# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 204427Orig1s000

# STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

| | |
|---|---|
| **NDA/Serial Number:** | 204427 / 000 |
| **Drug Name:** | Kerydin (tavaborole) solution 5% |
| **Indication(s):** | Onychomycosis |
| **Applicant:** | Anacor |
| **Dates:** | Submitted: 7/29/2013<br>PDUFA: 7/29/2014 |
| **Review Priority:** | Standard review |
| **Biometrics Division:** | Division of Biometrics III |
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**Keywords:** Onychomycosis

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# 1 Executive Summary

Tavaborole solution 5% was superior to vehicle in the treatment of onychomycosis in two studies. Studies 301 and 302 enrolled subjects age 18 and older with a clinical diagnosis of onychomycosis and positive mycology. Subjects applied treatment once daily for 48 weeks. The primary efficacy endpoint was complete cure at Week 52 (0% clinical involvement of target toenail plus negative KOH and negative culture). The secondary efficacy endpoints were: (1) completely clear or almost clear target nail at Week 52, (2) treatment success (completely clear or almost clear target nail and negative mycology) at Week 52, and (3) negative mycology (negative KOH and negative culture). Secondary endpoints were analyzed in sequential order. The primary and secondary efficacy endpoints were all statistically significant and the results are presented in Table 1.

**Table 1 – Primary and Secondary Efficacy Endpoints at Week 52**

| | Study 301 | | | Study 302 | | |
|---|---|---|---|---|---|---|
| | Tavaborole N = 399 | Vehicle N = 194 | p-value | Tavaborole N = 396 | Vehicle N = 205 | p-value |
| *Primary Endpoint* | | | | | | |
| Complete Cure | 26 (6.5%) | 1 (0.5%) | 0.001 | 36 (9.1%) | 3 (1.5%) | <0.001 |
| *Secondary Endpoints* | | | | | | |
| Completely Clear or Almost Clear Nail | 104 (26.1%) | 18 (9.3%) | <0.001 | 109 (27.5%) | 30 (14.6%) | <0.001 |
| Treatment Success* | 61 (15.3%) | 3 (1.5%) | <0.001 | 71 (17.9%) | 8 (3.9%) | <0.001 |
| Negative Mycology | 124 (31.1%) | 14 (7.2%) | <0.001 | 142 (35.9%) | 25 (12.2%) | <0.001 |

*Completely clear or Almost Clear Nail + Negative Mycology

The protocols were submitted as Special Protocol Assessments. The Agency and sponsor reached agreement on the study design and endpoints. The protocols were amended to add an additional 8-week follow-up for subjects with completely clear or almost clear nails at Week 48 to assess durability of effect. As this amendment was added during the study, only subjects who enrolled later in the trial had the additional follow-up. Because subjects who enrolled early in the recruitment period completed the study before the amendment went into effect, only one-fifth to one-third of tavaborole subjects (from Studies 301 and 302 respectively) who met the efficacy criteria that would have triggered the additional follow-up were actually followed up. With the limited number of subjects who were followed, it is impossible to assess whether the subjects who were followed up were similar to subjects enrolled earlier in the trial, and this additional analysis has limited utility.

# 2 Introduction

## *2.1 Overview*

### 2.1.1 Clinical Studies

Tavaborole solution 5% is a new molecular entity intended for the treatment of onychomycosis. This submission is a 505(b)(1) application. Tavaborole solution was evaluated in a double-blind dose-ranging Phase 2 study (Study 200/200A), two open-label cohort Phase 2 studies, where one dosing regimen cohort is fully enrolled before the next cohort is enrolled (Studies 201 and 203), and two identical vehicle-controlled Phase 3 studies (Studies 301 and 302). The Phase 2 studies evaluated dose levels of 1%, 2.5%, 5%, and 7.5% and various treatment regimens from once daily for 30 days followed by three times weekly for 150 days to once daily treatment for 360 days. The basic design details and treatment regimens assessed are summarized in Table 2.

**Table 2 – Clinical Studies Overview – Phase 2 Studies**

| Study number | 201 (Cohorts 1 &2) | 201 (Cohort 3) | 203 | 200/200A |
|---|---|---|---|---|
| Study design | Open-label rising dose cohort | Open-label dose cohort | Open-label rising dose cohort | Randomized, double-blind |
| Treatment regimen | Once daily for 180 days | Once daily for 360 days | Once daily for 180 days (1%) or once daily for 30 days, then 3x weekly for 150 days (5%) | Once daily for 90 days, then 3x weekly for 90 days |
| Treatment arms and sample size | Tavaborole 5% (17)<br>Tavaborole 7.5% (18)<br>(MITT) | Tavaborole 5% (29)<br>(ITT) | Tavaborole 1% (30)<br>Tavaborole 5% (30)<br>(ITT) | Tavaborole 2.5% (33)<br>Tavaborole 5% (31)<br>Tavaborole 7.5% (60)<br>Vehicle (63)<br>(ITT) |
| Study location | Mexico | Mexico | United States | U.S. and Mexico |
| Study dates | Nov. 2005 – Feb. 2007 | Mar. 2007 – July 2008 | June 2006 – Aug. 2007 | Feb. 2006 – Aug. 2007 |

The Phase 3 studies evaluated tavaborole solution 5% with a dosing regimen of once daily treatment with for 48 weeks. Study 301 randomized 400 tavaborole and 194 vehicle subjects (one tavaborole subject was randomized in error and did not receive medication). Study 302 randomized 399 tavaborole and 205 vehicle subjects (three tavaborole subjects were randomized in error and did not receive medication). Both studies enrolled subjects age 18 and older with 20-60% involvement of the target toenail, positive culture, and positive KOH. The primary efficacy endpoint was complete cure (0% clinical involvement of target toenail plus negative KOH and negative culture) at Week 52. Study 301 was conducted in the U.S. and Mexico. Study 302 was conducted in the U.S.

and Canada. An overview of the Phase 3 studies is presented in Table 3. This review will focus primarily on the two Phase 3 studies.

**Table 3 – Clinical Studies Overview – Phase 3 Studies**

| | |
|---|---|
| Study numbers | 301 and 302 |
| Study design | Randomized, double-blind, vehicle-controlled |
| Inclusion criteria | Adults with a clinical diagnosis of onychomycosis, 20-60% involvement of target nail, ≥ 3mm of clear nail from proximal fold, distal toenail plate thickness ≤ 3mm, positive KOH, and positive culture. |
| Treatment regimen | Once daily to all affected nails for 48 weeks. |
| Primary endpoint | Complete cure at Week 52 (no clinical evidence of onychomycosis, negative KOH, and negative culture) |
| Treatment arms and sample size | 301 / 302<br>Tavaborole 400* (399 ITT) / 399* (396 ITT)<br>Vehicle 194 / 205 |
| Study location | 301: US – 504, Mexico – 89<br>302: US – 480, Canada – 121 |
| Study dates | 301: Dec. 2010 – Jan 2013; 302: Feb. 2011 – Feb. 2013 |

*One tavaborole subject in Study 301and three tavaborole subjects in Study 302 were randomized in error and did not receive medication and were not included in the ITT population.

### 2.1.2 Regulatory History

The IND for tavaborole was opened in 2005 with a pharmacokinetics study. The following meetings were held with the sponsor:

- Pre-IND meeting (10/3/2005)
- Guidance meeting (6/11/2007)
- Guidance meeting (8/13/2008)
- End of Phase 2 meeting (10/28/2009)
- Guidance meeting (11/14/2012)
- Pre-NDA meeting (5/29/2013)

Protocol 301 was submitted as a Special Protocol Assessment (SPA) on 8/14/2010, and an agreement letter was issued on 9/13/2010. The Agency and sponsor reached agreement on the study design and endpoints. The protocols were amended two times, in November 2010 and in September 2012. The first amendment addressed issues such as providing additional details regarding missing data and sensitivity analyses. The second amendment added an additional 8-week follow-up for subjects with completely clear or almost clear nails. As this amendment was added during the study, only a portion of eligible subjects had the additional follow-up.

## *2.2 Data Sources*

This reviewer evaluated the applicant's clinical study reports, datasets, clinical summaries, and proposed labeling. This submission was submitted in eCTD format and was entirely electronic. Both SDTM and analysis datasets were submitted. The analysis datasets used in this review are archived at \\cdsesub1\evsprod\nda204427\0000\m5\datasets.

# 3 Statistical Evaluation

## *3.1 Data and Analysis Quality*

The databases for the studies required minimal data management prior to performing analyses and no requests for additional datasets were made to the applicant.

## *3.2 Evaluation of Efficacy*

### 3.2.1 Study Design and Statistical Analysis

Studies 301 and 302 were identically designed, randomized, double-blind, vehicle-controlled studies of the efficacy and safety of tavaborole solution, 5% in the treatment of onychomycosis. The studies enrolled subjects aged 18 and older with a clinical diagnosis of distal subungual onychomycosis affecting at least one great toenail and positive KOH and positive culture. The target nail was to have 20 to 60% involvement with at least 3 mm of clear nail measured from the proximal nail fold and distal plate thickness of ≤ 3 mm. Subjects were randomized in a 2:1 ratio to tavaborole or vehicle. Treatment was applied once daily for 48 weeks. Subjects were evaluated at screening, baseline, and Weeks 2, 6, 12, 18, 24, 30, 36, 42, 48, and 52. After a protocol amendment, some subjects were also evaluated at Week 60 (subjects who had not yet had a Week 52 visit when the amendment was implemented and who had a completely clear or almost clear nail at Week 48).

Efficacy assessments included extent of involvement of the target nail, extent and number of non-target nails with involvement, KOH and culture. Extent of involvement of the target nail was assessed on the following scale

Completely clear – 0% toenail involvement
Almost clear – disease present but involving ≤ 10% of the toenail
Mild – >10% to ≤ 20% toenail involvement
Moderate – >20% to ≤ 60% toenail involvement
Severe – >60% toenail involvement

The number of non-target toenails that were completely clear (0% involvement), almost clear (disease present but ≤ 10% involvement), and more than 10% affected were also recorded at each visit. KOH and culture were assessed at screening and Weeks 12, 24, 36, 48, 52, and 60. They were assessed at the other visits only if the target nail achieved ≤ 10% involvement for the first time at that visit. Local tolerability signs and symptoms for burning/stinging, induration/edema, oozing and crusting, pruritus, erythema, and scaling were recorded on 4-point scales (none, mild, moderate, severe) at each visit.

The primary efficacy endpoint was complete cure (completely clear nail, negative KOH, and negative culture) at Week 52 (4 weeks post-treatment). The secondary endpoints were (1) completely clear or almost clear target nail at Week 52, (2) treatment success (completely clear or almost clear target nail and negative mycology) at Week 52, and (3) negative mycology (negative KOH and negative culture). The 'other' efficacy endpoints were (1) change from baseline in the proportion of other nails (not including the target

nail) that were completely clear or almost clear at Week 52, and (2) durability of clinical benefit from Week 52 to Week 60.

Complete cure was analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by analysis center. The secondary endpoints of completely clear or almost clear target nail, treatment success, and negative mycology were also analyzed using the CMH test stratified by analysis center. To control multiplicity among the secondary endpoints, the hypotheses were tested in sequential order (completely clear or almost clear target nail, treatment success, and negative mycology).

Small centers were combined into analysis centers for the CMH analyses. Sites that enrolled fewer than 8 tavaborole and 4 vehicle subjects were pooled with another site from the geographic region. The site with the smallest enrollment was combined with the site with the largest enrollment among sites that did not meet the enrollment targets, and so forth with the second smallest and second largest, etc. until all analysis centers met the minimum size. Consistency of treatment response across analysis centers for the primary endpoint was assessed with the Breslow-Day test. If the Breslow-Day test was significant at 0.10, sensitivity analyses were conducted to assess the impact of extreme centers.

The ITT population was defined as all subjects randomized and dispensed study drug. The per protocol population included subjects who

- met all inclusion/exclusion criteria unless a waiver was granted prior to randomization
- did not take any interfering concomitant medications
- completed the Week 52 visit
- applied 80% to 120% of the total number of expected doses during the treatment period
- did not miss more than 14 consecutive doses during the treatment period
- did not miss 28 or more consecutive doses during the treatment period
- were not out of the visit window (± 7 days) for the Week 52 visit

Subjects who prematurely discontinued from the study due to worsening of onychomycosis or a treatment-related adverse event were included in the per protocol population with the last value carried forward. Subjects who missed doses due to a drug holiday but finished the study were excluded from the per protocol population if they missed more than 20% of the scheduled doses.

The primary method of handling missing data for the primary efficacy analysis was last observation carried forward (LOCF). As a sensitivity analysis, subjects with missing Week 52 complete cure assessments were imputed as failures. A second sensitivity analysis imputes subjects with missing values as successes. A third sensitivity analysis used multiple imputation. For the multiple imputation model, 5 complete data sets were imputed using logistic regression with treatment group as the independent factor. Each complete data set was analyzed with logistic regression and the results were combined for the inference.

### 3.2.2 Subject Disposition

Study 301 randomized 400 subjects to tavaborole and 194 subjects to vehicle. One subject (randomized to tavaborole) did not meet the inclusion criteria, but was denoted as 'randomized' rather than 'screen failure' in the IWRS (interactive web randomization system). This subject was not dispensed study medication and is not included in the ITT or safety population. Study 302 randomized 399 subjects to tavaborole and 205 subjects to vehicle. Two subjects (both randomized to tavaborole) did not meet the inclusion criteria, but were denoted as 'randomized' rather than 'screen failure' in the IWRS. Neither subject was dispensed medication or included in the ITT or safety population. One additional subject (also randomized to tavaborole) decided that they did not wish to commit to all study visits and was withdrawn from the study before treatment medication was dispensed. This subject was also not included in the ITT or safety population. Note that in the database, one out of the four subjects who were not dispensed medication was classified as 'discontinuing treatment', while the other three subjects were neither classified as 'discontinuing treatment' nor 'completing treatment' (item left blank). All four subjects were classified as discontinuing the study.

Similar proportions of tavaborole and vehicle subjects (around 13%) discontinued the study (did not return for further follow-up) in both Study 301 and 302. The disposition and reasons for discontinuation are presented in Table 4. Subjects who discontinued treatment early were encouraged to remain in the study and complete visits. The most common reasons for discontinuation are Subject Request – Unrelated to Study Treatment and Lost to Follow-up. Eleven subjects (9 tavaborole in Study 301, 1 tavaborole in Study 302, and 1 vehicle in Study 301) discontinued treatment due to adverse events, but completed the study. One subject (vehicle in Study 302) discontinued treatment due to non-compliance, but completed the study.

**Table 4 – Disposition of Subjects in Studies 301 and 302**

| | Study 301 | | Study 302 | |
|---|---|---|---|---|
| | Tavaborole | Vehicle | Tavaborole | Vehicle |
| *Subjects Randomized* | 400 | 194 | 399 | 205 |
| Not Dispensed Treatment | 1 (0.3%) | 0 (0%) | 3 (0.8%)[a] | 0 (0%) |
| Discontinued Treatment and Discontinued Study | 50 (12.5%) | 23 (11.9%) | 45 (11.3%)[a] | 27 (13.2%) |
| Discontinued Treatment but Completed Study | 9 (2.3%)[b] | 1 (0.5%)[b] | 1 (0.3%)[b] | 1 (0.5%)[c] |
| Completed Treatment but Discontinued Study | 1 (0.3%)[d] | 0 (0%) | 2 (0.5%)[d,e] | 1 (0.5%)[d] |
| Completed Treatment and Completed Study | 339 (84.8%) | 170 (87.6%) | 348 (87.2%) | 176 (85.9%) |
| *Reason for Treatment Discontinuation* | | | | |
| Adverse event | 10 (2.5%) | 3 (1.5%) | 3 (0.8%) | 1 (0.5%) |
| Lost to follow-up | 18 (4.5%) | 5 (2.6%) | 10 (2.5%) | 4 (2.0%) |
| Subject request – Unrelated to study treatment | 19 (4.8%) | 8 (4.1%) | 25 (6.3%) | 14 (6.8%) |
| Subject request – Related to study treatment | 4 (1.0%) | 3 (1.5%) | 2 (0.5%) | 5 (2.4%) |
| Non-compliance | 2 (0.5%) | 2 (1.0%) | 4 (1.0%) | 3 (1.5%) |
| Other | 6 (1.5%) | 3 (1.5%) | 3 (0.8%)[a] | 1 (0.5%) |
| *Reason for Study Discontinuation* | | | | |
| Adverse event | 1 (0.3%) | 2 (1.0%) | 2 (0.5%) | 1 (0.5%) |
| Lost to follow-up | 18 (4.5%) | 5 (2.6%) | 10 (2.5%) | 4 (2.0%) |
| Subject request – Unrelated to study treatment | 20 (5.0%) | 8 (4.1%) | 27 (6.8%) | 15 (7.3%) |
| Subject request – Related to study treatment | 4 (1.0%) | 3 (1.5%) | 3 (0.8%) | 5 (2.4%) |
| Non-compliance | 2 (0.5%) | 2 (1.0%) | 4 (1.0%) | 2 (1.0%) |
| Other | 7 (1.8%) | 3 (1.5%) | 4 (1.0%) | 1 (0.5%) |

[a] 1 subject (315-008) who was not dispensed medication was classified as discontinuing treatment and discontinuing the study. The subject is included as 'not dispensed treatment' rather than 'discontinued treatment and discontinued study' in the top part of this table, rather than as discontinuing treatment and discontinuing study (as listed in the database). This subject is included in the middle of the table as discontinuing treatment due to 'other' reasons (as listed in the database).
[b] All subjects discontinued treatment due to Adverse Events
[c] 1 subject discontinued treatment due to Non-compliance with Protocol
[d] 1 subject discontinued study due to Subject Request – Unrelated to Study Treatment
[e] 1 subject discontinued study due to Subject Request – Related to Study Treatment
Source: pg 82 of Study Report for Study 301, pg 81 of Study Report for Study 302, and reviewer analysis.

### 3.2.3 Baseline Characteristics

Baseline demographics were generally balanced across the treatment groups in the two studies. The mean age was about 54 years with approximately 19% of the subjects aged 65 or older. Approximately 82% of the subjects were male. In Study 301, approximately 79% of the subjects were white, and 5% were black. Twenty-six percent of subjects in Study 301 were of Hispanic/Latino ethnicity. The Mexican sites enrolled approximately 15% of subjects. In Study 302, approximately 90% of subjects were white and 5% were black. Fourteen percent of subjects in Study 302 were of Hispanic/Latino ethnicity. The Canadian sites enrolled approximately 20% of subjects. See Table 5.

**Table 5 – Demographics in Studies 301 and 302**

| | Study 301 | | Study 302 | |
|---|---|---|---|---|
| | Tavaborole N=399 | Vehicle N=194 | Tavaborole N=396 | Vehicle N=205 |
| *Age (years)* | | | | |
| Mean | 53.6 | 53.4 | 55.5 | 55.4 |
| Range | 18-88 | 19-81 | 20-81 | 27-81 |
| 18 to 64 years | 328 (82%) | 157 (81%) | 316 (80%) | 162 (79%) |
| 65 + years | 71 (18%) | 37 (19%) | 80 (20%) | 43 (21%) |
| *Gender* | | | | |
| Male | 324 (81%) | 158 (81%) | 323 (82%) | 174 (85%) |
| Female | 75 (19%) | 36 (19%) | 73 (18%) | 31 (15%) |
| *Race* | | | | |
| White | 316 (79%) | 152 (78%) | 355 (90%) | 183 (89%) |
| Black or Afric.-Amer. | 19 (5%) | 12 (6%) | 21 (5%) | 14 (7%) |
| Amer. Ind./AK Native | -- | -- | 2 (0.5%) | 1 (0.5%) |
| Asian | 2 (0.5%) | -- | 11 (3%) | 2 (1%) |
| Native HI/Pac. Islander | -- | -- | 2 (0.5%) | 1 (0.5%) |
| Other | 62 (16%) | 30 (15%) | 5 (1%) | 4 (2) |
| *Ethnicity* | | | | |
| Hispanic or Latino | 99 (25%) | 54 (28%) | 57 (14%) | 30 (15%) |
| Not Hispanic or Latino | 300 (75%) | 140 (72%) | 339 (86%) | 175 (85%) |
| *Country* | | | | |
| United States | 340 (85%) | 164 (85%) | 315 (80%) | 165 (80%) |
| Mexico | 59 (15%) | 30 (15%) | -- | -- |
| Canada | -- | -- | 81 (20%) | 40 (20%) |

Source: pg 84 of Study Report for Study 301, pg 83 of Study Report for Study 302, and reviewer analysis.

To be enrolled in the study subjects were to have 20 to 60% involvement of the great toenail, with positive KOH and culture. The vast majority of subjects had baseline cultures positive with *T. rubrum* (approximately 95%). A small percentage of subjects had <20% target toenail involvement or cultures negative for dermatophytes in violation of the inclusion criteria. See Table 6. All but one of the subjects with negative cultures were discontinued from treatment and the study early because of the negative cultures. The subject with a negative baseline culture who remained in the study (randomized to tavaborole) had 10 to 20% toenail involvement at the end of the study and was neither a

complete cure, nor a treatment success. Subjects had an average of 3.4 affected non-target affected toenails at baseline.

**Table 6 – Baseline Disease Characteristics in Studies 301 and 302**

| | Study 301 | | Study 302 | |
|---|---|---|---|---|
| | Tavaborole N=399 | Vehicle N=194 | Tavaborole N=396 | Vehicle N=205 |
| *Target Toenail Involvement* | | | | |
| Mild (>10% to ≤ 20%) | 8 (2%) | 3 (2%) | 5 (1%) | 3 (1%) |
| Moderate (>20% to ≤ 60%) | 391 (98%) | 191 (98%) | 390 (98%) | 202 (99%) |
| Severe (>60%) | -- | -- | 1 (0.3%) | -- |
| *Number of affected non-target toenails* | | | | |
| Mean (SD) | 3.4 (2.8) | 3.8 (2.7) | 3.3 (2.8) | 3.3 (2.6) |
| *Screening Culture* | | | | |
| *T. rubrum* | 379 (95%) | 184 (95%) | 376 (95%) | 188 (92%) |
| *T. mentagrophytes* | 8 (2%) | 5 (3%) | 14 (4%) | 12 (6%) |
| *E. floccosum* | 0 | 0 | 0 | 2 (1%) |
| Multiple | 3 (0.7%) | 4 (2%) | 4 (1%) | 2 (1%) |
| No dermatophyte | 4 (1%) | 1 (0.5%) | 2 (0.5%) | 1 (0.5%) |

Source: pg 85 of Study Report for Study 301, pg 84 of Study Report for Study 302, and reviewer analysis

### 3.2.4 Primary Efficacy Endpoint

Tavaborole was superior to vehicle on the primary efficacy endpoint of complete cure at Week 52 in both studies ($p \leq 0.001$). Complete cure is defined as completely clear target nail, negative KOH, and negative culture. The complete cure rate was analyzed with a CMH test stratified by analysis center. For the ITT analysis, the primary method of handling missing data was LOCF. The results from the ITT and per protocol analyses were similar. The ITT and per protocol results are presented in Table 7.

**Table 7 – Complete Cure at Week 52 in Studies 301 and 302**

| | Study 301 | | Study 302 | |
|---|---|---|---|---|
| | Tavaborole | Vehicle | Tavaborole | Vehicle |
| ITT | 26/399 (6.5%) | 1/194 (0.5%) | 36/396 (9.1%) | 3/205 (1.5%) |
| | p=0.001 | | p<0.001 | |
| Per Protocol | 23/312 (7.4%) | 1/156 (0.6%) | 30/299 (10.0%) | 2/157 (1.3%) |
| | p=0.001 | | p<0.001 | |

Source: pg 87 and 175 of Study Report for Study 301, pg 86 and 161of Study Report for Study 302.

### 3.2.5 Missing Data Handling

The protocols specified three sensitivity analyses for handling missing data: imputing missing as failures, imputing missing as successes, and using multiple imputation. Missing data rates were similar on the two arms: 13% for tavaborole and 12% for vehicle

in Study 301, and 12% for tavaborole and 14% for vehicle in Study 302. Under LOCF imputation, only 2 subjects were imputed as having success for complete cure. Both subjects were randomized to tavaborole in Study 302. One of the subjects had their last efficacy assessment on Day 211 and the other on Day 296 where they met the complete cure criteria. Thus, the missing as failure analysis is very similar to the LOCF analysis. Because a slightly higher proportion of tavaborole subjects than vehicle subjects had missing data in Study 301, while a slightly higher proportion of vehicle subjects than tavaborole subjects had missing data in Study 302, the 'missing as success' imputation leads to a slightly smaller treatment effect in Study 301 and a slightly larger treatment effect in Study 302, but in both cases the trend still favors tavaborole. For the multiple imputation analysis the applicant generated 5 complete data sets and used logistic regression with treatment group as the independent factor for the imputation model. The complete datasets were also analyzed with logistic regression and combined in a single inference. In general the treatment effects were consistent across the different sensitivity analyses. See Table 8.

**Table 8 – Complete Cure Rates Under Missing Data Sensitivity Analyses in Studies 301 and 302**

| | Study 301 | | Study 302 | |
|---|---|---|---|---|
| | Tavaborole N=399 | Vehicle N=194 | Tavaborole N=396 | Vehicle N=205 |
| Missing as Failure | 26 (6.5%) | 1 (0.5%) p=0.001 | 34 (8.6%) | 3 (1.5%) p=0.001 |
| Missing as Success | 77 (19.3%) | 24 (12.4%) p=0.026 | 81 (20.5%) | 31 (15.1%) p=0.128 |
| Multiple Imputation | 7.4% | 0.6% p=0.012 | 9.8% | 1.7% p=0.003 |

Source: pg 177 of Study Report for Study 301, pg 164 of Study Report for Study 302.

### 3.2.6 Secondary Efficacy Analyses

The secondary endpoints were (1) completely clear or almost clear target nail at Week 52, (2) treatment success (completely clear or almost clear target nail and negative mycology) at Week 52, and (3) negative mycology (negative KOH and negative culture). The secondary endpoints of completely clear or almost clear target nail, treatment success, and negative mycology were analyzed using the CMH test stratified by analysis center. To control multiplicity among the secondary endpoints, the hypotheses were tested in sequential order (completely clear or almost clear target nail, treatment success, and negative mycology). The secondary endpoint outcomes are consistent with the primary efficacy outcome, and all three were statistically significant in both studies when tested in sequential order. See Table 9.

**Table 9 - Secondary Efficacy Endpoints at Week 52 in Studies 302 and 302 (ITT)**

| | Study 301 | | | Study 302 | | |
|---|---|---|---|---|---|---|
| | Tavaborole N = 399 | Vehicle N = 194 | p-value | Tavaborole N = 396 | Vehicle N = 205 | p-value |
| Completely Clear or Almost Clear Nail | 104 (26.1%) | 18 (9.3%) | <0.001 | 109 (27.5%) | 30 (14.6%) | <0.001 |
| Treatment Success* | 61 (15.3%) | 3 (1.5%) | <0.001 | 71 (17.9%) | 8 (3.9%) | <0.001 |
| Negative Mycology | 124 (31.1%) | 14 (7.2%) | <0.001 | 142 (35.9%) | 25 (12.2%) | <0.001 |

*Completely Clear or Almost Clear Nail + Negative Mycology
Source: pg 88 of Study Report for Study 301, pg 87 of Study Report for Study 302.

