CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-030

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	22-030
Drug Name:	Toviaz™ (Fesoterodine Fumarate)
Indication(s):	Treatment of Overactive Bladder.
Applicant:	Pfizer Global Pharmaceuticals.
Date (s):	Submitted: 5/02/2008
	PDUFA: 11/2/2008
Review Priority:	Standard
Biometrics Division:	Division of Biometrics III (HFD-725)
Statistical Reviewer:	Mahboob Sobhan, Ph.D. (HFD-725)
Medical Division:	Division of Reproductive and Urological Drug Products (HFD-580)
Clinical Team:	Mark Hirsch, M.D. (HFD-580)
	Harry Handlesman, M.D. (HFD-580)
Project Manager:	Ceilia Peacock (HFD-580)
Keywords:	NDA review, Clinical studies.

NDA 20-030: Toviaz®

Statistical Reviewer's comment

This submission pertains to revised labeling, in most part, the clinical pharmacology and adverse reactions section of the label. There was no new efficacy data submitted for our statistical review. We agreed with the revised efficacy results in the clinical trial section. From a statistical perspective, there are no further efficacy comments pertaining to this submission.

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Mahboob Sobhan
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BIOMETRICS

STATISTICAL EVALUATION OF NEW NDAs - FILEABILITY

NDA:	22-030
Drug Name:	Fesoterodine
Sponsor:	Schwarz Pharma.
Indications:	Treatment of overactive bladder.
Medical Officer:	Suresh Kaul, M.D., HFD-580
Statistician:	Mahboob Sobhan, Ph.D., HFD-715
Project Manager:	Jean Makie
Submission Date:	3/17/2006
45 day Meeting Date:	5/10/2006

Two P3 controlled studies constitutes the main database to support the above indication. In addition, efficacy data from three ongoing open-label studies wee also submitted. The summary of the two P3 studies are as follows:

Brief Summary of Controlled Trials

Study	Site(s)	No. of Patients Randomized/ Treatments	Duration of Treatment	Endpoints (P-value*)
SP583	Europe, Australia, New Zealand, South Africa	Total: 1135 Placebo: 285 Feso 4mg: 272 Feso 8mg: 288 Tolt 4mg: 290	12 weeks	Co-primary: • Change in micturitions • Change in incontinence episodes Secondary • Change in urge incontinence • Volume voided • Health outcomes
S584	USA	Total: 836 Placebo: 274 Feso 4mg: 283 Feso 8mg: 279	12 weeks	Co-primary • Change in micturitions • Change in incontinence episodes Secondary • Change in urge incontinence • Volume voided • Health outcomes

The following items were checked to determine the fileability conclusion.

Items:	Check (Yes, No, N/A)	Comments:
Index sufficient to locate reports, tables, etc.	Yes	
Original protocols and subsequent amendments included in the submission.	Yes	
Designs utilized appropriate for the indications requested.	Yes	
Endpoints and methods of analyses spelled out in the protocols.	Yes	
Interim analyses (if present) planned in the protocol and appropriate adjustments in significance level made	No	Not planned
Appropriate references included for novel statistical methodology (if present)	yes	
Sufficient data listings and intermediate analysis tables to permit a statistical review	Yes	
Data from primary studies on diskettes and/or eCTD submitted	yes	eCTD
Effects of dropouts on primary analyses investigated.	yes	
Integrated summary of safety and efficacy included.	Yes	Safety only

Conclusion

After the preliminary review of the submission, we have not identified any deficiencies that would be a reason for refuse-to-file. The sponsor provided the required information in this NDA to perform statistical evaluation and therefore, this NDA is fileable.

Mahboob Sobhan, Ph.D.
Mathematical Statistician
Division of Biometrics 3, HFD-725

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/s/

Mahboob Sobhan
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BIOMETRICS

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
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Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	22-030
Drug Name:	[redacted] (Fesoterodine Fumarate) b(4)
Indication(s):	Treatment of Overactive Bladder.
Applicant:	Schwarz Pharma.
Date (s):	Submitted: 3/17/2006
	PDUFA: 1/27/2007
Review Priority:	Standard
Biometrics Division:	Division of Biometrics III (HFD-725)
Statistical Reviewer:	Mahboob Sobhan, Ph.D. (HFD-725)
Concurring Reviewer:	Lisa Kammerman, Ph.D. (HFD-725)
Medical Division:	Division of Reproductive and Urological Drug Products (HFD-580)
Clinical Team:	Mark Hirsch, M.D. (HFD-580)
	Suresh Kaul, M.D. (HFD-580)
Project Manager:	Jean Makie (HFD-580)
Keywords:	NDA review, Clinical studies, ANCOVA, Multiple comparisons/Multiplicities, Hierarchical Closed-testing Procedure.

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b(4)

1.0 EXECUTIVE SUMMARY

1.1 Conclusion and Recommendations

Based on the efficacy data submitted from two Phase 3 studies, our analysis showed that at week 12, compared with placebo, both doses (4 and 8mg) of ——— significantly ($p<.05$) reduced the average number of micturitions and number of urge incontinence episodes. ——— 8mg was also statistically significant in the reduction of endpoints as early as week 2, b(4)

From a statistical perspective, this application provided adequate data to support the efficacy of ——— 8mg ——— and 4mg at week 12 in the treatment of overactive bladder symptoms. b(4)

1.2 Brief Overview of Clinical Studies

The applicant, Schwarz BioSciences, GmbH, reports efficacy and safety data from two Phase 3 clinical trials (studies SP583 and SP584) to support sustained-release ——— in the treatment of overactive bladder symptoms (OAB). Study SP583 was conducted at 150 sites in Europe, South Africa, Australia and New Zealand while study SP584 was conducted at 50 sites in the United States. Both studies were parallel-group, randomized, double-blind, double-dummy, placebo-controlled studies, except for the inclusion of an additional active-controlled arm in study SP583. Subjects with signs and symptoms of OAB syndrome and with urinary urgency, but with or without incontinence for at least 6 months prior to enrollment, were randomized to receive either ——— 4mg, ——— 8 mg/day, tolterodine 4mg/day (study SP583 only), or placebo during the 12-week treatment period. b(4)

The protocol-specified primary efficacy endpoints included two co-primary endpoints: change in the average number of micturitions and urge incontinence episodes per 24 hours from baseline to week 12 of the treatment period. Both the outcomes were measured by a daily diary, where subjects recorded at least 3 consecutive days of number of micturitions, urge incontinence episodes, and the number of voidings per week during the course of the trial. The secondary efficacy endpoints were the change from baseline in the number of voidings, a responder analysis using a treatment benefit scale, change in the average number of micturitions during the day and sleeping time, change in severity of urinary urgency, and change in number of incontinent days.

The objective in both the studies was to demonstrate that sustained-release ——— 4 and 8mg/day is superior to placebo with respect to the two co-primary endpoints. Both studies were designed to detect a difference of ≥ 0.72/day in the mean change in micturitions and ≥ 0.57/day in the mean change in urge incontinence. A sample size of 270 per arm (adjusting for drop outs), for a total of 1080 in study SP583 and 810 in study SP584 was determined to be adequate to test the superiority hypothesis with 90% power. At the completion of the trial, a total of 1135 subjects were treated in study SP583 and 836 were treated in study SP584, respectively. b(4)

1.3 Statistical Issues and Principal Findings

Our review focused on several statistical issues: the impact of missing post-baseline diary data, adjustment for multiple comparisons (pair-wise comparison of each dose group versus placebo), multiplicity (multiple endpoints), and adequacy of study power with regards to all primary endpoints. Missing diaries were reported in less than 7% of the subjects (ranging from 3% to 7% across treatment groups) and did not appear to follow any missing pattern, i.e., missing either due to adverse events or lack of efficacy. The efficacy results using last-observation-carried-forward approach (LOCF) and per protocol (completers at endpoint) analysis population were similar. The sponsor's closed-testing procedure to control the false positive error rate for multiple comparison/multiplicity (co-primary endpoints) was acceptable. However, no such procedure was planned for evaluating efficacy at different time points (weeks) and for the secondary endpoints. Although, as per protocol we agreed that a closed-testing procedure is an appropriate method, alternative methods could be more intuitive and simpler to use. Under such an alternative method, there would be no need to order the sequence of family of hypotheses, which in some cases may not be appropriate from a clinical perspective, because efficacy must be demonstrated on both endpoints. Therefore, for exploratory and consistency purposes, we performed an alternative simple adjustment for multiple comparisons using Dunnett's test to test for each endpoint separately.

Based on the applicant's data and our independent analysis, the efficacy results could be summarized as follows:

(1) At week 12, compared with placebo, both doses of [redacted] (4 and 8mg) treatment resulted in a reduction in both the co-primary endpoints: the change in the average number of micturitions and the average number of urge incontinence episodes. Our analysis showed that both doses were statistically significantly superior to placebo ($p<.05$, adjusting for multiple dose/multiple endpoints). b(4)

(2) At week 12, compared with placebo, [redacted] 4 and 8mg were also significantly superior to placebo in the improvement of the secondary endpoint: the voided volume per micturitions in study SP583, but not in study SP584, where the 4mg dose was not statistically significantly superior to placebo ($p<.05$, adjusting for multiple dose/multiple endpoints). b(4)

(3) At week 2, compared with placebo, [redacted] 8mg was also effective in reducing [redacted] incontinence episodes in both studies. [redacted] 4mg dose of [redacted] was effective only in reducing the incontinence episodes ($p<.01$) [redacted] b(4)

NDA 20-030: ®

b(4)

2.0 INTRODUCTION

2.1 Overview

The applicant, Schwarz Pharma, is seeking approval of —, sustained-release (SR), for the treatment of overactive bladder syndrome (OAB). — has been developed as once-daily formulation with dosage strength of 4mg and 8mg. b(4)

To support the safety and efficacy of —, clinical data from two Phase 3 pivotal studies were submitted. In addition, safety data from open-label extension studies and a QT study were also submitted to rule out any abnormal QT prolongation or other cardiac abnormality post-dose. This review will focus on the efficacy data from the two Phase 3 trials listed in Table 2.1 below. b(4)

Table 2.1 Summary of Pivotal Studies

Study#	Study Site (number)	Study Design	Number Randomized /Study Regimen	Duration of Treatment
SP583	Europe, Australia, New Zealand, South Africa (150)	Multi-center, double-blind, placebo and active-controlled, Phase 3.	Total Randomized: 1135 Placebo: 285 —: 4mg: 272 —: 8mg: 288 Tolterodine 4mg: 290	12 weeks
SP584	US (83)	Multi-center, double-blind, placebo-controlled, Phase 3.	Total Randomized: 836 Placebo: 274 —: 4mg: 283 —: 8mg: 279	12 weeks

b(4)

2.2 Data Sources

The submission was in hard copy and partially electronic. Submitted data were stored in folder \\Cdsesub1\n22030\N_000\2006-03-17\crt\datasets in FDA's Electronic Document Room (EDR). The data quality of the submission was within acceptable limits.

2.3 Indication

— *fumarate is indicated for the treatment of overactive bladder symptoms with urge urinary incontinence, urgency, and urinary frequency.* b(4)

3.0 STATISTICAL EVALUATION

3.1 Overview of Study SP583 and Study SP584

3.1.1 Design and Objectives

Studies SP583 and SP584 were identical in design except that study SP583 included one additional active-controlled arm and was conducted using a separate protocol in several countries, while study SP584 was conducted at US sites. The methodologies used in both trials were the same; therefore, the study descriptions are applicable to both studies, unless otherwise indicated:

Design: Both studies SP583 and SP584 were multi-center, randomized, and placebo-controlled, and were conducted at 150 sites across Europe, South Africa, Australia and New Zealand, while study SP584 was conducted at 83 sites in the United States. In addition to a placebo treatment arm, study SP583 contained an active control treatment arm (tolterodine SR 4mg/day). The objectives of both studies were to evaluate the efficacy, tolerability and safety of [redacted] as compared to placebo in subjects with OAB. b(4)

Following enrollment and a two week placebo run-in, subjects with a known history of OAB symptoms with at least 8 micturitions per 24 hours for at least 6 months were randomized to one of the following treatment groups: [redacted], 4mg/day, [redacted], 8mg/day, tolterodine SR 4mg/day (study SP583) or placebo. b(4)

The planned duration of the trial was approximately 16 weeks: 2 weeks of run-in, 12 weeks of treatment, and 2 weeks of safety follow-up. Treatment compliance was assessed by instructing subjects to return all unused medication and micturition diaries at each applicable trial visit. For subjects taking less than 75% or more than 125% of the given dosage, a decision was to be made as to whether the subject should continue or withdraw from the study.

Primary Efficacy Endpoints: As per protocol, the following endpoints were considered co-primary:

1) Change in the average number of micturitions (frequency) per 24 hours (from baseline to week 12 of treatment period).

Number of micturitions was defined as the number of times a subject passed urine per day (not including incontinence episodes). Subjects were to record the number of micturitions using a diary for 3 consecutive days during the week immediately prior to scheduled visits. A time had to be recorded in the diary for the data to be included.

2) Change in average number of urge incontinence episodes per 24 hours.

Urge incontinence episode was defined as the complaint of a sudden compelling desire to pass urine,

a desire which is difficult to defer.

Secondary Efficacy Endpoints: The following endpoints were considered secondary in this study:

1) Change in average voided volume per micturition measured using the urine cup provided during 1 day collection period.
2) Treatment response (yes/no), derived from a 4-grade treatment benefit scale assessing subject condition: 1= greatly improved, 2=improved, 3=not changed, and 4=worsened. Treatment response was dichotomized as yes for category 1 and 2, no otherwise.
3) Change in number of micturitions during daytime.
4) Change in number of micturitions during sleeping time.
5) Change in number of urgency episodes per 24 hours defined as number of times a subject recorded an urgency episode with or without incontinence per day within the 3-day collection period.
6) Change in severity of urinary urgency based on 4-grade scale: 1=none, 2=mild, 3=moderate, and 4=severe, and
7) Change in health outcome parameters based on King's Health Questionnaire.

Determination of Sample Size: The sample size was calculated to test the superiority hypothesis for both co-primary endpoints. Using a clinically meaningful difference of ≥0.72 in daily number of micturitions between [redacted] and placebo with a mean square error of approximately 2.5 (based on Phase 2 study SP582), the protocol called for a planned sample size of 249 per group, to test the null hypothesis of no difference assuming a type-I error (2-sided) of 5% and a power of 90%. For the change in urge incontinence, at least 205 per arm subjects would be needed to detect a difference of equal or greater than 0.57 per 24 hours with 80% power at the type-I error of 5%.

Definition of Analysis Sets (Population): For efficacy analysis, two analysis sets were used: Full Analysis Set (FAS), and Per Protocol Set (PPS). FAS included subjects who were randomized using intent-to-treat principle, i.e., all subjects randomized regardless of actual treatment received. Subjects who did not obtain any dose of the medication or who did not have micturition measurements at baseline or under double-blind treatment period, were excluded from the FAS. PPS excluded subjects with major protocol violations and/or with duration of double-blind treatment shorter than 2 weeks.

Handling of Missing Data: Missing diary data on micturitions and urge incontinent episodes from the double-blind period of the treatment were imputed by LOCF method from the last available post-baseline diary data. For the missing treatment response variable, in addition to LOCF, a 'non-response' was set to subjects without post-baseline measurement data.

Pooling of Sites: Because of the small numbers of subjects per site, sites were pooled within each country and incorporated into statistical analyses to adjust for site variability by treatment.

Statistical Methods: For comparison of treatment groups with respect to both co-primary endpoints, the statistical methods included ANOVA models including country, treatment, and baseline by treatment interactions as factors. Pair-wise comparisons were reported as least square

(LS) means. To examine the robustness of the results, non-parametric analyses were also performed.

Multiple Comparisons/Multiplicities: To preserve the false positive error (alpha) rate for co-primary endpoints at multiple doses, the protocol-specified plan was to use a closed-testing procedure in a hierarchical sequentially rejective manner. In this method, the plan was to test for statistical significance at 0.05 (two-sided) for the comparison of mean change in micturitions between 8mg and placebo first, and if the p-value for this test was <.05, then the test would proceed for the next lower dose, i.e., testing fo 4mg and placebo comparison in the second step and so on for testing change in urge incontinence. If the test result was not statistically significant at any step, then all remaining tests would be considered statistically non-significant. b(4)

3.1.2 Reviewer's Comments on the Design

The sample size was adequate for testing the superiority hypothesis for both co-primary endpoints in both studies. The closed-testing procedure to preserve the false positive error was also acceptable, but it was not clearly indicated in the protocol why the test for micturitions would be conducted first, when the Division requires both primary endpoints for approval. Therefore, must demonstrate reduction in both primary endpoints compared to placebo. The use of a hierarchical closed-testing procedure was appropriate for controlling type-I error rate with regards to co-primary endpoints. However, no such plan was in the protocol for testing secondary endpoints or even to test for the co-primary endpoints at different weeks. In this review, we will use other methods while evaluating the secondary endpoints. b(4)

3.2 Results: Study SP583

3.2.1 Subject Disposition

At 150 sites, a total of 1135 subjects were randomized approximately equally to the treatment groups as shown in Table 3.2.1. Subject enrollment was similar across sites. No single site was predominant in terms of subject enrollment. For analysis, sites were clustered together by country. A total of 147 (13%) subjects discontinued the study prematurely. The major reasons for discontinuation were adverse event (3%) and withdrawal of consent (3.5%), followed by protocol deviation 2%. The discontinuation rates were similar across treatment groups, and did not appear to impact the efficacy results. The full analysis (ITT-LOCF) population of 1103 subjects is well over the required 1070 subjects, while the per protocol analysis (completers at endpoint) population of 1027 is also in the acceptable range.

