Summary of Male Mice Survival (dose/kg/day)**

Period (Weeks)	Cntrl1	Cntrl2	CIBP3	CIBP4	CIBP5	BP6	BP7	C18	C19
0-50	1/60 <sup>1</sup> 98.3% <sup>2</sup>	1/60 98.3%	2/60 96.7%	3/60 95.0%	3/60 95.0%	3/60 95.0%	1/60 98.3%	5/60 91.7%	4/60 93.3%
51-78	4/59 91.7%	11/59 80.0%	6/58 86.7%	11/57 76.7%	9/57 80.0%	3/57 90.0%	6/59 88.3%	6/55 81.7%	6/56 83.3%
79-91	3/55 86.7%	5/48 71.7%	9/52 71.7%	7/46 65.0%	5/48 71.7%	9/54 75.0%	7/52 76.7%	3/49 76.7%	11/50 65.0%
91-103	12/52 66.7%	10/43 55.0%	12/43 51.7%	8/39 51.7%	9/43 56.7%	11/45 56.7%	7/36 65.0%	5/46 68.3%	7/39 53.3%
Terminal 104	40	33	31	31	34	34	39	41	32

<sup>1</sup> number deaths / number at risk<sup>2</sup> per cent survival to end of period.**Table 15. Summary of Female Mice Survival (dose/kg/day)**

Period (Weeks)	Cntrl1	Cntrl2	CIBP3	CIBP4	CIBP5	BP6	BP7	C18	C19
0-50	4/60 <sup>1</sup> 92.3% <sup>2</sup>	2/60 96.7%	5/60 91.7%	1/60 98.3%	1/60 96.7%	7/60 88.3%	2/60 96.7%	6/60 90.0%	4/60 93.3%
51-78	12/56 73.3%	13/58 75.0%	3/55 86.7%	7/59 86.7%	8/59 85.0%	12/53 68.3%	8/58 83.3%	10/54 73.3%	16/56 66.7%
79-91	5/44 65.0%	8/45 61.7%	12/52 66.7%	10/52 70.0%	15/51 60.0%	8/41 55.0%	8/50 70.0%	7/44 61.7%	6/40 56.7%
92-102	12/39 45.0%	16/37 35.0%	16/40 40.0%	16/42 43.3%	7/36 48.3%	12/33 35.0%	15/42 45.0%	7/37 50.0%	6/34 46.7%
Terminal 103	27	21	24	26	29	21	27	30	28

<sup>1</sup> number deaths / number at risk<sup>2</sup> per cent survival to end of period.

Among the eight treatment groups in both mouse genders there was no strong evidence of heterogeneity in survival (all four p-values  $\geq 0.4693$ ). Results are similar in the treatment subgroups: in subgroup with both clindamycin and benzoyl peroxide increasing proportionally (all four p-values  $\geq 0.4221$ ), in the clindamycin only group (all four p-values  $\geq 0.1376$ ), and finally, in the benzoyl peroxide only group (all four p-values  $\geq 0.2823$ ). From these results and from the incidence tables (tables 14, and 15 above) or the Kaplan-Meier survival curves in Appendix 1, there seems to be no strong differences in survival, with intertwining of the survival curves.

b(4)

**Table 16. Statistical Significances of Tests of Homogeneity and Trend in Survival in Mice**

	Males		Females	
	LR/Wald	Wilcoxon	LR/Wald	Wilcoxon
Homogeneity over all 8 groups	0.5059	0.5474	0.6586	0.4693
Homogeneity over Cntrl1&2, BPC13-5	0.4966	0.4221	0.7830	0.6817
Trend over 4 groups Cntrl1&2, BPC13-5	0.6445		0.3918	
Departure from trend	0.3359		0.8544	
Homogeneity over Cntrl 1+2, BP6,BP7	0.6394	0.6515	0.2506	0.1376
Trend over 3 groups Cntrl 1+2, BP6,BP7	0.6110		0.3514	
Departure from trend	0.4232		0.1666	
Homogeneity over Cntrl 1+2, C18, C19	0.2823	0.3249	0.6471	0.7805
Trend over 3 groups Cntrl 1+2, C18, C19	0.2312		0.7702	
Departure from trend	0.3140		0.3785	

**Tumorigenicity analysis:**

Table 17 below shows the significant comparisons using the Haseman-Lin-Rahman rules. Note the tables are complicated, with interpretation as described in the executive summary, the rat study in 3.2.1.2, and in Appendix 2. In male mice the paired comparison of the high dose in the benzoyl peroxide alone group (i.e., BP7) to the pooled controls in liver hepatocellular adenoma was statistically significant (i.e.,  $p = 0.008 < 0.01$  for a common tumor). In female mice the paired comparison of the low dose of the both benzoyl peroxide and clindamycin (i.e. CIBP3) in focal hyperplasia of the pituitary was statistically significant (i.e.,  $p = 0.048 < 0.05$  for a rare tumor), as was the similar comparison of the low dose the both benzoyl peroxide and clindamycin in polyps of the uterus (i.e.,  $p = 0.005$  for a common tumor). Also in female mice the paired comparison between middle dose of the both benzoyl peroxide and clindamycin (i.e., CIBP4) and the pooled controls in terms of stromal sarcoma of the uterus was also exactly statistically significant (i.e.,  $p = 0.010$  for a common tumor). Note however, again, due to the large number of tests these are almost surely anticonservative, that is, the true overall error is likely to be considerably higher than the nominal roughly 10%.

**Table 17. Multiplicity Adjusted Statistically Significant Results in Mice**

Organ/tumor	Incidence/p-values																		
	Ctrl1	Ctrl2	C1BP3	C1BP4	C1BP5	BP6	BP7	C18	C19	pboth	pCvs3	pCvs4	pCvs5	pBP	pCvs6	pCvs7	pC1	pCvs8	pCvs9
<b>Male Mice</b>																			
<b>LIVER</b>																			
Hepatocellular Adenoma	12	6	11	11	10	15	19	9	6										
	.460	.342	.259	.453	.010	.069	.008	.225	.529	.301									
<b>Female Mice</b>																			
<b>PITUITARY GLAND</b>																			
Focal Hyperplasia	0	1	4	2	1	0	1	2	0										
	.447	.048	.288	.567	.471	.691	.580	.424	.261	.680									
<b>UTERUS</b>																			
Polyp	5	7	0	6	4	7	5	3	5										
	.436	.005	.539	.310	.282	.374	.401	.504	.182	.532									
Stromal Sarcoma	1	1	3	7	1	2	5	0	0										
	.259	.221	.010	.736	.032	.360	.053	.257	.443	.464									

**4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS**

NA

**5. SUMMARY AND CONCLUSIONS**

**5.1. Statistical Issues and Collective Evidence**

Please see Section 1.3 above.

**5.2. Conclusions and Recommendations**

Please see section 1.1 above.