While the studies were ongoing, the applicant modified the protocols to add an 8-week follow-up period (additional visit at Week 60) for subjects who had clinical assessments of completely clear or almost clear nail at Week 48. Only the subjects enrolled after the amendment was implemented and who met the efficacy criterion were followed-up. In Study 301, 86 tavaborole and 14 vehicle subjects had completely clear or almost clear nail at Week 48, but only 18 (20%) of tavaborole subjects and 2 (14%) of vehicle subjects who met this efficacy criterion reached this milestone after the protocol amendment went into effect and entered the follow-up period. Similarly in Study 302, 97 tavaborole and 21 vehicle subjects had completely clear or almost clear nail at Week 48, but only 31 (32%) of tavaborole subjects and 11 (52%) of vehicle subjects reached this milestone after the protocol amendment and entered the follow-up period. The greater proportion of subjects in Study 302 who were followed-up is likely due to the fact that Study 302 began recruitment 2 months after Study 301, and thus a greater proportion of subjects were still in the study when the protocol was amended. Most subjects maintained at least 'almost clear' status during the follow-up period, though two vehicle subjects in Study 301 and two tavaborole subjects in Study 302 worsened to mild or moderate status. However, because fewer than one-third of the tavaborole subjects that would have been eligible for follow-up if the plan had been in place when the study began were enrolled after the amendment, the available data is too limited to draw conclusions about the durability of effect. This durability of effect endpoint was considered an 'other' endpoint and was not statistically analyzed. See Table 10 and Table 11.

**Table 10 – Clinical Status during Follow-up Period in Study 301**

| | | Week 60 | | | |
|---|---|---|---|---|---|
| | Week 48 | Completely Clear | Almost Clear | Mild | Moderate |
| **Tavaborole** (N=18) | Completely Clear | 1 (5.6%) | 4 (22.2%) | -- | -- |
| | Almost Clear | 4 (22.2%) | 9 (50.0%) | -- | -- |
| **Vehicle** (N=2) | Completely Clear | -- | -- | -- | -- |
| | Almost Clear | -- | -- | 1 (50.0%) | 1 (50.0%) |

Source: pg 179 of Study Report for Study 301.

**Table 11 – Clinical Status during Follow-up Period in Study 302**

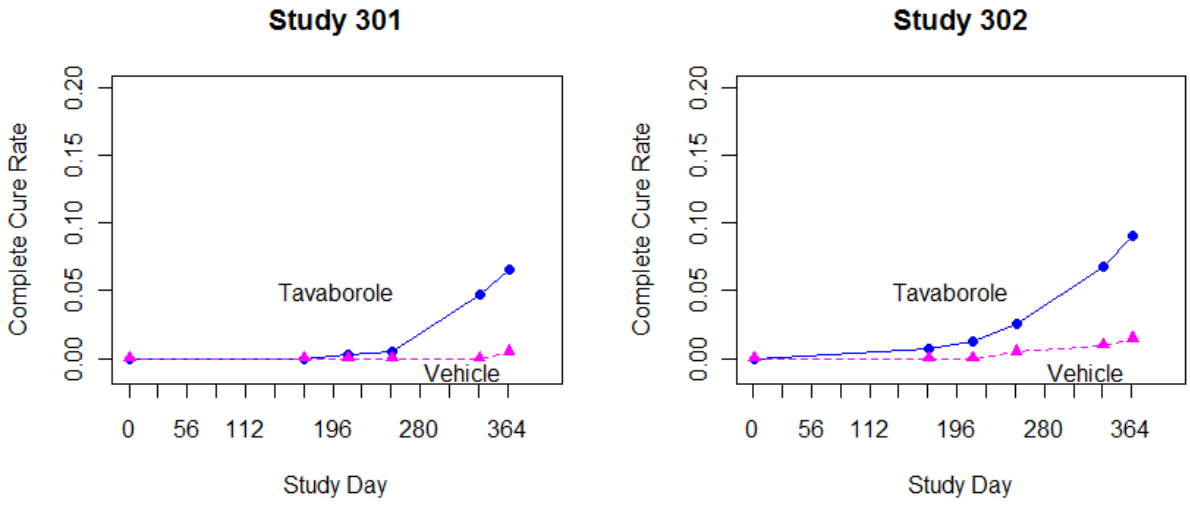
| | | Week 60 | | | |
|---|---|---|---|---|---|
| | Week 48 | Completely Clear | Almost Clear | Mild | Moderate |
| **Tavaborole** (N=31) | Completely Clear | 10 (32.3%) | 1 (3.2%) | -- | -- |
| | Almost Clear | 5 (16.1%) | 13 (41.9%) | 2 (6.5%) | -- |
| **Vehicle** (N=11) | Completely Clear | 1 (9.1%) | 1 (9.1%) | -- | -- |
| | Almost Clear | 2 (18.2%) | 7 (63.6%) | -- | -- |

Source: pg 166 of Study Report for Study 302.

### 3.2.7 Efficacy over Time

Complete cure rates (the primary efficacy endpoint) increased over time through Week 52 and the curves began to separate at the Week 48 visit (Day 337). The results were similar for the two studies. See Figure 1.

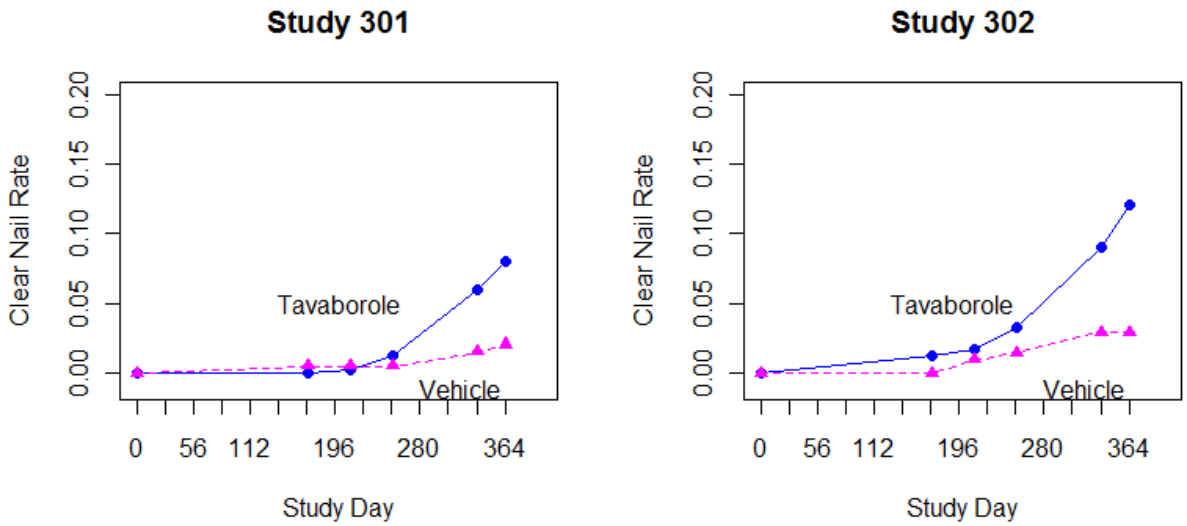
**Figure 1 – Complete Cure Rates over Time in Studies 301 and 302 (LOCF)**




Source: reviewer analysis

Assessment of complete cure involves three components: nail involvement, KOH result and culture result. The completely clear nail rate (0% affected area) has similar trends to the complete cure rate (clear nail plus negative mycology), with the curves separating at the Week 48 visit and rates increasing through Week 52. See Figure 2.

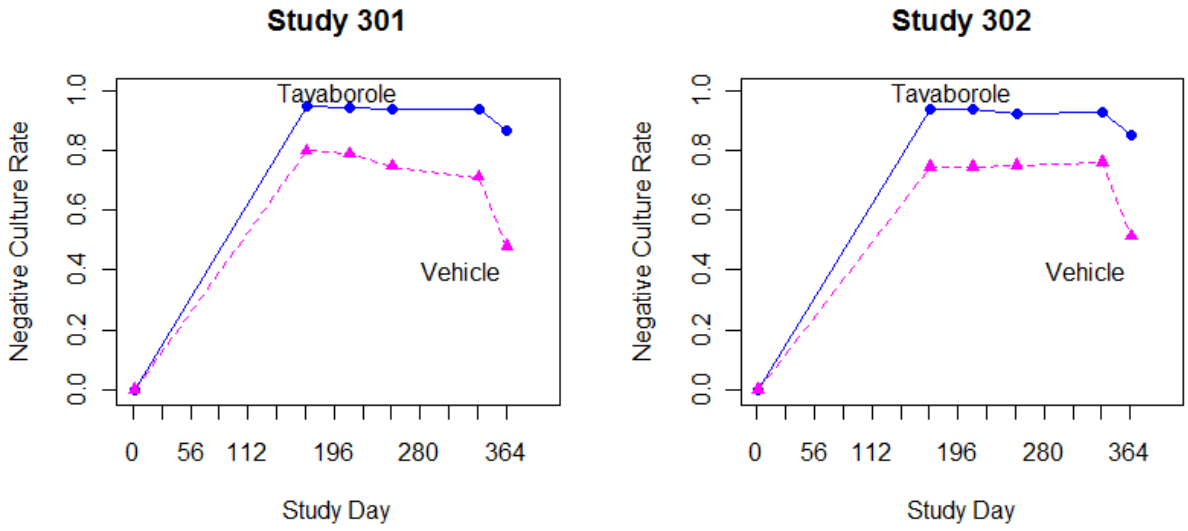
**Figure 2 – Clear Nail Rate over Time in Studies 301 and 302 (LOCF)**




Source: reviewer analysis

The majority of subjects had negative cultures at the first post-baseline culture assessment (Day 169 or Week 24), though the rate was slightly higher in the tavaborole arm. Of note, the negative culture rate dropped slightly at the Week 52 visit, which was four weeks after the last treatment application. The negative culture rate at Week 52 was similar in both studies and was 87% for tavaborole versus 48% for vehicle in Study 301 and 85% for tavaborole versus 51% for vehicle in Study 302. See Figure 3.

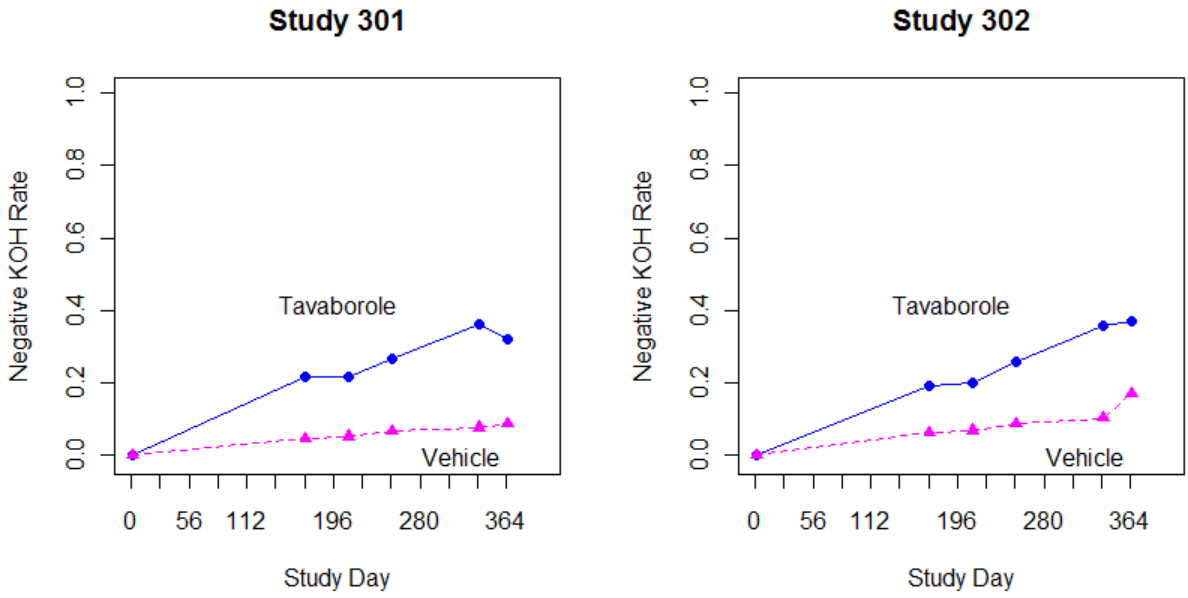
**Figure 3 – Negative Culture Rate over Time in Studies 301 and 302 (LOCF)**




Source: reviewer analysis

The negative KOH rate did not increase as rapidly as the negative culture rate, though it increased throughout the treatment period. The negative KOH rate at Week 52 was 32% for tavaborole versus 9% for vehicle in Study 301 and 37% for tavaborole versus 17% for vehicle in Study 302. See Figure 4.

**Figure 4 – Negative KOH Rate over Time in Studies 301 and 302 (LOCF)**

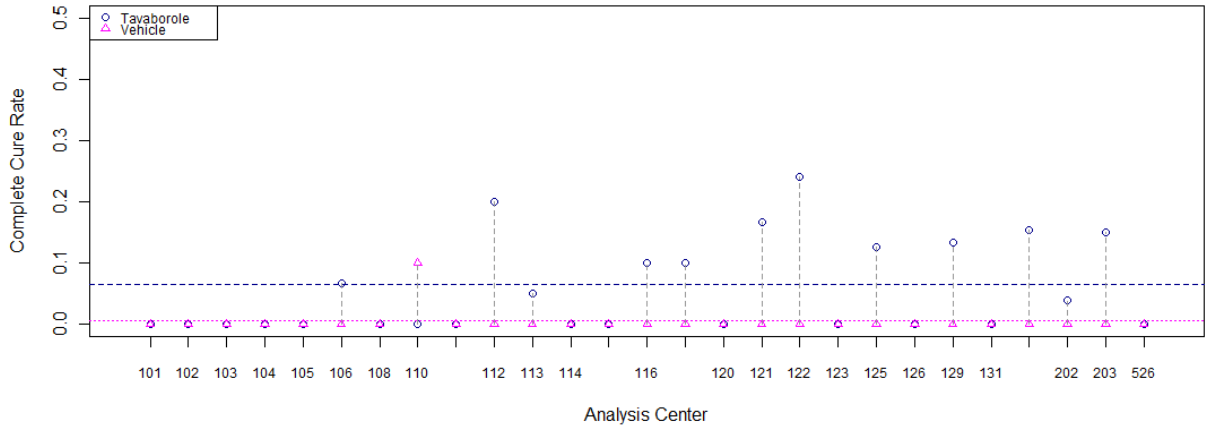



Source: reviewer analysis

### 3.2.8 Efficacy by Center

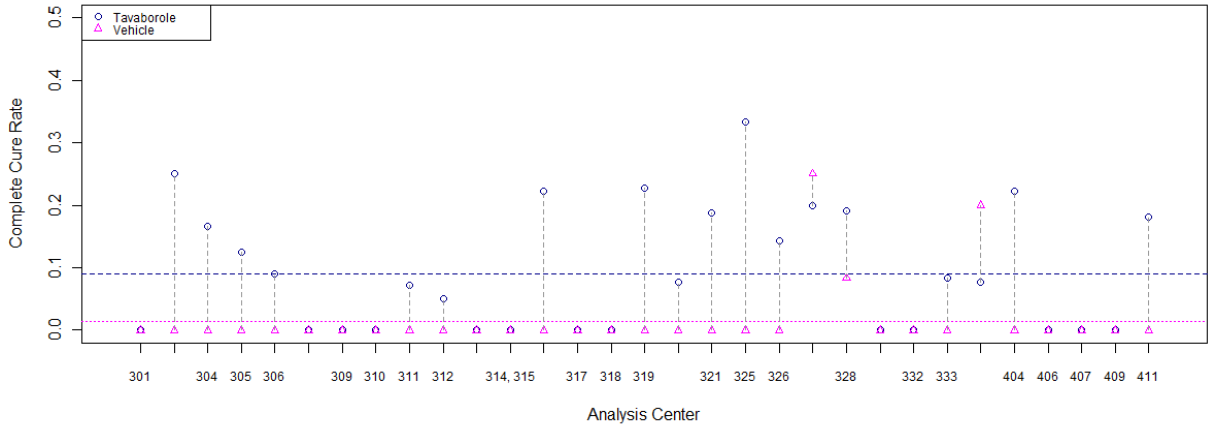
Study 301 was conducted at 34 centers, 28 in the United States and 6 in Mexico. After pooling, Study 301 had 27 analysis centers (24 U.S. and 3 Mexican). The centers with numbers in the 100s and 500s were U.S. centers and centers with numbers in the 200s were Mexican centers. Study 302 was conducted at 42 centers, 33 in the US and 9 in Canada. After pooling, Study 302 had 31 analysis centers (25 U.S. and 6 Canadian). The centers with numbers in the 300s were U.S. centers and centers with numbers in the 400s were Canadian centers. Because of the large number of centers and the low overall response rate on the vehicle arm no center is overly influential on the overall results. Many centers had no complete cures on either the tavaborole or vehicle arms. See Figure 5 and Figure 6. Per the protocol, the applicant conducted the Breslow-Day test for homogeneity. The p-values from the Breslow-Day test were 0.008 for Study 301 and 0.706 in Study 302. Note that the Breslow-Day test requires a large sample size within each center, and with only 1 vehicle subject in the whole study who had a complete cure in Study 301, the data on the vehicle arm are very sparse. Thus the significant result for the Breslow-Day test in Study 301 is not meaningful and is likely due to the very low vehicle response rate in that study.

**Figure 5 – Complete Cure Rate by Analysis Center (Study 301)**




Source: reviewer analysis

**Figure 6 – Complete Cure Rate by Analysis Center (Study 302)**




Source: reviewer analysis

Note that the list of investigators notes that centers 126 and 526 have the same primary investigator and location (Diane McConnehey, Boise, ID; see pg 4 of 1614-invest-list.pdf for Study 301). However the audit certificate lists a Nampa, ID address for Diane McConnehey (see pg 6 of 1618-audit-cert-report.pdf for Study 301). Thus although the application does not directly address the reason for one investigator having two center numbers, the distinction may be due to different locations. Center 126 enrolled 28 subjects with screening dates between 2/16/2011 and 9/22/2011. Center 526 enrolled 12 subjects with screening dates between 9/8/2011 and 10/19/2011. None of the tavaborole or vehicle subjects at either center achieved complete cure in the trial. Thus both of the McConnehey centers had an estimated treatment effect of 0. See Table 12.

**Table 12 – Complete Cure Rates at McConnehey Centers (Study 301)**

| | Tavaborole N = 399 | Vehicle N = 194 |
|---|---|---|
| Center 126 | 0/20 (0%) | 0/8 (0%) |
| Center 526 | 0/8 (0%) | 0/4 (0%) |
| Other Centers | 26/371 (7%) | 1/181 (0.6%) |

Source: reviewer analysis

## *3.3 Evaluation of Safety*

### 3.3.1 Extent of Exposure

Subjects on the tavaborole and vehicle arms used similar amounts of study treatment in the Studies 301 and 302. The planned number of study product applications was 336 and the mean number of applications was around 302 and 306 for the tavaborole arms in the two studies, and 307 and 305 for the vehicle arms in the two studies. Similarly, the mean amount of study product (grams) used in the two studies was around 108 to 110 g in the two tavaborole arms, and 112 to 115 g in the two vehicle arms. These calculations were computed in subjects with available data. See Table 13.

**Table 13 – Extent of Exposure in Studies 301 and 302 (Safety Population)**

| | Study 301 | | Study 302 | |
|---|---|---|---|---|
| | Tavaborole N = 396 | Vehicle N = 193 | Tavaborole N = 395 | Vehicle N = 202 |
| *Number of Applications* | *N=396* | *N=193* | *N=395* | *N=202* |
| Mean (SD) | 302.5 (73.3) | 307.4 (70.0) | 305.5 (74.7) | 304.9 (69.7) |
| Range | 4 - 357 | 0 - 357 | 1 - 354 | 15 - 348 |
| *Amount used (g)* | *N=329* | *N=158* | *N=343* | *N=173* |
| Mean (SD) | 110.0 (68.3) | 114.9 (66.4) | 107.7 (61.9) | 112.3 (64.8) |
| Range | 1.0 – 342.3 | 0.4 – 291.1 | 1.1 – 294.0 | 12.7 – 289.8 |

Source: pg 98 of of Study Report for Study 301and pg 96-97 of Study Report for Study 302.

### 3.3.2 Adverse Events

Approximately 58-64% of tavaborole and 54-70% of vehicle subjects experienced at least one adverse event, and approximately 2-3% of tavaborole and 1-4% of vehicle subjects experienced a serious adverse event. Approximately 1-3% of tavaborole subjects and 0.5-2% of vehicle subjects discontinued treatment due to adverse events. See Table 14.

**Table 14 – Adverse Events in Studies 301 and 302 (Safety Population)**

| | Study 301 | | Study 302 | |
|---|---|---|---|---|
| | Tavaborole N=396 | Vehicle N=193 | Tavaborole N=395 | Vehicle N=200 |
| Any Adverse Event | 255 (64%) | 135 (70%) | 227 (58%) | 109 (54%) |
| Serious Adverse Event | 12 (3%) | 8 (4%) | 7 (2%) | 2 (1%) |
| Discontinued treatment due to AEs | 10 (3%) | 3 (2%) | 3 (0.8%) | 1 (0.5%) |

Source: pg 100 of Study Report for Study 301and pg 99 of Study Report for Study 302.

Subjects on the tavaborole arm had a higher rate of application site adverse reactions than subjects on the vehicle arm, including application site exfoliation (2.7% vs. 0.3%), application site erythema (1.6% vs. 0%), application site dermatitis (1.3% vs. 0%), and application site pain (1.0% vs. 0.3%). Other administration site conditions and skin and subcutaneous tissues disorders observed in at least 0.5% of tavaborole subjects are presented in Table 15. Other adverse events observed in at least 1.5% of tavaborole subjects are presented in Table 16.

**Table 15 – Administration Site Conditions and Skin and Subcutaneous Tissue Disorders Observed in > 0.5% of Tavaborole Subjects (Based on Combined Studies 301 and 302, Safety Population)**

| | Study 301 | | Study 302 | | Combined | |
|---|---|---|---|---|---|---|
| | Tavaborole N=396 | Vehicle N=193 | Tavaborole N=395 | Vehicle N=202 | Tavaborole N=791 | Vehicle N=395 |
| Appl. site exfoliation | 16 (4.0%) | 1 (0.5%) | 5 (1.3%) | 0 (0%) | 21 (2.7%) | 1 (0.3%) |
| Appl. site erythema | 7 (1.8%) | 0 (0%) | 6 (1.5%) | 0 (0%) | 13 (1.6%) | 0 (0%) |
| Appl. site dermatitis | 8 (2.0%) | 0 (0%) | 2 (0.5%) | 0 (0%) | 10 (1.3%) | 0 (0%) |
| Appl. site pain | 5 (1.3%) | 1 (0.5%) | 3 (0.8%) | 0 (0%) | 8 (1.0%) | 1 (0.3%) |
| Appl. site discharge | 3 (0.8%) | 0 (0%) | 2 (0.5%) | 0 (0%) | 5 (0.6%) | 0 (0%) |
| Appl. site hematoma | 2 (0.5%) | 1 (0.5%) | 3 (0.8%) | 2 (1.0%) | 5 (0.6%) | 3 (0.8%) |
| Appl. site vesicles | 3 (0.8%) | 1 (0.5%) | 2 (0.5%) | 0 (0%) | 5 (0.6%) | 1 (0.3%) |
| Appl. site pruritus | 2 (0.5%) | 0 (0%) | 2 (0.5%) | 0 (0%) | 4 (0.5%) | 0 (0%) |
| Ingrowing nail | 14 (3.5%) | 1 (0.5%) | 6 (1.5%) | 0 (0%) | 20 (2.5%) | 1 (0.3%) |
| Contact dermatitis | 6 (1.5%) | 2 (1.0%) | 4 (1.0%) | 1 (0.5%) | 10 (1.3%) | 3 (0.8%) |
| Skin exfoliation | 3 (0.8%) | 0 (0%) | 2 (0.5%) | 0 (0%) | 5 (0.6%) | 0 (0%) |

Source: pg. 79-91 of summary-clin-safety.pdf

**Table 16 – Other Adverse Events Observed in > 1.5% of Tavaborole Subjects (Based on Combined Studies 301 and 302)**

| | Study 301 | | Study 302 | | Combined | |
|---|---|---|---|---|---|---|
| | Tavaborole N=396 | Vehicle N=193 | Tavaborole N=395 | Vehicle N=202 | Tavaborole N=791 | Vehicle N=395 |
| Tinea Pedis | 42 (10.6%) | 35 (18.1%) | 53 (13.4%) | 25 (12.4%) | 95 (12.0%) | 60 (15.2%) |
| Nasopharyngitis | 23 (5.8%) | 10 (5.3%) | 27 (6.8%) | 16 (7.9%) | 50 (6.3%) | 26 (6.6%) |
| Upper Resp. Tr. Inf. | 20 (5.0%) | 8 (4.1%) | 18 (4.6%) | 12 (5.9%) | 38 (4.8%) | 20 (5.1%) |
| Back Pain | 17 (4.3%) | 3 (1.6%) | 7 (1.8%) | 2 (1.0%) | 24 (3.0%) | 5 (1.3%) |
| Hypertension | 11 (2.8%) | 8 (4.1%) | 11 (2.8%) | 4 (2.0%) | 22 (2.8%) | 12 (3.0%) |
| Headache | 10 (2.5%) | 5 (2.6%) | 11 (2.8%) | 7 (3.5%) | 21 (2.7%) | 12 (3.0%) |
| Sinusitis | 12 (3.0%) | 5 (2.6%) | 6 (1.5%) | 5 (2.5%) | 18 (2.3%) | 10 (2.5%) |
| Muscle Strain | 8 (2.0%) | 1 (0.5%) | 10 (2.5%) | 6 (3.0%) | 18 (2.3%) | 7 (1.8%) |
| Procedural Pain | 8 (2.0%) | 1 (0.5%) | 10 (2.5%) | 4 (2.0%) | 18 (2.3%) | 5 (1.3%) |
| Arthralgia | 8 (2.0%) | 6 (3.1%) | 8 (2.0%) | 0 (0%) | 16 (2.0%) | 6 (1.5%) |
| Limb Injury | 10 (2.5%) | 3 (1.6%) | 3 (0.8%) | 1 (0.5%) | 13 (1.6%) | 4 (1.0%) |
| Influenza | 11 (2.8%) | 10 (5.3%) | 2 (0.5%) | 0 (0%) | 13 (1.6%) | 10 (2.5%) |

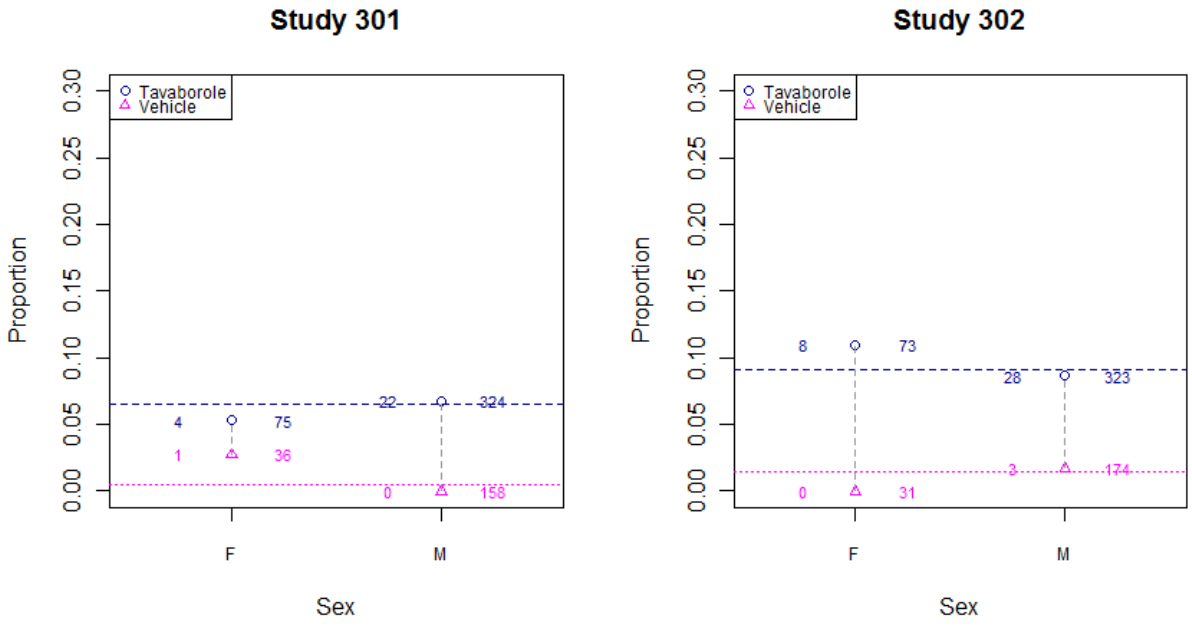
Source: pg. 79-91 of summary-clin-safety.pdf

# 4 Findings in Special/Subgroup Populations

## *4.1 Gender, Race, Age, and Geographic Region*

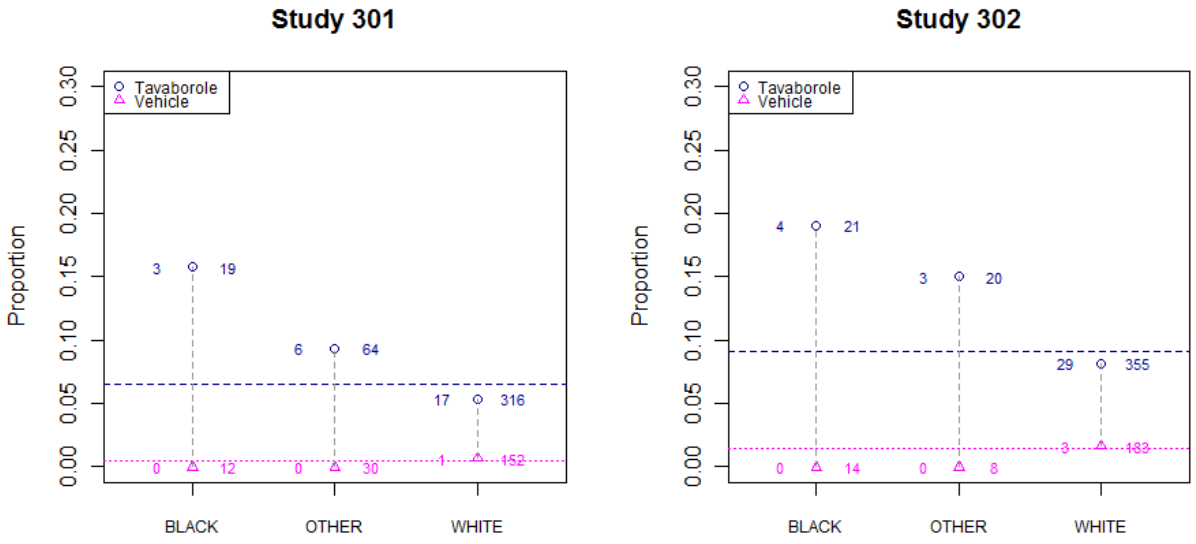
Treatment effects were generally consistent across gender, race, age, and country subgroups in Studies 301 and 302. See Figure 7 through Figure 10.