Table 3.2.1 Disposition of Subjects: Study SP583						b(4)
Subjects	Treatment groups					
	Placebo	~~~4mg	~~~8mg	Tolt 4mg	Total	
Total Randomized	285	272	288	290	1135	
Completed study						
Discontinued (%):	33(12)	41(15)	36(13)	37(13)	147(13)	
Adverse Event	6 (2)	9 (3)	14 (5)	10 (3)	39 (3)	
Lack of Efficacy	1 (<1)	2 (1)	2 (1)	3 (1)	8 (<1)	
Withdrawn Consent	12 (4)	9 (3)	9 (3)	10 (3)	40 (3.5)	
Protocol deviation	6 (2)	9 (3)	4(1)	5 (2)	24 (2)	
Compliance	0	2 (1)	3 (1)	1 (<1)	6 (<1)	
Lost to follow-up	2 (1)	1 (<1)	0	4 (1)	7 (<1)	
Other Reasons	6 (2)	9 (3)	4 (1)	4 (1)	23 (2)	
Full Analysis population (ITT-LOCF)	279	265	276	283	1103	
Per Protocol Population	262	246	253	266	1027	

* ITT population included all randomized subjects who received treatments and had diary response for at least 3 consecutive days.

3.2.2 Patient demographics and baseline characteristics

The baseline characteristics such as age, race, gender, body mass index were similar across treatment groups. Concomitant medication use and prior drug treatment for OAB were also similar between treatment groups.

3.2.3 Primary Efficacy

Two endpoints were considered primary in this study: the change in micturitions and change in urge incontinence episodes per 24 hours from baseline to week 12. As per protocol, a hierarchical closed-testing procedure was used to control false positive error rate (type-I) for multiplicity. To use this method, a family of hypotheses with respect to multiple endpoints and doses are hierarchically ordered and the hypotheses are tested in a sequence. In this protocol, the sponsor ordered the sequence starting with the micturition hypothesis at the highest dose of ~~~ followed by lower dose and so on for the urge incontinence hypotheses. For the secondary endpoints, no testing was planned in a hierarchical order. Therefore, we used Dunnett's test to adjust for multiple dose comparisons. b(4)

To evaluate the treatment difference between ~~~ doses and placebo, we also performed a statistical analysis similar to the sponsor's analysis using a analysis of covariance (ANCOVA) model b(4)

with factors for baseline, treatment, country (sites pooled by country), and baseline by treatment interactions. We do not disagree with the sponsor's approach, but need to look at other methods for consistency of the results, although it is highly unlikely to differ in conclusions. Our analysis was also based on the ITT population using last observation carried forward (LOCF) for missing post baseline data. We used LOCF because the percentages of subjects with post baseline missing diary ranged from 3%-7%. It was similar across treatment groups and did not appear to follow any systematic pattern that could either be considered as missing not at random or otherwise.

Change in micturitions: Results of our analyses are shown in Table 3.2.3. At week 12, the average reductions from baseline in micturitions were -1.9 and -2.0, for —— (4mg and 8mg) doses, compared with -1.1 for placebo. The reductions for both doses o —— were statistically significant ($p<.05$, after adjusting for multiple comparisons) compared to placebo. However, there were no statistically significant differences between the ——doses and both doses appeared equally effective in improving micturitions per 24 hours.

Change in Urge Incontinence: Similar effects were also noted for average reductions in urge incontinence at week 12 of -1.94 and -2.2 for ——, doses, compared with -1.14 for placebo. The reductions were again statistically significantly different from placebo after adjusting for multiple comparisons.

Results using from the completers (not shown here), similar to the sponsor's definition of per protocol set, were similar to ITT using the LOCF analysis population. Both analysis population sets showed consistent efficacy results with respect to both endpoints in support of —— compared to placebo.

Table 3.2.3
Change⁺ from Baseline to Week 12 in the Mean Number of Micturitions and Urge Incontinence Episodes per 24 hours: ITT-LOCF Population, Study SP583

	Treatment groups (N)	Baseline Mean	Change (LS Mean)	Treatment Difference	P-value⁺⁺ (unadjusted)
Number of Micturitions per 24 hours	Placebo (279)	11.96	-1.08	--	
	——4mg (265)	11.56	-1.90	-0.82	<.05
	—— 8mg (276)	11.90	-1.99	-0.91	<.05
	Tolt 4mg (283)	11.49	-1.87	-0.79	<.05
Urge Incontinence	Placebo (211)	3.67	-1.14	--	--
	——4mg (199)	3.83	-1.94	-0.80	<.05
	—— 8mg (223)	3.68	-2.22	-1.08	<.05
	Tolt 4mg (223)	3.81	-1.74	-0.60	<.05

⁺ Change from baseline based on LS mean difference from ANCOVA model with factors for baseline values, treatment, country, and baseline by treatment interaction.
⁺⁺Unadjusted

3.2.4 Secondary Efficacy

Several outcomes, as noted in section 3.1.1, were considered secondary in this study. Among them, the clinical team considered the changes in voided volume per mictutritions as one of the important secondary endpoints and, therefore, we have performed an analysis of voided volume using the same ANOVA models. The results of our analysis are shown in Table 3.2.4. Relative to placebo, [redacted] (4mg and 8mg) improved the mean voided volume per micturition from baseline to endpoint by 27mL and 33 mL, respectively. The improvements for both doses were statistically significant compared to placebo. b(4)

Table 3.2.4
Change+ from Baseline to Week 12 in the Mean Volume Voided:
ITT-LOCF Population, Study SP583

	Treatment Groups (N)	Baseline Mean	Change (LS Mean)	Treatment Difference	P-value++
Voided Volume per micturition	Placebo (278)	150.0	9.0	--	--
	[redacted] 4mg (265)	160.0	27.0	18.0	<.001
	[redacted] 8mg (275)	154.0	33.0	24.0	<.001
	Tolt 4mg (282)	154.0	24.0	15.0	<.02

+ Change from baseline based on LS mean difference from ANCOVA model with factors for treatment and site.
++P-values, adjusted for multiple comparisons with placebo by Dunnett's Test.

b(4)

3.2.5 Efficacy at Week 2

At week 2, [redacted] both doses of [redacted] did reduce the average [redacted] urge incontinence, [redacted] b(4)

3.2.6 Adjustment for Multiple Comparisons/Multiplicities

As mentioned in previous sections, a hierarchical closed-testing procedure was used to control the false positive error rate (type-I) for multiple doses and multiple endpoints. To use this method, a family of hypotheses with respect to multiple endpoints and doses are hierarchically ordered and the hypotheses are tested in a sequence. In this method, the plan was to test for statistical significance at 0.05 (two-sided) for the comparison of mean change in micturitions between [redacted] 8mg and placebo first, and if the p-value for this test was <.05, then the test would proceed for the next lower dose, i.e., testing for [redacted] 4mg and placebo comparison in the second step and so on for testing change in urge incontinence. If the test result was not statistically significant at any step, then all remaining tests would be considered statistically non-significant. Table 3.2.6 shows the ordering of the hypotheses and the significance level at each step of the test. At each step, the p-value for the b(4)

treatment difference was less than the pre-specified two-sided p-value of 0.05, meaning after adjusting for both multiple dose and co-primary endpoints, ——treatment improved in the number of micturitions and urge incontinence episodes in a statistically significant manner compared to placebo. b(4)

For consistency purpose, we also performed an alternative adjustment for multiple comparisons for doses by Dunnett's test for each co-primary endpoint separately, because we thought efficacy must be demonstrated for both co-primary endpoints without a need for ordering the hypotheses. The results and the conclusions by both adjustment methods remained the same.

Table 3.2.6
Statistical Significance of Primary Efficacy Endpoints (Week 12) with adjustment for Multiple Comparisons/Multiplicities: Study SP583

Sponsor's adjustment using Closed-Testing Procedure		Adjustment using Dunnett's Test		
Testing Steps	Nominal P-value (unadjusted)	Endpoints	Comparison	P-value++
Step 1: Number of Micturitions (——, 8mg vs placebo)	<.001	Micturitions	——, 4mg vs placebo	<.05
			——, 8mg vs placebo	<.05
Step 2: Number of Micturitions (——, 4mg vs placebo)	<.001		Tolt vs placebo	<.05
		Urge Incontinence	——, 4mg vs placebo	<.05
Step 3: Number of Urge Incontin (——, 8mg vs placebo)	<.001		——, 8mg vs placebo	<.05
			Tolt vs placebo	<.05
Step 4: Number of Urge Incontin (——, 4mg vs placebo)	<.01			

b(4)

+ Change from baseline based on LS mean difference from ANCOVA model with factors for baseline values, treatment, country, and baseline by treatment interaction.
++P-value, adjusted for pair wise comparisons by Dunnett's test.

3.2.7 Reviewer's Comment on the Efficacy Results

Results of our independent analysis showed that compared to placebo, —— (4 and 8mg) treatment resulted in a reduction in the average number of micturitions and urge incontinence episodes at week 12. These differences from placebo were statistically significant (adjusting for type-I error rate). ——

—— (4 and 8mg) was also efficacious with respect to the important secondary endpoint: the voided volume per micturition.

b(4)

b(4)

3.3 Results: Study SP584

3.3.1 Subject Disposition

A total of 836 subjects were randomized approximately equally to the treatment groups as shown in Table 3.3.1. Subject enrollment was similar across sites. No single site was predominant in terms of subject enrollment. For analysis, sites were clustered together by country. A total of 155 (18%) subjects discontinued the study prematurely. The major reasons for discontinuation were adverse event (7%) and withdrawal of consent (4%), followed by protocol deviation (2%). The discontinuation rates were similar across treatment groups, and did not appear to impact the efficacy results. The full analysis (ITT-LOCF) population of 800 subjects is well over the required 750 subjects, while the per protocol analysis (completers at endpoint) population of 709 is also in the acceptable range of required sample size for this study.

Table 3.3.1 Disposition of Subjects: Study SP584

Subjects	Treatment groups			
	Placebo	4mg	8mg	Total
Total Randomized	274	283	279	836
Discontinued (%):	41(15)	58(21)	56(20)	155(18)
Adverse Event	13(5)	18 (6)	27 (10)	58 (7)
Lack of Efficacy	4 (2)	2 (1)	2 (1)	8 (1)
Withdrawn Consent	8 (3)	10 (4)	13 (5)	31(4)
Protocol deviation	4 (2)	6 (2)	3 (1)	13 (<2)
Lack of Compliance	0	5 (2)	2 (1)	7 (1)
Lost to follow-up	4 (2)	10(4)	3 (1)	17 (2)
Other Reasons	8 (3)	7 (3)	6 (2)	21 (2)
Full Analysis population (ITT-LOCF)	266 (97)	267 (94)	267 (96)	800 (96)
Per Protocol Population	241 (88)	230 (81)	238 (85)	709 (85)

* ITT population included all randomized subjects who received treatments and had diary response for at least 3 consecutive days.

(b)(4)

3.3.2 Patient demographics and baseline characteristics

The baseline characteristics such as age, race, gender, and body mass index were similar across treatment groups. Concomitant medication use and prior drug treatment for OAB were also similar between treatment groups.

3.3.3 Primary Efficacy

b(4)

Change in micturitions: At week 12, the average reductions from baseline in micturitions were -1.62 and -2.1 (Table 3.3.3) for the (4 and 8mg) doses and -1.09 for placebo. The reductions for both doses of were statistically significant ($p<.05$) compared to placebo.

Change in Urge Incontinence: A similar reductions in urge incontinence at week 12 of -1.6 and -2.2 were noted for the doses and 1.05 for placebo. The average reductions were again statistically significantly different from placebo after adjusting for multiplicity by a closed-testing method.

b(4)

Table 3.3.3
Change+ from Baseline to Week 12 in the Mean Number of Micturitions and Urge Incontinence Episodes per 24 hours: ITT-LOCF Population, Study SP584

	Treatment groups (N)	Baseline Mean	Endpoint LS Mean	Treatment Difference	P-value++ (unadjusted)
Number of micturitions	Placebo (266)	12.2	-1.09	--	--
	4mg (267)	12.8	-1.62	-0.53	0.032
	8mg (267)	12.0	-2.10	-1.00	<.05
Urge Incontinence	Placebo (205)	3.6	-0.83	--	--
	4mg (228)	3.9	-1.60	-0.77	<.05
	8mg (218)	3.8	-2.21	-1.38	<.05

+ Change from baseline based on LS mean difference from ANCOVA model with factors for baseline values, treatment, and baseline by treatment interaction.
++Unadjusted P-values for pair-wise comparisons with placebo.

b(4)

3.3.4 Secondary Efficacy

As per the clinical team, voided volume is considered the most important secondary endpoint of all the secondary endpoints considered by the sponsor. We performed an analysis on this secondary endpoint only and the results are shown in Table 3.3.4. In this study, only 8mg dose of showed statistically significant ($p<.05$) improvement in the voided volume compared to placebo.

b(4)

Table 3.3.4
Change from Baseline to Week 12 in the Mean Voided Volume per Micturition: ITT-LOCF Population, Study SP584

	Treatment groups (N)	Baseline Mean	Change (LS Mean)	Treatment Difference	P-value+
Voided Volume per micturition	Placebo (260)	159.4	8.7	--	--
	4mg (266)	152.0	16.0	7.3	0.24
	8mg (265)	156.0	33.0	24.3	<.05

+ Adjusted for multiple comparisons by Dunnett's test.

b(4)

3.3.5 Efficacy at Week 2

In study SP584, b(4)
However, the 4mg dose was significantly better than placebo with respect to incontinence the 8mg dose was significantly better for the secondary endpoint at week 2.

3.3.6 Adjustment for Multiple Comparisons/Multiplicities

Adjusting for type-I error rate by the hierarchical closed-testing procedure, both doses of b(4)
were statistically significantly superior to placebo with respect to both co-primary endpoints. Adjusting the p-values by Dunnett's test for pair-wise comparisons, the p-value for the 4mg dose was marginally significant (p=.0591).

Table 3.3.6
Statistical Significance of Primary Efficacy Endpoints (Week 12) with adjustment for Multiple comparisons between Sponsor and our Analysis: Study SP584

Sponsor's adjustment using Closed-Testing Procedure		Adjustment using Dunnett's Test		
Testing Steps	**P-value**	Endpoints	Comparison	P-value++
Step 1: Number of Micturitions (8mg vs placebo)	0.032	Micturitions	4mg vs plbo 8mg vs plbo	.0591 <.05
Step 2: Number of Micturitions (4mg vs placebo)	<.05	Urge Incontinence	4mg vs plbo 8mg vs plbo	<.05 <.05
Step 3: Number of Urge Incontin (8mg vs placebo)	<.05			
Step 4:Number of Urge Incontin (4mg vs placebo)	<.05			

+ Change from baseline based on LS mean difference from ANCOVA model with factors for baseline values, treatment, country, and baseline by treatment interaction.
++P-value for adjusted for pair wise comparisons by Dunnett's test.

b(4)

3.3.7 Reviewer's Comments on the Efficacy Results

In this study, the results of our independent analysis confirmed that compared with placebo, (4mg and 8mg) treatment resulted in statistically significant reductions in the average number of micturitions and urge

b(4)

incontinence at endpoint (week 12, adjusting for type-I error rate). The higher dose (8mg) was significantly superior to placebo as early as early as week 2 with respect to endpoints.

4.0 SUMMARY AND CONCLUSIONS

We have reviewed efficacy data from two Phase 3 studies (SP583 and SP584) in support of sustained-release (4 and 8mg/day) in the treatment of overactive bladder symptoms. Both studies SP583 and SP584 were similar in design: randomized, placebo-controlled, parallel-group, except that in study SP583 one additional active-controlled arm was included. Study SP583 was conducted in different countries (Europe, South Africa, Australia and New Zealand), while study SP584 was conducted in the United States. b(4)

In study SP583, a total of 1135 subjects were randomized to the following 4 treatment groups: 4mg (272), 8mg (288), tolterodine 4mg (290), and placebo (285). In study SP584, a total 836 subjects were randomized to the following 3 treatment groups 4mg (283), 8mg (279), and placebo (274). b(4)

We performed statistical analyses with respect to two protocol-specified co-primary endpoints: changes in the average number of micturitions and number of urge incontinence episodes per 24 hours from baseline to week 12 of the treatment period, and one secondary endpoint: changes in the voided volume per micturition at week 12. We also performed analyses on the above endpoints at week 2

Our analysis showed that compared with placebo, 4mg and 8mg doses resulted in statistically significant ($p<.05$, after controlling for type-I error) reductions in the average number of micturitions and urge incontinence episodes at week 12 in both studies. Both doses of also showed, compared with placebo, statistically significant ($p<.05$) improvement in the secondary endpoint, i.e., voided volume per micturition in study SP583. But in study SP584, only 8mg dose showed significant improvement in voided volume per micturition. b(4)

The 4mg dose was significantly better with respect to incontinence as early as week 2 in both studies. The 8mg dose was also efficacious in terms of both co-primary endpoints starting at week 2. b(4)

From a statistical perspective, the efficacy data provided in this application do support the efficacy of (4mg and 8mg) in the treatment of overactive bladder symptoms after 12 weeks of treatment.