**Figure 7 – Complete Cure Rate by Gender in Studies 301 and 302**



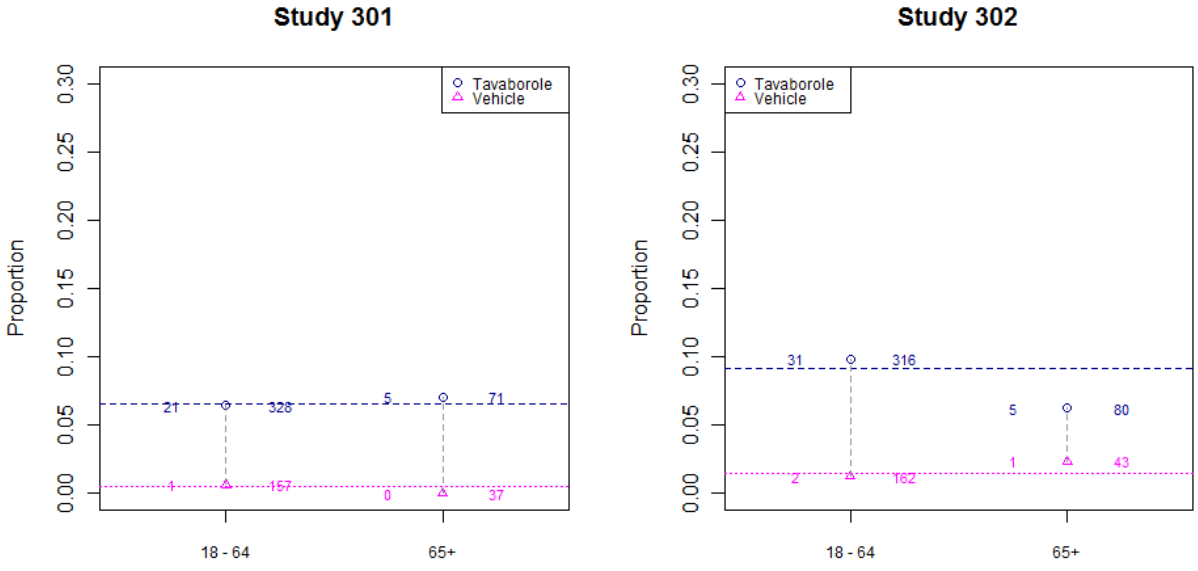

Note: number to the left of the symbol is the number of responders and the number to the right of the symbol is the total number of subjects within each group. (Source: reviewer analysis)

**Figure 8 – Complete Cure Rate by Race in Studies 301 and 302**



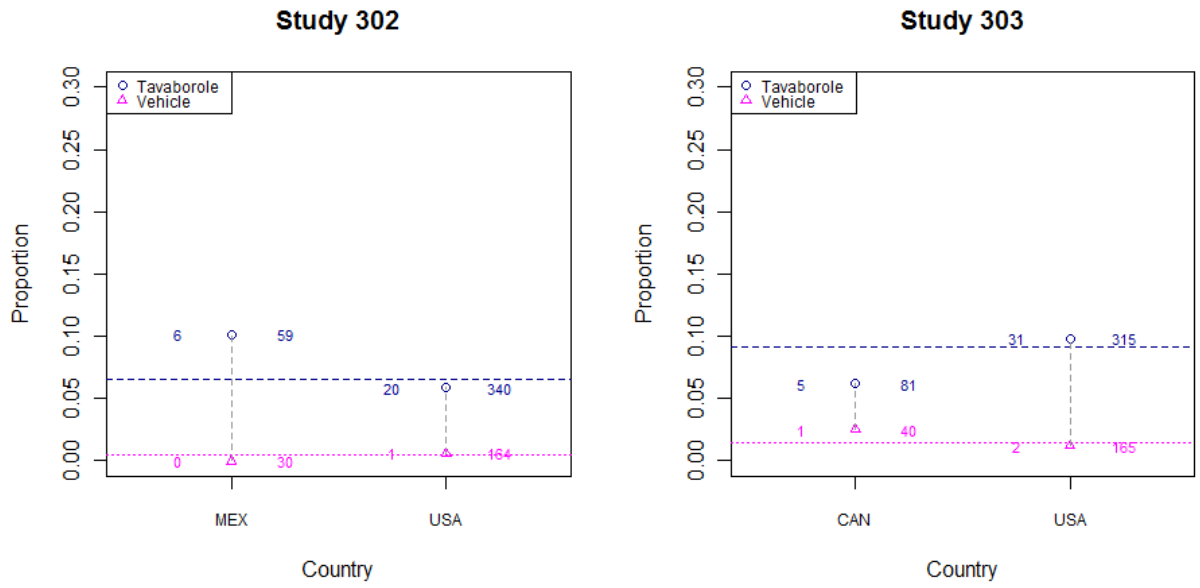

Note: number to the left of the symbol is the number of responders and the number to the right of the symbol is the total number of subjects within each group.
Source: reviewer analysis

**Figure 9 – Complete Cure Rate by Age Group in Studies 301 and 302**




Note: number to the left of the symbol is the number of responders and the number to the right of the symbol is the total number of subjects within each group.
Source: reviewer analysis

**Figure 10 - Complete Cure Rate by Country in Studies 301 and 302**




Note: number to the left of the symbol is the number of responders and the number to the right of the symbol is the total number of subjects within each group.
Source: reviewer analysis

### *4.2 Other Special/Subgroup Populations*

None.

## 5 Summary and Conclusions

### *5.1 Statistical Issues and Collective Evidence*

The applicant has evaluated the efficacy of tavaborole solution 5% in two vehicle-controlled studies for the treatment of onychomycosis. Both studies were statistically significant for the primary efficacy endpoint of complete cure at Week 52 ($p \leq 0.001$). Treatment effects were generally consistent across subgroups and centers, and the conclusions were consistent across various assumptions regarding missing data.

The protocols were submitted as Special Protocol Assessments. The Agency and sponsor reached agreement on the study design and endpoints. The protocols were amended to add an additional 8-week follow-up for subjects with completely clear or almost clear nails at Week 48 to assess durability of effect. As this amendment was implemented during the study, only a portion of eligible subjects had the additional follow-up. Because subjects who enrolled early in the recruitment period completed the study before the amendment went into effect, only one-fifth to one-third of tavaborole subjects (from Studies 301 and 302 respectively) who met the efficacy criteria that would have triggered the additional follow-up were actually followed up. With the limited number of subjects

who were followed, it is impossible to assess whether the subjects who were followed up were similar to subjects enrolled earlier in the trial, and this additional analysis has limited utility.

### *5.2 Conclusions and Recommendations*

Tavaborole solution 5% was superior to vehicle in the treatment of onychomycosis in two studies. The studies enrolled subjects age 18 and older with a clinical diagnosis of onychomycosis and positive mycology. Subjects applied treatment once daily for 48 weeks. The primary efficacy endpoint was complete cure at Week 52 (0% clinical involvement of target toenail plus negative KOH and negative culture). The complete cure rate for tavaborole vs. vehicle was 6.5% vs. 0.5% in Study 301 and 9.1% vs. 1.5% in Study 302. The secondary efficacy endpoints defined in the protocol were supportive of the primary endpoint. The primary and secondary efficacy endpoints were all statistically significant ($p \leq 0.001$).

## Signatures/Distribution List

Primary Statistical Reviewer: Kathleen Fritsch, Ph.D.
Date: 3/7/2014

Statistical Team Leader: Mohamed Alosh, Ph.D.

cc:
DDDP/Walker
DDDP/Kettl
DDDP/Lolic
DDDP/Attinello
OBIO/Patrician
DBIII/Wilson
DBIII/Alosh
DBIII/Fritsch

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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KATHLEEN S FRITSCH
03/07/2014

MOHAMED A ALOSH
03/07/2014

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:** | 204427 |
| **Drug Name:** | TAVABOROLE® topical solution, 5% (AN2690) (1,3-dihydro-5-fluoro-1-hydroxyl-2,1-benzoxaborole) |
| **Indication:** | Topical treatment of the treatment of onychomycosis (b) (4) [redacted] |
| | Anacor Pharmaceuticals, Inc., Palo Alto, California |
| | CRO rats: (b) (4) [redacted] |
| | mice: (b) (4) [redacted] |
| **Date:** | Submitted 9 January 2013 |
| **Review Priority:** | Standard (NME) |
| **Biometrics Division:** | Division 6 |
| **Statistical Reviewer:** | Steve Thomson |
| **Concurring Reviewer:** | Team Leader: Karl Lin, Ph. D. |
| **Medical Division:** | Dermatological and Dental Drug Products |
| **Toxicologist:** | Reviewer: Linda Pellicore, Ph.D<br>Team Leader: Barbara A. Hill, Ph.D. |
| **Project Manager:** | Christina Attinello, MPH |
| **Keywords:** | Carcinogenicity, Cox regression, Kaplan-Meier product limit, Survival analysis, Trend test |

# Table of Contents

# 1. EXECUTIVE SUMMARY

According to the reports provided by (b) (4), these 104 week studies were intended to assess the carcinogenic potential of the drug Tavaborole, labled AN2690 in the reports, following oral (gavage) administration once daily to Sprague-Dawley rats and when administered once daily by topical application to the dorsal skin of mice. The rat study was conducted by (b) (4), and the mouse study at (b) (4)

## 1.1. Conclusions and Recommendations

This submission summarizes the results of a rat study with daily oral gavage dosing and a mouse study with topical dosing. Gross aspects of the study design for the study animals in rats are summarized in Table 1 be1ow:

**Table 1. Design of Rat Study** (dose volume 10 mL/kg)

| Treatment Group | # Main study animals (# TK[1] animals)/gender | Nominal Dose (mg/kg/day) | Nominal Dosing Concentra-tion (mg/mL) |
|---|---|---|---|
| 1. Vehicle[2] | 65 ( 12) | 0 | 0 |
| 2. Low | 65 ( 12) | 12.5 | 1.25 |
| 3. Medium | 65 ( 12) | 25 | 2.5 |
| 4. High | 65 ( 12) | 50 | 5 |

[1] Toxicokinetic phase animals began dosing during Week 1. Blood samples were collected from on Day 1 and in Week 26 of the carcinogenicity phase. Surviving toxicokinetic phase animals were euthanized following collection of the last blood sample.

[2] Aqueous 1% [w/v] Medium Viscosity Carboxymethylcellulose 1% in purified water).

In mice the topical route of administration was selected since this is the intended route of dosing in humans. General aspects of the study design for the mice study are summarized in Table 2 be1ow:

**Table 2. Design of Mice Study** (dose volume 5 µL/cm$^2$ from days 1-14)

1 μL/g from day 15 to study end

| Treatment Group | # Main study animals (# TK[1,2] animals)/gender | Nominal Dose[3] from day 8 | Nominal Dosing[3] Concentration (mg/mL) |
|---|---|---|---|
| 1. Vehicle[4] | 65 ( 40[1]/ 22[2]) | 0% | 0 |
| 2. Low | 65 ( 40[1]/ 22[2]) | 5% ( 1%) | 50 (10) |
| 3. Medium | 65 ( 40[1]/ 22[2]) | 10% (2.5%) | 100 (25) |
| 4. High | 65 ( 40[1]/ 22[2]) | 15% (10 %) | 150 (100) |

[1] Toxicokinetic phase animals began dosing during Week 1, and blood samples were collected on Days 1 and 180.
[2] Toxicokinetic single dose groups.
[3] Dosage in parentheses from days 1-7, main dosage (outside parentheses) from day 8.
[4] 80% ethanol (USP, 190 proof)/20% propylene glycol.

Kaplan-Meier survival curves for these studies are presented in Appendix 1. Summary incidence of death tables are presented on pages 18, 19, and 25 of this report. From Figure A.1.1 in that appendix, in male rats the Kaplan-Meier estimated survival curves of the four dose groups including vehicle are all close and none of the curves seem to consistently dominate the others. From Figure A.1.2 for female rats, although the vehicle control generally has slightly higher survival, the actual survival curves differ little, with the curves for the other dose groups generally intertwined.

These observations explain the results in the tests of differences in survival given below:

**Table 3. Statistical Significances of Tests of Homogeneity and Trend in Survival in Rats**

| Hypotheses | Males | | Females | |
|---|---|---|---|---|
| | Logrank | Wilcoxon | Logrank | Wilcoxon |
| Homogeneity over all four groups | 0.5913 | 0.5935 | 0.6919 | 0.6404 |
| No Trend over all four groups | 0.4206 | 0.4246 | 0.6067 | 0.4566 |
| No difference between high dose and vehicle | 0.4462 | 0.4661 | 0.6569 | 0.4923 |

In male or female rats, whether analyzing among all four dose groups, trend in dose, and in the comparison between the high dose and control, none of the tests of differences in survival or trend were even close to the usual 0.05 level of statistical significance (i.e., in males all six $p \geq 0.4206$, in females all six $p \geq 0.4566$). While absence of proof is not proof of absence, the lack of evidence for such differences in survival was quite consistent with the hypotheses of no differences or trends.

Figures A.1.3 and A.1.4, respectively, in the Appendix 1, show estimated Kaplan-Meier survival curves for male and female mice. In male mice the vehicle control group generally has the highest survival, although largely intertwined with the remaining dose groups. Near the end of the study, the low dose group eventually has the lowest survival. In female mice, although the

low dose generally has slightly the highest or near the highest survival, while the vehicle control generally the lowest. The other dose groups are generally intertwined.

**Table 4. Statistical Significances of Tests of Homogeneity and Trend in Survival in Mice**

| Hypotheses | Males | | Females | |
|---|---|---|---|---|
| | Logrank | Wilcoxon | Logrank | Wilcoxon |
| Homogeneity over all four groups | 0.2591 | 0.4010 | 0.8719 | 0.8151 |
| No Trend over all four groups | 0.9489 | 0.8354 | 0.7144 | 0.6512 |
| No difference between high dose and vehicle | 0.5915 | 0.5596 | 0.7699 | 0.6250 |

Thus, as with rats, in male or female mice none of the tests of no trend over dose or tests of no difference between the high doses and controls were even close to the usual 0.05 level of statistical significance (i.e., in males all six $p \geq 0.2591$, in females all six $p \geq 0.6250$).

Note that a large number of tumors are typically identified in the analysis of neoplasms, implying a large number of statistical tests. Following the frequentist paradigm, when interpreting significance levels (i.e., p-values), this reviewer would recommend one of the Haseman-Lin-Rahman (HLR) rules to adjust for the multiplicity of tests. Two approaches have been investigated, one for testing dose related trend and pairwise comparison between the high dose and control seperately and the other these hypotheses jointly (please see Section 1.3.1.4, below, for details). Usual statistical practice would be to test hypotheses separately, but some scientists want to control Type I error only when testing both the trend and pairwise hypotheses simultaneously. That is, when testing for trend over dose and, separately, the difference between the highest dose group with a control group, to control the overall Type I error rate for the joint tests in a two species submission to roughly 10%, one compares the unadjusted significance level of the trend test to 0.005 for common tumors and 0.025 for rare tumors, and the pairwise test to 0.01 for common tumors and 0.05 for rare tumors. For the testing these hypothese jointly for common tumors one compares the unadjusted significance level of the trend test to 0.005 and the pairwise test to 0.05, and for rare tumors 0.025 for tests of trend and 0.10 the pairwise comparison. Using these adjustments for other tests, like testing the comparisons between the Low and Medium dose groups versus vehicle can be expected to increase the overall type I error rate to some value above the nominal rough 10% level, possibly considerably higher than the nominal 10% rate.

Tables 5 and 6, below, shows the tumors that had at least one non-multiplicity adjusted test that was statistically significant at or close to a 0.10 level.

**Table 5. Potentially Statistically Significant Results for Organ-Tumor Combinations in Rats** Overall Results

| Organ/ Tumor | Veh | Low | Med | High | ptrend | phigh vsVeh | pmed vsVeh | plow vsVeh |
|---|---|---|---|---|---|---|---|---|
| Male Rats | | | | | | | | |
| PITUITARY GLAND | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 55.7 | 54.1 | 54.3 | 57.0 | | | | |
| PARS INTERMEDIA ADENOMA [B]. | 0 | 0 | 4 | 1 | .2107 | .5045 | .0568 | . |
| Systemic | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 55.7 | 54.1 | 54.2 | 57.9 | | | | |
| Malignant Fibrous Histiocytoma | 0 | 0 | 0 | 2 | .0663 | .2568 | . | . |
| TESTES | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 55.7 | 54.4 | 55.0 | 57.7 | | | | |
| INTERSTITIAL CELL ADENOMA [B]. | 1 | 1 | 4 | 7 | .0059 | .0341 | .1760 | .7477 |
| THYROID GLAND | | | | | | | | |
| # Evaluated | 64 | 63 | 64 | 65 | | | | |
| Adj. # at Risk | 54.8 | 52.9 | 53.2 | 57.0 | | | | |
| C-CELL ADENOMA [B]. | 1 | 5 | 2 | 3 | .4251 | .3298 | .4929 | .0942 |
| | | | | | | | | |
| Female Rats | | | | | | | | |
| MAMMARY GLANDS | | | | | | | | |
| # Evaluated | 64 | 65 | 63 | 65 | | | | |
| Adj. # at Risk | 53.6 | 53.8 | 50.2 | 52.1 | | | | |
| FIBROADENOMA [B]. | 11 | 22 | 15 | 13 | .5939 | .3877 | .1970 | .0176 |
| OVARIES | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 52.8 | 51.0 | 48.7 | 50.8 | | | | |
| TUBULOSTROMAL ADENOMA [B]. | 0 | 0 | 0 | 3 | .0149 | .1142 | . | . |
| PANCREAS | | | | | | | | |
| # Evaluated | 64 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 51.8 | 51.0 | 48.7 | 49.7 | | | | |
| ISLET CELL A DENOMA [B]. | 0 | 2 | 1 | 3 | .0821 | .1139 | .4848 | .2426 |
| UTERUS | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 64 | | | | |
| Adj. # at Risk | 53.9 | 52.5 | 51.6 | 50.8 | | | | |
| ENDOMETRIAL STROMAL POLYP [B]. | 4 | 6 | 11 | 8 | .0968 | .1518 | .0386 | .3585 |

Using the tumor incidence in the vehicle to determine whether a tumor should be classified as rare or common, in male rats, benign interstitial cell adenoma of the testes would be classified as common, so the test of trend would be quite close to statistical significance ( $p = 0.0059 \approx 0.005$). Seperately or jointly testing the associated pairwise test between the high dose and the vehicle ( $p = 0.0341 < 0.05$ ) in this adenoma in the testes would be statistically significant. In female rats the simple test of trend in benign tubulostromal adenoma in the ovaries was also statistically significant ( $p = 0.0149 < 0.025$), since the tumor would be classified as rare. For joint testing, but not for separate testing, the corresponding pairwise comparison would be close to significance ( $p = 0.1142 \approx 0.10$).

For separate testing of hypotheses, if we accept the, possibly quite considerable, increase in error for including pairwise tests other than the comparison between the high dose and vehicle, in female rats the simple pairwise difference between the low dose and vehicle in benign fibroadenoma of the mammaries would be statistically significant ( $p = 0.0176 < 0.05$ ), as would be the pairwise difference between the medium dose and vehicle in benign endometrial stromal

polyp ( p=0.0386 < 0.05). No other tests satisfied the Haseman-Lin-Rahman adjustments for multiplicity for seperate tests on the trend and pairwise difference parameters.

**Table 6. Potentially Statistically Significant Results for Organ-Tumor Combinations in Mice**

| Organ/ Tumor | Overall Results Veh | Low | Med | High | ptrend | phigh vsVeh | pmed vsVeh | plow vsVeh |
|---|---|---|---|---|---|---|---|---|
| Male Mice | | | | | | | | |
| Systemic | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.7 | 41.2 | 46.0 | 45.9 | | | | |
| HEMANGIOSARCOMA | 2 | 3 | 7 | 4 | .1546 | .3279 | .0789 | .4450 |
| Adj. # at Risk | 46.7 | 41.7 | 46.1 | 45.9 | | | | |
| Hemangioma/Hemangiosacroma | 2 | 4 | 8 | 4 | .1679 | .3279 | .0450 | .2847 |
| epididymides | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.1 | 40.9 | 43.8 | 44.9 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 0 | 0 | 2 | .0636 | .2362 | . | . |
| liver | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.7 | 41.0 | 46.0 | 45.9 | | | | |
| HEMANGIOSARCOMA | 2 | 1 | 7 | 4 | .0935 | .3279 | .0789 | .8517 |
| Adj. # at Risk | 46.9 | 44.7 | 44.7 | 44.9 | | | | |
| Hepato.Adenoma/Carcinoma | 6 | 12 | 10 | 7 | .4606 | .4650 | .1775 | .0769 |
| multicentric neoplasm | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.7 | 41.2 | 46.0 | 45.9 | | | | |
| HEMANGIOSARCOMA | 2 | 3 | 7 | 4 | .1546 | .3279 | .0789 | .4450 |
| Female Mice | | | | | | | | |
| Systemic | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.4 | | | | |
| GRANULOSA CELL TUMOR | 0 | 0 | 0 | 2 | .0628 | .2646 | . | . |
| brain | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.9 | 48.9 | 45.3 | 47.5 | | | | |
| LYMPHOMA | 1 | 3 | 0 | 6 | .0649 | .0746 | 1 | .3604 |
| large intestine, cecum | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 46.4 | | | | |
| LYMPHOMA | 0 | 0 | 0 | 2 | .0650 | .2704 | . | . |
| ovaries | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.4 | | | | |
| GRANULOSA CELL TUMOR | 0 | 0 | 0 | 2 | .0628 | .2646 | . | . |
| salivary gland, mandibula | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 43.7 | 47.3 | 47.3 | 48.2 | | | | |
| LYMPHOMA | 2 | 1 | 4 | 6 | .0465 | .1721 | .3819 | .8950 |
| skin, subcutis | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 43.0 | 48.6 | 47.1 | 47.7 | | | | |
| LYMPHOMA | 3 | 3 | 6 | 7 | .0799 | .1965 | .2891 | .7127 |
| uterus with cervix | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.4 | | | | |
| GRANULOSA CELL TUMOR | 0 | 0 | 0 | 2 | .0628 | .2646 | . | . |

As with rats, we use the tumor incidence in the vehicle to determine whether a tumor should be classified as rare or common. Whether defined as rare or common, no separate tests or joint tests of trend or pairwise comparison between the high dose and control in mice achieved the Haseman-Lin-Rahman bounds to be classified as statistically significant (please see Section 1.3.1.4, below). However, if we accept the possibly quite considerable increase in error for including pairwise tests other than the comparison between the high dose and vehicle, in male mice the simple pairwise difference between the medium dose and vehicle in pooled hemangioma and hemangiosarcoma would be barely statistically significant ( $p = 0.045 < 0.05$ ). No other tests in mice satisfied the Haseman-Lin-Rahman adjustments for multiplicity. Further no joint test of trend and pairwise comparison between the high dose and control achieved the HLR levels.

Complete results of statistical poly-k tests of tumor trend and differences between dose groups are given in Tables A.2.3 through A.2.6 in Appendix 2.

## 1.2. Brief Overview of the Studies

Two studies were submitted:

**(b) (4) Study 7783 - AN2690: A 104-Week Oral Carcinogenicity Study in Sprague-Dawley Rats**

and,

**(b) (4) Study 1124-016 - A 104-Week Dermal Oncogenicity Study of AN2690 in Mice**

These studies were designed to assess the carcinogenic potential of tavaborole. In each study, the actual dose groups are labeled in this report as the Low, Medium, and High dose groups, respectively, plus the Vehicle control group. The Sponsor summarized results by noting that in their analysis there were no AN2690 related neoplastic findings, and further noted that in "conclusion, the oral administration of AN2690 once daily for 104 consecutive weeks was well-tolerated by Sprague-Dawley rats and there were no indications that AN2690 had carcinogenic potential." (page 15 of rat report).

Topical results in the mouse report were similarly summarized as follows: "Once daily topical administration of 5, 10, or 15% AN2690 did not affect survival or cause a statistically significant increase in the incidence of any neoplasm. All neoplasms present were typical of those seen in mice of this strain and age, and were considered incidental." (page 33 of mouse report)

## 1.3. Statistical Issues and Findings

### 1.3.1. Statistical Issues

In this section, several issues, typical of statistical analyses of these studies, are considered. These issues include comments on the details of the survival analyses, tests on tumorigenicity, multiplicity of tests on neoplasms, and the validity of the designs.

#### 1.3.1.1. Survival Analysis:

The survival analyses presented here are based on both the log rank test and the Wilcoxon test comparing survival curves. The Wilcoxon statistic provided by SAS® (technically the Gehan-Wilcoxon statistic) can be cast as a log rank test weighted by the number of subjects at risk, and thus is more sensitive to earlier differences (when more subjects are at risk). The logrank test is most powerful when the survival curves track each other, and thus the hazards, i.e., the conditional probability of the event in the next infinitesimal interval, would be roughly proportional. Note the logrank test seems to be the test usually recommended by statisticians, and is one of the tests used by the Sponsor (in rats in addition to Tarone's test). Both the logrank and the Wilcoxon tests are used in the FDA analysis of mortality. Appendix 1 reviews the specific FDA animal survival analyses in more detail. The results of the Sponsor's analysis are summarized in Sections 3.2.1.1 and 3.2.2.1.

#### 1.3.1.2. Multiplicity of Tests on Survival:

Using both the logrank and Wilcoxon tests, for each gender in each species there are six tests of survival differences. Assuming tests were performed at the usual 0.05 level, and the tests were stochastically independent, but there were actually absolutely no differences in survival across groups (so one would hope no tests would be statistically significant), the probability of at least one statistically significant result in each gender in each species was about 0.27, and an overall result of about 0.46 in each species. These bounds assume the tests are stochastically independent, which they clearly are not, but these values can give some idea of the possible price paid for the multiplicity of hypothesis tests in the statistical frequentist paradigm.

#### 1.3.1.3. Tests on Neoplasms:

The data sets requested for the analysis of rodent carcinogenicity studies are supposed to include a record for each animal organ combination that was not evaluated. If a number of the animals are not examined, but the proportions of animals showing the tumor under study in each treatment group is roughly the same as in the subset of animals actually reported the calculated p-values will generally be too large, i.e., results will be less statistically significant than they should be, possibly much less. If we can assume the process that determines whether or not a tumor is analyzed in each specific tumor is random, it is perhaps appropriate to consider such endpoints to be both analyzed and have the tumor.

Ignoring these possible problems, the Sponsor's analyses of tumorigenicity in rats are Peto tests, with incidental and fatal plus mortality independent tumors. In mice, trend over dose

was tested by Peto methods and unadjusted (i.e., not poly-k) Cochran-Armitage tests. Pairwise comparisons were made using Fisher exact tests. Note that Peto methods require accurate determination of whether a tumor is fatal or incidental.

The FDA analysis is based on a modification of the Cochran-Armitage test of trend in mortality (please see Bailer & Portier, 1988, Bieler & Williams, 1993). Inspecting a large number of studies, Bailer and Portier noted that survival time seemed to fit a Weibull distribution, generally with a shape parameter of between 1 and 5, with 3 a typical value. With $t_{max}$ denoting the maximal time to terminal sacrifice and $t_{obs}$ the time to detection of the tumor in the animal, they proposed weighting the animal by $(t_{obs}/t_{max})^k$, so that an animal that survives for say 52 weeks in 104 week study without the tumor being analyzed is counted as $(1/2)^k$ of an animal in the risk set for that tumor. For k = 3, that means that particular animal would count as 1/8 of an animal. Further, the k = 3 specification seems to represent tumor incidence where some animals are perhaps more sensitive and respond earlier to the insult than the remining animals. Under this structure time to incidence would tend to follow a cubic expression. Thus an animal with the specific tumor being studied or who survives to terminal sacrifice without the tumor will be given a weight of 1 when counting the number of animals at risk. However, animals that die early without the tumor are down weighted when counting the number of animals in the risk set for that specific tumor. With differential mortality, this can mean a substantial reduction in the size of that risk set. Note this seems to be an appropriate adjustment for dose groups that are terminated early. The report of the Society of Toxicological Pathology "town hall" meeting in June 2001 recommeded the use of this poly-k modification of the so-called Cochran-Armitage tests of trend over the corresponding Peto tests used by the Sponsor.

The computed significance levels are based on small sample exact permutation tests of tumor incidence. In the tumor incidence tables the effective size of the risk set for each tumor is listed in the row labeled "Adjusted # at risk ", and seems to be a more appropriate denominator when comparing incidence rates than the simple unadjusted number evaluated.

**1.3.1.4. Multiplicity of Tests on Neoplasms:**

Testing dose related treatment differences for each species by gender by organ by tumor combination involves a large number of comparisons. One way to distinguish the hypotheses being tested is as follows:

1. Analyze the test of trend and the pairwise comparison between the high dose and control as separately. This seems to be congruent with usual statistical practice.
2. Analyze the test of trend and the pairwise comparison between the high dose and control as a single joint event. This fits the case where the toxicologist only concludes a statistically significant effect if both tests are significant.
3. Analyze other hypotheses, e.g. comparisons between the other dose groups with each other or with control, trend deleting one or more high doses, etc.

Current FDA practice is based on the Haseman-Lin-Rahman (HLR) multiplicity

adjustments, targeted at the first two sets of hypothese above. These adjustments are based on the original multiplicity adjustment of Haseman (1983) and extended by Lin and Rahman with various simulations. Based on his extensive experience with such analyses, for pairwise tests in a two species study 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. Lin & Rahman (1998) proposed a further 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. Other specifications are presented in the Table 4 below. 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).

The proposed Haseman-Lin-Rahman bounds are taken from *Guidance for Industry Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals*, (HHS, 2013). The bounds on the right in table 7, below, are grouped so that the last four columns correspond to testing either trend or pairwise comparison between the high dose and control seperately. The previous four columns ( columns 2-5), correspond to testing both overall trend and pairwise tests between the high dose and control together. Within each group there is a column giving the corresponding bounds for a two species study and another column for a one species study. In this analysis we emphasize the usual statistical practice of testing parameters separately, so the bounds in the leftmost columns are used, athough results from joint tests are also mentioned. The observed tumor incidence in the vehicle group is used to decide if a tumor is classified rare or common.

**Table 7. Recommended Multiplicity Adjusted Bounds on Significance Levels**

| | Testing trend or pairwise difference | | | | Joint testing of trend and pairwise | | | |
|---|---|---|---|---|---|---|---|---|
| | Two Species | | One Species | | Two Species | | One Species | |
| | Trend | Pairwise | Trend | Pairwise | Trend | Pairwise | Trend | Pairwise |
| Common Tumor | 0.005 | 0.01 | 0.01 | 0.025 | 0.005 | 0.05 | 0.01 | 0.05 |
| Rare Tumor | 0.025 | 0.05 | 0.05 | 0.10 | 0.025 | 0.10 | 0.05 | 0.10 |

The significance levels of the pairwise tests between the vehicle control with the Low and Medium dose groups are also provided in the tumor analysis tables below. Applying the HLR rules to these comparisons can be expected to increase the overall type I error rate to some level above the usual rough 10% level, possibly considerably larger. Again, because of the possibility of genetic drift and for convenience the vehicle group is used to determine if the tumor is classified as rare or common.

**1.3.1.6. Validity of the Designs:**

When determining the validity of designs there are two key points:
1) adequate drug exposure
2) tumor challenge to the tested animals.

1) is related to whether or not sufficient animals survived long enough to be at risk of forming late-developing tumors and 2) is related to the Maximum Tolerated Dose (MTD), designed to achieve the greatest likelihood of tumorigenicity.

Lin and Ali (2006), quoting work by Haseman, have suggested that in standard laboratory rodent species, a survival rate of about 25 animals, out of 50 or more animals (i.e. 50%), 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 table 17, as a percentage of the High dose group animals that survived to week 91, met and considerably exceded in male rats (high dose: 89.2%). From tables 18 in female rats, 23 in male mice, and 24 in female mice this criterion is solidly met (Female rats 69.2%, Male mice 60.0%, Female mice 61.5%) but not excessively as with male rats. This may be evidence that the MTD was never achieved, particularly in male rats, but such a determination requires the expertise of the toxicologist.

The mean weight values used to derive differences and ratios in the following tables were taken directly from the Sponsor's reports ( Rat Table 2A, pages 255-258, and Mice Table 5, pages 105-110). The change from baseline in the table below is the simple difference between the means at the specified dates, and thus animals that die early are only counted at the study initiation, not at the end of the study.

**Table 8. Mean Weights and Changes (in g) in Male Rats**

| Dose Group | Dose mg/kg/day | Day | | Change from Baseline | % change relative to vehicle |
|---|---|---|---|---|---|
| | | -1 | 729 | | |
| 1. Vehicle | 0 | 216 | 513 | 297 | |
| 2. Low | 12.5 | 217 | 499 | 282 | 94.9 % |
| 3. Medium | 25 | 217 | 507 | 290 | 97.6 % |
| 4. High | 50 | 217 | 501 | 284 | 95.6 % |

**Table 9. Mean Weights and Changes (in g) in Female Rats**

| Dose Group | Dose mg/kg/day | Day | | Change from Baseline | % change relative to vehicle |
|---|---|---|---|---|---|
| | | -1 | 729 | | |
| 1. Vehicle | 0 | 160 | 513 | 353 | |
| 2. Low | 12.5 | 160 | 499 | 339 | 96.0 % |
| 3. Medium | 25 | 161 | 507 | 346 | 98.0 % |
| 4. High | 50 | 160 | 501 | 341 | 96.6 % |

**Table 10. Mean Weights and Changes (in g) in Male Mices**

| Dose | | Week | Change | % change |
|---|---|---|---|---|

| Group | Dose[1] | -1 | 104 | from Baseline | relative to vehicle |
|---|---|---|---|---|---|
| 1. Vehicle | 0% | 26.88 | 41.57 | 14.69 | |
| 2. Low | 5% ( 1%) | 26.53 | 41.56 | 15.03 | 102.3% |
| 3. Medium | 10% (2.5%) | 26.90 | 42.20 | 15.30 | 104.2% |
| 4. High | 15% (10 %) | 26.91 | 40.85 | 13.94 | 94.9% |

[1] Dosage in parentheses from days 1-14, main dosage (outside parentheses) from day 15.

**Table 11. Mean Weights and Changes (in g) in Female Mice**

| Dose Group | Dose[1] | Week | | Change from Baseline | % change relative to vehicle |
|---|---|---|---|---|---|
| | | -1 | 104 | | |
| 1. Vehicle | 0% | 21.46 | 36.34 | 14.88 | |
| 2. Low | 5% ( 1%) | 21.45 | 36.43 | 14.98 | 102.3% |
| 3. Medium | 10% (2.5%) | 21.50 | 36.03 | 14.53 | 104.2% |
| 4. High | 15% (10 %) | 21.65 | 35.37 | 13.72 | 94.9% |

[1] Dosage in parentheses from days 1-14, main dosage (outside parentheses) from day 15.

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' " From Tables 8 through 11 above, it seems that the weight criterion is satisfied in both genders in both species.

More generally, in the rat study, the Sponsor summarizes weight results as "Body weights were unaffected by treatment of AN2690 as values were generally comparable across all groups over the duration of the treatment period." (page 32 of rat report) In mice the conclusion was similar: "Mean body weights in males and females in all treatment groups were comparable to controls and unaffected by treatment." (page 26 of mice report)

Again from 2) above, excess mortality not associated with any tumor or sacrifice in the higher dose groups might suggest that the MTD was exceeded. This suggests that a useful way to assess whether or not the MTD was achieved is to measure early mortality not associated with any identified tumor. If this is high in the higher dose groups it suggests that animals tend to die before having time to develop tumors. Table 12, below, displays the number of rats in each dose group that died of a natural death or moribund sacrifice, but did not show any tumors (i.e., the "Event"):

**Table 12. Natural Death with No Identified Tumor in Rats (Male/Female)**

| | 1.Vehicle | 2. Low | 3. Medium | 4. High |
|---|---|---|---|---|
| Males Event | 2 | 3 | 6 | 6 |

| | | | | |
|---|---|---|---|---|
| No event | 63 | 62 | 59 | 59 |
| Females Event | 0 | 3 | 2 | 2 |
| No event | 65 | 62 | 63 | 63 |

Actually, it is clear from the simple incidence table above that in both genders in rats, particularly in females, but also in male rats, there is no strong evidence of heterogeneity over dose in the event, dying prior to developing detectable tumors. Although hardly necessary, statistical tests are unnecessary, it is consistent with the results of Fisher exact tests of homogeneity across dose groups (Males p = 0.3766, Females p = 0.5271).

**Table 13. Natural Death with No Identified Tumor in Mice (Male/Female)**

| | 1.Vehicle | 2. Low | 3. Medium | 4. High |
|---|---|---|---|---|
| Males Event | 17 | 20 | 17 | 21 |
| No event | 48 | 45 | 48 | 44 |
| Females Event | 17 | 15 | 18 | 12 |
| No event | 48 | 50 | 47 | 43 |

As with rats, it is clear from the simple incidence above that in both genders in mice there is no evidence of heterogeneity in the event, dying before developing detectable tumors. And similarly, although unecessary, this is consistent with the results of both Pearson chi-square tests of homogeneity (Males p = 0.8120, Females p = 0.6195).

Like the other observations above, this requires the expertise of the toxicologist, but these tests and tables seem to provide evidence that the MTD was not exceeded in either gender in either species.

### 1.3.2. Statistical Findings

Please see Section 1.1 above.

# 2. INTRODUCTION

## 2.1. Overview

Results from two-year studies, one in Sprague-Dawley rats with daily gavage and the other in CD1 mice with daily topical application were submitted to assess the carcinogenic potential of Tavaborole, labeled as AN2690 in the Sponsor's reports.

## 2.2. Data Sources

A SAS data set for rats tumor.sas7bdat was translated from SAS transport file labeled (b) (4) 7783-tumor.xpt. For mice the following transport files were converted to SAS data sets with the same prefix and the usual ".sas7bdat" suffix:

| | | | |
|---|---|---|---|
| food.xpt | micro.xpt | signsf.xpt | tumor.xpt |
| macro.xpt | mortal.xpt | signsm.xpt | weights.xpt |

# 3. STATISTICAL EVALUATION

## 3.1. Evaluation of Efficacy

NA

## 3.2. Evaluation of Safety

More detailed results on the study are presented below.

### 3.2.1 Study (b) (4) Study 7783 - AN2690: A 104-Week Oral Carcinogenicity Study in Sprague-Dawley Rats

CRO: (b) (4)
STUDY DURATION: 105 weeks.
DOSING STARTING DATE: July 24, 2006.
DOSING TERMINATION: August 1, 2008.
RAT STRAIN: Sprague-Dawley [Crl:CD (SD) IGS BR] Rats
ROUTE: Daily Oral gavage

The drug vehicle is carboxymethylcellulose 1% in water. Animals were dosed once daily by oral gavage. Gross aspects of the study designs for the main study animals are summarized in Table 14 be1ow (a repeat of Table 1 above):

**Table 14. Design of Rat Study** (dose volume 10 mL/kg)

| Treatment Group | # Main study animals (# TK[1] animals)/gender | Nominal Dose (mg/kg/day) | Nominal Dosing Concentra-tion (mg/mL) |
|---|---|---|---|
| 1. Vehicle[2] | 65 ( 12) | 0 | 0 |
| 2. Low | 65 ( 12) | 12.5 | 1.25 |
| 3. Medium | 65 ( 12) | 25 | 2.5 |
| 4. High | 65 ( 12) | 50 | 5 |

[1] Toxicokinetic phase animals began dosing during Week 1. Blood samples were collected from on Day 1 and in Week 26 of the carcinogenicity phase. Surviving toxicokinetic phase animals were euthanized following collection of the last blood sample.

[2] Aqueous 1% [w/v] Medium Viscosity Carboxymethylcellulose 1% in purified water).

Dosing and aspects of the design were described by the Sponsor as follows: "The oral route of administration was selected to maximize systemic exposure of the compound and was in concert with Pre-IND discussions with the Division of Dermatology and Dental Products, ODE III, CDER of the FDA. The final protocol was reviewed by the FDA and conforms with the recommendations of the Executive Carcinogenicity Assessment Committee.

"The Sprague-Dawley rat was chosen for this study as it is a preferred species and strain for preclinical oral toxicity testing by U.S. and international regulatory agencies.

"The total number of animals used in this study was the minimum required to properly characterize the effects of the test article. Group size and the number of groups were based on guidelines of the FDA Redbook. Based on statistical sample size calculations, the number of animals per group is the minimum necessary to detect a tumor incidence of 21.5% as statistically significant compared to a control tumor incidence of 2% at an $\alpha$ level of 0.05 and a $\beta$ level of 0.1. From a toxicological perspective, this degree of statistical resolution was considered sufficient for this study design.

"The dose levels were selected in an attempt to produce graded responses to the test article. The highest dose level selected for this study was based on the results of a 6 month oral toxicity study in rats with AN2690 (002-NCL TX-007-01) in which a dosage of 30 mg/kg/day was determined to be the NOAEL. Administration of AN2690 to male and female rats at dosages of 50 mg/kg/day and higher resulted in hyperplasia and hyperkeratosis of the epithelium in the non-glandular stomach in a dose-related manner. As proposed by the FDA Executive CAC review, the dosage levels for this study were established as 0 (Vehicle Control), 12.5, 25 and 50 mg/kg/day. The Mid-Dose and Low-Dose levels are one-half and one-quarter of the highest dose level. The Mid-Dose level was considered to have the possibility to produce minimal signs of effects. The Low-Dose level was selected to produce no observable indications of toxicity." (page 15 of rat report)

Animals were approximately six to seven weeks old at first dosing. During the study animals were housed individually in wire mesh rodent cages. Food, namely four or five rodent pellers, and water were available ad libitum except during procedures. The Sponsor states that weekly physical examinations were on main study animals in both studies.

### 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 rats.

**Survival analysis:**

The Sponsor summarized survival results as follows: "There were no differences in the number of mortalities across the groups and cumulative survival at the end of the study was considered to be acceptable at 66 to 77% for males and 45 to 54% for females." (page 31 of report)

**Table 15. Sponsor's Text Table (**page 31**): Mortality table**

The mortality and survival data were summarized as follows:

| Group Number | Group Designation | Sex | Mean Survival (Days) | Cumulative Survival (%) Week 53 | Week 104 |
|---|---|---|---|---|---|
| 1 | Control | ♂ | 693 | 100 | 71 |
| | | ♀ | 682 | 100 | 54 |
| 2 | Low Dose | ♂ | 681 | 97 | 69 |
| | | ♀ | 686 | 97 | 52 |
| 3 | Mid Dose | ♂ | 686 | 98 | 66 |
| | | ♀ | 652 | 97 | 45 |
| 4 | High Dose | ♂ | 697 | 98 | 77 |
| | | ♀ | 642 | 97 | 52 |

The corresponding statistical report noted that "For the statistical analysis of the mortality data, there was no early death or sacrifice that needed to be censored. . . .

"The significance of group effects on mortality rates was assessed by applying the logrank test at the 5% significance level. The Logrank test was performed as a two-sided homogeneity test. For both female and male datasets, this test revealed no significant difference among the four groups, with $p = 0.6919$, and $p = 0.5913$, respectively." (page 13702 of report, page 10 of Statistics Report)

**Tumorigenicity analysis:**

"For each dataset of interest within each sex, the significance of an overall linear dose-related increase in tumor occurrence rates across the four groups was evaluated using Peto's survival-adjusted one-tailed trend test at the 5% significance level. This overall trend test was performed using the respective group scores of 0, 125, 250 and 500. For females and males, the

one-sided overall trend tests were found to be significant in any cases ($p > 0.05$). . . . . The results show significance only for the Interstitial Cell Adenoma [B] in Testes ($p = 0.0035$) and for Tubulostromal Adenoma [B] in Ovaries ($p = 0.0189$). According to the recommendations of Lin and Rahman (Lin and Rahman, 1998), the dose-related increase in tumor incidence should be considered significant if the p-value $\leq 0.025$ for rare tumors and $\leq 0.005$ for common tumors (historical incidence of more than 1%). Based on these criteria, the overall dose-related increase in tumor incidence corresponding to Tubulostromal Adenoma [B] in Ovaries is considered to be statistically significant only if this tumor is classified as rare since the p-value is between 0.005 and 0.025. However, the trend test is considered to be significant for Interstitial Cell Adenoma [B] in Testes independently of its classification since the p-value is lower than 0.005.

"In addition to the overall trend test, pairwise group comparisons were made using Peto's onesided trend test at the 5% significance level in order to determine if the tumor rate in each treated group is significantly higher than the one in the control Group 1. For each pairwise comparison, only the two considered groups were used in the analysis. All p-value results from the comparisons of each treated group with Group 1 are presented under the respective group in Table 2 for males and Table 3 for females. The following table, [taken from the statistical report] presents the list of tumors for which the p-value from the pairwise comparison was $\leq 0.05$." (page 13703 of report, page 10 of statistical report)

**Table 16. (Extract Sponsor Text Table 3) List of pairwise comparisons with p-value ≤ 0.05**

| Sex | Organ Name | Tumor Name | Comparison | P-value |
|---|---|---|---|---|
| Male | Testes Interstitial Cell | Adenoma [B] | 1 vs 4 | 0.0320 |
| Female | Mammary Glands | Fibroadenoma [B] | 1 vs 2 | 0.0101 |
| Female | Uterus | Endometrial Stromal Polyp [B] | 1 vs 3 | 0.0168 |

"The obtained p-values are all greater than 0.01 but lower than or equal to 0.05. According to the recommendations of Lin and Rahman (Lin and Rahman, 1998), the increased tumor rate in a treated group when compared with the control group is considered significant when the p-value is $\leq$ 0.05 for a rare tumor, or $\leq$ 0.01 for a common tumor. Using these criteria, the increased incidence of tumors in the above listed pairwise comparisons are considered to be statistically significant only if these tumor are classified as rare since the p-values are between 0.01 and 0.05.

"As mentioned by Lin [Lin, 1997], the discrete permutation distribution was used to compute the corresponding p-value for each statistical test performed on a dataset containing 10 or less tumor occurrences." (page 13703 of report, page 10 of Statistics Report)

### 3.2.1.2 FDA Reviewer's Results

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

**Survival analysis:**

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 17 for male rats, Table 18 for female rats) summarize the mortality results for the dose groups. The data were grouped for the specified time period, and present the number of deaths during the time interval over the number at risk at the beginning of the interval. The percentage cited is the percent survived at the end of the interval.

**Table 17. Summary of Male Rats Mortality (dose/kg/day)**

| Period | 1.Vehicle | 2.Low | 3.Medium | 4.High |
|---|---|---|---|---|
| 0-52 | 0/65<br>100.0% | 2/65<br>96.9% | 1/65<br>98.5% | 1/65<br>98.5% |
| 53-78 | 4/65<br>93.8% | 4/63<br>90.8% | 4/64<br>92.3% | 3/64<br>93.8% |
| 79-91 | 6/61<br>84.6% | 8/59<br>78.5% | 8/60<br>80.0% | 3/61<br>89.2% |
| 92-104 | 9/55<br>70.8% | 6/51<br>69.2% | 9/52<br>66.2% | 8/58<br>76.9% |
| terminal | 46 | 45 | 43 | 50 |

[1] number deaths / number at risk
[2] per cent survival to end of period.

**Table 18. Summary of Female Rats Mortality (dose/kg/day)**

| Period | 1.Vehicle | 2.Low | 3.Medium | 4.High |
|---|---|---|---|---|
| 0-52 | 0/65<br>100.0% | 2/65<br>96.9% | 2/65<br>96.9% | 2/65<br>96.9% |
| 53-78 | 5/65<br>92.3% | 7/63<br>86.2% | 10/63<br>81.5% | 7/63<br>86.2% |
| 79-91 | 11/60<br>75.4% | 9/56<br>72.3% | 8/53<br>69.2% | 11/56<br>69.2% |
| 92-104 | 14/49<br>53.8% | 13/47<br>52.3% | 16/45<br>44.6% | 11/45<br>52.3% |
| terminal | 35 | 34 | 29 | 34 |

[1] number deaths / number at risk
[2] per cent survival to end of period.

The results of statistical tests in survival differences are presented below (and in Appendix 1):

**Table 19. Statistical Significances of Tests of Homogeneity and Trend in Survival in Rats**

| Hypotheses | Males | | Females | |
|---|---|---|---|---|
| | Logrank | Wilcoxon | Logrank | Wilcoxon |
| Homogeneity over all four groups | 0.5913 | 0.5935 | 0.6919 | 0.6404 |
| No Trend over all four groups | 0.4206 | 0.4246 | 0.6067 | 0.4566 |
| No difference between high dose and vehicle | 0.4462 | 0.4661 | 0.6569 | 0.4923 |

Thus, in male or female rats, whether analyzing among all four dose groups, trend in dose, and in the comparison between the high dose and control none of the tests of differences in survival or trend were even close to the usual 0.05 level of statistical significance (i.e., in males all six $p \geq 0.4206$, in females all six $p \geq 0.4566$). While absence of proof is not proof of absence, the lack of evidence for such differences in survival was quite consistent with the hypotheses of no differences or trends.

The statistical tests seem to be explained by the Kaplan-Meier survival curves displayed Appendix 1. In male rats none of the curves seem to consistently dominate, and are largely intertwined. In female rats, although the vehicle control generally has slightly higher survival, the actual survival curves differ little, with the curves for the other dose groups generally intertwined. Again, this seems consistent with the results of the tests presented above.

**Tumorigenicity analysis:**

Table 20 below, a repeat of Table 3 above and Table A.2.1 below, shows the tumors that had at least one non-multiplicity adjusted test that was statistically significant at a 0.10 level.