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/s/

Mahboob Sobhan
1/10/2007 12:26:48 PM
BIOMETRICS

Lisa A. Kammerman
1/10/2007 02:19:59 PM
BIOMETRICS
I concur with Dr. Sobhan's review.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CARCINOGENICITY STUDY

NDA Number:	22,030 / Serial 000
Drug Name:	TRADENAME™ (Fesoterodine Fumarate)
Indication(s):	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency
Applicant:	Schwarz Biosciences, Inc.
Date(s):	Submitted 03/17/06
Review Priority:	Standard
Biometrics Division:	Division 6, HFD-705
Statistical Reviewer:	Steve Thomson, HFD-705
Concurring Reviewer:	Team Leader: Karl Lin, Ph. D., HFD-705
Medical Division:	Reproductive and Urologic Products, HFD-580
Toxicologist:	Reviewer: Laurie McLeod-Flynn, Ph.D., HFD-580 Team Leader: Lynnda Reid, Ph.D., HFD-580
Project Manager:	Jean Mackie, HFD-580
Keywords:	Bayesian analysis, Carcinogenicity, Cox regression, Kaplan-Meier product limit, Survival analysis, Trend test

Table of Contents

1. EXECUTIVE SUMMARY

This submission was intended to assess the carcinogenic potential of daily administration of fesoterodine fumarate when administered orally (by gavage) to mice and rats for two years.

1.1. Conclusions and Recommendations

The submission reports on the results of two animal studies of carcinogenicity. In both studies there were four treatment groups (i.e., a control, and three nominal dosages of fesoterodine fumarate: Control, 5, 15, and 45/60 mg/kg/day), labeled as Control, Low, Medium, and High dose groups respectively. The nominal dose 45/60 represents increases in dose in the high dose group as, according to the Sponsor, the 45 mg/kg/day did not seem to result in sufficient toxicity "as required by ICH guidelines." Due to increased mortality in male rats these doses were decreased "in agreement with the CAC of the FDA."

In males of both species the high dose group generally had the highest mortality rate. For both genders in mice and in male rats the control group generally had the lowest mortality rate. In female rats the low dose had the generally lowest mortality. For each gender and species the other treatment groups were generally close and intertwined. In mice the tests of homogeneity in survival were only clearly statistically significant in males (Males: Logrank p = 0.0363, Wilcoxon p = 0.0018, proportional hazards test of trend p = 0.0104). Differences were not significant in female mice (Females: Logrank p = 0.2796, Wilcoxon p = 0.2395, trend p = 0.1965). Results were similar in rats (Male rats: Logrank p = 0.0328, Wilcoxon p = 0.0308, proportional hazards test of trend p = 0.0256, Female rats: Logrank p = 0.2399, Wilcoxon p = 0.2052, trend p = 0.3339). Plots and some details are provided in Appendix 1. A Bayesian analysis of survival gave similar results (please see Appendix 2).

For the tests for tumorigenicity, in both gender of mice and in female rats, no tests of trend over the four treatment group (with control) and no tests between the high dose group and control were statistically significant. The unadjusted test of trend for unilateral cortical adenoma in male mice was close to being statistically significant (p = 0.0518). The control group incidence suggests that this would be classed a rare tumor. However, using the Haseman-Lin-Rahman rules to adjust for multiplicity (see Section 1.3.1 below) would suggest that this not statistically significant (since it is not less than 0.025). The corresponding asymptotic test was statistically significant (p = 0.0061), as was the corresponding asymptotic test for the test of differences between the high dose group (p = 0.0455). However the total number of tumors was two in the high dose group and none elsewhere. With such a small number of events the assumptions needed for the asymptotic tests are not likely to be met, and the exact test cited above is more appropriate. In rats, prior to adjusting for multiplicity, the corresponding test of trend for unilateral cortical adenoma in male mice was statistically significant (p = 0.0088). Using the control group incidence as a guide this would be classified as a common tumor, and since significance level is not less than 0.005, after adjusting for multiplicity this would not be

considered statistically significant at a roughly 10% level of significance, though close. The Sponsor cites several other trends in rats as being statistically significant. However these were not confirmed in the FDA analysis (please see Appendix 3 for details).

1.2. Brief Overview of the Studies

Two studies, both typical rodent studies, were submitted:

Study 13399/00: A 104-Week Carcinogenicity Study of SPM 8272 By Oral Administration to CD-1 Mice,

and,

Study 13400/00: A 104-Week Carcinogenicity Study of SPM 8272 By Oral Administration to CD®- Rats.

In both studies there were four treatment groups (i.e., a control, and three nominal dosages of fesoterodine fumarate: Control, 5, 15, and 45/60 mg/kg/day), labeled as Control, Low, Medium, and High dose groups respectively. Vehicle was deoinized water. In both studies treatment was administered orally by gavage for up to 24 months. Due to mortality in the high dose treatment group in male mice, dosing was terminated at 94 weeks. Animals in the other female mice dosing groups were treated to the end of the study (104 weeks). Similarly, for female rats in the medium and high dose groups, dosing was stopped at 98 weeks. For controls and the low dose group, dosing in female rats was continued to 103 weeks.

1.3. Statistical Issues and Findings

1.3.1. Statistical Issues

Several issues, typical of such analyses, are considered in the following discussion. These include details of the survival analyses, tests on tumorigenicity, multiplicity of tests on neoplasms, and the validity of the designs.

1. Survival Analysis:

Both logrank and Wilcoxon tests were used to test homogeneity of survival among the treatment groups, including the control group. Tests of dose related trend using a Cox proportional odds model were also performed. These involved testing multiple hypotheses, but from the point of view of finding differences among treatment groups (i.e., minimizing Type II error) would be conservative. Appendix 1 reviews the animal survival analyses in some detail. Appendix 2 provides an alternative Bayesian analysis of survival.

2. Tests in Neoplasms:

The Sponsor indicates that in both studies, for most organs, all animals at risk were exhaustively analyzed in all the four treatment groups. In the FDA analysis both the exact, permutation tests and symptotic tests were computed but for tumors where total incidence over the four treatment groups was 10 or less only the results of the exact test are presented. For tumors with incidence greater than 10 the results of the asymptotic test are presented. The Peto tumorigenicity analyses were conducted using the FDA WebCarcin program.

Note that for each species the initial dose given to the high dose group was 45 mg/kg/day. At Week 26 this was raised to 60 mg/kg/day. Female mice and both genders in rats had longer experience with this higher dose, and this is the dose weight used in tests of trend. However, the dose for male mice the dose was gradually reduced to 30 mg/kg/day by Week 47. For this group the nominal 45 mg/kg/day dose was used as the dose weight. For each neoplasm, incidental tumors were grouped into weekly intervals 0 -50, 51-78, 79-91, 91-103, and finally the terminal sacrifice group. Further details are included in the description of each study.

The Sponsor report describes several "Peto" tests of trend in tumor incidence female rats as being statistically significant. However these results are not confirmed in the FDA analysis, and there may be some reason to suspect they may not be appropriate (please see Appendix 3 for details).

3. Multiplicity of Tests on Neoplasms:

Testing the various neoplasms involves a large number of statistical tests, which in turn necessitates an adjustment in experiment-wise Type I error. Current FDA practice is based on the Haseman-Lin-Rahman rules. Namely, based on his extensive experience with such analyses, for pairwise tests comparing control to the high dose group, Haseman (1983) claimed that for a roughly 0.10 (10%) overall false positive error rate, rare tumors should be tested at a 0.05 (5%) level, and common tumors (with a historical control incidence greater than 1%) at a 0.01 level. Based on simulations and their experience, Lin & Rahman (1998) proposed a p-value adjustment for tests of trend. That is, for a roughly 0.10 (10%) overall false positive error rate in tests of trend, rare tumors should be tested at a 0.025 (2.5%) level and common tumors at a 0.005 (0.5%) level. In this analysis we will use the observed incidence in the pooled vehicle groups to decide if a tumor is rare or common. This approach is intended to balance both Type I error and Type II error (i.e., the error of concluding there is no evidence of a relation to tumorgenicity when there actually is such a relation).

4. Validity of the Designs:

Traditionally, in analyses performed in the United States, the highest dose should be close to the Maximum Tolerated Dose (MTD) to achieve the greatest likelihood of tumorigenicity. Chu, Ceuto, and Ward (1981), citing earlier work by Sontag et al. (1976) recommend that the MTD "is taken as 'the highest dose that causes no more than a 10% weight decrement as compared to the appropriate control groups, and does not produce mortality,

clinical signs of toxicity, or pathologic lesions (other than those that may be related to a neoplastic response) that would be predicted to shorten the animal's natural life span' "

Further, Lin and Ali (1994), quoting work by Haseman, have suggested that a survival rate of about 25 animals, out of 50 or more animals, between weeks 80-90 of a two-year study may be considered a sufficient number of survivors as well as one measure of adequate exposure. From the survival plots in the Appendix, it is evident that in both genders in rats and in female mice more than 25 animals survived to this date. However in male mice fewer than 25 animals survived to this date. Near the end of the study mortality was such that several doses were reduced (Please Table 2 in Section 3.2.1 for details).

The Sponsor did not provide data sets for the animal weights. However, summary data was provided in the Sponsor's reports. In male mice dosing in the high dose group was terminated at 84 weeks. The entries for each gender and species include mean weights at the baseline and at the end of study (EOS). The last column shows the ratio of the change from baseline in each treatment group relative to the change from baseline in the control group change. More than a 10% weight deficit in the high dose group relative to controls may indicate problems. For mice males the decrement relative to controls is almost 30%, while for female mice it is 45%. In both genders of rats the decrement is roughly 25%. This, plus the mortality in the high dose group suggests that the MTD may have been exceeded in each species.

Table 1. Summary of Weights and Weight Changes in Dose Groups

Mice Males

Dose	Baseline		Week 85		EOS (Week 104)		Differ-	% Change Rel-
	N	Mean	N	Mean	N	Mean	Ence	ative to Control
Control	50	30.3	37	38.5	24	38.8	8.5	-
Low	50	30.7	34	37.6	18	38.3	7.6	89.4%
Medium	50	30.7	31	38.1	13	37.6	6.9	81.2%
High	50	30.6	19	36.7	16	36.7	6.1	71.8%

Mice Females

Dose	Baseline		EOS (Week 103)		Differ-	% Change Rel-
	N	Mean	N	Mean	Ence	ative to Control
Control	50	23.0	24	34.1	11.1	-
Low	50	23.9	21	32.9	9.0	81.1%
Medium	50	23.4	29	33.4	10.0	90.1%
High	50	23.7	19	29.8	6.1	55.0%

Rat Males

Dose	Baseline		EOS (Week 103)		Differ-	% Change Rel-
	N	Mean	N	Mean	Ence	ative to Control
Control	50	222.9	39	540.7	317.8	-
Low	50	224.8	29	555.9	331.1	104.2%
Medium	50	221.7	34	523.9	302.2	95.1%
High	50	220.5	26	457.5	237.0	74.6%

Table 1. (cont.) Summary of Weights and Weight Changes in Dose Groups
Rat Females

Dose	Baseline		EOS (Week 103)		Differ-	% Change Rel-
	50	Mean	N	Mean	Ence	ative to Control
Control	50	163.7	39	390.1	226.4	-
Low	50	162.5	42	390.5	228.0	100.7%
Medium	50	164.3	34	398.0	233.7	103.2%
High	50	160.9	36	324.4	163.5	72.2%

The combination of the body weight gain data and the mortality information indicate that the high dose used in the mouse study may have exceeded the MTD. For the rat study the weight gain suggests the MTD may have been exceeded, however, mortality was relatively low.

The above evaluation of the appropriateness of the designs and whether or not the doses were sufficiently close to the MTD is based on some rules derived from data of 200 NCI carcinogen bioassays. Information regarding clinical signs and histopathological data, plus other possible considerations, are well beyond the expertise of this reviewer, but presumably would be used by the toxicologist in the final assessment of the adequacy of these experiments.

1.3.2. Statistical Findings

Please see Section 1.1 above.

2. INTRODUCTION

2.1. Overview

Results from a study in \ CD-1® (ICR) BR mice and a study in \CD®(SD)IGS BR rats were submitted to assess the carcinogenic potential of Fesoterodine. b(4)

2.2. Data Sources

For both studies, the Sponsor initially sent data sets that were nominally SAS transport data sets labeled as follows:

382018FT, 38201MT, 38009FT, and 38009MT.

However these names violate the naming conventions of SAS, and were not readable by SAS. When notified of this problem, the Sponsor sent tumor data sets, one for each study, following SAS data set conventions (e.g. TUMOR.XPT). No other data sets were provided for analysis.

3. STATISTICAL EVALUATION

3.1. Evaluation of Efficacy

NA

3.2. Evaluation of Safety

Results on both studies are presented below.

3.2.1. Study 13399/00: 104-Week Carcinogenicity Study of SPM8272 by Oral Administration to CD-1 Mice,

MOUSE STUDY DURATION: 2 adaption weeks, 104 test weeks.
STUDY STARTING DATE: June 6, 2001.
STUDY ENDING DATE: June 5, 2003.
MOUSE STRAIN: CD-1 / CD®-1 (ICR)BR Mice.
ROUTE: Oral (gavage). b(4)
DOSE LEVELS: Control Medium: 15 mg/kg/day
Low: 5 mg/kg/day High 45/60 mg/kg/day
Number of Animals: 50 male and 50 female mice per treatment group (400 animals)
Satellite animals:
18 male and 18 female mice per dose level group (108 animals)

There were four treatment groups (i.e., a vehicle control, and three nominal dosages of the fumurate salt (SPM 8272): Control, 5, 15, and 45/60 mg/kg b.w./day), labeled as the Control, Low, Medium, and High dose groups respectively. Vehicle was "aqua ad iniectabilia." Each treatment group initially had 50 mice, with 18 additional mice per dose group as satellite animals. After four weeks of dosing, animals were selected at random to achieve a level of 60 animals per dose group. The Sponsor states dosing in the high dose group was increased from 45 to 60 mg/kg b.w./day from Week 28 onwards as the high dose group did not seem to show sufficient toxicity. "As the increased high dose level of 60 mg/kg b.w./day led to an increased mortality in the male animals the dose level was reduced from 60 mg/kg b.w./day to 45 mg/kg b.w./day for the males from test day 328 (TW 47) onwards after consultation of the sponsor and in agreement with the CAC (Carcinogenicity Assessment Committee, FDA." (page 33 of report)

"However, a slightly increased mortality was still noted after this dose reduction in the high dosed animals. Therefore, after consultation of the sponsor and in agreement with the CAC (Carcinogenicity Assessment Committee, FDA the dose level for the male animals of the high dose group was reduced to 30 mg/kg b.w./day as of test day 476 (TW 68). In addition, a mortality rate of 60% was set to be the criterion for the termination of administration. As a

mortality rate of 60% was reached on test day 584 in the high dosed male animals, the administration of the test item was terminated on test day 585 (TW 84). " (page 33 of report).

The Sponsor provided the following description of the following modifications of dosing.

Table 2. Modifications of Dosing

Group/sex	Dose mg/kg b.w. /day	Treatment Interval (days)	Treatment Interval (Weeks)
Low/male	5	1 - 708	1 - 102
	0	709 on	102 on
Medium/male	15	1 - 702	1 - 101
	0	703 on	101 on
High/male	45	1 - 189	1 - 27
	60	190 - 327	28 - 47
	45	328 - 475	47 - 68
	30	476 - 584	68 - 84
	0	585 on	84 on
High/female	45	1 - 189	1 - 27
	60	190 - 721	28 - 103
	0	709 on	104 on

Animals were approximately six weeks old at first dosing. During the study animals were housed individually. Food and water were available ad libitum. The Sponsor states that detailed physical examinations were made on all animals each week. Body weights were recorded weekly, beginning approximately one week before initiation of dosing.

3.2.1.1 Sponsor's Results and Conclusions

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

Survival analysis:

The Sponsor mortality results are summarized in the following table, Table 3. For each treatment group, at the end of each time period, the number of animals who died of any cause and the percentage who died up to that time point are presented.

Table 3. Summary of Mortality in Mice: Cumulative Deaths (Cumlative Percentage)

Males Time Interval	Control	Low 5 mg/kg/day	Medium 15 mg/kg/day	High 45/60 mg/kg/day
0-50	0 (0%)	2 (4%)	4 (8%)	11 (22%)
51-78	7 (14%)	12 (24%)	17 (34%)	26 (58%)
79-91	22 (44%)	21 (42%)	24 (48%)	32 (64%)
92-EOS	26 (52%)	32 (64%)	37 (74%)	34 (68%)

Table 3. (cont.) Summary of Mortality in Mice: Cumulative Deaths (Cumlative Percentage)

Females Time Interval	Control	Low 5 mg/kg/day	Medium 15 mg/kg/day	High 45/60 mg/kg/day
0-50	0 (0%)	3 (6%)	2 (4%)	2 (4%)
51-78	3 (6%)	12 (24%)	13 (26%)	10 (20%)
79-91	9 (18%)	21 (42%)	24 (48%)	32 (64%)
92-EOS	26 (52%)	29 (58%)	21 (42%)	31 (62%)

The Sponsor provided the following mortality table (in a different format) for mice:

Table 4. Survival rates at Study Termination

	Control	Low	Medium	High
Males	48%	36%	26%**	32%*
Females	48%	42%	58%	38%

* significant different from the control at $p \leq 0.05$ (FISHER test)
** significant different from the control at $p \leq 0.01$ (FISHER test)

Tumorigenicity analysis:

The Sponsor conducted summaries of all tumors and Peto type analyses of dose related trend to compare the incidence of various neoplasms (see Tables A.3.1 and A.3.2 in Appendix 3). Even without adjusting for the multiplicity of comparisons, no tests of trend were statistically significant.