**Table 20. Potentially Statistically Significant Results for Organ-Tumor Combinations in Rats**

| Organ/ Tumor | Overall Results Veh | Low | Med | High | ptrend | phigh vsVeh | pmed vsVeh | plow vsVeh |
|---|---|---|---|---|---|---|---|---|
| Male Rats | | | | | | | | |
| PITUITARY GLAND | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 55.7 | 54.1 | 54.3 | 57.0 | | | | |
| PARS INTERMEDIA ADENOMA [B]. | 0 | 0 | 4 | 1 | .2107 | .5045 | .0568 | . |
| Systemic | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 55.7 | 54.1 | 54.2 | 57.9 | | | | |
| Malignant Fibrous Histiocytoma | 0 | 0 | 0 | 2 | .0663 | .2568 | . | . |
| TESTES | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 55.7 | 54.4 | 55.0 | 57.7 | | | | |
| INTERSTITIAL CELL ADENOMA [B]. | 1 | 1 | 4 | 7 | .0059 | .0341 | .1760 | .7477 |
| THYROID GLAND | | | | | | | | |
| # Evaluated | 64 | 63 | 64 | 65 | | | | |
| Adj. # at Risk | 54.8 | 52.9 | 53.2 | 57.0 | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| C-CELL ADENOMA [B]. | 1 | 5 | 2 | 3 | .4251 | .3298 | .4929 | .0942 |

**Table 20. (cont.) Potentially Statistically Significant Results for Organ-Tumor Combinations in Rats**

| Organ/ Tumor | Veh | Low | Med | High | Overall Results ptrend | phigh vsVeh | pmed vsVeh | plow vsVeh |
|---|---|---|---|---|---|---|---|---|
| Female Rats | | | | | | | | |
| MAMMARY GLANDS | | | | | | | | |
| # Evaluated | 64 | 65 | 63 | 65 | | | | |
| Adj. # at Risk | 53.6 | 53.8 | 50.2 | 52.1 | | | | |
| FIBROADENOMA [B]. | 11 | 22 | 15 | 13 | .5939 | .3877 | .1970 | .0176 |
| OVARIES | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 52.8 | 51.0 | 48.7 | 50.8 | | | | |
| TUBULOSTROMAL ADENOMA [B]. | 0 | 0 | 0 | 3 | .0149 | .1142 | . | . |
| PANCREAS | | | | | | | | |
| # Evaluated | 64 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 51.8 | 51.0 | 48.7 | 49.7 | | | | |
| ISLET CELL ADENOMA [B]. | 0 | 2 | 1 | 3 | .0821 | .1139 | .4848 | .2426 |
| UTERUS | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 64 | | | | |
| Adj. # at Risk | 53.9 | 52.5 | 51.6 | 50.8 | | | | |
| ENDOMETRIAL STROMAL POLYP [B]. | 4 | 6 | 11 | 8 | .0968 | .1518 | .0386 | .3585 |

Using the tumor incidence in the vehicle to determine whether a tumor should be classified as rare or common, in male rats, benign interstitial cell adenoma of the testes would be classified as common, so the test of trend would be quite close to statistical significance ( $p = 0.0059 \approx 0.005$). Seperately or jointly testing the associated pairwise test between the high dose and the vehicle ( $p = 0.0341 < 0.05$ ) would be statistically significant. In female rats the simple test of trend in benign tubulostromal adenoma in the ovaries was also statistically significant ( $p = 0.0149 < 0.025$), since the tumor would be classified as rare. For joint testing, but not for separate testing, the corresponding pairwise comparison would be close to significance ( $p = 0.1142 \approx 0.10$).

For separate testing of hypotheses, if we accept the, possibly quite considerable, increase in error for including pairwise tests other than the comparison between the high dose and vehicle, in female rats the simple pairwise difference between the low dose and vehicle in benign fibroadenoma of the mammaries would be statistically significant ( $p = 0.0176 < 0.05$ ), as would be the pairwise difference between the medium dose and vehicle in benign endometrial stromal polyp ( $p=0.0386 < 0.05$). No other tests satisfied the Haseman-Lin-Rahman adjustments for multiplicity for seperate tests on the trend and pairwise difference parameters.

Complete results of statistical poly-k tests of tumor trend and differences between dose groups in male rats and female rats are given in Tables A.2.3 and A.2.4 in appendix 2.

## 3.2.2 Study (b) (4) Study 1124-016 - A 104-Week Dermal Oncogenicity Study of AN2690 in Mice

CRO: (b) (4)
STUDY DURATION: 104 weeks.
STUDY STARTING DATE: October 27, 2006.
STUDY ENDING DATE: October 24, 2008.
RAT STRAIN: Crl:CD1®(Icr) Mice.
ROUTE: Daily topical application

The drug vehicle is 80% ethanol/20% propylene glycol. Animals were dosed once daily. Gross aspects of the study designs are summarized in Table 21 (a repeat of Table 2 above) be1ow:

**Table 21. Design of Mice Study** (dose volume 5 µL/cm$^2$ from days 1-14)
1 µL/g from day 15

| Treatment Group | # Main study animals (# TK[1,2] animals)/gender | Nominal Dose[3] from day 8 | Nominal Dosing[3] Concentration (mg/mL) |
|---|---|---|---|
| 1. Vehicle[4] | 65 ( 40[1]/ 22[2]) | 0% | 0 |
| 2. Low | 65 ( 40[1]/ 22[2]) | 5% ( 1%) | 50 (10) |
| 3. Medium | 65 ( 40[1]/ 22[2]) | 10% (2.5%) | 100 (25) |
| 4. High | 65 ( 40[1]/ 22[2]) | 15% (10 %) | 150 (100) |

[1] Toxicokinetic phase animals began dosing during Week 1, and blood samples were collected on Days 1 and 180.
[2] Toxicokinetic single dose groups.
[3] Dosage in parentheses from days 1-7, main dosage (outside parentheses) from day 8.
[4] 80% ethanol (USP, 190 proof)/20% propylene glycol.

The Sponsor summarizes the study conduct as follows: "Four main study treatment groups 65 Crl:CD1®(Icr) mice/sex/group received the vehicle, 80% ethanol/20% propylene glycol, or test article at approximately the same time (±2 hours) once per day for approximately 104 weeks at dose levels of 0, 1, 2.5, or 10% from Days 1 to 7, and 0, 5, 10, or 15% beginning on Day 8. Four toxicokinetic (TK) groups of 40 animals/sex/group received the vehicle or test article for up to 180 days in the same manner as the main study groups. The dose volume for all groups was 5 µL/cm2 from Days 1 to 14 and 1 µL/g beginning on Day 15. Four additional TK groups of 22 animals/sex/group were also included and received a single dose of the vehicle or test article at the revised dose levels of 0, 5, 10, and 15%, administered at a dose volume of 1 µL/g." (page 10 of Sponsor's report)

Mice were allocated to treatment sing a block randomization procedure, apparently balancing on weight. . "Separate block randomizations were performed for the main study, toxicokinetic (TK), and sentinel groups. A computer randomization was also used to select four animals/sex for a pretest serological health screen. Additionally, 88 male and 88 female animals (weighing 26.4 to 33.2 g and 20.3 to 25.8 g, respectively, at randomization) were assigned by block randomization to TK groups added to repeat the Day 1 blood collections for plasma analysis at the revised dose levels." (page 14 of Sponsor's report)

Animals were approximately six weeks old at first dosing. After three days where animals were housed in groups of three or four animals for acclimation, animals were housed individually. The Sponsor states that detailed physical examinations were made on all animals twice weekly for the first month, then weekly for the next three months, and finally biweekly and then monthly. Body weights were recorded weekly for the first 14 weeks, beginning approximately one week before initiation of dosing, every other week from Weeks 16 to 28, and every 4 weeks thereafter.

### 3.2.2.1 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 summarized mortality results in mice as follows: "A slight decrease in survival was observed in males treated with 5% AN2690 as compared to controls; however, this finding was not dose dependent or associated with any assigned cause of death. Forty-six, 29, 43, and 42% of the males and 38, 40, 45, and 38% of the females at 0, 5, 10, and 15% AN2690, respectively, survived to scheduled termination (Week 105). There were no test article-related differences in mortality between control and treated males and females. Causes of death were of the type commonly seen in mice of this strain and age." (page 25 of rat report)

**Tumorigenicity analysis:**

The Sponsor's statistical analysis of tumorigenicity is based on the Cochran-Armitage trend test, and Fisher's exact tests to compare each treatment group with the control group, and Peto's survival adjusted test (apparently) of trend. Those results that had a significance level of 0.10 or less were extracted from the Sponsor's text table 11 (pages 289-306) and are presented below:

**Table 22. Sponsor Table 11 Statistical Analysis of Neoplasma (Extract)**

| Tissue Diagnosis | 0% AN2690 | 5% AN2690 | 10% AN2690 | 15% AN2690 |
|---|---|---|---|---|
| Males | | | | |
| Lung | | | | |
| adenoma, bronchiolar alveolar, benign | | | | |
| Overall Rates (a) | 8/65 (12.31%) | 2/65 (3.08%) | 9/65 (13.85%) | 10/65 (15.38%) |
| Fisher Exact Test; P-value | | 0.0958 | 1.0000 | 0.8002 |
| Cochran - Armitage Trend Test; P-value | 0.2530 | | | |
| Peto Test; P-value | 0.2356 | | | |
| carcinoma, bronchiolar alveolar, malignant | | | | |
| Overall Rates (a) | 7/65 (10.77%) | 10/65 (15.38%) | 1/65 (1.54%) | 7/65 (10.77%) |
| Fisher Exact Test; P-value | | 0.6040 | 0.0619 | 1.0000 |
| Cochran - Armitage Trend Test; P-value | 0.3981 | | | |
| Peto Test; P-value | 0 4217 | | | |
| Females | | | | |
| ovaries | | | | |
| granulosa cell tumor, malignant | | | | |
| Overall Rates (a) | 0/64 (0.00%) | 0/65 (0.00%) | 0/64 (0.00%) | 2/65 (3.08%) |
| Fisher Exact Test; P-value | | 1.0000 | 1.0000 | 0.4961 |
| Cochran - Armitage Trend Test; P-value | 0.0579 | | | |
| Peto Test; P-value | 0.0652 | | | |

Note that none of the tests of trend or pairwise differences between the high dose and control satisfy the Haseman-Lin-Rahman criteria for statistical significance when adjusting for multiplicity. The Sponsor summarizes tumorigenicity results as follows: "There were no test article-related neoplastic effects observed in treated males or females. Neoplasms in this study were of the type typically seen in this strain and age of mouse. Any differences in tumor incidence between control and treated animals were small and not considered biologically or statistically significant.

"Squamous cell carcinoma of the treated skin was observed in three animals: one male at 5% AN2690 (animal number 1092), one male at 10% AN2690 (animal number 1168), and one female at 15% AN2690 (animal number 1655). A squamous cell papilloma was observed in the untreated skin of one female each at 5% and 10% AN2690 (animal numbers 1489 and 1596, respectively).

"A low incidence of cutaneous squamous cell carcinomas in female control mice and cutaneous squamous cell papillomas in male and female control mice has been reported in historical control data of Crl:CD1 (ICR)BR mice from (b) (4) The squamous cell carcinomas and squamous cell papilloma in the treated and untreated skin, respectively, of this study were considered incidental and not test article related due to the low number of tumors, the lack of statistical significance, lack of dose responsiveness, and previous evidence of these type of tumors in historical control data.

"Several mice had large, aggressive, poorly differentiated subcutaneous sarcomas consisting of fibrosarcoma, undifferentiated sarcoma, fibrous histiocytoma, liposarcoma, and osteosarcoma. The majority of these subcutaneous tumors were located in the untreated skin regions. These tumors in the untreated skin were described under skin, subcutis. One female each at 5% and 10% AN2690 (animal numbers 1543 and 1591, respectively) had subcutaneous tumors in the treated region, liposarcoma and undifferentiated sarcoma, respectively." (page 28-29 of report)

"Subcutaneous soft tissue tumors have been reported at the site of implanted microchips in mice. . . . Of the subcutaneous sarcomas observed in this study, half of the tumors were associated with implanted microchips. Therefore, it is likely that these tumors were induced by the presence of the microchip. The subcutaneous liposarcoma observed in the treated skin area of animal 1543 was associated with an implanted microchip and was considered not test article related. The association with a microchip in the subcutaneous undifferentiated sarcoma of animal number 1591 could not be determined as no description of microchip location in the relation to the tumor was made for this animal. Due to the low incidence of subcutaneous sarcomas in the treated skin area and the possible association with implanted microchips, the subcutaneous sarcomas in the treated skin area were considered incidental and not test article related." (page 29 of report)

**3.2.1.2 FDA Reviewer's Results**

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

**Survival analysis:**

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 23 for male mice, Table 24 for female mice) summarize the mortality results for the dose groups. The data were grouped for the specified time period, and present the number of deaths during the time interval over the number at risk at the beginning of the interval. The percentage cited is the percent survived at the end of the interval.

**Table 23. Summary of Male Mice Mortality (dose/kg/day)**

| Period | 1.Vehicle | 2.Low | 3.Medium | 4.High |
|---|---|---|---|---|
| 0-52 | 3/65<br>95.4% | 5/65<br>92.3% | 6/65<br>90.8% | 6/65<br>90.8% |
| 53-78 | 9/62<br>81.5% | 12/60<br>73.8% | 12/59<br>72.3% | 8/59<br>78.5% |
| 79-91 | 13/53<br>61.5% | 15/48<br>50.8% | 8/47<br>60.0% | 12/51<br>60.0% |
| 92-104 | 10/40<br>46.2% | 14/33<br>29.2% | 11/39<br>43.1% | 12/39<br>41.5% |
| terminal | 30 | 19 | 28 | 27 |

[1] number deaths / number at risk
[2] per cent survival to end of period.

**Table 24. Summary of Female Mice Mortality (dose/kg/day)**

| Period | 1.Vehicle | 2.Low | 3.Medium | 4.High |
|---|---|---|---|---|
| 0-52 | 6/65<br>90.8% | 3/65<br>95.4% | 5/65<br>92.3% | 5/65<br>92.3% |
| 53-78 | 14/59<br>69.2% | 7/62<br>84.6% | 13/60<br>72.3% | 9/60<br>78.5% |
| 79-91 | 9/45<br>55.4% | 16/55<br>60.0% | 6/47<br>63.1% | 11/51<br>61.5% |
| 92-104 | 11/36<br>38.5% | 13/39<br>40.0% | 12/41<br>44.6% | 15/40<br>38.5% |
| Terminal | 25 | 26 | 29 | 25 |

[1] number deaths / number at risk
[2] per cent survival to end of period.

The results of statistical tests of overall homogeneity, no tend, and no differences between the High dose and Vehicle are given below (a repeat of Table 4 and Table A.1.2):

**Table 25. Statistical Significances of Tests of Homogeneity and Trend in Survival in Mice**

| Hypotheses | Males | | Females | |
|---|---|---|---|---|
| | Logrank | Wilcoxon | Logrank | Wilcoxon |
| Homogeneity over all four groups | 0.2591 | 0.4010 | 0.8719 | 0.8151 |
| No Trend over all four groups | 0.9489 | 0.8354 | 0.7144 | 0.6512 |
| No difference between high dose and vehicle | 0.5915 | 0.5596 | 0.7699 | 0.6250 |

As was observed in rats, in either gender, none of the tests of overall differences among dose groups, trend in dose, or comparison between high dose and control were even close to the usual 0.05 level of statistical significance (i.e., in males all six $p \geq 0.2591$, in females all six $p \geq 0.6250$). Again, while not actual proving no difference, it is consistent with such a hypothesis

These statistical results are consistent with the Kaplan-Meier curves for mice in Appendix 1. In male mice the vehicle control generally has the highest survival, although largely intertwined with the remaining dose groups. Near the end of the study, the low dose group eventually has the lowest survival. In female mice, although the low dose generally has slightly the highest or near the highest survival, while the vehicle control generally the lowest. The other dose groups are generally intertwined.

**Tumorigenicity analysis:**

Table 26 below, a repeat of Table 3 above and Table A.2.2 below, shows the tumors that had at least one non-multiplicity adjusted test that was statistically significant at a 0.10 level.

**Table 26. Potentially Statistically Significant Results for Organ-Tumor Combinations in Mice**

| Organ/ Tumor | Overall Results Veh | Low | Med | High | ptrend | phigh vsVeh | pmed vsVeh | plow vsVeh |
|---|---|---|---|---|---|---|---|---|
| Male Mice | | | | | | | | |
| Systemic | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.7 | 41.2 | 46.0 | 45.9 | | | | |
| HEMANGIOSARCOMA | 2 | 3 | 7 | 4 | .1546 | .3279 | .0789 | .4450 |
| Adj. # at Risk | 46.7 | 41.7 | 46.1 | 45.9 | | | | |
| Hemangioma/Hemangiosacroma | 2 | 4 | 8 | 4 | .1679 | .3279 | .0450 | .2847 |
| epididymides | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.1 | 40.9 | 43.8 | 44.9 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 0 | 0 | 2 | .0636 | .2362 | . | . |
| liver | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.7 | 41.0 | 46.0 | 45.9 | | | | |
| HEMANGIOSARCOMA | 2 | 1 | 7 | 4 | .0935 | .3279 | .0789 | .8517 |
| Adj. # at Risk | 46.9 | 44.7 | 44.7 | 44.9 | | | | |
| Hepato.Adenoma/Carcinoma | 6 | 12 | 10 | 7 | .4606 | .4650 | .1775 | .0769 |
| multicentric neoplasm | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.7 | 41.2 | 46.0 | 45.9 | | | | |
| HEMANGIOSARCOMA | 2 | 3 | 7 | 4 | .1546 | .3279 | .0789 | .4450 |

**Table 26. (cont.) Potentially Statistically Significant Results for Organ-Tumor Combinations in Mice**

| Organ/ Tumor | Veh | Low | Med | High | Overall Results ptrend | phigh vsVeh | pmed vsVeh | plow vsVeh |
|---|---|---|---|---|---|---|---|---|
| Female Mice | | | | | | | | |
| Systemic | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.4 | | | | |
| GRANULOSA CELL TUMOR | 0 | 0 | 0 | 2 | .0628 | .2646 | . | . |
| brain | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.9 | 48.9 | 45.3 | 47.5 | | | | |
| LYMPHOMA | 1 | 3 | 0 | 6 | .0649 | .0746 | 1 | .3604 |
| large intestine, cecum | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 46.4 | | | | |
| LYMPHOMA | 0 | 0 | 0 | 2 | .0650 | .2704 | . | . |
| ovaries | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.4 | | | | |
| GRANULOSA CELL TUMOR | 0 | 0 | 0 | 2 | .0628 | .2646 | . | . |
| salivary gland, mandibula | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 43.7 | 47.3 | 47.3 | 48.2 | | | | |
| LYMPHOMA | 2 | 1 | 4 | 6 | .0465 | .1721 | .3819 | .8950 |
| skin, subcutis | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 43.0 | 48.6 | 47.1 | 47.7 | | | | |
| LYMPHOMA | 3 | 3 | 6 | 7 | .0799 | .1965 | .2891 | .7127 |
| uterus with cervix | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.4 | | | | |
| GRANULOSA CELL TUMOR | 0 | 0 | 0 | 2 | .0628 | .2646 | . | . |

As with rats, we use the tumor incidence in the vehicle to determine whether a tumor should be classified as rare or common. Whether defined as rare or common, no tests of trend or pairwise comparison between the high dose and control achieved the Haseman-Lin-Rahman bounds to be considered as statistically significant. However, if we accept the possibly quite considerable increase in error for including pairwise tests other than the comparison between the high dose and vehicle, in male mice the simple pairwise difference between the medium dose and vehicle in pooled hemangioma and hemangiosarcoma would be barely statistically significant ( $p = 0.045 < 0.05$ ). Since none of the tests of trend were statistically significant, none of the joint tests would be statistically significant. No other tests in mice satisfied the Haseman-Lin-Rahman adjustments for multiplicity.

Complete results of statistical poly-k tests of tumor trend and differences between dose groups in male and female mice are given in Table A.2.5 and Table A.2.6 in Appendix 2.

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

**NA**

# 5. SUMMARY AND CONCLUSIONS

## 5.1. Statistical Issues and Collective Evidence

Please see Section 1.3 above.

## 5.2. Conclusions and Recommendations

Please see section 1.1.

# APPENDICES:

## Appendix 1. Survival Analyses

Simple summary life tables in mortality are presented in the report (Tables 12 and 13, above). Kaplan-Meier estimated survival curves across study groups for each gender in rats are displayed below in Figures A.1.1 and A.1.2. The plots include 95% confidence intervals around each survival curve (colored area around each curve). These plots are also supported by tests of homogeneity in survival over the treatment groups. The statistical significance levels (i.e., p-values) are provided in Table A.1.1., below. One might note that the log rank tests place greater weight on later events, while the Wilcoxon test tends to weight them more equally, and thus, in tends to place more weight on differences in earlier events than does the log rank test.

**Table A.1.1 Statistical Significances of Tests of Homogeneity and Trend in Survival in Rats**

| Hypotheses | Males | | Females | |
|---|---|---|---|---|
| | Logrank | Wilcoxon | Logrank | Wilcoxon |
| Homogeneity over all four groups | 0.5913 | 0.5935 | 0.6919 | 0.6404 |
| No Trend over all four groups | 0.4206 | 0.4246 | 0.6067 | 0.4566 |
| No difference between high dose and vehicle | 0.4462 | 0.4661 | 0.6569 | 0.4923 |

In male or female rats, whether analyzing among all four dose groups, trend in dose, and in the comparison between the high dose and control none of the tests of differences in survival or trend were even close to the usual 0.05 level of statistical significance (i.e., in males all six $p \geq 0.4206$, in females all six $p \geq 0.4566$). While absence of proof is not proof of absence, the lack of evidence for such differences in survival was quite consistent with the hypotheses of no differences or trends.

The statistical tests seem to be explained by the Kaplan-Meier survival curves displayed below. In male rats none of the curves seem to consistently dominate, and are largely intertwined. In female rats, although the vehicle control generally has slightly higher survival, the actual survival curves differ little, with the curves for the other dose groups generally intertwined. Again, this seems consistent with the results above.

**Figure A.1.1 Kaplan-Meier Survival Curves for Male Rats**

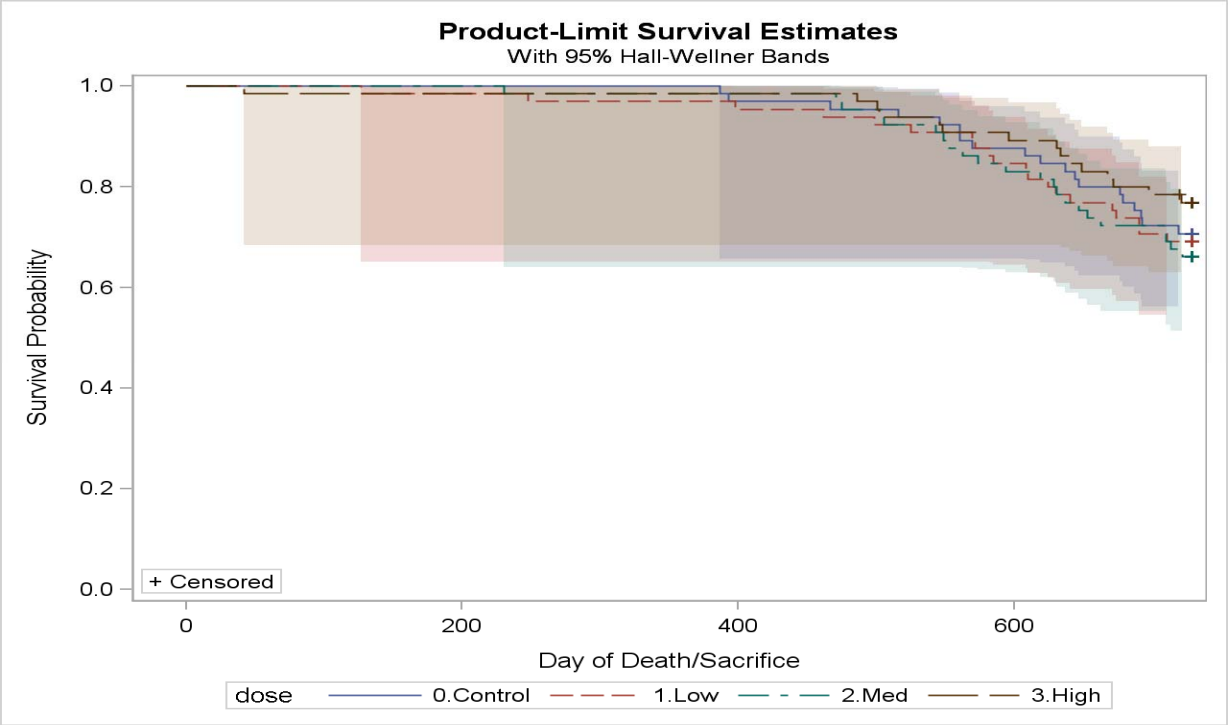
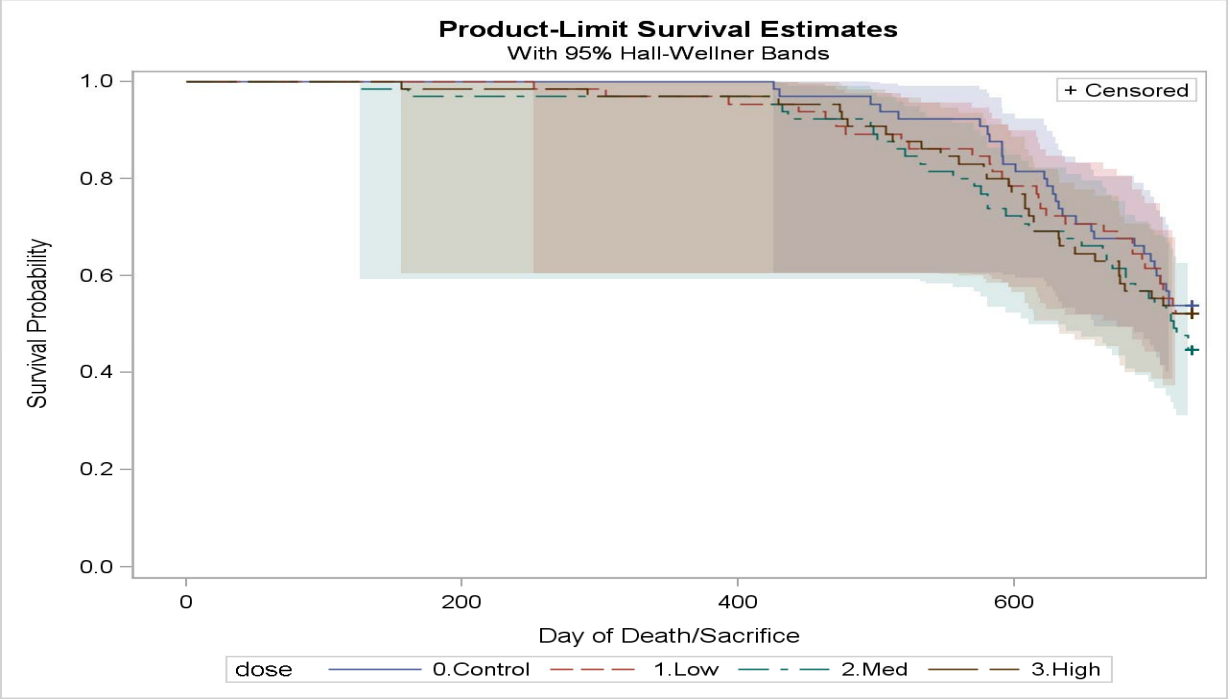



**Figure A.1.2 Kaplan-Meier Survival Curves for Female Rats**



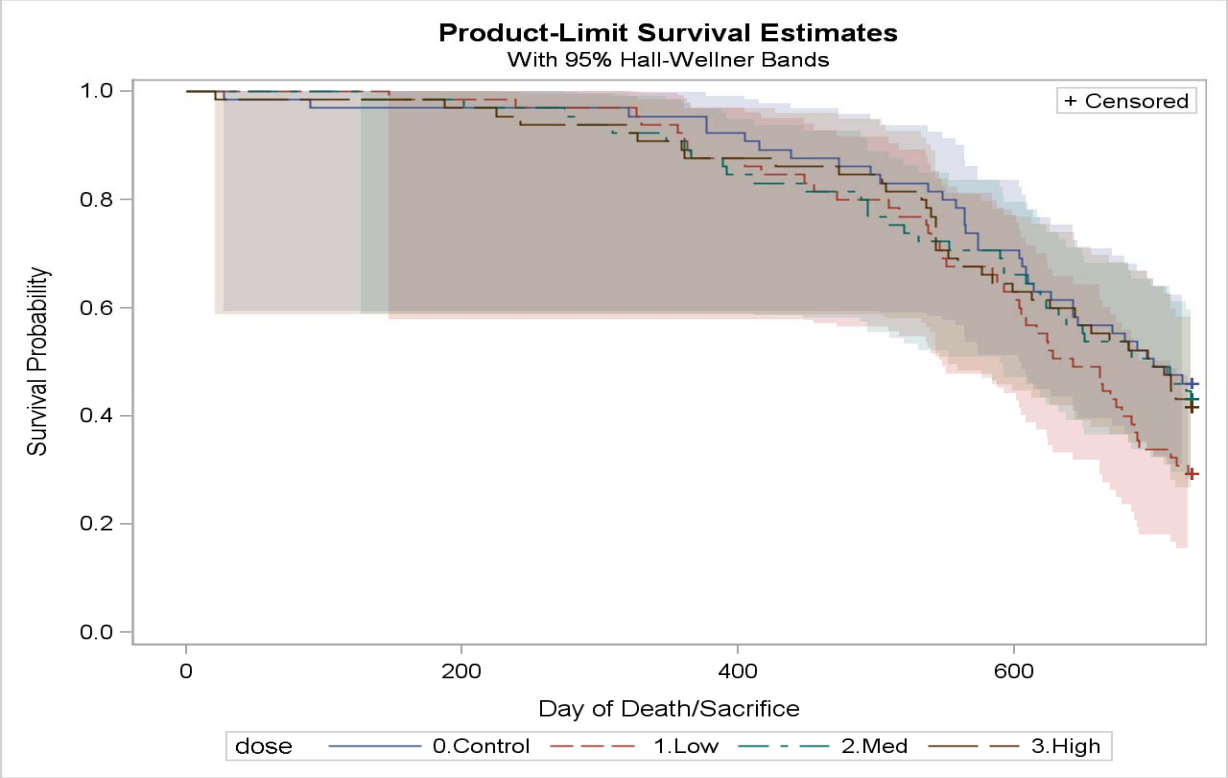
Results are quite similar in mice.