3.2.1.2 FDA Reviewer's Results

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

Survival analysis:

In mice the tests of homogeneity in survival were only clearly statistically significant in males (Males: Logrank p = 0.0363, Wilcoxon p = 0.0018, proportional hazards test of trend p = 0.0104). Differences were not significant in female mice (Females: Logrank p = 0.2796, Wilcoxon p = 0.2395, trend p = 0.1965).

Kaplan-Meier plots comparing treatment groups in both studies are given in Appendix 1, along with more details of the analysis. The following tables (Table 5 for male mice, Table 6 for female mice) summarize the mortality results for the dose groups. The data were grouped for the specified time period, and give the number of deaths during the time interval over the number at risk at the beginning of the interval. The percentage is the percent survived at the end of the interval, as estimated using a Kaplan-Meier estimate on the ungrouped data. Note again the high dose group seems to have higher mortality.

Table 5. Summary of Male Mice Mortality (dose/kg/day)

Period (Weeks)	Control	Low 5 mg/kg/day	Medium 15 mg/kg/day	High 45 mg/kg/day
1-50	0/50 [1] 100%[2]	2/50 46%	4/50 92%	11/50 78%
51-78	8/50 84%	11/48 74%	13/46 66%	18/39 42%
79-91	14/42 66%	8/37 58%	7/33 52%	3/21 36%
92-104	4/28 48%	11/29 36%	13/26 26%	2/18 32%
Terminal	24	18	13	16

[1] number deaths / number at risk

[2] Kaplan-Meier estimate of cumulative survival at end of interval (not the percentage corresponding to number deaths / number at risk).

Table 6. Summary of Female Mice Mortality (dose/kg/day)

Period (Weeks)	Control	Low 5 mg/kg/day	Medium 15 mg/kg/day	High 45/60 mg/kg/day
1-50	0/50 [1] 100%[2]	3/50 94%	2/50 96%	2/50 96%
51-78	3/50 94%	9/47 76%	12/48 72%	8/48 80%
79-91	6/47 82%	9/38 58%	6/36 60%	12/40 54%
92-104	18/41 46%	8/29 42%	1/30 58%	9/28 38%
Terminal	23	21	29	19

[1] number deaths / number at risk

[2] Kaplan-Meier estimate of cumulative survival (not the percentage corresponding to number deaths / number at risk).

Tumorigenicity analysis:

Even without adjusting for multiplicity, there were no statistically significant tests of trend or pairwise differences between the control group and the high dose group in either mouse gender. Tables A.4.1 and A.4.2 (see Appendix 4) review the overall tumor incidence in each treatment for each neoplasm organ combination. The unadjusted test of trend for unilateral cortical adenoma in male mice was close to being statistically significant ($p = 0.0518$). The control group incidence suggests that this would be classed a rare tumor. However, using the Haseman-Lin-Rahman rules to adjust for multiplicity (see Section 1.3.1 above) would suggest that this not statistically significant (since it is not less than 0.025). The corresponding asymptotic test was statistically significant ($p = 0.0061$), as was the corresponding asymptotic test for the test of differences between the high dose group ($p = 0.0455$). However the total

number of tumors was two in the high dose group and none elsewhere. With such a small number of events the assumptions needed for the asymptotic tests are not likely to be met, and the exact test cited above is more appropriate. Again, absence of proof is not proof of absence. Nonetheless, these results are consistent with the notion of no particular carcinogenic signal.

3.2.2. Study 13400/00: A 104-Week Carcinogenicity Study of SPM 8272 by Oral Administration to CD®- Rats.

RAT STUDY DURATION: 12 adaption days, 104 test weeks.
STUDY STARTING DATE: May 21, 2001.
STUDY ENDING DATE: May 22, 2003.
MOUSE STRAIN: CD® / \ CD® Rats. b(4)
ROUTE: Oral (gavage).
DOSE LEVELS: Control Medium: 15 mg/kg/day
Low: 5 mg/kg/day High 45/60 mg/kg/day
Number of Animals: 50 male and 50 female rats per treatment group (400 animals)
Satellite animals:
10 male and 10 female rats per dose level group (60 animals)

As in the mouse study, there were four treatment groups (i.e., a vehicle control, and three nominal dosages of the fumurate salt (SPM 8272): Control, 5, 15, and 45/60 mg/kg b.w./day), labeled as the Control, Low, Medium, and High dose groups respectively. From test week 30 on the dose level in the high dose group was increased from 45 mg/kg b.w./day to 60 mg/kg b.w./day as the lower dose did "not result in a sufficient degree of toxicity as required by the ICH guidelines on the dose selection for carcinogenicity studies of pharmaceuticals" (page 32 of report) Vehicle was "aqua ad iniectabilia." Each treatment group initially had 50 mice, with 10 additional rats per dose group as satellite or replacement animals.

Animals were housed individually with food and water available ad libitum.

3.2.2.1 Sponsor's Results and Conclusions for Rats

This section presents a summary of the Sponsor's analysis of survivability and tumorigencity in rats.

Survival analysis:

The Sponsor mortality results are summarized in the following table, Table 7. For each treatment group, at the end of each time period, the number of animals who died of any cause and the percentage who died up to that time point are presented.

Table 7. Summary of Mortality in Rats: Cumulative Deaths (Cumlative Percentage)

Males Time Interval	Control	Low 5 mg/kg/day	Medium 15 mg/kg/day	High 45/60 mg/kg/day
0-50	1 (2%)	1 (2%)	2 (4%)	4 (8%)
51-78	2 (4%)	5 (10%)	5 (10%)	12 (24%)
79-91	5 (10%)	13 (26%)	8 (16%)	14 (28%)
92-EOS	11 (22%)	21 (42%)	16 (32%)	24 (48%)

Females Time Interval	Control	Low 5 mg/kg/day	Medium 15 mg/kg/day	High 45/60 mg/kg/day
0-50	1 (2%)	0 (0%)	1 (2%)	1 (2%)
51-78	4 (8%)	0 (0%)	3 (6%)	4 (8%)
79-91	8 (16%)	3 (6%)	10 (20%)	11 (22%)
92-EOS	11 (22%)	8 (16%)	16 (32%)	14 (28%)

The Sponsor provided the following summary mortality table (in a different format) for rats:

Table 8. Survival rates at study termination

	Control	Low	Medium	High
Males	78%	58%**	68	52%**
Females	78%	84%	68%	72%

** significant different from the control at $p \leq 0.01$ (FISHER test)

Tumorigenicity analysis:

The Sponsor also conducted Peto type analyses of dose related trend in tumorigenicity in rats (see Table A.3.4 in Appendix 3). However, as discussed in Appendix 3 there may be problems with the Sponsor's analysis. The Sponsor's results in rats are summarized in the following table:

Table 9. Nominally significant trend tests in tumor incidence

	Control	Low 5 mg/kg	Medium 15 mg/kg	High 60 mg/kg	p-value
Male Rats					
Adrenals					
Phaeochromocytoma, unilat.	4	2	1	7	0.02500
Female Rats					
Mammary Gland					
Fibroadenoma	9	8	8	4	0.02500
Ovariies					
Sex Cord, Stromal Tumor	3	0	2	2	0.02000
Pancreas					
Adenoma, Islet Cell	0	5	1	2	0.02000
Vagina					
Schwannoma	0	0	0	1	0.04000

Although it is not clear from the Sponsor's report, presumably these significance levels are not adjusted for multiplicity. The results for male rats are consistent with the FDA analysis. However, in female rats there are differences. Note that the computed significance level for Schwannoma in the Vagina, would seem to be in error. It is difficult to see how one tumor could lead to such a statistically significant result. Perhaps an asymptotic test was used, when,due to the small number of events, an exact test would have been more appropriate. The trends in fibroadenoma in the mammary glands and stromal tumor in the ovaries correspond to decreasing dose and, if correct, are presumably artifactual results. Since the highest incidence of islet cell adenoma in the pancreas occurs in the low dose group, it is difficult to see how there could be a statistically significant trend. Note that none of the last four results were confirmed in the corresponding FDA analyses and may be due to different choices in time intervals or weights. Finally, note that while p-values are displayed to five decimal places they are apparently rounded to the nearest 5 or 0 in the third decimal place.

3.2.2.2 FDA Reviewer's Results

This section summarizes the Agency results on survival and tumorigenicity in male and female rats.

Survival analysis:

Results were similar in rats (Male rats: Logrank p = 0.0328, Wilcoxon p = 0.0308, proportional hazards test of trend p = 0.0256, Female rats: Logrank p = 0.2399, Wilcoxon p = 0.2052, trend p = 0.3339). Plots and some details are provided in Appendix 1.

These results are summarized in the following tables (Tables 10 and 11). The data are grouped for the specified time period, and give the number of deaths during the time interval over the number at risk at the beginning of the interval. The percentage is the percent surviving at the end of the interval, as estimated using a Kaplan-Meier estimate on the ungrouped data.

Table 10. Summary of Male Rat Mortality (dose/kg/day)

Period (Weeks)	Control	Low 5 mg/kg/day	Medium 15 mg/kg/day	High 45/60 mg/kg/day
1-50	1/50 [1] 98%[2]	1/50 98%	2/50 96%	4/50 92%
51-78	1/49 96%	4/49 90%	3/48 90%	8/46 76%
79-91	3/48 90%	8/45 74%	3/45 84%	3/38 70%
92-104	6/45 78%	8/37 58%	8/42 68%	9/35 52%
Terminal	39	29	34	26

[1] number deaths / number at risk

[2] Kaplan-Meier estimate of cumulative survival (not the percentage corresponding to number deaths / number at risk).

Table 11. Summary of Female Rat Mortality (dose/kg/day)

Period (Weeks)	Control	Low 5 mg/kg/day	Medium 15 mg/kg/day	High 45/60 mg/kg/day
1-50	1/50 [1] 98%[2]	0/50 100%	1/50 98%	1/50 98%
51-78	3/49 92%	0/50 100%	2/49 94%	3/49 92%
79-91	4/46 84%	3/50 94%	7/47 80%	7/46 78%
92-104	3/42 78%	6/47 82%	7/40 66%	3/39 72%
Terminal	39	41	33	36

[1] number deaths / number at risk

[2] Kaplan-Meier estimate of cumulative survival (not the percentage corresponding to number deaths / number at risk).

Tumorigenicity analysis:

Prior to adjusting for multiplicity, the only tests of tumor incidence that were statistically significant were unilateral Phaeocromocytoma in the adrenals of males rats (trend p=0.0088). However, this is classified as a common tumor (since control group incidence is greater than 1%), and hence to adjust for multiplicity should only be considered statistically significant if $p \leq 0.005$, though it is close. Thus no trends or pairwise differences between the high dose group and control were considered to be statistically significant. Again, absence of proof is not proof of absence. Nonetheless these results are consistent with the notion of no particular carcinogenic signal. Tables A.4.3 and A.4.4 in Appendix 4 provide details on the overall tumor incidence in each treatment for each neoplasm organ combination.

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

In males of both species the high dose group generally had the highest mortality rate. For both genders in mice and in male rats the control group generally had the lowest mortality rate. In female rats the low dose had the generally lowest mortality. For each gender and species the other treatment groups were generally close and intertwined. The significance levels of the tests of homogeneity among the treatment groups are presented in Table 12 below (please see Appendix 1 for details).

Table 12. Tests of Homogeneity and Trend in Survival

	Mice			Rats		
Gender	Log Rank	Wilcoxon	Trend	Log Rank	Wilcoxon	Trend
Male	0.0363	0.0018	0.0104	0.0328	0.0308	0.0256
Female	0.2796	0.2395	0.1965	0.2399	0.2052	0.3339

Note that in both species the tests of homogeneity in survival were statistically significant in males, but not in females.

For the tests for tumorigenicity, in both gender of mice and in female rats, no tests of trend over the four treatment group (with control) and no tests between the high dose group and control were statistically significant. Without adjusting for multiplicity, the test for trend in unilateral cortical adenoma in male rats was close statistically significant ($p = 0.0088$). However, using the control group incidence as a guide this would be classed as a common tumor, and since significance level is not less than 0.005, this would not be considered statistically significant at a roughly 10% level of significance, though close. The Sponsor cites several other trends in female rats as being possibly statistically significant. However these were not confirmed in the FDA analysis (please see Appendix 3 for details).

APPENDICES:

Appendix 1. Survival Analysis

In males of both species the high dose group generally had the highest mortality rate. For both genders in mice and in male rats the control group generally had the lowest mortality rate. In female rats the low dose had the generally lowest mortality. For each gender and species the other treatment groups were generally close and intertwined. In mice the tests of homogeneity in survival were only clearly statistically significant in males (Males: Logrank p = 0.0363, Wilcoxon p = 0.0018, proportional hazards test of trend p = 0.0104). Differences were not significant in female mice (Females: Logrank p = 0.2796, Wilcoxon p = 0.2395, trend p = 0.1965). Results were similar in rats (Male rats: Logrank p = 0.0328, Wilcoxon p = 0.0308, proportional hazards test of trend p = 0.0254, Female rats: Logrank p = 0.2399, Wilcoxon p = 0.2052, trend p = 0.3339).

The figures below display the Kaplan-Meier estimated survival curves for the four different species by gender combinations. These curves include the time of censoring, including sacrifice or acidental death, as an event.

Figure A.1.1 Male Mice

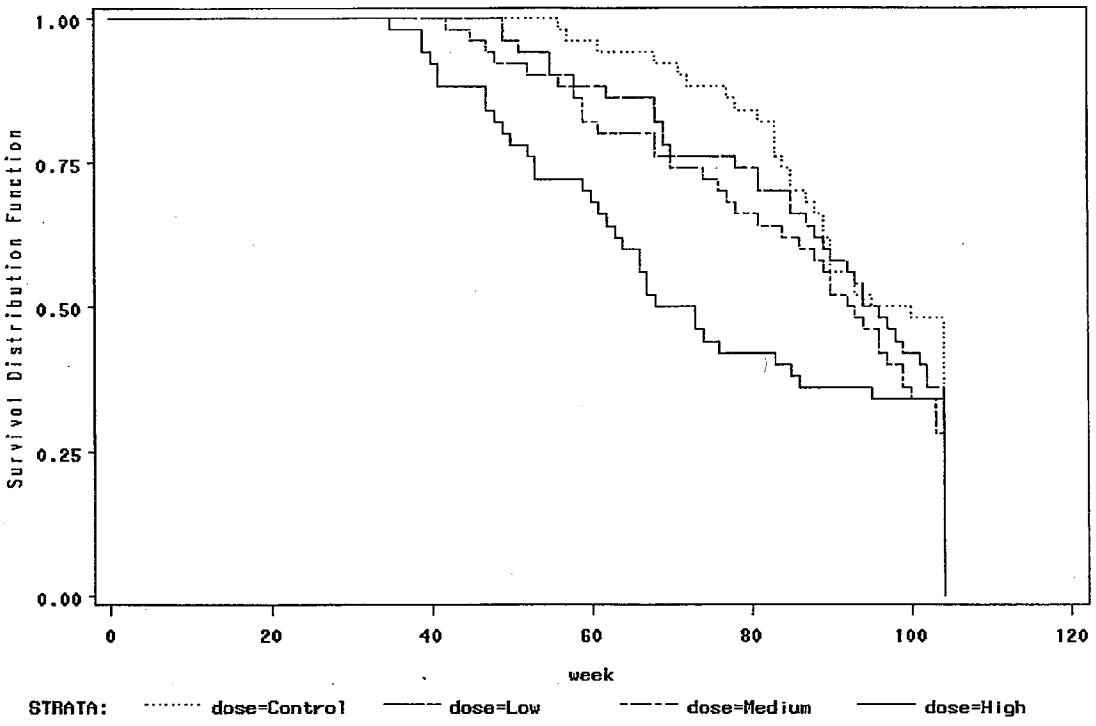


Figure A.1.2 Female Mice

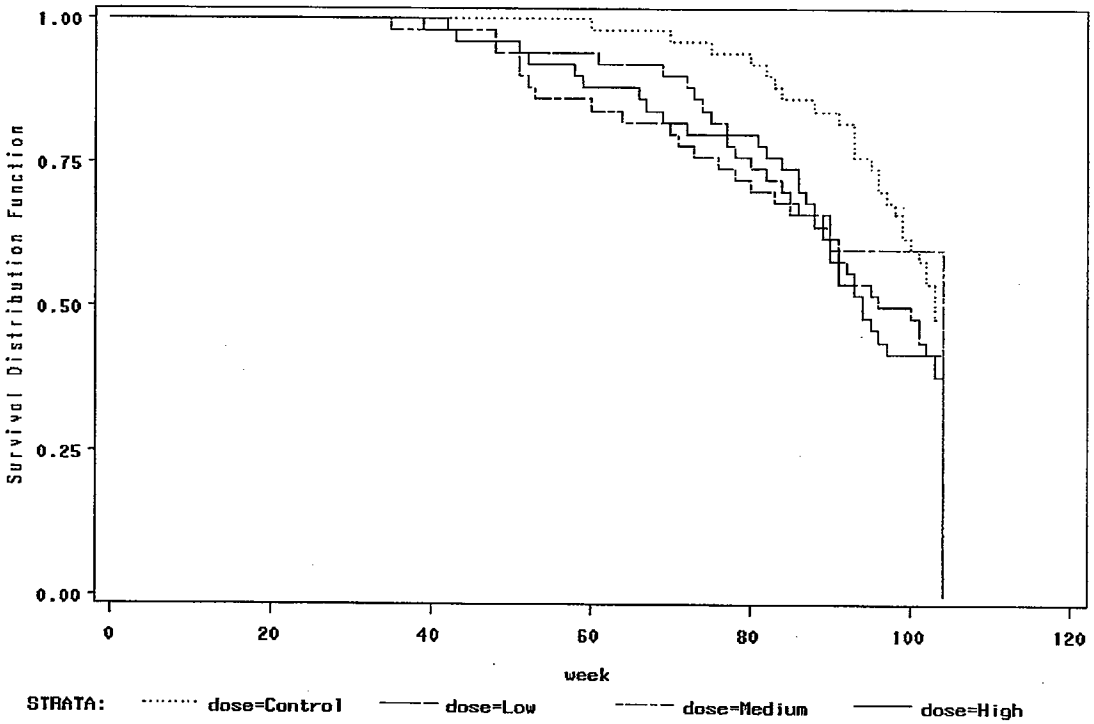


Figure A.1.3 Male Rats

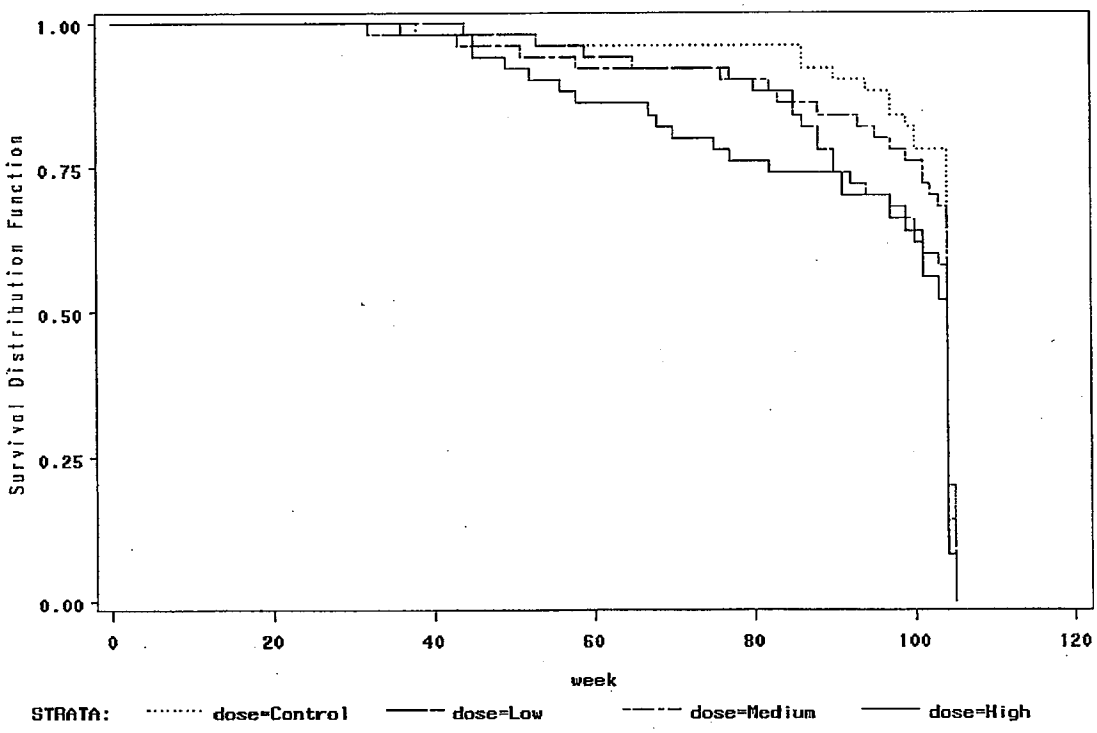
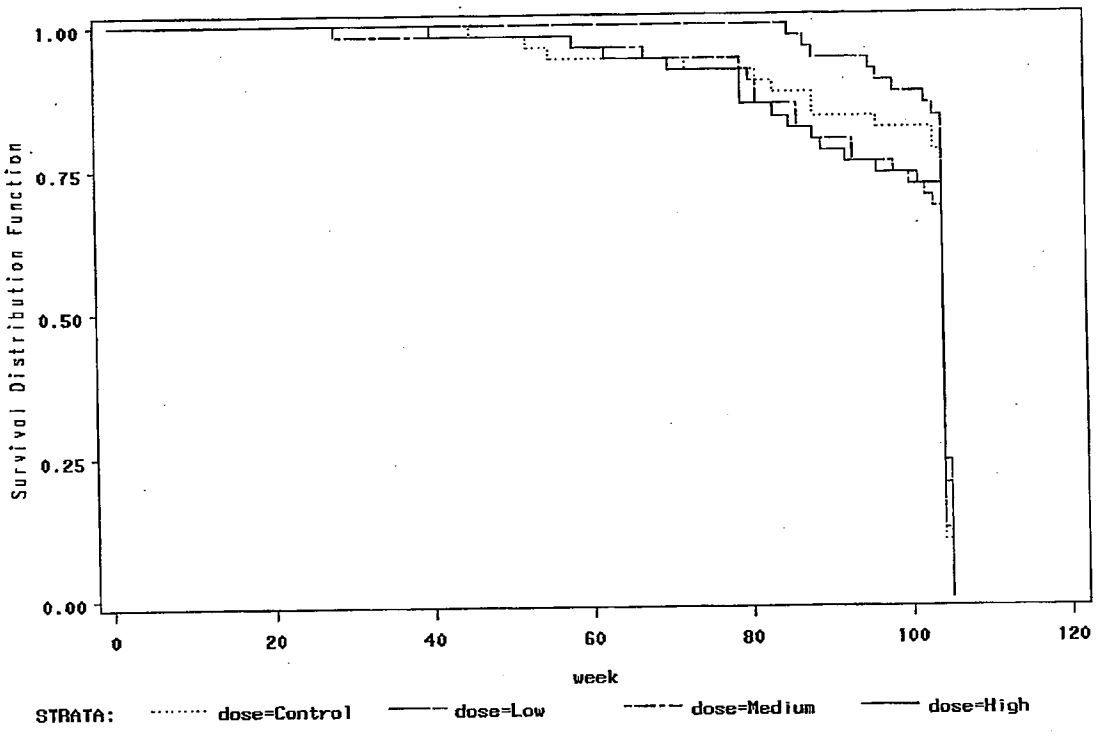


Figure A.1.4 Female Rats



So the integrated cumulative baseline hazard can be written as:

$$H_o(t_i) = e^{x'\beta}\int_0^{t_i} h_0(u)du = e^{x'\beta}\{\sum_{k=1}^{j-1}\lambda_k(a_k - a_{k-1}) + \lambda_j(t_i - a_{j-1})\},$$

with hazard $h_o(t_i) = e^{x'\beta}\lambda_j$.

Then the likelihood for subject i can be written as:

$$L_i(\lambda,\beta) \propto \begin{cases} e^{-H_0(t_i)} & \textit{if ith subject is censored at time } t_i \\ \lambda_j e^{x'\beta} e^{-H_0(t_i)} & \textit{if ith subject fails at time } t_i \end{cases}$$

Because this looks like a sample of exponential interarrival times we would expect the simple fail/not fail distributions to correspond to Poisson random variables.

For subject i censored or failed at time t_j, let $\gamma_{ik} = \begin{cases} \lambda_k(a_k - a_{k-1}) & \textit{for } t_j > a_k \\ \lambda_j(t_j - a_{j-1}) & \textit{for } a_{j-1} \le t_j < a_j \\ 0 & \textit{otherwise} \end{cases}$

Note since the subject i is censored or failed at time t_j, for intervals above a_j, $-e^{x'\beta}\gamma_{ik} = 0$.

Then for these intervals, $\exp(-e^{x'\beta}\gamma_{ik})$ does not contribute to the product.

Thus $S(t) = e^{-H(t)} = \prod_{k=1}^{T}\exp(-e^{x'\beta}\gamma_{ik})$. Further, with respect to parameters $(t_j - a_{j-1})$ is constant, and hence can be incorporated in the likelihood for subjects who fail by multiplying λ_j by this difference. Thus, for subject i, the likelihood can also be written as:

$$L_i(\lambda,\beta) \propto \begin{cases} \prod_{k=1}^{T}\exp(-e^{x'\beta}\gamma_{ik}) & \textit{if ith subject is censored at time } t_i \\ \gamma_{ij} e^{x'\beta}\prod_{k=1}^{T}\exp(-e^{x'\beta}\gamma_{ik}) & \textit{if ith subject fails at time } t_i \end{cases}$$

Note this corresponds to the likelihood of T independent Poisson random variables with mean $e^{x'\beta}\gamma_{ik}$ where all responses are zero except at time j with the occurrence of a failure in the jth interval $(a_{j-1}, a_j]$. This is only a computational convenience but allows easy estimation of the appropriate parameters using standard software (e.g., WINBUGS)..

Thus we need to specify an appropriate prior for the baseline hazard. Note that the baseline hazard is essentially the hazard of the control group. A gamma prior would be skewed to the right and would seem to be an appropriate choice. The two year study is broken down into

twelve two month periods. Sacrifice or accidental death is treated as a reduction in the risk set, but not as a mortality event. To reflect the expectation of an increasing hazard we specify a baseline hazard of 0.01 increasing by 0.01 each two month period. This implies an integrated baseline hazard of 0.78, and baseline expected cumulative survival close to 0.5 (i.e., we expect about half the sham group to survive two years). However, to have a relatively noninformative prior we specify a variance of about .25. Under the parameterization used by WINBUGS, for time period t, this corresponds to a Gamma($0.04*t$, $0.0004*t^2$) distribution, as is used in the programs below.

One approach to model selection in Bayesian models is to use the Deviance Information Criterion (DIC). Effectively, for $D(\theta)$ denoting the usual deviance, $DIC \approx E(D(\theta)) + 1/2$ (Var $(D(\theta))$. For a given data set the model with the smallest DIC would be preferred.

Deviance Information Criterion for Mice	Males	Females
Model with all four treatment groups heterogeneous.	11.846	11.777
Model with trend in BenzaClin Gel groups, 0=vehicle.	9.890	9.846
Model with all four treatment groups homogeneous.	8.833	8.790

Deviance Information Criterion for Rats	Males	Females
Model with all four treatment groups heterogeneous.	687.492	526.772
Model with trend in BenzaClin Gel groups, 0=vehicle.	687.384	525.721
Model with all four treatment groups homogeneous.	690.026	524.546

Note again that the model with treatment effects homogeneous actually means that all treatment effects are confounded with the baseline hazard. For mice the models with all four treatment groups homogeneous have the smallest DICs, suggesting that the model with no treatment effects would be chosen. However, for male mice see the comments on the parameters of the models below. The same holds for female rats. However, for male rats the models with all four treatment groups heterogeneous and the model with a trend in dose have virtually the same DICs, both considerably less than the DIC of the model with homogeneous treatment. So these models seem to fit best. However, again, see the comments below on the parameters of these models.

Male Mice testing homogeneity over four parameter groups

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
beta[1]	0.1668	0.2572	0.004888	-0.3369	0.163	0.6776	4001	17000
beta[2]	0.3869	0.2479	0.004912	-0.0979	0.3877	0.8777	4001	17000
beta[3]	0.5819	0.2531	0.00484	0.09697	0.5807	1.077	4001	17000

The 95% credible interval for beta[3], (i.e. 0.09677 to 1.077), corresponding to the difference in treatment effect between the high dose group and vehicle, is bounded away from 0. This is a strong indication that the treatment groups in male mice are not homogeneous, or at least that the treatment effect of the high dose group is different from the control effect. The

DIC is smallest for the model with homogeneous treatment. However, the DIC is an asymptotic test, and despite the essentially three degree of freedom difference between the models with heterogeneous treatment effects and homogeneous effects, the parameter estimates should take precedence. Thus we would conclude that the survival in the high dose group is clearly less than in the control group.

Male Mice model for trend over treatment groups

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
beta	0.01142	0.004956	8.356E-5	0.00161	0.01146	0.02093	4001	12000

The 95% credible interval for beta, the linear effect in dose, (i.e. 0.00161 to 0.02093), is bounded away from 0. This is a strong indication that the there is a linear effect in dose. Since the DIC is for this model is considerably less than the model with general heteroegeneity in treatments, we would conclude that this model actually is the best of the three, i.e. there is reasonable evidence of a decreasing trend in survival over dose.

Female Mice testing homogeneity over four parameter groups

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
beta[1]	0.1478	0.2633	0.005337	-0.3692	0.1504	0.6738	4001	12000
beta[2]	-0.2138	0.2869	0.004811	-0.7839	-0.2116	0.3363	4001	12000
beta[3]	0.2557	0.2589	0.00486	-0.2538	0.2559	0.7678	4001	12000

Female Mice model for trend over treatment groups

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
beta	0.003905	0.003948	6.268E-5	-0.003952	0.003976	0.01155	4001	12000

The 95% credible intervals for the treatment parameters in both models have zero solidly within the intervals, suggesting that the evidence that the parameter is not zero is not strong. This, coupled with the observations about the DICs above are very consistent with the hypothesis that for female mice the models the model with all four treatment groups homogeneous is the most appropriate model. This would imply no treatment effects on survival.

Male rats testing homogeneity over four parameter groups

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
beta[1]	0.5137	0.3463	0.008347	-0.1614	0.5146	1.213	4001	12000
beta[2]	0.1639	0.3687	0.008376	-0.5546	0.1658	0.8982	4001	12000
beta[3]	0.7163	0.3388	0.008306	0.07307	0.7089	1.389	4001	12000

The 95% credible interval for beta[3], (i.e. 0.07307 to 1.389), corresponding to the difference in treatment effect between the high dose group and vehicle, is bounded away from 0. This is a strong indication that the treatment groups in male rats are not homogeneous.

Male rats model for trend over treatment groups

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
beta	0.008485	0.004612	7.22E-5	-7.462E-4	0.008544	0.01737	4001	12000

The 95% credible interval for beta, the linear effect in dose, (i.e. -0.0007462 to 0.01737), is almost bounded away from 0. This, plus the almost three degree of freedom superiority over

the model with no treatment effects, suggests that either the model with a linear effect in dose or heterogeneous treatment effects are most appropriate.

Female rats testing homogeneity over four parameter groups

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
beta[1]	-0.6006	0.4365	0.007972	-1.501	-0.5857	0.2293	4001	12000
beta[2]	0.1968	0.3637	0.007675	-0.5086	0.1973	0.9172	4001	12000
beta[3]	0.00197	0.3819	0.00755	-0.7503	0.004979	0.7413	4001	12000

Female rats model for trend over treatment groups

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
beta	0.002661	0.005573	7.795E-5	-0.008599	0.002794	0.01343	4001	12000

The 95% credible intervals for the treatment parameters in both models have zero solidly within the intervals, suggesting that the evidence that the parameter is not zero is not strong. This, coupled with the DICs above are very consistent with the hypothesis that for female rats there are no treatment effects on survival.