**Table A.1.2 Statistical Significances of Tests of Homogeneity and Trend in Survival in Mice**

| Hypotheses | Males | | Females | |
|---|---|---|---|---|
| | Logrank | Wilcoxon | Logrank | Wilcoxon |
| Homogeneity over all four groups | 0.2591 | 0.4010 | 0.8719 | 0.8151 |
| No Trend over all four groups | 0.9489 | 0.8354 | 0.7144 | 0.6512 |
| No difference between high dose and vehicle | 0.5915 | 0.5596 | 0.7699 | 0.6250 |

As with rats, in male or female mice, none of the tests of overall differences among dose groups, trend in dose, or comparison between high dose and control were even close to the usual 0.05 level of statistical significance (i.e., in males all six $p \geq 0.2591$, in females all six $p \geq 0.6250$). Again, while not actual proving no difference, it is consistent with such a hypothesis.

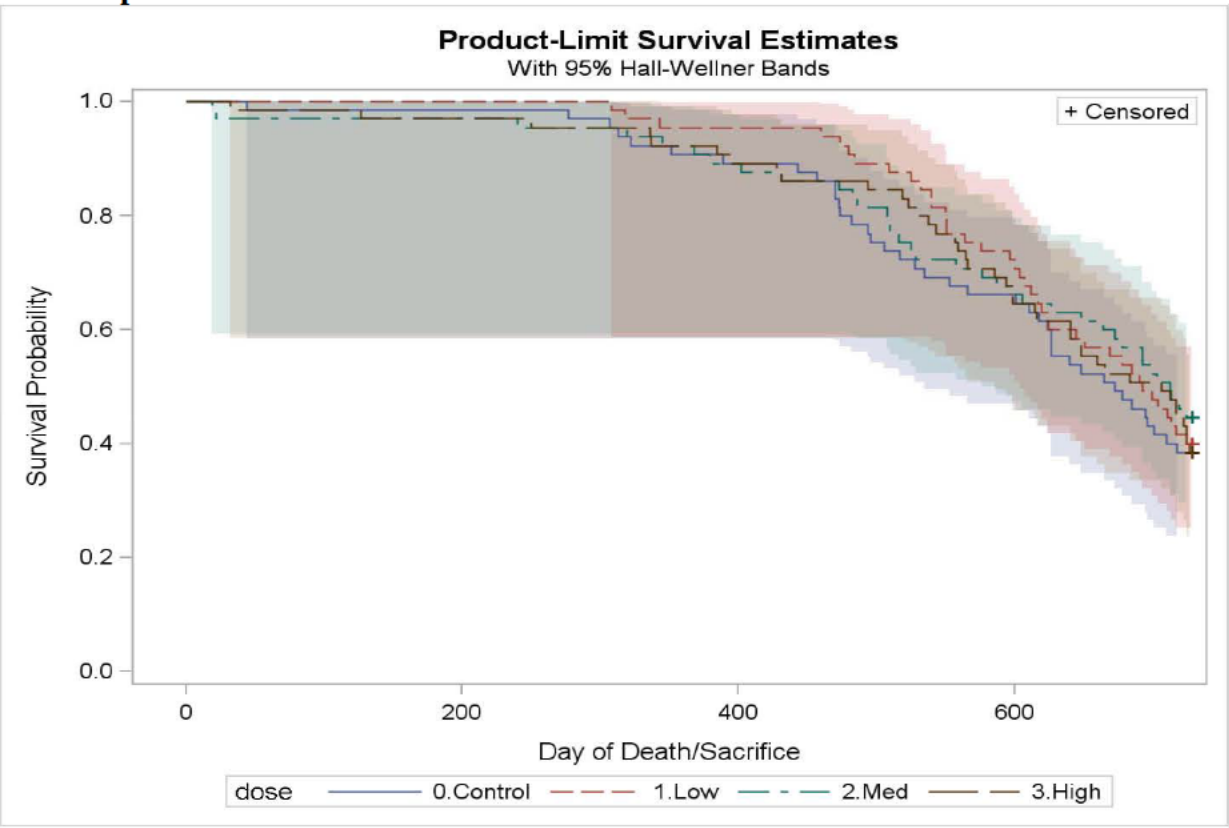
**Figure A.1.3 Kaplan-Meier Survival Curves for Male Mice**




Again, the statistical results are consistent with the Kaplan-Meier curves above and below. In male mice the vehicle control generally has the highest survival, although largely intertwined with the remaining dose groups. Near the end of the study, the low dose group eventually has the lowest survival. In female mice, although the low dose generally has slightly

the highest or near the highest survival, while the vehicle control generally the lowest. The other dose groups are generally intertwined.

### A.1.4 Kaplan-Meier Survival Curves for Female Mice



## Appendix 2. FDA Poly-k Tumorigenicity Analysis

The poly-k test, here with k=3, modifies the original Cochran-Armitage test to adjust for differences in mortality (please see Bailer & Portier, 1988, Bieler & Williams, 1993). The tests used here are small sample exact permutation tests of tumor incidence. When there were no tumors of the specific type being analyzed in either column of the 2x2 table corresponding to a pairwise comparison an argument could be made that the p-value for this test should be 1.0. However, largely for readability, in the tables below these p-values are considered as missing (i.e., corresponding to a null test), denoted by a period ".". Note that the StatXact program used for these analyses adjusts for the variance, which would be 0. Then the significance levels of the test statistics are based on the result of a division by 0, i.e., undefined, and hence StatXact codes these p-values as missing.

For each gender by organ the number of animals microscopically analyzed is presented first. Note that indicating an organ was not examined requires a specification in the data (please see section 2.2 above). It is possible that this specification could be missing in some of this data. Then the number of animals at risk could be inflated, and the proportion of animals with tumor would be artificially decreased. Thus, as discussed in Section 1.5 above, for some of these organs it is possibly more appropriate to define the actual endpoint used in the statistical analysis be the condition of being microscopically analyzed and show the tumor. This does have problems unless treatment groups are not treated equally except for actual treatment. The entry for each tumor is preceded by the adjusted number of animals at risk for that endpoint. It seems clear that an animal that dies early without having displaying that endpoint reduces the size of the risk set for that getting that particular endpoint. The poly-k test down weights such animals, and as discussed in Section 1.3.1.4, above, the sum of these poly-k weights seems to be a better estimate of the number of animals at risk of getting that tumor than the simple number of animals analyzed. This sum is given in the row labeled "Adjusted # at risk ". Tumor incidence is presented next, with the significance levels of the tests of trend, and the results of pairwise tests between the high and medium dose groups versus vehicle. The next row continues with the p-values of the pairwise test between the low and vehicle dose groups and the p-values between the vehicle dose group and high dose group with water, respectively. For these analyses, incidence in the water only group is used to assess background tumor incidence, and thus whether a tumor is considered to be rare (background incidence <1%) or common. Note that for this analysis a tumor is only classified as rare if the vehicle group shows none of that particular tumor.

A large number of tumors are typically identified in the analysis of neoplasms, implying a large number of statistical tests. Following the frequentist paradigm, when interpreting significance levels (i.e., p-values), this reviewer would recommend one of the Haseman-Lin-Rahman (HLR) rules to adjust for the multiplicity of tests. Two primary approaches have been investigated, one for testing dose related trend and pairwise comparison between the high dose and control seperately and the other these hypotheses jointly (please see Section 1.3.1.4, above). Usual statistical practice would be to test hypotheses separately, but some scientists want to

control Type I error when only testing both the trend and pairwise hypotheses simultaneously. That is, when testing for trend over dose and, separately, the difference between the highest dose group with a control group, to control the overall Type I error rate for the joint tests in a two species submission to roughly 10%, one compares the unadjusted significance level of the trend test to 0.005 for common tumors and 0.025 for rare tumors, and the pairwise test to 0.01 for common tumors and 0.05 for rare tumors. For the testing these hypothese jointly for common tumors one compares the unadjusted significance level of the trend test to 0.005 and the pairwise test to 0.05, and for rare tumors 0.025 for tests of trend and 0.10 the pairwise comparison. Using these adjustments for other tests, like testing the comparisons between the Low and Medium dose groups versus vehicle can be expected to increase the overall type I error rate to some value above the nominal rough 10% level, possibly considerably higher than the nominal 10% rate.

Table A.2.1 below, displays the tumors in rats that had at least one non-multiplicity adjusted test that was statistically significant at or close to a 0.10 level. Table A.2.2 shows similar results in mice. Complete results of statistical poly-k tests of tumor trend and differences between dose groups in male and female rats are given in Tables A.2.3 and A.2.4, respectively, with similar results for mice in Tables A.2.5 and A.2.6, respectively.

**Table A.2.1. Potentially Statistically Significant Results for Organ-Tumor Combinations in Rats**

| Organ/ Tumor | Overall Results Veh | Low | Med | High | ptrend | phigh vsVeh | pmed vsVeh | plow vsVeh |
|---|---|---|---|---|---|---|---|---|
| Male Rats | | | | | | | | |
| PITUITARY GLAND | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 55.7 | 54.1 | 54.3 | 57.0 | | | | |
| PARS INTERMEDIA ADENOMA [B]. | 0 | 0 | 4 | 1 | .2107 | .5045 | .0568 | . |
| Systemic | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 55.7 | 54.1 | 54.2 | 57.9 | | | | |
| Malignant Fibrous Histiocytoma | 0 | 0 | 0 | 2 | .0663 | .2568 | . | . |
| TESTES | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 55.7 | 54.4 | 55.0 | 57.7 | | | | |
| INTERSTITIAL CELL ADENOMA [B]. | 1 | 1 | 4 | 7 | .0059 | .0341 | .1760 | .7477 |
| THYROID GLAND | | | | | | | | |
| # Evaluated | 64 | 63 | 64 | 65 | | | | |
| Adj. # at Risk | 54.8 | 52.9 | 53.2 | 57.0 | | | | |
| C-CELL ADENOMA [B]. | 1 | 5 | 2 | 3 | .4251 | .3298 | .4929 | .0942 |
| Female Rats | | | | | | | | |
| MAMMARY GLANDS | | | | | | | | |
| # Evaluated | 64 | 65 | 63 | 65 | | | | |
| Adj. # at Risk | 53.6 | 53.8 | 50.2 | 52.1 | | | | |
| FIBROADENOMA [B]. | 11 | 22 | 15 | 13 | .5939 | .3877 | .1970 | .0176 |
| OVARIES | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 52.8 | 51.0 | 48.7 | 50.8 | | | | |
| TUBULOSTROMAL ADENOMA [B]. | 0 | 0 | 0 | 3 | .0149 | .1142 | . | . |
| PANCREAS | | | | | | | | |
| # Evaluated | 64 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 51.8 | 51.0 | 48.7 | 49.7 | | | | |
| ISLET CELL ADENOMA [B]. | 0 | 2 | 1 | 3 | .0821 | .1139 | .4848 | .2426 |

**Table A.2.1. (cont.) Potentially Statistically Significant Results for Organ-Tumor Combinations in Rats**

| Organ/ Tumor | Overall Results Veh | Low | Med | High | ptrend | phigh vsVeh | pmed vsVeh | plow vsVeh |
|---|---|---|---|---|---|---|---|---|
| Female Rats(cont.) | | | | | | | | |
| UTERUS | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 64 | | | | |
| Adj. # at Risk | 53.9 | 52.5 | 51.6 | 50.8 | | | | |
| ENDOMETRIAL STROMAL POLYP [B]. | 4 | 6 | 11 | 8 | .0968 | .1518 | .0386 | .3585 |

Using the tumor incidence in the vehicle to determine whether a tumor should be classified as rare or common, in male rats, benign interstitial cell adenoma of the testes would be classified as common, so the test of trend would be quite close to statistical significance ( $p = 0.0059 \approx 0.005$). The associated pairwise test between the high dose and the vehicle ( $p = 0.0341 < 0.05$ ) would be statistically significant. In female rats the test of trend in benign tubulostromal adenoma in the ovaries was also statistically significant ( $p = 0.0149 < 0.025$), while the joint test would be close to statistical significance since the pairwise test would be close to significance ($p = 0.1142 \approx 0.10$).

If we accept the, possibly quite considerable, increase in error for including pairwise tests other than the comparison between the high dose and vehicle, in female rats the simple pairwise difference between the low dose and vehicle in benign fibroadenoma of the mammaries would be statistically significant ( $p = 0.0176 < 0.05$ ), as would be the pairwise difference between the medium dose and vehicle in benign endometrial stromal polyp ( $p=0.0386 < 0.05$). No other tests satisfied the Haseman-Lin-Rahman adjustments for multiplicity.

**Table A.2.2. Potentially Statistically Significant Results for Organ-Tumor Combinations in Mice**

| Organ/ Tumor | Overall Results Veh | Low | Med | High | ptrend | phigh vsVeh | pmed vsVeh | plow vsVeh |
|---|---|---|---|---|---|---|---|---|
| Male Mice | | | | | | | | |
| Systemic | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.7 | 41.2 | 46.0 | 45.9 | | | | |
| HEMANGIOSARCOMA | 2 | 3 | 7 | 4 | .1546 | .3279 | .0789 | .4450 |
| Adj. # at Risk | 46.7 | 41.7 | 46.1 | 45.9 | | | | |
| Hemangioma/Hemangiosacroma | 2 | 4 | 8 | 4 | .1679 | .3279 | .0450 | .2847 |
| epididymides | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.1 | 40.9 | 43.8 | 44.9 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 0 | 0 | 2 | .0636 | .2362 | . | . |
| liver | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.7 | 41.0 | 46.0 | 45.9 | | | | |
| HEMANGIOSARCOMA | 2 | 1 | 7 | 4 | .0935 | .3279 | .0789 | .8517 |
| Adj. # at Risk | 46.9 | 44.7 | 44.7 | 44.9 | | | | |
| Hepato.Adenoma/Carcinoma | 6 | 12 | 10 | 7 | .4606 | .4650 | .1775 | .0769 |
| multicentric neoplasm | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.7 | 41.2 | 46.0 | 45.9 | | | | |
| HEMANGIOSARCOMA | 2 | 3 | 7 | 4 | .1546 | .3279 | .0789 | .4450 |

**Table A.2.2. (cont.) Potentially Statistically Significant Results for Organ-Tumor Combinations in Mice**

| Organ/ Tumor | Veh | Low | Med | High | Overall Results ptrend | phigh vsVeh | pmed vsVeh | plow vsVeh |
|---|---|---|---|---|---|---|---|---|
| Female Mice | | | | | | | | |
| Systemic | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.4 | | | | |
| GRANULOSA CELL TUMOR | 0 | 0 | 0 | 2 | .0628 | .2646 | . | . |
| brain | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.9 | 48.9 | 45.3 | 47.5 | | | | |
| LYMPHOMA | 1 | 3 | 0 | 6 | .0649 | .0746 | 1 | .3604 |
| large intestine, cecum | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 46.4 | | | | |
| LYMPHOMA | 0 | 0 | 0 | 2 | .0650 | .2704 | . | . |
| ovaries | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.4 | | | | |
| GRANULOSA CELL TUMOR | 0 | 0 | 0 | 2 | .0628 | .2646 | . | . |
| salivary gland, mandibular | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 43.7 | 47.3 | 47.3 | 48.2 | | | | |
| LYMPHOMA | 2 | 1 | 4 | 6 | .0465 | .1721 | .3819 | .8950 |
| skin, subcutis | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 43.0 | 48.6 | 47.1 | 47.7 | | | | |
| LYMPHOMA | 3 | 3 | 6 | 7 | .0799 | .1965 | .2891 | .7127 |
| uterus with cervix | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.4 | | | | |
| GRANULOSA CELL TUMOR | 0 | 0 | 0 | 2 | .0628 | .2646 | . | . |

As with rats, we use the tumor incidence in the vehicle to determine whether a tumor should be classified as rare or common. Whether defined as rare or common, no tests of trend or pairwise comparison between the high dose and control achieved the Haseman-Lin-Rahman bounds to be considered as statistically significant. However, if we accept the possibly quite considerable increase in error for including pairwise tests other than the comparison between the high dose and vehicle, in male mice the simple pairwise difference between the medium dose and vehicle in pooled hemangioma and hemangiosarcoma would be barely statistically significant ( $p = 0.045 < 0.05$ ). Since none of the tests of trend were statistically significant, none of the joint tests would be statistically significant. No other tests in mice satisfied the Haseman-Lin-Rahman adjustments for multiplicity.

Tables A.2.3 and A.2.4 below, give overall results in rats.

**Table A.2.3. Overall Results for Organ-Tumor Combinations in Male Rats**

| Organ/ Tumor | Overall Results Veh | Low | Med | High | ptrend | phigh vsVeh | pmed vsVeh | plow vsVeh |
|---|---|---|---|---|---|---|---|---|
| ABDOMINAL CAVITY | | | | | | | | |
| # Evaluated | 3 | 0 | 2 | 0 | | | | |
| Adj. # at Risk | 3.0 | 0.0 | 0.6 | 0.0 | | | | |
| ADENOCARCINOMA [M], metastatic site | 1 | 0 | 0 | 0 | 1 | . | . | . |
| ADRENAL GLANDS | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 64 | | | | |
| Adj. # at Risk | 55.7 | 54.1 | 54.9 | 56.0 | | | | |
| ADENOCARCINOMA [M], metastatic site | 0 | 0 | 1 | 0 | .5000 | . | .4954 | . |
| Adj. # at Risk | 55.7 | 54.8 | 54.2 | 56.1 | | | | |
| ADENOMA [B]. | 0 | 3 | 3 | 3 | .1480 | .1250 | .1182 | .1182 |
| Adj. # at Risk | 55.7 | 54.1 | 54.2 | 56.0 | | | | |
| C-CELL CARCINOMA [M], metastatic site | 0 | 0 | 0 | 1 | .2557 | .5045 | . | . |
| Adj. # at Risk | 55.7 | 54.1 | 54.2 | 56.4 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 0 | 0 | 0 | 1 | .2557 | .5045 | . | . |
| Adj. # at Risk | 55.7 | 54.1 | 54.2 | 56.6 | | | | |
| MALIGNANT FIBROUS HISTIOCYTOMA | 0 | 0 | 0 | 1 | .2557 | .5045 | . | . |
| Adj. # at Risk | 55.8 | 55.0 | 54.2 | 57.1 | | | | |
| PHEOCHROMOCYTOMA [B]. | 4 | 4 | 3 | 7 | .1769 | .2848 | .7736 | .6420 |
| AORTA | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 55.7 | 54.1 | 54.2 | 57.3 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 0 | 0 | 0 | 1 | .2591 | .5089 | . | . |
| Adj. # at Risk | 55.7 | 54.1 | 54.2 | 57.6 | | | | |
| MALIGNANT FIBROUS HISTIOCYTOMA | 0 | 0 | 0 | 1 | .2591 | .5089 | . | . |
| BONE | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 55.7 | 54.1 | 54.7 | 57.0 | | | | |
| SQUAMOUS CELL CARCINOMA [M]. | 0 | 0 | 1 | 0 | .5023 | . | .4954 | . |
| BONE MARROW | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 55.7 | 54.1 | 54.2 | 57.3 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 0 | 0 | 0 | 1 | .2591 | .5089 | . | . |
| BRAIN | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 55.8 | 54.5 | 55.6 | 57.0 | | | | |
| ASTROCYTOMA [M]. | 3 | 2 | 3 | 0 | .9496 | 1 | .6607 | .8126 |
| Adj. # at Risk | 55.7 | 54.8 | 54.2 | 57.0 | | | | |
| GRANULAR CELL TUMOR [B]. | 0 | 1 | 0 | 0 | .7489 | . | . | .4954 |
| Adj. # at Risk | 56.1 | 54.1 | 54.2 | 57.0 | | | | |
| LEIOMYOSARCOMA [M], metastatic site | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 56.0 | 54.1 | 54.2 | 57.0 | | | | |
| SQUAMOUS CELL CARCINOMA [M], metast. | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| EPIDIDYMIDES | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 55.7 | 54.1 | 54.2 | 57.3 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 0 | 0 | 1 | 1 | .1940 | .5089 | .4954 | . |
| ESOPHAGUS | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 55.7 | 54.1 | 54.2 | 57.3 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 0 | 0 | 1 | 1 | .1940 | .5089 | .4954 | . |
| HEART | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 55.7 | 54.1 | 54.2 | 57.3 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 0 | 0 | 0 | 1 | .2591 | .5089 | . | . |
| Adj. # at Risk | 55.7 | 54.3 | 54.2 | 57.2 | | | | |
| SCHWANNOMA [M]. | 0 | 1 | 0 | 1 | .3218 | .5089 | . | .4954 |

**Table A.2.3. (cont.) Overall Results for Organ-Tumor Combinations in Male Rats**

| Organ/ Tumor | Overall Results Veh | Low | Med | High | ptrend | phigh vsVeh | pmed vsVeh | plow vsVeh |
|---|---|---|---|---|---|---|---|---|
| KIDNEYS | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 55.7 | 54.1 | 54.9 | 57.0 | | | | |
| ADENOCARCINOMA [M]. | 0 | 0 | 1 | 0 | .5023 | . | .4954 | . |
| Adj. # at Risk | 55.7 | 54.1 | 54.2 | 57.0 | | | | |
| ADENOMA [B]. | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 55.7 | 54.1 | 54.9 | 57.0 | | | | |
| Adenoma/Adenocarcinoma | 1 | 0 | 1 | 0 | .8134 | 1 | .7477 | 1 |
| Adj. # at Risk | 55.7 | 54.7 | 54.2 | 57.7 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 0 | 1 | 1 | 2 | .1274 | .2568 | .4954 | .4954 |
| Adj. # at Risk | 55.7 | 54.1 | 54.2 | 57.6 | | | | |
| MALIGNANT FIBROUS HISTIOCYTOMA | 0 | 0 | 0 | 1 | .2591 | .5089 | . | . |
| Adj. # at Risk | 56.3 | 54.1 | 54.2 | 57.0 | | | | |
| RHABDOMYOSARCOMA [M], metastatic site | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| LARGE INTESTINE | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 55.7 | 54.1 | 54.2 | 57.3 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 0 | 0 | 1 | 1 | .1940 | .5089 | .4954 | . |
| LIVER | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 55.7 | 54.2 | 54.2 | 57.0 | | | | |
| Adenoma/Carcinoma, Hepatocellular | 1 | 1 | 3 | 0 | .7466 | 1 | .3021 | .7477 |
| Adj. # at Risk | 55.7 | 54.1 | 54.2 | 57.0 | | | | |
| HEPATOCELLULAR ADENOMA [B]. | 1 | 0 | 3 | 0 | .6865 | 1 | .3021 | 1 |
| Adj. # at Risk | 55.7 | 54.2 | 54.2 | 57.0 | | | | |
| HEPATOCELLULAR CARCINOMA [M]. | 0 | 1 | 0 | 0 | .7489 | . | . | .4954 |
| Adj. # at Risk | 55.7 | 54.7 | 54.2 | 57.7 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 0 | 1 | 1 | 2 | .1274 | .2568 | .4954 | .4954 |
| Adj. # at Risk | 56.1 | 54.1 | 54.2 | 57.0 | | | | |
| LEIOMYOSARCOMA [M], metastatic site | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 56.3 | 54.1 | 54.2 | 57.0 | | | | |
| RHABDOMYOSARCOMA [M], metastatic site | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| LUNGS | | | | | | | | |
| # Evaluated | 64 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 55.3 | 54.1 | 54.9 | 57.0 | | | | |
| BRONCHIOLO-ALVEOLAR ADENOMA [B]. | 0 | 0 | 1 | 0 | .5023 | . | .4954 | . |
| Adj. # at Risk | 55.3 | 54.1 | 54.2 | 57.0 | | | | |
| C-CELL CARCINOMA [M], metastatic site | 0 | 0 | 0 | 1 | .2557 | .5045 | . | . |
| Adj. # at Risk | 55.3 | 54.7 | 54.2 | 57.7 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 0 | 1 | 1 | 2 | .1274 | .2568 | .4954 | .4954 |
| Adj. # at Risk | 55.6 | 54.1 | 54.2 | 57.0 | | | | |
| LEIOMYOSARCOMA [M], metastatic site | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 55.3 | 54.1 | 54.2 | 57.6 | | | | |
| MALIGNANT FIBROUS HISTIOCYTOMA | 0 | 0 | 0 | 1 | .2591 | .5089 | . | . |
| Adj. # at Risk | 55.8 | 54.1 | 54.2 | 57.0 | | | | |
| RHABDOMYOSARCOMA [M], metastatic site | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| LYMPH NODES | | | | | | | | |
| # Evaluated | 9 | 3 | 6 | 8 | | | | |
| Adj. # at Risk | 8.1 | 2.9 | 5.8 | 6.5 | | | | |
| C-CELL CARCINOMA [M], metastatic site | 0 | 0 | 0 | 1 | .2857 | .4286 | . | . |
| Adj. # at Risk | 8.1 | 2.9 | 5.9 | 6.8 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 0 | 0 | 1 | 1 | .2143 | .4286 | .3846 | . |