Testing homogeneity over four parameter groups:

```
# Fesoterodine Male Rats Homogeneity
model{
   for (j in 1:T+1) {
          a[j] <- (j-1)*56                                    }
   for (i in 1:N) {
          lin.pred[i] <- beta[1]*equals(dose[i],2)+ beta[2]*
              equals(dose[i],3) + beta[3]*equals(dose[i],4)
   for (j in 1:T) {
          d[i,j]<- fail[i]*step(obs.t[i]-a[j])*step(a[j+1]-obs.t[i])
          gamma[i,j] <- (a[j+1]-a[j])*step(obs.t[i] - a[j+1])+
               (obs.t[i]-a[j])*step(a[j+1]-obs.t[i])*step(obs.t[i]-a[j])
          theta[i,j] <- lambda[j] * exp(lin.pred[i])
          d[i,j]~ dpois(mu[i,j])
          mu[i,j] <- theta[i,j]*gamma[i,j]
                  }}
   for ( j in 1:T) {
           mn[j] <- 0.04*j
           r[j]  <- 0.0004*j*j
           lambda[j] ~ dgamma(mn[j],r[j])
           part[j] <- lambda[j]*(a[j+1]-a[j])
                   }
    for (m in 1:3)  {
           beta[m] ~ dnorm (0.0,0.001)
                   }
    for ( k in 1:T) {
          sum[k] <- sum(part[1:k])
          S.high[k] <- exp( -(exp(beta[3])*sum[k]))
          S.med[k]  <- exp( -(exp(beta[2])*sum[k]))
          S.low[k]  <- exp( -(exp(beta[1])*sum[k]))
          S.veh[k]  <- exp( -(sum[k]))
                  }}
inits
list(beta=c(-.5,0,0.5))

data
```

```
list(N=200,T=13)
dose[ ] obs.t[ ] fail[ ]
  1      263    1
  1      371    1
  - data -
  4      727    0
END
```

Testing for trend in dose.

```
# Fesoterodine Male Rats Slope
model{
   for (j in 1:T+1) {
          a[j] <- (j-1)*56                                    }
   for (i in 1:N) {
          lin.pred[i]  <-  beta*(5*equals(dose[i],2)+ 15*equals(dose[i],3) +
              60*equals(dose[i],4) )
   for (j in 1:T) {
          d[i,j]<- fail[i]*step(obs.t[i]-a[j])*step(a[j+1]-obs.t[i])
          gamma[i,j] <- (a[j+1]-a[j])*step(obs.t[i] - a[j+1])+
               (obs.t[i]-a[j])*step(a[j+1]-obs.t[i])*step(obs.t[i]-a[j])
          theta[i,j] <-  lambda[j] * exp(lin.pred[i])
          d[i,j]~ dpois(mu[i,j])
          mu[i,j] <- theta[i,j]*gamma[i,j]
                  }}
   for ( j in 1:T) {
            mn[j] <- 0.04*j
            r[j]  <- 0.0004*j*j
            lambda[j] ~ dgamma(mn[j],r[j])
            part[j] <- lambda[j]*(a[j+1]-a[j])
                  }
   beta ~ dnorm (0.0,0.001)
   for ( k in 1:T) {
           sum[k] <- sum(part[1:k])
           S.high[k] <- exp( -(exp(60*beta)*sum[k]))
           S.med[k]  <- exp( -(exp(15*beta)*sum[k]))
           S.low[k]  <- exp( -(exp( 5*beta)*sum[k]))
           S.veh[k] <- exp( -(sum[k]))
                   }}
inits
list(beta=0.5)

data
list(N=200,T=13)
dose[ ] obs.t[ ] fail[ ]
  1      263    1
  1      371    1
  - data -
  4      727    0
END
```

Appendix 3. Sponsor's Tumorigenicity Analysis

Tables A.3.1 and A.3.3 below display the summaries of the overall tumor incidence, where all different neoplasms are pooled. Tables A.3.2 and A.3.4 below display the results of the Peto tests of trend. The Sponsor's submission also includes tables of tumor incidence, but they seem to be consistent with those provided in the FDA analysis, and are too presented in a manner to be too extensive to include in this report.

In the tables of trend statistics the Sponsor displays the computed value of the trend test statistic, but only reports the corresponding p-values for comparisons that are possibly statistically significant (according to the Sponsor, $p \leq 0.01$ for common tumors, $p \leq 0.05$ for rare tumors). Using this rule, apparently Haseman's rule for tests of pairwise differences between the high dose group and control, the sponsor reports there are no statistically significant trends in the incidence of neoplasms in either mouse gender. For rats, the Sponsor indicates the following significance levels (with tumor incidence added);

	Control	Low	Medium	High	p-value
Male Rats					
Adrenals					
Phaeochromocytoma, unilat.	4	2	1	7	0.02500
Female Rats					
Mammary Gland					
Fibroadenoma	9	8	8	4	0.02500
Ovariies					
Sex Cord, Stromal Tumor	3	0	2	2	0.02000
Pancreas					
Adenoma, Islet Cell	0	5	1	2	0.02000
Vagina					
Schwannoma	0	0	0	1	0.04000

Although it is not clear from the Sponsor's report, presumably these significance levels are not adjusted for multiplicity, and to assess statistical significance the FDA would recommend the use of the Haseman-Lin-Rahman rules described in Section 1.3. The results for Male rats are consistent with the FDA analysis. However, in female rats there are differences. Note that the computed significance level for Schwannoma in the Vagina would seem to be in error. It is difficult to see how one tumor could lead to such a statistically significant result. Perhaps an asymptotic test statistic was used when, because of the small number of events, one should use an exact permutation tets. Unless there are similar errors, the trends in fibroadenoma in the mammary glands and stromal tumor in the ovaries correspond to decreasing dose and, if correct, are presumably artifactual results. Since the highest incidence of islet cell adenoma in the pancreas occurs in the low dose group, it is difficult to see how there could be a statistically significant trend as reported by the Sponsor. Note that none of the last four results were confirmed in the corresponding FDA analyses.

Table A.3.1 Summary Tumor Incidence in Mice

PROJECT ID: 13399	SEX: MALE							
GROUP:	Control		II		III		IV	
	#	%	#	%	#	%	#	%
Total Animals/Group	50		50		50		50	
Total Primary Tumors	41	(82)	27	(54)	28	(56)	12	(24)
Total Animals with Tumors #	33	(66)	22*	(44)	20*	(40)	10***	(20)
Total Animals with Multiple Tumors #	6	(12)	5	(10)	6	(12)	2	(4)
Total Benign ##	22	(53)	12	(44)	11	(39)	5	(41)
Total Malignant ##	19	(46)	15	(55)	17	(60)	8	(58)
Total Malignant with Metastasis ###	11	(57)	6	(40)	11	(64)	5	(57)

PROJECT ID: 13399	SEX: FEMALE							
GROUP:	Control		II		III		IV	
	#	%	#	%	#	%	#	%
Total Animals/Group	50		50		50		50	
Total Primary Tumors	54	(108)	43	(86)	48	(96)	25	(50)
Total Animals with Tumors #	36	(72)	29	(58)	31	(62)	25	(50)
Total Animals with Multiple Tumors #	15	(30)	10	(20)	13	(26)	0***	(0)
Total Benign ##	32	(59)	24	(55)	22	(45)	9	(36)
Total Malignant ##	22	(41)	19	(44)	26	(54)	16	(64)
Total Malignant with Metastasis ###	16	(72)	11	(57)	18	(69)	11	(68)

 # Comparison of groups 2 to 4 with group 1 (Control)
*** significantly different from control ($p \leq 0.05$)**
**** significantly different from control ($p \leq 0.01$)**
***** significantly different from control ($p \leq 0.001$)**
Percentage value is Total Benign or Malignant Tumors divided by the Total Primary Tumors
Percentage value is Total Metastasized Tumors divided by the Total Malignant Tumors

Table A.3.2 Study 13399 Mice Trend Test Statistics on Neoplastic Lesions

Combined Prevalence and Death Rate Methode (PETO et al., 1980)

Mouse

Groups: Control group (1) and dose groups 2, 3 and 4 Sex: Male

Organ/Tissue	Type of Neoplastic Lesion	Trend	p-Value#
Incidental Analysis: premature death/sacrifice			
Adrenals	PHAECHROMOCYTOMA	-19.62500	
Adrenals	CORTICAL ADENOMA,unilat.	0.00000	
Adrenals	ADENOMA,subcapsular	4.10448	
Epididymides	LEYDIG CELL ADENOMA	-11.75439	
Haematopoietic system	LYMPHOMA, LYMPHOCYTIC TYPE	26.55547	
Haematopoietic system	LYMPHOMA, PLEOMORPHIC TYPE	-74.30715	
Haematopoietic system	LYMPHOMA, LYMPHOBLASTIC TYPE	2.35294	
Harderian glands	ADENOMA,unilat.	-52.94298	
Hind / Fore leg	OSTEOSARCOMA	0.00000	
Hind / Fore leg	PLASMACYTOMA	0.00000	
Liver	HEPATOCELLULAR ADENOMA	-16.41912	
Liver	HEPATOCELLULAR CARCINOMA	-25.25025	
Liver	HAEMANGIOSARCOMA	-13.51351	

Table A.3.2 (cont.) Study 13399 Mice Trend Test Statistics on Neoplastic Lesions

Combined Prevalence and Death Rate Methode (PETO et al., 1980)

Mouse

Groups: Control group (1) and dose groups 2, 3 and 4 Sex: Male

Organ/Tissue	Type of Neoplastic Lesion	Trend	p-Value#
Lungs with bronchi/bronchiole	CARCINOMA, BRONCHIOLO-ALVEOLAR	-21.92543	
Lungs with bronchi/bronchiole	ADENOMA, BRONCHIOLO-ALVEOLAR	17.51767	
Lymph node (mesenteric)	HAEMANGIOMA	-5.25641	
Mononuclear phagocytic tissue	HISTIOCYTIC SARCOMA	0.83333	
Pancreas	ADENOMA, ISLET CELL	-11.25000	
Pituitary	ADENOMA, PARS DISTALIS	-24.19419	
Spleen	HAEMANGIOSARCOMA	-13.39286	
Tail/Back, skin	HAEMANGIOSARCOMA	0.00000	
Thymus	THYMOMA	-6.37255	

for positive significant trend

Table A.3.2 (cont.) Study 13399 Mice Trend Test Statistics on Neoplastic Lesions

Mouse

Groups: Control group (1) and dose groups 2, 3 and 4 Sex: Female

Organ/Tissue	Type of Neoplastic Lesion	Trend	p-Value#
Abdomen/Thorax site, skin	FIBROSARCOMA	0.00000	
Bone (os femoris with joint)	OSTEOMA	-6.07143	
Genital area	KERATOACANTHOMA	0.00000	
Haematopoietic system	LYMPHOMA, LYMPHOCYTIC TYPE	-45.53829	
Haematopoietic system	LYMPHOMA, PLEOMORPHIC TYPE	-13.24519	
Haematopoietic system	LYMPHOMA, LYMPHOBLASTIC TYPE	-6.78571	
Harderian glands	ADENOMA,unilat.	-26.77245	
Hind / Fore leg	ADENOCARCINOMA,metas.mamma	0.00000	
Liver	HEPATOCELLULAR ADENOMA	-6.53846	
Liver	HAEMANGIOSARCOMA	41.17022	
Lungs with bronchi/bronchioles	CARCINOMA, BRONCHIOLO-ALVEOLAR	-59.80187	
Lungs with bronchi/bronchioles	ADENOMA, BRONCHIOLO-ALVEOLAR	16.60474	
Lymph node (mesenteric)	HAEMANGIOMA	42.11538	
Mononuclear phagocytic tissue	HISTIOCYTIC SARCOMA	67.13203	
Nasal cavity with nasopharynx	OSTEOMA	-6.07143	
Ovaries	GRANULOSA CELL TUMOR,bilat.	-22.32780	
Ovaries	GRANULOSA CELL TUMOR,unilat.	-18.75000	
Ovaries	TUBULOSTROMAL ADENOMA	0.00000	
Ovaries	LUTEOMA, unilat.	-14.55128	
Ovaries	LEIOMYOSARCOMA	-6.92308	
Pituitary	ADENOMA, PARS DISTALIS	-16.11650	
Shoulder	ADENOCARCINOMA, mamma	0.00000	
Skin (left flank)	KERATOACANTHOMA	-16.20370	
Spleen	HAEMANGIOSARCOMA	-15.48611	
Thymus	THYMOMA	-13.42675	
Thyroids	ADENOMA,FOLLICUL.CELL,unil.	-21.20690	
Uterus (incl.cervix)	FIBROMA	-8.08824	
Uterus (incl.cervix)	HAEMANGIOMA	22.50000	
Uterus (incl.cervix)	LEIOMYOMA	-9.00000	
Uterus (incl.cervix)	POLYP, GLANDULAR	-75.08650	
Uterus (incl.cervix)	POLYP,ENDOMETRIAL,STROMAL	-31.56076	

Table A.3.2 Study 13399 Mice Trend Test Statistics on Neoplastic Lesions

Combined Prevalence and Death Rate Methode (PETO et al., 1980)

Mouse

Groups: Control group (1) and dose groups 2, 3 and 4 Sex: Female

Organ/Tissue	Type of Neoplastic Lesion	Trend	p-Value#
Uterus (incl.cervix)	ENDOMETRIAL STROMAL SARCOMA	-25.28572	
Uterus (incl.cervix)	LEIOMYOSARCOMA	41.47727	
Vagina	FIBROSARCOMA	-18.00000	
Vagina	SCHWANNOMA,malignant	30.56451	
Vagina	HAEMANGIOMA	-20.00000	
Vagina	UTERIN POLYP,haemorrhagic	-13.50000	

for positve significant trend

Table A.3.3 Summary Tumor Incidence in Rats

104-Week Carcinogenicity Study of SPM 8272 by Oral Administration to Rats

PROJECT ID: 13400 / GROUP:	SEX: MALE Control		II		III		IV	
	#	%	#	%	#	%	#	%
Total Animals/Group	50		50		50		50	
Total Primary Tumors	65	(130)	65	(130)	45	(90)	45	(90)
Total Animals with Tumors #	37	(74)	35	(70)	31	(62)	30	(60)
Total Animals with Multiple Tumors	#22	(44)	21	(42)	13	(26)	9**	(18)
Total Benign ##	47	(72)	48	(73)	30	(66)	36	(80)
Total Malignant ##	18	(27)	17	(26)	15	(33)	9	(20)
Total Malignant with Metastasis ###	5	(27)	8	(47)	7	(46)	5	(55)

PROJECT ID: 13400 / GROUP:	SEX: FEMALE Control		II		III		IV	
	#	%	#	%	#	%	#	%
Total Animals/Group	50		50		50		50	
Total Primary Tumors	81	(162)	79	(158)	101	(202)	38	(76)
Total Animals with Tumors #	40	(80)	41	(82)	43	(86)	28*	(56)
Total Animals with Multiple Tumors	#25	(50)	19	(38)	33	(66)	9**	(18)
Total Benign ##	63	(77)	63	(79)	66	(65)	26	(68)
Total Malignant ##	18	(22)	16	(20)	34	(34)	12	(31)
Total Malignant with Metastasis ###	8	(44)	8	(50)	18	(51)	6	(50)

 # Comparison of groups 2 to 4 with group 1 (Control)
*** significantly different from control ($p \leq 0.05$)**
**** significantly different from control ($p \leq 0.01$)**
***** significantly different from control ($p \leq 0.001$)**
Percentage value is Total Benign or Malignant Tumors divided by the Total Primary Tumors
Percentage value is Total Metastasized Tumors divided by the Total Malignant Tumors

Table A.3.2 Study 13400 Rats Trend Test Statistics on Neoplastic Lesions

Combined Prevalence and Death Rate Methode (PETO et al., 1980)

Mouse

Groups: Control group (1) and dose groups 2, 3 and 4 Sex: Male

Organ/Tissue	Type of Neoplastic Lesion	Trend	p-Value#
Adrenals	PHAEOCHROMOCYTOMA, unilat.	86.53986	0.025
Adrenals	CORTICAL ADENOMA,unilat.	38.75000	
Adrenals	PHAEOCHROMOCYTOMA,malignant	-24.10714	
Adrenals	PHAEOCHROMACYTOMA,bilat.	0.00000	
Brain (cerebellum)	ASTROCYTOMA,malignant	-15.85366	
Brain (cerebellum)	CHOROID PLEXUS CARCINOMA	24.16667	
Brain (cerebrum)	ASTROCYTOMA,malignant	-24.11765	
Brain (cerebrum)	MENINGEAL SARCOMA	-18.14516	
Brain stem	ASTROCYTOMA,malignant	17.31482	
Duodenum	MESOTHELIOMA	27.22223	
Haematopoietic system	LYMPHOMA, LYMPHOCYTIC TYPE	25.67176	
Haematopoietic system	LYMPHOMA, PLEOMORPHIC TYPE	-19.78959	
Haematopoietic system	LYMPHOMA, LYMPHOBLASTIC TYPE	-6.56250	
Head	HAEMANGIOSARCOMA	0.00000	
Head/Neck	HAEMANGIOSARCOMA	0.00000	
Head/Neck	SQUAMOUS CELL CARCINOMA	-1.00000	
Heart (l./r.ventr.,septum)	ENDOCARDIAL SCHWANNOMA,MALIGN.	-34.95879	
Liver	HEPATOCELLULAR ADENOMA	-10.00000	
Lungs with bronchi/bronchioles	KERATINI.CYSTIC SQUAM.C.TUMOR	-18.70370	
Lungs with bronchi/bronchioles	SCHWANNOMA	-20.33333	
Lymph node (mesenteric)	HAEMANGIOSARCOMA	-20.62500	
Lymph node (mesenteric)	HAEMANGIOMA	-5.00000	
Mammary gland	MALIG.FIBROC.HISTIOCYTOMA(MFH)	-33.47826	
Mononuclear phagocytic tissue	HISTIOCYTIC SARCOMA	0.00000	
Nasal cavity with nasopharynx	SQUAMOUS CELL CARCINOMA	28.00000	
Nasal cavity with nasopharynx	KERATOACANTHOMA	-18.05556	
Neck/Flank	FIBROMA	0.00000	
Pancreas	ADENOMA, ISLET CELL	-26.00000	
Pancreas	ADENOMA, ACINAR CELL	18.33333	
Pituitary	ADENOMA,PARS DISTALIS	-191.83453	
Pituitary	ADENOCARCINOMA,PARS DISTALIS	-21.90476	
Preputial gland	ADENOMA	-16.00000	
Prostate	ADENOCARCINOMA	-17.83784	
Skin (left flank)	FIBROMA	-25.00000	
Skin (left flank)	SCHWANNOMA	-18.57143	
Spinal cord (3 sections)	MALIGNANT GLIOMA	-21.37500	
Tail/back, skin	KERATOACANTHOMA	0.00000	
Tail/back, skin	RHABDOMYOSARCOMA	-22.50000	
Testicle	ADENOMA,LEYDIG CELL,unilat.	42.98118	
Thymus	THYMOMA	-17.77778	
Thymus	HAEMANGIOMA	-20.96774	
Thyroids	ADENOMA,FOLLICUL.CELL,unil.	-28.84615	
Thyroids	HAEMANGIOSARCOMA	-26.00000	
Tongue (incl.base)	SQUAMOUS CELL CARCINOMA	-18.44828	

for positive significant trend

Table A.3.4 (cont.) Study 13400 Rats Trend Test Statistics on Neoplastic Lesions

Trend Test Statistics on Neoplastic Lesions
Combined Prevalence and Death Rate Methode (PETO et al., 1980)

Rat

Groups: Control group (1) and dose groups 2, 3 and 4 Sex: Female

Organ/Tissue	Type of Neoplastic Lesion	Trend	p-Value#
Adrenals	PHAEOCHROMOCYTOMA, unilat.	1.50000	
Adrenals	CORTICAL ADENOMA,unilat.	-6.62791	
Adrenals	PHAEOCHROMACYTOMA,bilat.	-6.25000	
Axilla	MALIG.FIBROC.HISTIOCYTOMA(MFH)	33.33333	
Axilla	FIBROADENOMA,MAMMA	5.00000	
Axilla	ADENOCARCINOMA,MAMMA	-5.00000	
Brain (cerebrum)	ASTROCYTOMA,malignant	-12.27273	
Brain (cerebrum)	OLIGODENDROGLIOMA	0.00000	
Haematopoietic system	LYMPHOMA, LYMPHOCYTIC TYPE	79.70711	
Haematopoietic system	LYMPHOMA, PLEOMORPHIC TYPE	-4.27003	
Haematopoietic system	LYMPHOMA, LYMPHOBLASTIC TYPE	-2.50000	
Ileum	SARCOMA NOS	7.00000	
Liver	HEPATOCELLULAR ADENOMA	-2.17391	
Liver	BILE DUCT CARCINOMA	-17.85714	
Lymph node (mesenteric)	HAEMANGIOSARCOMA	-2.47059	
Mammary gland	FIBROADENOMA	84.52723	0.02500
Mammary gland	ADENOMA	4.50000	
Mammary gland	ADENOCARCINOMA	-33.51250	
Mammary gland	ADENOMA, CYSTIC	-18.20000	
Mononuclear phagocytic tissue	HISTIOCYTIC SARCOMA	0.00000	
Ovaries	SEX CORD STROMAL TUMOR	42.35294	0.02000
Pancreas	ADENOMA, ISLET CELL	40.16129	0.04000
Pituitary	ADENOMA,PARS DISTALIS	23.30738	
Thymus	THYMOMA	-6.66667	
Thyroids	ADENOMA,C-CELL, unilat.	-8.55556	
Thyroids	CARCINOMA,FOLLICUL.CELL,unila.	31.13821	
Tongue (incl.base)	SQUAMOUS CELL CARCINOMA	-12.69231	
Tongue (incl.base)	SQUAMOUS CELL PAPILLOMA	-7.91667	
Urinary bladder	SARCOMA	-3.97059	
Uterus (incl.cervix)	HAEMANGIOMA	-22.65957	
Uterus (incl.cervix)	ADENOCARCINOMA	-39.61905	
Uterus (incl.cervix)	SCHWANNOMA	38.21429	
Uterus (incl.cervix)	ADENOMA,cyst	-6.62791	
Uterus (incl.cervix)	POLYP, GLANDULAR	-19.21875	
Uterus (incl.cervix)	POLYP,ENDOMETRIAL,STROMAL	-24.86666	
Uterus (incl.cervix)	GRANULOSA CELL TUMOR	-11.42857	
Uterus (incl.cervix)	MALIG.FIBROC.HISTIOCYTOMA(MFH)	-3.33333	
Uterus (incl.cervix)	ENDOMETRIAL STROMAL SARCOMA	-3.97059	
Vagina	SCHWANNOMA	40.26316	0.04000

Appendix 4. FDA Tumorigenicity Analysis

Tables A.3.1 through A.3.2 below display the number of neoplasms in each organ and tumor combination in mice taken from the datasets provided by the Sponsor. Tables A.3.3 and A.3.4 below display similar results for rats. For each dose group, the numbers in the table are the number of animals where histopathological analysis detected a tumor. For both species and each gender there were 50 animals, most of whom were analyzed histopathologically. The significance levels of both the tests of trend over the four treatment groups and the tests comparing the high dose groups to control are presented. For more than 10 animals the results are from asymptotic tests. For 10 or fewer animals the results are from exact tests, with fixed marginal totals.

The Haseman-Lin-Rahman rules summarized below are designed to adjust for the multiplicity of tests over the organ by tumor combinations and determine if the observed p-value is statistically significant. That is, to control the overall Type I error rate to roughly 10% for each type of comparison, one compares the unadjusted significance level to the appropriate bound below:

Haseman - Lin - Rahman Bounds: Comparison	Rare Tumor (Incidence ≤ 1%)	Common Tumor (Incidence > 1%)
Trend (over 3 or more groups)	0.025	0.005
Pairwise	0.05	0.01

So, for example, for a rare tumor (with incidence in the pooled control groups ≤ 1%, i.e. 0 or 1 tumor), a trend would be considered statistically significant if the computed significance level was at or less than 0.025, while a comparison between the high dose group and the pooled controls (i.e., a pairwise comparison) would be statistically significant if the computed significance level was no more than 0.05.

The following tables show the tumor incidence and the significance levels of the tests of trend and the high dose group versus the vehicle controls. When there are no observed values in the controls and the high dose group, the test of differences is not defined and thus no p-value is given.

Table A.3.1. Tumorgenicity in Male Mice

Organ / Tumor	Control	Low	Medium	High	p-values: Trend	Hi vs Cntrl
Adrenals						
ADENOMA subcapsular	0	0	1	0	0.6200	
CORTICAL ADENOMA unilat	0	0	0	2	0.0518	0.1659
PHAEOCHROMOCYTOMA	1	0	1	0	0.6317	1.0000
Caecum						
LEIOMYOMA	0	0	1	0	0.4247	
Epididymides						
LEYDIG CELL ADENOMA	1	0	0	0	1.0000	1.0000
Haematopoietic system						
LYMPHOMA LYMPHOBLASTIC TYPE	0	0	1	0	0.4247	
LYMPHOMA LYMPHOCYTIC TYPE	3	1	0	3	0.1886	0.4327
LYMPHOMA PLEOMORPHIC TYPE	4	3	8	1	0.8638	0.9307
LYMPHOMA LYMPHOBLASTIC TYPE	0	0	1	0	0.4444	
Harderian glands						
ADENOMA unilat	3	0	4	0	0.7725	1.0000
Lesion (hind fore leg)						
OSTEOSARCOMA	0	1	0	0	0.7326	
PLASMACYTOMA	0	1	0	0	0.8400	
Lesion (tail back skin)						
HAEMANGIOSARCOMA	1	0	0	0	1.0000	1.0000
Liver						
HAEMANGIOSARCOMA	1	0	0	0	1.0000	1.0000
HEPATOCELLULAR ADENOMA	3	3	2	1	0.8160	0.8951
HEPATOCELLULAR CARCINOMA	3	7	3	1	0.8777	0.8436
Hepat Adenoma/Carcinoma	6	10	5	2	0.9369	0.9008
Lungs with bronchi						
ADENOMA BRONCHIOLO ALVEOLAR	4	6	0	2	0.8510	0.8218
Adenoma/Carcinoma	8	7	4	4	0.7709	0.6447
CARCINOMA BRONCHIOLO ALVEOLAR	4	1	4	2	0.4719	0.6700
Lymph node (mesenteric)						
HAEMANGIOMA	0	1	0	0	0.6000	
Mononuclear phagocytic tissue						
HISTIOCYTIC SARCOMA	2	1	0	0	0.9870	1.0000
Nasal cavity with nasopharynx						
ODONTOMA	1	0	0	0	1.0000	1.0000
Pancreas						
ADENOMA ISLET CELL	1	0	1	0	0.6045	1.0000
Pituitary						
ADENOMA PARS DISTALIS	3	0	0	0	1.0000	1.0000
Rectum						
LEIOMYOSARCOMA	0	1	0	0	0.6712	

Table A.3.1. (cont.) Tumorgenicity in Male Mice

Organ / Tumor	Control	Low	Medium	High	p-values: Trend	Hi vs Cntrl
Spleen						
HAEMANGIOMA	1	0	0	0	1.0000	1.0000
HAEMANGIOSARCOMA	1	0	0	0	1.0000	1.0000
Systemic						
HAEMANGIOMA	2	1	0	0	0.9541	1.0000
HAEMANGIOSARCOMA	3	0	0	0	1.0000	1.0000
Hemangioma/-sarcoma	5	1	0	0	0.9998	1.0000
Testicle						
ADENOMA LEYDIG CELL bilat	1	0	0	0	1.0000	1.0000
ADENOMA LEYDIG CELL unilat	2	0	1	0	0.8285	1.0000
HAEMANGIOMA	1	0	0	0	1.0000	1.0000
Thymus						
THYMOMA	0	1	0	0	0.9091	

Table A.3.2. Tumorgenicity in Female Mice

Organ / Tumor	Control	Low	Medium	High	p-values: Trend	Hi vs Cntrl
Adrenals						
PHAEOCHROMOCYTOMA	0	1	1	1	0.2539	0.4419
Bone (os femoris with joint)						
OSTEOMA	0	1	0	0	0.4848	
Brain (cerebrum)						
ASTROCYTOMA malignant	0	0	1	0	0.5213	
Caecum						
LEIOMYOMA	0	0	1	0	0.5213	
Gallbladder						
ADENOMA	0	1	1	0	0.6088	
Haematopoietic system						
LYMPHOMA LYMPHOCYTIC TYPE	2	3	6	1	0.8087	0.8360
LYMPHOMA PLEOMORPHIC TYPE	11	5	5	4	0.8572	0.8927
LYMPHOMA LYMPHOBLASTIC TYPE	0	0	1	0	0.4765	
Harderian glands						
ADENOMA unilat	1	1	1	1	0.4776	0.6114
Lesion (abdomen thorax site s						
FIBROSARCOMA	0	1	0	0	0.4848	
FIBROSARCOMA MYXOMATOUS TYP	0	0	1	0	0.5213	
Lesion (genital area)						
KERATOACANTHOMA	0	1	0	0	0.8235	
SQUAMOUS CELL CARCINOMA	1	0	0	0	1.0000	1.0000
Lesion (hind fore leg)						
ADENOCARCINOMA mamma	0	0	0	1	0.2500	0.7273
CHONDROMA	1	0	0	0	1.0000	1.0000
Lesion (neck flank)						
MALIG FIBROC HISTIOCYTOMA(MFH)	0	0	1	0	0.5213	
Lesion (shoulder)						
ADENOCARCINOMA mamma	1	0	0	0	1.0000	1.0000
Lesion (tail back skin)						
OSTEOSARCOMA	0	1	0	0	0.7447	

Table A.3.2. (cont.) Tumorgenicity in Female Mice

Organ / Tumor	Control	Low	Medium	High	p-values: Trend	Hi vs Cntrl
Liver						
HAEMANGIOSARCOMA	0	0	0	1	0.3824	0.6842
HEPATOCELLULAR ADENOMA	0	2	0	0	0.6915	
HEPATOCELLULAR CARCINOMA	1	0	1	0	0.7735	1.0000
Hepat Adenoma/Carcinoma	1	2	1	0	0.8149	1.0000
Lungs with bronchi						
ADENOMA BRONCHIOLO ALVEOLA	2	2	0	1	0.7139	0.7410
Adenoma/Carcinoma	5	3	2	1	0.9057	0.9707
CARCINOMA BRONCHIOLO ALVEO	3	1	2	0	0.9242	1.0000
Lymph node (mesenteric)						
HAEMANGIOMA	1	1	0	1	0.4840	0.6588
Mononuclear phagocytic tissue						
HISTIOCYTIC SARCOMA	2	3	5	5	0.2174	0.3889
Nasal cavity with nasopharynx						
OSTEOMA	0	1	0	0	0.4848	
Ovaries						
CYSTADENOMA	0	0	1	0	0.5269	
GRANULOSA CELL TUMOR bilat	1	0	1	0	0.7067	1.0000
GRANULOSA CELL TUMOR unilat	1	0	0	1	0.5085	0.8271
LEIOMYOSARCOMA	0	1	0	0	0.4848	
LUTEOMA unilat	0	1	1	0	0.6899	
TUBULOSTROMAL ADENOMA	1	0	0	1	0.3686	0.7062
Pituitary						
ADENOMA PARS DISTALIS	1	1	1	0	0.8849	1.0000
Skin (left flank)						
KERATOACANTHOMA	0	1	0	0	0.8235	
Spinal cord (3 sections)						
ASTROCYTOMA	0	1	0	0	0.7447	
Spleen						
HAEMANGIOSARCOMA	0	1	0	0	0.9063	
Systemic						
HAEMANGIOMA	4	1	1	1	0.8024	0.9622
HAEMANGIOSARCOMA	0	1	0	2	0.1442	0.3023
Hemangioma/-sarcoma	4	2	1	3	0.4337	0.7606
Thymus						
THYMOMA	2	3	7	1	0.7682	0.7968
Thyroids						
ADENOMA FOLLICUL CELL unil	1	0	0	0	1.0000	1.0000
Uterus (incl cervix)						
ADENOCARCINOMA	0	0	3	1	0.2060	0.4419
ENDOMETRIAL STROMAL SARCOMA	0	2	0	0	0.7841	
FIBROMA	1	0	1	0	0.6373	1.0000
HAEMANGIOMA	2	0	1	0	0.8401	1.0000
HAEMANGIOSARCOMA	0	0	0	1	0.2021	0.4419
LEIOMYOMA	1	1	0	1	0.4982	0.8478
LEIOMYOSARCOMA	0	0	0	1	0.3824	0.6842
POLYP GLANDULAR	7	2	2	0	0.9866	1.0000
POLYP ENDOMETRIAL STROMAL	5	3	2	0	0.9901	1.0000
SCHWANNOMA	0	0	0	1	0.2021	0.4419

Table A.3.2. (cont.) Tumorgenicity in Female Mice

Organ / Tumor	Control	Low	Medium	High	p-values: Trend	Hi vs Cntrl
Vagina						
FIBROSARCOMA	0	1	0	0	0.8125	
HAEMANGIOMA	1	0	0	0	1.0000	1.0000
LEIOMYOMA	2	0	0	0	1.0000	1.0000
PAPILLOMA	0	0	1	0	0.5222	
SCHWANNOMA malignant	1	0	0	1	0.4559	0.5652
UTERIN POLYP haemorrhagic	1	0	0	0	1.0000	1.0000

Table A.3.3. Tumorgenicity in Male Rats

Organ / Tumor	Control	Low	Medium	High	p-values: Trend	Hi vs Cntrl
Adrenals						
CORTICAL ADENOMA unilat	0	3	1	1	0.5786	0.8889
PHAEOCHROMACYTOMA bilat	0	1	0	0	0.8065	
PHAEOCHROMOCYTOMA unilat	4	2	1	7	0.0088	0.0887
PHAEOCHROMOCYTOMA malignant	1	0	0	0	1.0000	1.0000
Phaeochromacytoma	5	3	1	7	0.0398	0.1764
Bone (os femoris with joint)						
FIBROMA	0	0	0	1	0.1969	0.3906
Brain (cerebellum)						
ASTROCYTOMA malignant	0	1	0	0	0.7176	
CHOROID PLEXUS CARCINOMA	0	0	0	1	0.2903	0.6000
Brain (cerebrum)						
ASTROCYTOMA malignant	1	0	0	0	1.0000	1.0000
MENINGEAL SARCOMA	0	1	0	0	0.9375	
Brain stem						
ASTROCYTOMA malignant	0	0	1	1	0.1638	0.4667
Duodenum						
MESOTHELIOMA	0	0	0	1	0.2214	0.4429
Epididymides						
MESOTHELIOMA	0	1	0	0	0.6953	
Haematopoietic system						
LYMPHOMA LYMPHOBLASTIC TYP	0	0	1	0	0.4749	
LYMPHOMA LYMPHOCYTIC TYPE	0	2	1	2	0.2442	0.3938
LYMPHOMA PLEOMORPHIC TYPE	0	1	2	0	0.5991	
Heart						
ENDOCARDIAL SCHWANNOMA BENIGN	0	0	1	1	0.1487	0.4000
ENDOCARDIAL SCHWANNOMA MALIGNANT	0	2	0	0	0.7861	
Kidneys						
TUBULAR ADENOCARCINOMA unilat	0	1	0	0	0.6953	
Lacrimal glands						
MALIG FIBROC HISTIOCYTOMA	1	0	0	0	1.0000	1.0000
SCHWANNOMA	0	0	1	0	0.4688	
Lesion (abdomen thorax site sk						
FIBROMA	1	1	0	0	0.9088	1.0000
FIBROMA MYXOMATOUS TYPE	0	1	0	0	0.6953	
Lesion (abdominal cavity)						
SCHWANNOMA	1	0	0	0	1.0000	1.0000
Lesion (ear)						
SCHWANNOMA	0	1	0	0	0.7303	