**Table A.2.3. (cont.) Overall Results for Organ-Tumor Combinations in Male Rats**

| Organ/ Tumor | Overall Results Veh | Low | Med | High | ptrend | phigh vsVeh | pmed vsVeh | plow vsVeh |
|---|---|---|---|---|---|---|---|---|
| MAMMARY GLANDS | | | | | | | | |
| # Evaluated | 51 | 59 | 56 | 51 | | | | |
| Adj. # at Risk | 44.1 | 48.9 | 46.3 | 44.5 | | | | |
| ADENOMA [B]. | 1 | 0 | 1 | 0 | .8143 | 1 | .7638 | 1 |
| Adj. # at Risk | 44.1 | 48.9 | 46.3 | 44.5 | | | | |
| FIBROADENOMA [B]. | 0 | 0 | 1 | 0 | .4945 | . | .5111 | . |
| Adj. # at Risk | 44.1 | 48.9 | 46.2 | 44.9 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 0 | 0 | 0 | 1 | .2418 | .5000 | . | . |
| MANDIBULAR LYMPH NODE(S) | | | | | | | | |
| # Evaluated | 65 | 62 | 62 | 63 | | | | |
| Adj. # at Risk | 55.7 | 51.9 | 52.4 | 55.6 | | | | |
| SQUAMOUS CELL CARCINOMA [M],metastat. | 0 | 0 | 1 | 0 | .5023 | . | .4860 | . |
| MESENTERIC LYMPH NODE(S) | | | | | | | | |
| # Evaluated | 65 | 61 | 64 | 64 | | | | |
| Adj. # at Risk | 55.7 | 50.7 | 53.2 | 56.6 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 0 | 0 | 0 | 1 | .2617 | .5045 | . | . |
| Adj. # at Risk | 55.7 | 50.7 | 53.2 | 56.3 | | | | |
| LIPOMA [B]. | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| PANCREAS | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 64 | | | | |
| Adj. # at Risk | 55.7 | 54.1 | 54.2 | 56.0 | | | | |
| ACINAR CELL ADENOMA [B]. | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 56.2 | 54.6 | 54.8 | 56.0 | | | | |
| Adenoma/Carcinoma,Islet Cell | 8 | 5 | 5 | 2 | .9788 | .9919 | .8671 | .8671 |
| Adj. # at Risk | 55.7 | 54.1 | 54.2 | 56.4 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 0 | 0 | 1 | 1 | .1912 | .5045 | .4954 | . |
| Adj. # at Risk | 56.2 | 54.5 | 54.8 | 56.0 | | | | |
| ISLET CELL ADENOMA [B]. | 8 | 4 | 5 | 2 | .9744 | .9919 | .8671 | .9296 |
| Adj. # at Risk | 55.7 | 54.1 | 54.2 | 56.0 | | | | |
| ISLET CELL CARCINOMA [M]. | 0 | 1 | 0 | 0 | .7477 | . | . | .4954 |
| Adj. # at Risk | 55.7 | 54.1 | 54.2 | 56.0 | | | | |
| MESOTHELIOMA [M], metastatic site | 0 | 0 | 0 | 1 | .2557 | .5045 | . | . |
| PARATHYROID GLANDS | | | | | | | | |
| # Evaluated | 59 | 61 | 60 | 56 | | | | |
| Adj. # at Risk | 51.1 | 51.7 | 50.3 | 50.4 | | | | |
| ADENOMA [B]. | 1 | 0 | 0 | 1 | .4950 | .7475 | 1 | 1 |
| PITUITARY GLAND | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 55.7 | 54.1 | 54.2 | 57.0 | | | | |
| CRANIOPHARYNGIOMA [B]. | 0 | 1 | 0 | 0 | .7489 | . | . | .4954 |
| Adj. # at Risk | 61.3 | 59.8 | 57.2 | 59.5 | | | | |
| PARS DISTALIS ADENOMA [B]. | 39 | 33 | 34 | 33 | .7718 | .8601 | .7481 | .8601 |
| Adj. # at Risk | 55.7 | 54.1 | 54.3 | 57.0 | | | | |
| PARS INTERMEDIA ADENOMA [B]. | 0 | 0 | 4 | 1 | .2107 | .5045 | .0568 | . |
| PRIMARY SITE UNDETERMINED | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 55.8 | 54.1 | 54.2 | 57.0 | | | | |
| FIBROSARCOMA [M]. | 2 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 55.7 | 54.7 | 54.2 | 57.7 | | | | |
| HISTIOCYTIC SARCOMA [M]. | 0 | 1 | 1 | 2 | .1274 | .2568 | .4954 | .4954 |
| Adj. # at Risk | 55.7 | 54.1 | 54.2 | 57.6 | | | | |
| MALIGNANT FIBROUS HISTIOCYTOMA | 0 | 0 | 0 | 1 | .2591 | .5089 | . | . |
| Adj. # at Risk | 55.7 | 54.1 | 54.2 | 57.0 | | | | |
| MESOTHELIOMA [M]. | 0 | 0 | 0 | 1 | .2557 | .5045 | . | . |

**Table A.2.3. (cont.) Overall Results for Organ-Tumor Combinations in Male Rats**

| Organ/ Tumor | Overall Results Veh | Low | Med | High | ptrend | phigh vsVeh | pmed vsVeh | plow vsVeh |
|---|---|---|---|---|---|---|---|---|
| PROSTATE GLAND | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 55.9 | 54.1 | 54.2 | 57.7 | | | | |
| ADENOCARCINOMA [M]. | 1 | 0 | 0 | 1 | .5113 | .7611 | 1 | 1 |
| Adj. # at Risk | 55.7 | 54.1 | 54.2 | 57.3 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 0 | 0 | 1 | 1 | .1940 | .5089 | .4954 | . |
| SALIVARY GLANDS | | | | | | | | |
| # Evaluated | 65 | 64 | 65 | 65 | | | | |
| Adj. # at Risk | 55.7 | 53.1 | 54.2 | 57.0 | | | | |
| ADENOCARCINOMA [M]. | 0 | 0 | 1 | 0 | .5046 | . | .4954 | . |
| Adj. # at Risk | 55.7 | 53.1 | 54.2 | 57.6 | | | | |
| MALIGNANT FIBROUS HISTIOCYTOMA | 0 | 0 | 0 | 1 | .2603 | .5089 | . | . |
| SEMINAL VESICLES | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 55.9 | 54.1 | 54.2 | 57.0 | | | | |
| ADENOCARCINOMA [M], metastatic site | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 55.7 | 54.1 | 54.2 | 57.3 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 0 | 0 | 0 | 1 | .2591 | .5089 | . | . |
| SKELETAL MUSCLE | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 55.7 | 54.1 | 54.2 | 57.0 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 0 | 0 | 1 | 0 | .5023 | . | .4954 | . |
| Adj. # at Risk | 56.1 | 54.1 | 54.2 | 57.0 | | | | |
| LEIOMYOSARCOMA [M], metastatic site | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| SKIN | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 55.7 | 54.1 | 54.2 | 57.0 | | | | |
| BASAL CELL TUMOR [B]. | 0 | 0 | 3 | 0 | .4595 | . | .1182 | . |
| Adj. # at Risk | 55.9 | 54.1 | 54.2 | 57.0 | | | | |
| FIBROMA [B]. | 1 | 0 | 1 | 1 | .4595 | .7568 | .7477 | 1 |
| Adj. # at Risk | 55.7 | 54.7 | 54.2 | 57.3 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 0 | 1 | 1 | 1 | .3069 | .5089 | .4954 | .4954 |
| Adj. # at Risk | 55.7 | 55.1 | 54.2 | 57.7 | | | | |
| KERATOACANTHOMA [B]. | 1 | 2 | 2 | 3 | .2110 | .3227 | .4931 | .5000 |
| Adj. # at Risk | 55.7 | 54.1 | 54.2 | 57.0 | | | | |
| LIPOMA [B]. | 1 | 1 | 1 | 3 | .1466 | .3227 | .7477 | .7477 |
| Adj. # at Risk | 55.7 | 54.1 | 54.2 | 57.3 | | | | |
| MALIGNANT FIBROUS HISTIOCYTOMA | 0 | 0 | 0 | 1 | .2591 | .5089 | . | . |
| Adj. # at Risk | 55.7 | 54.1 | 54.2 | 57.0 | | | | |
| OSTEOMA [B]. | 0 | 0 | 0 | 1 | .2557 | .5045 | . | . |
| Adj. # at Risk | 55.7 | 54.1 | 54.2 | 57.0 | | | | |
| OSTEOSARCOMA [M]. | 0 | 0 | 0 | 1 | .2557 | .5045 | . | . |
| Adj. # at Risk | 55.7 | 54.1 | 54.9 | 57.0 | | | | |
| PAPILLOMA [B]. | 1 | 1 | 2 | 0 | .7946 | 1 | .4931 | .7477 |
| Adj. # at Risk | 56.1 | 54.1 | 54.9 | 57.0 | | | | |
| Papilloma/Sq.Cell Carcinoma | 2 | 1 | 2 | 0 | .9027 | 1 | .6771 | .8716 |
| Adj. # at Risk | 56.3 | 54.1 | 54.2 | 57.0 | | | | |
| RHABDOMYOSARCOMA [M]. | 1 | 0 | 1 | 0 | .8105 | 1 | .7431 | 1 |
| Adj. # at Risk | 56.0 | 54.1 | 54.2 | 57.0 | | | | |
| SQUAMOUS CELL CARCINOMA [M]. | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| SMALL INTESTINE | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 55.7 | 54.1 | 54.2 | 57.3 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 0 | 0 | 0 | 1 | .2591 | .5089 | . | . |
| Adj. # at Risk | 56.1 | 54.1 | 54.2 | 57.0 | | | | |
| LEIOMYOSARCOMA [M], metastatic site | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 55.7 | 54.1 | 54.2 | 57.0 | | | | |
| MESOTHELIOMA [M], metastatic site | 0 | 0 | 0 | 1 | .2557 | .5045 | . | . |

**Table A.2.3. (cont.) Overall Results for Organ-Tumor Combinations in Male Rats**

| Organ/ Tumor | Overall Results Veh | Low | Med | High | ptrend | phigh vsVeh | pmed vsVeh | plow vsVeh |
|---|---|---|---|---|---|---|---|---|
| SPINAL CORD | | | | | | | | |
| # Evaluated | 65 | 64 | 65 | 65 | | | | |
| Adj. # at Risk | 55.7 | 53.1 | 54.6 | 57.0 | | | | |
| ASTROCYTOMA [M]. | 0 | 0 | 1 | 0 | .5046 | . | .4954 | . |
| SPLEEN | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 55.7 | 54.7 | 54.2 | 57.7 | | | | |
| HISTOCYTIC SARCOMA [M], metastatic | 0 | 1 | 1 | 2 | .1274 | .2568 | .4954 | .4954 |
| STOMACH | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 55.7 | 54.1 | 54.2 | 57.3 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 0 | 0 | 1 | 1 | .1940 | .5089 | .4954 | . |
| Adj. # at Risk | 56.1 | 54.1 | 54.2 | 57.0 | | | | |
| LEIOMYOSARCOMA [M]. | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Systemic | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 55.7 | 54.7 | 54.2 | 57.7 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 0 | 1 | 1 | 2 | .1274 | .2568 | .4954 | .4954 |
| Adj. # at Risk | 55.7 | 54.1 | 54.2 | 57.9 | | | | |
| Malignant Fibrous Histiocytoma | 0 | 0 | 0 | 2 | .0663 | .2568 | . | . |
| TESTES | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 55.7 | 54.4 | 55.0 | 57.7 | | | | |
| INTERSTITIAL CELL ADENOMA [B]. | 1 | 1 | 4 | 7 | .0059 | .0341 | .1760 | .7477 |
| THYMUS | | | | | | | | |
| # Evaluated | 56 | 51 | 49 | 52 | | | | |
| Adj. # at Risk | 48.9 | 44.6 | 42.8 | 46.7 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 0 | 0 | 1 | 1 | .1842 | .4894 | .4667 | . |
| Adj. # at Risk | 48.9 | 44.6 | 42.7 | 46.9 | | | | |
| MALIGNANT FIBROUS HISTIOCYTOMA | 0 | 0 | 0 | 1 | .2556 | .4894 | . | . |
| THYROID GLAND | | | | | | | | |
| # Evaluated | 64 | 63 | 64 | 65 | | | | |
| Adj. # at Risk | 54.7 | 52.8 | 53.2 | 57.0 | | | | |
| Adenoma/Carcinoma,C-Cell | 0 | 1 | 0 | 1 | .3225 | .5091 | . | .4906 |
| Adj. # at Risk | 54.8 | 52.9 | 53.2 | 57.0 | | | | |
| C-CELL ADENOMA [B]. | 1 | 5 | 2 | 3 | .4251 | .3298 | .4929 | .0942 |
| Adj. # at Risk | 54.7 | 52.8 | 53.2 | 57.0 | | | | |
| C-CELL CARCINOMA [M]. | 0 | 1 | 0 | 1 | .3225 | .5091 | . | .4906 |
| Adj. # at Risk | 54.7 | 52.7 | 53.2 | 57.0 | | | | |
| FOLLICULAR CELL ADENOMA [B]. | 0 | 0 | 0 | 1 | .2605 | .5091 | . | . |
| TONGUE | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 55.7 | 54.1 | 54.7 | 57.0 | | | | |
| SQUAMOUS CELL CARCINOMA [M], metast. | 0 | 0 | 1 | 0 | .5023 | . | .4954 | . |
| TRACHEA | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 55.7 | 54.1 | 54.2 | 57.0 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 0 | 0 | 1 | 0 | .5023 | . | .4954 | . |
| URINARY BLADDER | | | | | | | | |
| # Evaluated | 65 | 64 | 65 | 65 | | | | |
| Adj. # at Risk | 55.7 | 53.5 | 54.2 | 57.0 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 0 | 0 | 1 | 0 | .5046 | . | .4954 | . |

**Table A.2.4. Overall Results for Organ-Tumor Combinations in Female Rats**

Overall Results

| Organ/ Tumor | Veh | Low | Med | High | ptrend | phigh vsVeh | pmed vsVeh | plow vsVeh |
|---|---|---|---|---|---|---|---|---|
| ABDOMINAL CAVITY | | | | | | | | |
| # Evaluated | 1 | 1 | 1 | 1 | | | | |
| Adj. # at Risk | 0.9 | 0.5 | 1.0 | 0.5 | | | | |
| ADENOCARCINOMA [M], metastatic site | 0 | 0 | 1 | 0 | 1 | . | . | . |
| Adj. # at Risk | 1.0 | 0.5 | 0.6 | 0.5 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 1 | 0 | 0 | 0 | 1 | . | . | . |
| Adj. # at Risk | 0.9 | 1.0 | 0.6 | 0.5 | | | | |
| LYMPHOMA [M], metastatic site. | 0 | 1 | 0 | 0 | 1 | . | . | . |
| ADRENAL GLANDS | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 64 | | | | |
| Adj. # at Risk | 53.4 | 51.2 | 49.0 | 48.6 | | | | |
| ADENOMA [B]. | 4 | 2 | 1 | 2 | .8014 | .8732 | .9638 | .8884 |
| Adj. # at Risk | 52.8 | 51.5 | 48.7 | 48.6 | | | | |
| LYMPHOMA [M], metastatic site. | 0 | 1 | 0 | 0 | .7387 | . | . | .4951 |
| Adj. # at Risk | 52.9 | 51.0 | 48.7 | 48.6 | | | | |
| PHEOCHROMOCYTOMA [B]. | 2 | 2 | 0 | 0 | .9779 | 1 | 1 | .6763 |
| AORTA | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 52.8 | 51.0 | 49.1 | 49.6 | | | | |
| ADENOCARCINOMA [M], metastatic site | 0 | 0 | 1 | 0 | .4900 | . | .4851 | . |
| Adj. # at Risk | 52.8 | 51.5 | 48.7 | 49.6 | | | | |
| LYMPHOMA [M], metastatic site. | 0 | 1 | 0 | 0 | .7400 | . | . | .4951 |
| BONE MARROW | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 53.0 | 51.0 | 48.7 | 49.6 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 52.8 | 51.5 | 48.7 | 49.6 | | | | |
| LYMPHOMA [M], metastatic site. | 0 | 1 | 0 | 0 | .7400 | . | . | .4951 |
| BRAIN | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 52.8 | 51.0 | 48.9 | 49.6 | | | | |
| ADENOCARCINOMA [M], metastatic site | 0 | 0 | 1 | 0 | .4874 | . | .4800 | . |
| Adj. # at Risk | 52.8 | 51.0 | 49.0 | 50.3 | | | | |
| ASTROCYTOMA [M]. | 0 | 1 | 1 | 1 | .2894 | .4902 | .4851 | .4902 |
| Adj. # at Risk | 52.8 | 51.0 | 48.7 | 49.6 | | | | |
| GRANULAR CELL TUMOR [M]. | 0 | 0 | 1 | 0 | .4874 | . | .4800 | . |
| Adj. # at Risk | 52.8 | 51.5 | 48.7 | 49.6 | | | | |
| LYMPHOMA [M], metastatic site. | 0 | 1 | 0 | 0 | .7400 | . | . | .4951 |
| Adj. # at Risk | 52.8 | 51.9 | 48.9 | 49.6 | | | | |
| PARS DISTALIS CARCINOMA [M], metast. | 0 | 2 | 1 | 1 | .4027 | .4851 | .4800 | .2427 |
| ESOPHAGUS | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 52.8 | 51.5 | 48.7 | 49.6 | | | | |
| LYMPHOMA [M], metastatic site. | 0 | 1 | 0 | 0 | .7400 | . | . | .4951 |
| EYES | | | | | | | | |
| # Evaluated | 60 | 60 | 63 | 59 | | | | |
| Adj. # at Risk | 49.5 | 48.3 | 47.7 | 46.7 | | | | |
| LYMPHOMA [M], metastatic site. | 0 | 1 | 0 | 0 | .7421 | . | . | .4948 |
| HARDERIAN GLANDS | | | | | | | | |
| # Evaluated | 64 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 51.8 | 51.5 | 48.7 | 49.6 | | | | |
| LYMPHOMA [M], metastatic site. | 0 | 1 | 0 | 0 | .7437 | . | . | .5000 |
| HEART | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 52.8 | 51.5 | 48.7 | 49.6 | | | | |
| LYMPHOMA [M], metastatic site. | 0 | 1 | 0 | 0 | .7400 | . | . | .4951 |
| Adj. # at Risk | 53.3 | 51.0 | 48.7 | 49.6 | | | | |
| SCHWANNOMA [B]. | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |

**Table A.2.4. (cont.) Overall Results for Organ-Tumor Combinations in Female Rats**

Overall Results

| Organ/ Tumor | Veh | Low | Med | High | ptrend | phigh vsVeh | pmed vsVeh | plow vsVeh |
|---|---|---|---|---|---|---|---|---|
| KIDNEYS | | | | | | | | |
| # Evaluated | 64 | 65 | 64 | 63 | | | | |
| Adj. # at Risk | 51.9 | 51.5 | 47.7 | 48.6 | | | | |
| LYMPHOMA [M], metastatic site. | 0 | 1 | 0 | 0 | .7411 | . | . | .5000 |
| LARGE INTESTINE | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 64 | | | | |
| Adj. # at Risk | 52.8 | 51.0 | 49.1 | 48.8 | | | | |
| ADENOCARCINOMA [M], metastatic site | 0 | 0 | 1 | 0 | .4874 | . | .4851 | . |
| LIVER | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 52.8 | 51.0 | 48.7 | 49.6 | | | | |
| CHOLANGIOMA [B]. | 0 | 0 | 1 | 0 | .4874 | . | .4800 | . |
| Adj. # at Risk | 52.8 | 51.0 | 48.7 | 49.6 | | | | |
| HEPATOCELLULAR ADENOMA [B]. | 0 | 2 | 0 | 0 | .8007 | . | . | .2378 |
| Adj. # at Risk | 53.3 | 51.1 | 48.7 | 49.6 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 2 | 1 | 0 | 0 | .9824 | 1 | 1 | .8714 |
| Adj. # at Risk | 52.8 | 51.5 | 48.7 | 49.6 | | | | |
| LYMPHOMA [M], metastatic site. | 0 | 1 | 0 | 0 | .7400 | . | . | .4951 |
| LUNGS | | | | | | | | |
| # Evaluated | 65 | 65 | 64 | 65 | | | | |
| Adj. # at Risk | 52.8 | 51.0 | 48.1 | 50.4 | | | | |
| ADENOCARCINOMA [M], metastatic site | 0 | 0 | 1 | 1 | .1822 | .4902 | .4800 | . |
| Adj. # at Risk | 53.3 | 51.1 | 47.7 | 49.6 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 2 | 1 | 0 | 0 | .9822 | 1 | 1 | .8714 |
| Adj. # at Risk | 52.8 | 51.5 | 47.7 | 49.6 | | | | |
| LYMPHOMA [M], metastatic site. | 0 | 1 | 0 | 0 | .7387 | . | . | .4951 |
| LYMPH NODES | | | | | | | | |
| # Evaluated | 9 | 6 | 14 | 8 | | | | |
| Adj. # at Risk | 7.8 | 4.5 | 10.2 | 6.1 | | | | |
| ADENOCARCINOMA [M], metastatic site | 1 | 1 | 0 | 0 | .9402 | 1 | 1 | .6182 |
| Adj. # at Risk | 7.9 | 4.0 | 10.2 | 6.1 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 7.8 | 4.5 | 10.2 | 6.1 | | | | |
| LYMPHOMA [M], metastatic site. | 0 | 1 | 0 | 0 | .7407 | . | . | .3636 |
| MAMMARY GLANDS | | | | | | | | |
| # Evaluated | 64 | 65 | 63 | 65 | | | | |
| Adj. # at Risk | 53.9 | 51.6 | 49.7 | 51.9 | | | | |
| ADENOCARCINOMA [M]. | 8 | 6 | 10 | 10 | .2006 | .3636 | .3285 | .7830 |
| Adj. # at Risk | 54.1 | 53.8 | 49.3 | 51.3 | | | | |
| ADENOMA [B]. | 13 | 11 | 10 | 12 | .5145 | .6153 | .7520 | .7396 |
| Adj. # at Risk | 55.7 | 54.5 | 51.1 | 53.6 | | | | |
| Adenoma/Adenocarcinoma | 20 | 17 | 18 | 21 | .3084 | .4401 | .6242 | .7703 |
| Adj. # at Risk | 53.6 | 53.8 | 50.2 | 52.1 | | | | |
| FIBROADENOMA [B]. | 11 | 22 | 15 | 13 | .5939 | .3877 | .1970 | .0176 |
| Adj. # at Risk | 52.3 | 51.0 | 47.6 | 49.6 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 52.1 | 51.5 | 47.6 | 49.6 | | | | |
| LYMPHOMA [M], metastatic site. | 0 | 1 | 0 | 0 | .7387 | . | . | .4951 |
| MANDIBULAR LYMPH NODE(S) | | | | | | | | |
| # Evaluated | 63 | 65 | 62 | 62 | | | | |
| Adj. # at Risk | 51.6 | 51.5 | 47.3 | 48.1 | | | | |
| LYMPHOMA [M], metastatic site. | 0 | 1 | 0 | 0 | .7411 | . | . | .5000 |

**Table A.2.4. (cont.) Overall Results for Organ-Tumor Combinations in Female Rats**

Overall Results

| Organ/ Tumor | Veh | Low | Med | High | ptrend | phigh vsVeh | pmed vsVeh | plow vsVeh |
|---|---|---|---|---|---|---|---|---|
| MESENTERIC LYMPH NODE(S) | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 52.8 | 51.0 | 49.1 | 50.1 | | | | |
| ADENOCARCINOMA [M], metastatic site | 0 | 0 | 1 | 1 | .1828 | .4902 | .4851 | . |
| Adj. # at Risk | 53.0 | 51.0 | 48.7 | 49.6 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 52.8 | 51.5 | 48.7 | 49.6 | | | | |
| LYMPHOMA [M], metastatic site. | 1 | 1 | 0 | 0 | .9334 | 1 | 1 | .7476 |
| OVARIES | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 53.0 | 51.0 | 48.7 | 49.6 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 52.8 | 51.0 | 48.7 | 49.6 | | | | |
| LUTEOMA [B]. | 0 | 0 | 1 | 0 | .4874 | . | .4800 | . |
| Adj. # at Risk | 52.8 | 51.5 | 48.7 | 49.6 | | | | |
| LYMPHOMA [M], metastatic site. | 0 | 1 | 0 | 0 | .7400 | . | . | .4951 |
| Adj. # at Risk | 52.8 | 51.0 | 48.7 | 50.8 | | | | |
| TUBULOSTROMAL ADENOMA [B]. | 0 | 0 | 0 | 3 | .0149 | .1142 | . | . |
| PANCREAS | | | | | | | | |
| # Evaluated | 64 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 51.8 | 51.0 | 49.1 | 49.6 | | | | |
| ADENOCARCINOMA [M], metastatic site | 0 | 0 | 1 | 0 | .4925 | . | .4900 | . |
| Adj. # at Risk | 51.8 | 51.1 | 48.7 | 49.6 | | | | |
| DUCTAL CELL ADENOMA [B]. | 0 | 1 | 0 | 0 | .7437 | . | . | .5000 |
| Adj. # at Risk | 52.0 | 51.0 | 48.7 | 49.6 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 51.8 | 51.0 | 48.7 | 49.7 | | | | |
| ISLET CELL ADENOMA [B]. | 0 | 2 | 1 | 3 | .0821 | .1139 | .4848 | .2426 |
| Adj. # at Risk | 51.8 | 51.5 | 48.7 | 49.6 | | | | |
| LYMPHOMA [M], metastatic site. | 0 | 1 | 0 | 0 | .7437 | . | . | .5000 |
| Adj. # at Risk | 51.8 | 51.0 | 48.7 | 49.6 | | | | |
| SARCOMA [M], not otherwise specified | 0 | 0 | 1 | 0 | .4899 | . | .4848 | . |
| PARATHYROID GLANDS | | | | | | | | |
| # Evaluated | 54 | 55 | 53 | 56 | | | | |
| Adj. # at Risk | 45.9 | 45.1 | 41.6 | 44.5 | | | | |
| ADENOMA [B]. | 0 | 0 | 1 | 1 | .1806 | .4944 | .4767 | . |
| PITUITARY GLAND | | | | | | | | |
| # Evaluated | 65 | 64 | 65 | 65 | | | | |
| Adj. # at Risk | 52.8 | 50.6 | 48.7 | 49.6 | | | | |
| LYMPHOMA [M], metastatic site. | 0 | 1 | 0 | 0 | .7387 | . | . | .4902 |
| Adj. # at Risk | 62.9 | 59.2 | 59.3 | 60.0 | | | | |
| PARS DISTALIS ADENOMA [B]. | 50 | 48 | 52 | 49 | .4241 | .5350 | .1892 | .5529 |
| Adj. # at Risk | 52.8 | 51.0 | 48.9 | 49.6 | | | | |
| PARS DISTALIS CARCINOMA [M]. | 0 | 2 | 1 | 1 | .4027 | .4851 | .4800 | .2427 |
| PRIMARY SITE UNDETERMINED | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 52.8 | 51.0 | 48.8 | 49.6 | | | | |
| GRANULOCYTIC LEUKEMIA [M]. | 0 | 0 | 1 | 0 | .4874 | . | .4800 | . |
| Adj. # at Risk | 53.3 | 51.1 | 48.7 | 49.6 | | | | |
| HISTIOCYTIC SARCOMA [M]. | 2 | 1 | 0 | 0 | .9824 | 1 | 1 | .8714 |
| Adj. # at Risk | 52.8 | 51.5 | 48.7 | 49.6 | | | | |
| LYMPHOMA [M]. | 1 | 1 | 0 | 0 | .9334 | 1 | 1 | .7476 |
| SALIVARY GLANDS | | | | | | | | |
| # Evaluated | 65 | 65 | 64 | 65 | | | | |
| Adj. # at Risk | 52.8 | 51.5 | 47.7 | 49.6 | | | | |
| LYMPHOMA [M], metastatic site. | 0 | 1 | 0 | 0 | .7387 | . | . | .4951 |