Table A.3.3. (cont.) Tumorgenicity in Male Rats

Organ / Tumor	Control	Low	Medium	High	p-values: Trend	Hi vs Cntrl
Lesion (femur Skin)						
FIBROADENOMA MAMMA	1	0	0	0	1.0000	1.0000
Lesion (head neck)						
HAEMANGIOSARCOMA	1	0	0	0	1.0000	1.0000
KERATOACANTHOMA	1	0	0	0	1.0000	1.0000
SARCOMA NOS	1	0	0	0	1.0000	1.0000
SQUAMOUS CELL CARCINOMA	0	1	0	0	0.8235	
Lesion (head)						
HAEMANGIOSARCOMA	0	1	0	0	0.7209	
SCHWANNOMA MALIGNANT	1	0	0	0	1.0000	1.0000
Lesion (hind fore leg)						
HAEMANGIOSARCOMA	0	0	1	0	0.4688	
Lesion (lymph node body mandib						
HAEMANGIOSARCOMA	1	0	0	0	1.0000	1.0000
Lesion (neck flank)						
FIBROMA	1	1	0	0	0.9462	1.0000
KERATOACANTHOMA	2	0	0	1	0.4970	0.7908
SARCOMA NOS	0	0	0	1	0.2031	0.4000
SCHWANNOMA MALIGNANT	0	1	0	0	0.6953	
TRICHOFOLLICULOMA	0	1	0	0	0.6953	
Lesion (shoulder)						
KERATOACANTHOMA	1	0	0	0	1.0000	1.0000
Lesion (tail back skin)						
HAEMANGIOSARCOMA	1	0	0	0	1.0000	1.0000
KERATOACANTHOMA	0	0	0	1	0.2903	0.6000
RHABDOMYOSARCOMA	0	0	1	0	0.5484	
Liver						
HEPATOCELLULAR ADENOMA	0	1	1	0	0.6300	
Lungs with bronchi						
KERATINI CYSTIC SQUAM C TUM	0	1	0	0	0.9333	
SCHWANNOMA	0	1	0	0	0.8000	
Lymph node (mesenteric)						
HAEMANGIOMA	0	3	2	2	0.2254	0.1562
HAEMANGIOSARCOMA	2	0	2	1	0.4662	0.8381
Mammary gland						
ADENOCARCINOMA	1	0	0	0	1.0000	1.0000
FIBROADENOMA	1	0	0	1	0.3663	0.6437
MALIG FIBROC HISTIOCYTOMA	1	0	1	0	0.8043	1.0000
Mononuclear phagocytis tissue						
HISTIOCYTIC SARCOMA	0	0	1	1	0.1613	0.4783
Nasal cavity with nasopharynx						
KERATOACANTHOMA	0	1	0	0	0.8235	
SQUAMOUS CELL CARCINOMA	0	0	1	1	0.2870	0.8889
Pancreas						
ADENOMA ACINAR CELL	0	2	0	2	0.1551	0.2400
ADENOMA ISLET CELL	3	3	1	0	0.9757	1.0000
MALIG FIBROC HISTIOCYTOMA	1	0	0	0	1.0000	1.0000
Pituitary						
ADENOCARCINOMA PARS DISTALIS	1	0	0	0	1.0000	1.0000
ADENOMA PARS DISTALIS	13	9	12	5	0.9513	0.9231
ADENOMA PARS INTERMEDIA	0	0	0	1	0.2033	0.3968

Table A.3.3. (cont.) Tumorgenicity in Male Rats

Organ / Tumor	Control	Low	Medium	High	p-values: Trend	Hi vs Cntrl
Preputial gland						
ADENOMA	2	1	2	1	0.5721	0.7908
HISTIOCYTIC SARCOMA	0	1	0	0	0.6953	
Prostate						
ADENOCARCINOMA	0	1	0	0	0.8125	
ADENOMA	1	0	1	0	0.8043	1.0000
Skin (left flank)						
FIBROMA	0	1	0	0	0.8065	
SCHWANNOMA	0	1	0	0	0.8235	
Spinal cord (3 sections)						
MALIGNANT GLIOMA	1	0	0	0	1.0000	1.0000
Systemic						
HAEMANGIOMA	0	4	2	2	0.3111	0.1562
HAEMANGIOSARCOMA	7	1	3	1	0.9266	0.9957
Hemangioma/-sarcoma	7	5	5	3	0.8104	0.9181
Testicle						
ADENOMA LEYDIG CELL bilat	2	2	0	4	0.0501	0.1680
ADENOMA LEYDIG CELL unilat	5	5	5	5	0.3405	0.4965
HAEMANGIOSARCOMA	1	0	0	0	1.0000	1.0000
MESOTHELIOMA	0	1	0	0	0.6953	
Thymus						
HAEMANGIOMA	0	1	0	0	0.8571	
THYMOMA	0	2	1	0	0.7474	
THYMOMA malignant	0	0	1	0	0.4758	
Thyroids						
ADENOMA C CELL unilat	7	2	1	2	0.8038	0.9433
ADENOMA FOLLICUL CELL unil	2	1	1	1	0.6073	0.8473
HAEMANGIOSARCOMA	1	0	0	0	1.0000	1.0000
Tongue (incl base)						
SQUAMOUS CELL CARCINOMA	0	1	0	0	0.7134	
Zymbal glands						
SCHWANNOMA	0	0	1	0	0.4724	
SQUAMOUS CELL CARCINOMA	0	1	0	0	0.7008	

Table A.3.4. Tumorgenicity in Female Rats

Organ / Tumor	Control	Low	Medium	High	p-values: Trend	Hi vs Cntrl
Adrenals						
CORTICAL ADENOMA bilat	0	0	1	0	0.4636	
CORTICAL ADENOMA unilat	0	2	2	0	0.7655	
MYELOLIPOMA	1	0	0	0	1.0000	1.0000
PHAEOCHROMACYTOMA bilat	1	0	0	0	1.0000	1.0000
PHAEOCHROMOCYTOMA unilat	2	2	1	0	0.9401	1.0000
Phaeochromacytoma	3	2	1	0	0.9792	1.0000
Brain (cerebrum)						
ASTROCYTOMA benign	1	0	0	0	1.0000	1.0000
ASTROCYTOMA malignant	0	1	0	0	0.8095	
HAEMANGIOMA	0	0	1	0	0.4636	
MENINGIOMA	0	0	0	1	0.2384	0.4800
OLIGODENDROGLIOMA	0	1	0	0	0.7417	

Table A.3.4. (cont.) Tumorgenicity in Female Rats

Organ / Tumor	Control	Low	Medium	High	p-values: Trend	Hi vs Cntrl
Haematopoietic system						
LYMPHOMA LYMPHOBLASTIC TYPE	0	1	0	0	0.8235	
LYMPHOMA LYMPHOCYTIC TYPE	2	1	2	3	0.2565	0.5596
LYMPHOMA PLEOMORPHIC TYPE	0	1	4	0	0.7908	
Harderian glands						
ADENOCARCINOMA unilat	0	0	1	0	0.4636	
ADENOMA unilat	0	0	1	0	0.4636	
HAEMANGIOSARCOMA	0	0	0	1	0.2384	0.4800
Heart						
ENDOCARDIAL SCHWANNOMA BENIGN	0	0	1	0	0.4636	
Ileum						
FIBROSARCOMA	0	1	0	0	0.7417	
SARCOMA NOS	0	0	1	0	0.4581	
Kidneys						
ADENOMA TUBULAR unilat	0	0	1	0	0.4636	
PELVIC CARCINOMA	0	0	1	0	0.4636	
Lesion (abdomen thorax site sk						
LIPOMA	0	1	2	0	0.6136	
OSTEOSARCOMA	0	0	1	0	0.4636	
Lesion (abdominal cavity)						
SCHWANNOMA	0	0	1	0	0.4921	
Lesion (axilla)						
ADENOCARCINOMA MAMMA	0	0	1	0	0.6667	
FIBROADENOMA MAMMA	0	3	2	0	0.7892	
MALIG FIBROC HISTIOCYTOMA	0	0	0	1	0.1765	0.5000
Lesion (chest wall)						
LIPOMA	0	0	1	0	0.4636	
Lesion (clitorial gland)						
ADENOMA	1	0	0	0	1.0000	1.0000
Lesion (ear)						
FIBROSARCOMA	0	0	1	0	0.4636	
Lesion (genital area)						
FIBROADENOMA MAMMA	2	2	3	1	0.6911	0.8647
Lesion (head neck)						
SARCOMA NOS	0	0	0	1	0.2384	0.4800
Lesion (hind fore leg)						
MALIG FIBROC HISTIOCYTOMA	1	0	0	0	1.0000	1.0000
Lesion (neck flank)						
ADENOCARCINOMA MAMMA	0	2	0	0	0.7899	
FIBROADENOMA MAMMA	1	1	0	0	0.9346	1.0000
FIBROMA	0	1	0	0	0.7417	
Lesion (shoulder)						
ADENOMA MAMMA	0	1	0	0	0.7417	
FIBROADENOMA	1	0	0	0	1.0000	1.0000
LIPOMA	0	1	0	0	0.7417	
Lesion (tail back skin)						
HAEMANGIOSARCOMA	0	1	0	0	0.7417	
Lesion (vagina area)						
FIBROADENOMA MAMMA	0	0	1	0	0.4636	
Liver						
BILE DUCT CARCINOMA	1	0	0	0	1.0000	1.0000
HEPATOCELLULAR ADENOMA	1	0	1	0	0.8212	1.0000

Table A.3.4. (cont.) Tumorgenicity in Female Rats

Organ / Tumor	Control	Low	Medium	High	p-values: Trend	Hi vs Cntrl
Lungs with bronchi						
ADENOMA BRONCHIOLO ALVEOLAR	0	0	0	1	0.2384	0.4800
Lymph node (mesenteric)						
HAEMANGIOMA	1	0	2	1	0.3297	0.7330
HAEMANGIOSARCOMA	0	1	2	0	0.5799	
Mammary gland						
ADENOCARCINOMA	4	2	4	1	0.8674	0.9754
ADENOMA	0	1	7	0	0.7550	
ADENOMA CYSTIC	2	0	0	0	1.0000	1.0000
CARCINOMA arising in FIBROA	1	0	0	0	1.0000	1.0000
FIBROADENOMA	9	8	8	4	0.9261	0.9243
FIBROMA	1	1	0	0	0.9346	1.0000
SCHWANNOMA	0	0	0	1	0.2384	0.4800
Adenoma/Adencarcinoma	4	3	11	1	0.9124	0.9754
Mononuclear phagocytis tissue						
HISTIOCYTIC SARCOMA	1	0	1	0	0.7332	1.0000
Ovaries						
GRANULOSA CELL TUMOR	0	0	1	0	0.4636	
SERTOLI CELL TUMOR unilat	1	0	1	0	0.7139	1.0000
SEX CORD STROMAL TUMOR	3	0	2	2	0.4348	0.8241
Oviducts						
ADENOMA	1	0	0	1	0.4212	0.7330
PAPILLOMA	1	1	0	1	0.5136	0.7330
Pancreas						
ADENOMA ISLET CELL	0	5	1	2	0.4907	0.3055
CARCINOMA ISLET CELL	0	0	1	0	0.4636	
Parathyroids						
ADENOMA	1	0	0	0	1.0000	1.0000
Pituitary						
ADENOCARCINOMA PARS DISTALIS	1	0	3	0	0.6933	1.0000
ADENOMA PARS DISTALIS	17	11	10	6	0.9830	0.9976
Skin (left flank)						
HISTIOCYTOMA	0	0	1	0	0.4636	
Systemic						
HAEMANGIOMA	2	0	3	2	0.3216	0.6671
HAEMANGIOSARCOMA	0	2	2	1	0.3963	0.4800
Hemangioma/-sarcoma	2	2	5	3	0.3557	0.4696
Thymus						
THYMOMA	2	3	4	1	0.7422	0.8545
Thyroids						
ADENOMA C CELL bilat	0	1	0	0	0.7467	
ADENOMA C CELL unilat	4	7	5	3	0.8004	0.7620
C CELL CARCINOMA unilat	1	0	0	0	1.0000	1.0000
CARCINOMA FOLLICUL CELL unilat	1	0	0	2	0.1716	0.4932
Tongue (incl base)						
SQUAMOUS CELL CARCINOMA	0	1	0	0	0.8095	
SQUAMOUS CELL PAPILLOMA	0	1	0	0	0.8235	
Urinary bladder						
SARCOMA	0	0	1	0	0.6667	

Table A.3.4. (cont.) Tumorgenicity in Female Rats

Organ / Tumor	Control	Low	Medium	High	p-values: Trend	Hi vs Cntrl
Uterus (incl cervix)						
ADENOCARCINOMA	4	3	3	0	0.9896	1.0000
ADENOMA cyst	0	0	1	0	0.6250	
ENDOMETRIAL STROMAL SARCOMA	0	0	1	0	0.6667	
GRANULOSA CELL TUMOR	1	1	0	0	0.9544	1.0000
HAEMANGIOMA	1	0	0	1	0.5240	0.7400
MALIG FIBROC HISTIOCYTOMA	0	0	1	0	0.4811	
POLYP GLANDULAR	2	4	2	0	0.9624	1.0000
POLYP ENDOMETRIAL STROMAL	6	4	6	1	0.9579	0.9939
SCHWANNOMA	0	0	0	1	0.3750	0.5000
Vagina						
SCHWANNOMA	0	0	0	1	0.3500	0.6364
Zymbal glands						
SQUAMOUS CELL CARCINOMA	0	1	0	0	0.7417	

Appendix 5. References

Chu, K.C., Ceuto, C., and Ward, J.M. (1981), Factors in the Evaluation of 200 National Cancer Institute Carcinogen Bioassays, *Journal of Toxicology and Environmental Health,* 8, 251-280

Haseman, J. K. (1983), A Reexamination of False-positive Rates for Carcinogenicity Studies, *Fundamental and Applied Toxicology,* 3, 334-339.

Lin, K. K. and Ali, M.W. (2006), Statistical Review and Evaluation of Animal Tumorigenicity Studies, *Statistics in the Pharmaceutical Industry,Third Edition,* edited by C.R. Buncher and J.Y. Tsay, Marcel Dekker, Inc. New York.

Lin, K. K. and Rahman, M.A. (1998), Overall False Positive Rates in Tests for Linear Trend in Tumor Incidence in Animal Carcinogenicity Studies of New Drugs, *Journal of Biopharmaceutical Statistics.* 8(1), 1-15.

Peto, R., Pike, M.C., Day, N.E., Gray, R.G., Lee, P.N., Parrish, S., Peto, J., Richards, S., and Wahrendorf, J. (1980). Guidelines for sample sensitive significance tests for carcinogenic effects in long-term animal experiments, *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, supplement 2: Long term and Short term Screening Assays for Carcinogens: A Critical Appraisal,* International Agency for Research Against Cancer, 311-426.

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/s/

Steven Thomson
7/18/2006 03:55:41 PM
BIOMETRICS

Karl Lin
7/18/2006 04:45:25 PM
BIOMETRICS
Concur with review

Executive CAC
Date of Meeting: July 11, 2006

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Joseph Contrera, Ph.D., OPS, Member
John Leighton, Ph.D., DDOP, Alternate Member
Lynnda Reid, Ph.D., DRUP, Team Leader
Laurie McLeod-Flynn, Ph.D., DRUP, Presenting Reviewer

Author of Draft: Laurie McLeod-Flynn

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA # 22030
Drug Name: Fesoterodine
Sponsor: Schwartz

Background:

b(4)

Mouse Carcinogenicity Study: A two-year bioassay was conducted in CD-1/ / CD®-1(ICR)BR mice up to a maximally tolerated dose under GLP conditions. FDA concurrence was given to dose reduction in high dose males from 60 to 45 mg/kg/day in week 42 and from 45 to 30 mg/kg/day in week 66. Dosing was reduced to 0 mg/kg/day in week 84, as per CAC instructions, as tabulated in table below. The administration of test item was terminated in the high dose males, in agreement with CAC, and in high dose females and in low dose males after a mortality rate of 60% was reached. Mice were demonstrated to be exposed to an accurate concentration of the prodrug SPM 8272 and to adequate concentrations of the active drug SPM 7605 and its major human metabolites SPM 5509 and SPM7790. An adequate number of animals survived to perform histopathological examinations and statistical analysis. No treatment related increases in the type or incidence of neoplastic and/or hyperplastic lesions were observed.

Rat Carcinogenicity Study: A two-year bioassay was conducted in the CD® / / CD® rat up to a maximally tolerated dose (FDA concurrence was given to an interim analysis of body weight and mortality after week 53) under GLP conditions. Rats were demonstrated to be exposed to an accurate concentration of the prodrug SPM 8272 and to adequate concentrations of the active drug SPM 7605 and its major human metabolites SPM 5509 and SPM7790. An adequate number of animals survived to perform histopathological examinations and statistical analysis. No treatment related increases in the type or incidence of neoplastic and/or hyperplastic lesions were observed.

b(4)

Executive CAC Recommendations and Conclusions:

Mouse:

* The Committee agreed that the study was adequate, noting prior Exec CAC concurrence.

* The Committee noted that males had a particularly high mortality rate, but agreed that there were no statistically significant tumor findings.

Rat:

* The Committee agreed that the study was adequate, noting prior Exec CAC concurrence.

* The Committee agreed that there were no statistically significant tumor findings.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\
/Division File, DRUP
Lynnda Reid, Ph.D./Team leader, DRUP
Laurie McLeod-Flynn, Ph.D,/Reviewer, DRUP
Jean Makie, M.S., R.D./PM, DRUP
/ASeifried, OND IO

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David Jacobson-Kram
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