**Table A.2.4. (cont.) Overall Results for Organ-Tumor Combinations in Female Rats**

Overall Results

| Organ/ Tumor | Veh | Low | Med | High | ptrend | phigh vsVeh | pmed vsVeh | plow vsVeh |
|---|---|---|---|---|---|---|---|---|
| SKELETAL MUSCLE | | | | | | | | |
| # Evaluated | 64 | 65 | 65 | 64 | | | | |
| Adj. # at Risk | 52.0 | 51.0 | 48.7 | 48.6 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 51.8 | 51.5 | 48.7 | 48.6 | | | | |
| LYMPHOMA [M], metastatic site. | 0 | 1 | 0 | 0 | .7424 | . | . | .5000 |
| SKIN | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 52.8 | 51.0 | 48.7 | 49.6 | | | | |
| BASAL CELL TUMOR [B]. | 0 | 0 | 0 | 1 | .2462 | .4851 | . | . |
| Adj. # at Risk | 52.8 | 51.1 | 48.7 | 49.6 | | | | |
| CARCINOMA [M]. | 0 | 1 | 0 | 0 | .7400 | . | . | .4951 |
| Adj. # at Risk | 52.8 | 51.0 | 48.7 | 49.6 | | | | |
| FIBROMA [B]. | 0 | 0 | 1 | 0 | .4874 | . | .4800 | . |
| Adj. # at Risk | 52.8 | 51.0 | 49.0 | 49.6 | | | | |
| FIBROSARCOMA [M]. | 0 | 0 | 2 | 0 | .4900 | . | .2279 | . |
| Adj. # at Risk | 53.3 | 51.0 | 48.7 | 49.6 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 2 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 52.8 | 51.0 | 48.7 | 49.6 | | | | |
| KERATOACANTHOMA [B]. | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 52.8 | 51.5 | 48.7 | 49.6 | | | | |
| LYMPHOMA [M], metastatic site. | 0 | 1 | 0 | 0 | .7400 | . | . | .4951 |
| Adj. # at Risk | 52.9 | 51.0 | 48.7 | 49.6 | | | | |
| MALIGNANT FIBROUS HISTIOCYTOMA | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 52.8 | 51.0 | 48.7 | 49.6 | | | | |
| PAPILLOMA [B]. | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 52.8 | 51.9 | 48.7 | 49.6 | | | | |
| SCHWANNOMA [M]. | 0 | 1 | 0 | 0 | .7400 | . | . | .4951 |
| SMALL INTESTINE | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 64 | | | | |
| Adj. # at Risk | 52.8 | 51.0 | 48.7 | 49.3 | | | | |
| ADENOCARCINOMA [M], metastatic site | 0 | 0 | 0 | 1 | .2462 | .4851 | . | . |
| Adj. # at Risk | 52.8 | 51.5 | 48.7 | 48.8 | | | | |
| LYMPHOMA [M], metastatic site. | 0 | 1 | 0 | 0 | .7387 | . | . | .4951 |
| SPINAL CORD | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 52.8 | 51.5 | 48.7 | 49.6 | | | | |
| LYMPHOMA [M], metastatic site. | 0 | 1 | 0 | 0 | .7400 | . | . | .4951 |
| SPLEEN | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 52.8 | 51.0 | 48.7 | 50.1 | | | | |
| ADENOCARCINOMA [M], metastatic site | 0 | 0 | 0 | 1 | .2500 | .4902 | . | . |
| Adj. # at Risk | 52.8 | 51.0 | 48.8 | 49.6 | | | | |
| GRANULOCYTIC LEUKEMIA[M], metastatic | 0 | 0 | 1 | 0 | .4874 | . | .4800 | . |
| Adj. # at Risk | 53.3 | 51.0 | 48.7 | 49.6 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 2 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 52.8 | 51.5 | 48.7 | 49.6 | | | | |
| LYMPHOMA [M], metastatic site. | 0 | 1 | 0 | 0 | .7400 | . | . | .4951 |
| STOMACH | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 52.8 | 51.0 | 49.1 | 49.6 | | | | |
| ADENOCARCINOMA [M], metastatic site | 0 | 0 | 1 | 0 | .4900 | . | .4851 | . |
| Adj. # at Risk | 53.0 | 51.0 | 48.7 | 49.6 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 52.8 | 51.5 | 48.7 | 49.6 | | | | |
| LYMPHOMA [M], metastatic site. | 0 | 1 | 0 | 0 | .7400 | . | . | .4951 |
| Adj. # at Risk | 52.8 | 51.0 | 48.7 | 49.6 | | | | |
| SARCOMA [M], not otherwise specified | 0 | 0 | 1 | 0 | .4874 | . | .4800 | . |

**Table A.2.4. (cont.) Overall Results for Organ-Tumor Combinations in Female Rats**

Overall Results

| Organ/ Tumor | Veh | Low | Med | High | ptrend | phigh vsVeh | pmed vsVeh | plow vsVeh |
|---|---|---|---|---|---|---|---|---|
| Systemic | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 53.3 | 51.1 | 48.7 | 49.6 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 2 | 1 | 0 | 0 | .9824 | 1 | 1 | .8714 |
| Adj. # at Risk | 52.8 | 51.5 | 48.7 | 49.6 | | | | |
| LYMPHOMA [M], metastatic site. | 1 | 1 | 0 | 0 | .9334 | 1 | 1 | .7476 |
| THYMUS | | | | | | | | |
| # Evaluated | 49 | 53 | 51 | 49 | | | | |
| Adj. # at Risk | 39.9 | 43.0 | 37.8 | 38.3 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 39.8 | 43.5 | 37.8 | 38.3 | | | | |
| LYMPHOMA [M], metastatic site. | 0 | 1 | 0 | 0 | .7516 | . | . | .5244 |
| THYROID GLAND | | | | | | | | |
| # Evaluated | 64 | 65 | 64 | 64 | | | | |
| Adj. # at Risk | 52.7 | 51.0 | 48.3 | 48.9 | | | | |
| C-CELL ADENOMA [B]. | 1 | 0 | 4 | 1 | .3557 | .7321 | .1571 | 1 |
| Adj. # at Risk | 52.6 | 51.0 | 47.8 | 48.8 | | | | |
| FOLLICULAR CELL ADENOMA [B]. | 0 | 0 | 1 | 0 | .4822 | . | .4747 | . |
| TONGUE | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 52.8 | 51.5 | 48.7 | 49.6 | | | | |
| LYMPHOMA [M], metastatic site. | 0 | 1 | 0 | 0 | .7400 | . | . | .4951 |
| URINARY BLADDER | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 64 | | | | |
| Adj. # at Risk | 52.8 | 51.0 | 49.3 | 48.6 | | | | |
| ENDOMETRIAL STROMAL SARCOMA [M], | 0 | 0 | 1 | 0 | .4874 | . | .4851 | . |
| Adj. # at Risk | 53.0 | 51.0 | 48.7 | 48.6 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 52.8 | 51.5 | 48.7 | 48.6 | | | | |
| LYMPHOMA [M], metastatic site. | 0 | 1 | 0 | 0 | .7387 | . | . | .4951 |
| UTERUS | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 64 | | | | |
| Adj. # at Risk | 52.8 | 51.0 | 49.1 | 48.8 | | | | |
| ADENOCARCINOMA [M]. | 1 | 0 | 1 | 1 | .4338 | .7321 | .7374 | 1 |
| Adj. # at Risk | 52.8 | 51.0 | 48.7 | 48.6 | | | | |
| ADENOMA [B]. | 0 | 0 | 0 | 1 | .2424 | .4800 | . | . |
| Adj. # at Risk | 52.8 | 51.0 | 49.1 | 48.8 | | | | |
| Adenoma/Adenocarcinoma | 1 | 0 | 1 | 2 | .1899 | .4697 | .7374 | 1 |
| Adj. # at Risk | 53.9 | 52.5 | 51.6 | 50.8 | | | | |
| ENDOMETRIAL STROMAL POLYP [B]. | 4 | 6 | 11 | 8 | .0968 | .1518 | .0386 | .3585 |
| Adj. # at Risk | 52.8 | 51.0 | 49.3 | 49.0 | | | | |
| ENDOMETRIAL STROMAL SARCOMA [M]. | 0 | 0 | 1 | 1 | .1797 | .4851 | .4851 | . |
| Adj. # at Risk | 53.0 | 51.0 | 48.7 | 48.6 | | | | |
| HISTIOCYTIC SARCOMA [M], metastatic | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 52.8 | 51.5 | 48.7 | 48.6 | | | | |
| LYMPHOMA [M], metastatic site. | 0 | 1 | 0 | 0 | .7387 | . | . | .4951 |
| Adj. # at Risk | 52.8 | 51.0 | 48.7 | 48.6 | | | | |
| SCHWANNOMA [M]. | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 52.8 | 51.0 | 48.7 | 48.6 | | | | |
| SQUAMOUS CELL PAPILLOMA [B]. | 0 | 0 | 0 | 1 | .2424 | .4800 | . | . |

**Table A.2.4. (cont.) Overall Results for Organ-Tumor Combinations in Female Rats**

Overall Results

| Organ/ Tumor | Veh | Low | Med | High | ptrend | phigh vsVeh | pmed vsVeh | plow vsVeh |
|---|---|---|---|---|---|---|---|---|
| VAGINA | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 64 | | | | |
| Adj. # at Risk | 52.8 | 51.3 | 48.7 | 48.6 | | | | |
| ENDOMETRIAL STROMAL POLYP [B]. | 0 | 1 | 0 | 0 | .7387 | . | . | .4951 |
| Adj. # at Risk | 52.8 | 51.0 | 49.3 | 48.6 | | | | |
| ENDOMETRIAL STROMAL SARCOMA [M], | 0 | 0 | 1 | 0 | .4874 | . | .4851 | . |
| Adj. # at Risk | 52.8 | 51.5 | 48.7 | 48.6 | | | | |
| LYMPHOMA [M], metastatic site. | 0 | 1 | 0 | 0 | .7387 | . | . | .4951 |
| Adj. # at Risk | 52.8 | 51.0 | 48.7 | 48.6 | | | | |
| SCHWANNOMA [M], metastatic site. | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 52.8 | 51.0 | 48.7 | 48.6 | | | | |
| SCHWANNOMA [M]. | 0 | 1 | 0 | 0 | .7374 | . | . | .4902 |
| Adj. # at Risk | 52.8 | 51.0 | 48.7 | 48.6 | | | | |
| SQUAMOUS CELL CARCINOMA [M]. | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 52.8 | 51.0 | 48.9 | 48.6 | | | | |
| SQUAMOUS CELL PAPILLOMA [B]. | 0 | 0 | 1 | 0 | .4848 | . | .4800 | . |

## Table A.2.5. Overall Results for Organ-Tumor Combinations in Male Mice

| | Overall Results | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Organ/ Tumor | Veh | Low | Med | High | ptrend | phigh vsVeh | pmed vsVeh | plow vsVeh |
| Systemic | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.1 | 40.9 | 43.8 | 44.9 | | | | |
| ADENOCARCINOMA | 0 | 1 | 0 | 1 | .3697 | .4889 | . | .4651 |
| Adj. # at Risk | 46.1 | 41.4 | 43.8 | 44.3 | | | | |
| HEMANGIOMA | 0 | 1 | 1 | 0 | .6200 | . | .4831 | .4713 |
| Adj. # at Risk | 46.7 | 41.2 | 46.0 | 45.9 | | | | |
| HEMANGIOSARCOMA | 2 | 3 | 7 | 4 | .1546 | .3279 | .0789 | .4450 |
| Adj. # at Risk | 46.7 | 41.7 | 46.1 | 45.9 | | | | |
| Hemangioma/Hemangiosacroma | 2 | 4 | 8 | 4 | .1679 | .3279 | .0450 | .2847 |
| Adj. # at Risk | 46.5 | 40.9 | 43.8 | 44.3 | | | | |
| LEUKEMIA, GRANULOCYTIC | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 47.6 | 42.1 | 45.2 | 45.6 | | | | |
| LYMPHOMA | 4 | 3 | 5 | 4 | .4423 | .6182 | .4720 | .7337 |
| Adj. # at Risk | 46.4 | 40.9 | 43.8 | 44.3 | | | | |
| MAST CELL TUMOR | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 46.1 | 41.8 | 43.8 | 44.9 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 0 | 2 | .1535 | .2362 | . | .4713 |
| adipose tissue, brown, periaorti | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.1 | 40.9 | 43.8 | 45.2 | | | | |
| LYMPHOMA | 0 | 0 | 0 | 1 | .2586 | .4945 | . | . |
| adrenal glands | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.1 | 40.9 | 43.8 | 44.3 | | | | |
| ADENOMA, CORTICAL | 1 | 0 | 1 | 0 | .8068 | 1 | .7357 | 1 |
| Adj. # at Risk | 46.1 | 41.3 | 43.8 | 44.3 | | | | |
| ADENOMA, SUBCAPSULAR CELL | 1 | 2 | 0 | 0 | .9332 | 1 | 1 | .4564 |
| Adj. # at Risk | 46.5 | 40.9 | 43.8 | 44.3 | | | | |
| LEUKEMIA, GRANULOCYTIC | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 46.9 | 40.9 | 44.6 | 44.3 | | | | |
| LYMPHOMA | 1 | 0 | 1 | 0 | .8090 | 1 | .7416 | 1 |
| Adj. # at Risk | 46.1 | 41.8 | 43.8 | 44.7 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 0 | 1 | .3684 | .4889 | . | .4713 |

## Table A.2.5. (cont.) Overall Results for Organ-Tumor Combinations in Male Mice

| | Overall Results | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Organ/ | Veh | Low | Med | High | ptrend | phigh | pmed | plow |

| Tumor | | | | | | vsVeh | vsVeh | vsVeh |
|---|---|---|---|---|---|---|---|---|
| aorta | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.1 | 41.8 | 43.8 | 44.3 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 0 | 0 | .7356 | . | . | .4713 |
| bone | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.1 | 40.9 | 43.8 | 45.2 | | | | |
| LYMPHOMA | 0 | 0 | 0 | 1 | .2586 | .4945 | . | . |
| bone marrow, femur | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.5 | 40.9 | 43.8 | 44.3 | | | | |
| LEUKEMIA, GRANULOCYTIC | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 47.4 | 40.9 | 43.9 | 44.3 | | | | |
| LYMPHOMA | 2 | 0 | 1 | 0 | .9311 | 1 | .8620 | 1 |
| Adj. # at Risk | 46.4 | 40.9 | 43.8 | 44.3 | | | | |
| MAST CELL TUMOR | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| bone marrow, sternum | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.5 | 40.9 | 43.8 | 44.3 | | | | |
| LEUKEMIA, GRANULOCYTIC | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 47.4 | 40.9 | 43.9 | 45.2 | | | | |
| LYMPHOMA | 2 | 0 | 1 | 1 | .7348 | .8709 | .8620 | 1 |
| Adj. # at Risk | 46.4 | 40.9 | 43.8 | 44.3 | | | | |
| MAST CELL TUMOR | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| bone, sternum | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.1 | 41.8 | 44.3 | 44.3 | | | | |
| LYMPHOMA | 0 | 1 | 1 | 0 | .6213 | . | .4889 | .4713 |
| brain | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.1 | 41.7 | 43.8 | 44.3 | | | | |
| CARCINOMA, PARS DISTALIS | 0 | 1 | 0 | 0 | .7356 | . | . | .4713 |
| Adj. # at Risk | 46.1 | 40.9 | 44.3 | 44.3 | | | | |
| LYMPHOMA | 0 | 0 | 1 | 0 | .5057 | . | .4889 | . |
| cavity, abdominal | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.9 | 41.8 | 43.8 | 44.3 | | | | |
| LYMPHOMA | 1 | 1 | 1 | 0 | .8379 | 1 | .7357 | .7233 |
| Adj. # at Risk | 46.1 | 41.8 | 43.8 | 44.3 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 0 | 0 | .7356 | . | . | .4713 |
| cavity, thoracic | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.1 | 40.9 | 43.8 | 45.2 | | | | |
| LYMPHOMA | 0 | 0 | 0 | 1 | .2586 | .4945 | . | . |
| coagulating glands | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.1 | 40.9 | 43.9 | 44.3 | | | | |
| LYMPHOMA | 0 | 0 | 2 | 0 | .3697 | . | .2306 | . |

**Table A.2.5. (cont.) Overall Results for Organ-Tumor Combinations in Male Mice**

| Organ/ | Overall Results Veh | Low | Med | High | ptrend | phigh | pmed | plow |
|---|---|---|---|---|---|---|---|---|

| Tumor | | | | | | vsVeh | vsVeh | vsVeh |
|---|---|---|---|---|---|---|---|---|
| epididymides | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.1 | 41.5 | 43.8 | 44.3 | | | | |
| CARCINOMA, SQUAMOUS CELL | 0 | 1 | 0 | 0 | .7356 | . | . | .4713 |
| Adj. # at Risk | 46.1 | 41.3 | 43.8 | 44.3 | | | | |
| FIBROSARCOMA | 0 | 1 | 0 | 0 | .7356 | . | . | .4713 |
| Adj. # at Risk | 47.1 | 40.9 | 43.9 | 44.3 | | | | |
| LYMPHOMA | 2 | 0 | 2 | 0 | .8535 | 1 | .6573 | 1 |
| Adj. # at Risk | 46.1 | 40.9 | 43.8 | 44.9 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 0 | 0 | 2 | .0636 | .2362 | . | . |
| esophagus | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.1 | 40.9 | 44.4 | 44.3 | | | | |
| LYMPHOMA | 0 | 0 | 2 | 0 | .3713 | . | .2362 | . |
| eyes | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.1 | 40.9 | 43.8 | 44.9 | | | | |
| ADENOCARCINOMA | 0 | 0 | 0 | 1 | .2543 | .4889 | . | . |
| Adj. # at Risk | 46.1 | 40.9 | 44.4 | 44.3 | | | | |
| LYMPHOMA | 0 | 0 | 2 | 0 | .3713 | . | .2362 | . |
| gallbladder | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 47.4 | 40.9 | 43.8 | 44.3 | | | | |
| LYMPHOMA | 2 | 1 | 0 | 0 | .9812 | 1 | 1 | .8470 |
| Adj. # at Risk | 46.1 | 41.8 | 43.8 | 44.3 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 0 | 0 | .7356 | . | . | .4713 |
| harderian glands | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 47.3 | 41.8 | 44.2 | 44.4 | | | | |
| ADENOMA | 6 | 2 | 3 | 2 | .9284 | .9637 | .9047 | .9550 |
| Adj. # at Risk | 46.5 | 40.9 | 43.8 | 44.3 | | | | |
| LEUKEMIA, GRANULOCYTIC | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 46.9 | 40.9 | 45.1 | 44.3 | | | | |
| LYMPHOMA | 1 | 1 | 3 | 0 | .6496 | 1 | .3000 | .7168 |
| heart | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 47.1 | 42.0 | 43.9 | 45.2 | | | | |
| LYMPHOMA | 2 | 2 | 2 | 1 | .7365 | .8709 | .6573 | .6480 |
| kidneys | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.1 | 41.2 | 43.8 | 44.3 | | | | |
| ADENOMA, TUBULAR CELL | 0 | 2 | 0 | 0 | .8059 | . | . | .2192 |
| Adj. # at Risk | 46.1 | 40.9 | 43.8 | 44.4 | | | | |
| CARCINOMA, TUBULAR CELL | 0 | 0 | 0 | 1 | .2543 | .4889 | . | . |
| Adj. # at Risk | 46.5 | 40.9 | 43.8 | 44.3 | | | | |
| LEUKEMIA, GRANULOCYTIC | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 47.6 | 41.8 | 44.4 | 45.3 | | | | |
| LYMPHOMA | 3 | 2 | 3 | 2 | .6552 | .8056 | .6295 | .7742 |
| Adj. # at Risk | 46.4 | 40.9 | 43.8 | 44.3 | | | | |
| MAST CELL TUMOR | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 46.1 | 41.8 | 43.8 | 44.7 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 0 | 1 | .3684 | .4889 | . | .4713 |

**Table A.2.5. (cont.) Overall Results for Organ-Tumor Combinations in Male Mice**

| | Overall Results | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Organ/ | Veh | Low | Med | High | ptrend | phigh | pmed | plow |

| Tumor | | | | | | vsVeh | vsVeh | vsVeh |
|---|---|---|---|---|---|---|---|---|
| lacrimal glands, exorbital | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.5 | 40.9 | 43.8 | 44.3 | | | | |
| LEUKEMIA, GRANULOCYTIC | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 47.1 | 40.9 | 43.9 | 44.3 | | | | |
| LYMPHOMA | 2 | 0 | 1 | 0 | .9311 | 1 | .8620 | 1 |
| Adj. # at Risk | 46.1 | 40.9 | 43.8 | 44.7 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 0 | 0 | 1 | .2543 | .4889 | . | . |
| large intestine, cecum | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.6 | 40.9 | 44.6 | 44.3 | | | | |
| LYMPHOMA | 1 | 0 | 1 | 0 | .8090 | 1 | .7416 | 1 |
| Adj. # at Risk | 46.1 | 41.8 | 43.8 | 44.3 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 0 | 0 | .7356 | . | . | .4713 |
| larynx | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.1 | 40.9 | 44.4 | 44.3 | | | | |
| LYMPHOMA | 0 | 0 | 2 | 0 | .3713 | . | .2362 | . |
| liver | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.9 | 42.8 | 44.7 | 44.5 | | | | |
| ADENOMA, HEPATOCELLULAR | 5 | 8 | 10 | 5 | .4410 | .6015 | .1099 | .2181 |
| Adj. # at Risk | 46.1 | 42.8 | 43.8 | 44.7 | | | | |
| CARCINOMA, HEPATOCELLULAR | 1 | 4 | 0 | 2 | .6178 | .4831 | 1 | .1531 |
| Adj. # at Risk | 46.1 | 41.4 | 43.8 | 44.3 | | | | |
| HEMANGIOMA | 0 | 1 | 0 | 0 | .7356 | . | . | .4713 |
| Adj. # at Risk | 46.7 | 41.0 | 46.0 | 45.9 | | | | |
| HEMANGIOSARCOMA | 2 | 1 | 7 | 4 | .0935 | .3279 | .0789 | .8517 |
| Adj. # at Risk | 46.9 | 44.7 | 44.7 | 44.9 | | | | |
| Hepato.Adenoma/Carcinoma | 6 | 12 | 10 | 7 | .4606 | .4650 | .1775 | .0769 |
| Adj. # at Risk | 46.5 | 40.9 | 43.8 | 44.3 | | | | |
| LEUKEMIA, GRANULOCYTIC | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 47.6 | 41.8 | 44.4 | 45.4 | | | | |
| LYMPHOMA | 3 | 1 | 3 | 3 | .4346 | .6405 | .6295 | .9235 |
| Adj. # at Risk | 46.1 | 41.8 | 43.8 | 44.9 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 0 | 2 | .1535 | .2362 | . | .4713 |
| lung | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.1 | 40.9 | 43.8 | 44.9 | | | | |
| ADENOCARCINOMA | 0 | 0 | 0 | 1 | .2543 | .4889 | . | . |
| Adj. # at Risk | 48.5 | 41.1 | 46.8 | 45.4 | | | | |
| ADENOMA, BRONCHIOLAR ALVEOLAR | 8 | 2 | 9 | 10 | .1300 | .3389 | .4610 | .9852 |
| Adj. # at Risk | 50.3 | 43.4 | 47.3 | 46.3 | | | | |
| Bronch.Alv.Adenoma/Carcinoma | 15 | 12 | 10 | 17 | .3527 | .3065 | .8879 | .6730 |
| Adj. # at Risk | 47.9 | 43.2 | 44.3 | 45.2 | | | | |
| CARCINOMA, BRONCHIOLAR ALVEOL | 7 | 10 | 1 | 7 | .8110 | .5791 | .9963 | .2289 |
| Adj. # at Risk | 46.1 | 41.5 | 43.8 | 44.3 | | | | |
| CARCINOMA, HEPATOCELLULAR | 0 | 1 | 0 | 0 | .7356 | . | . | .4713 |
| Adj. # at Risk | 46.1 | 41.3 | 43.8 | 44.3 | | | | |
| FIBROSARCOMA | 0 | 1 | 0 | 0 | .7356 | . | . | .4713 |
| Adj. # at Risk | 46.5 | 40.9 | 43.8 | 44.3 | | | | |
| LEUKEMIA, GRANULOCYTIC | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 47.1 | 42.0 | 44.4 | 45.5 | | | | |
| LYMPHOMA | 2 | 2 | 3 | 2 | .4879 | .6750 | .4684 | .6480 |
| Adj. # at Risk | 46.1 | 41.8 | 43.8 | 44.9 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 0 | 2 | .1535 | .2362 | . | .4713 |
| Adj. # at Risk | 46.1 | 41.7 | 43.8 | 44.3 | | | | |
| SARCOMA, UNDIFFERENTIATED | 0 | 1 | 0 | 0 | .7356 | . | . | .4713 |

**Table A.2.5. (cont.) Overall Results for Organ-Tumor Combinations in Male Mice**

| | Overall Results | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Organ/ | Veh | Low | Med | High | ptrend | phigh | pmed | plow |

| Tumor | | | | | vsVeh | vsVeh | vsVeh |
|---|---|---|---|---|---|---|---|
| lymph node, axillary | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | |
| Adj. # at Risk | 46.1 | 40.9 | 44.2 | 44.3 | | | |
| FIBROUS HISTIOCYTOMA | 0 | 0 | 1 | 0 | .5057 | . | .4889 | . |
| Adj. # at Risk | 46.1 | 40.9 | 43.8 | 44.3 | | | |
| LYMPHOMA | 0 | 0 | 1 | 1 | .1908 | .4889 | .4831 | . |
| Adj. # at Risk | 46.1 | 40.9 | 43.8 | 44.7 | | | |
| SARCOMA, HISTIOCYTIC | 0 | 0 | 0 | 1 | .2543 | .4889 | . | . |
| lymph node, hepatic | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | |
| Adj. # at Risk | 46.1 | 40.9 | 43.9 | 44.3 | | | |
| LYMPHOMA | 0 | 0 | 2 | 0 | .3697 | . | .2306 | . |
| Adj. # at Risk | 46.1 | 40.9 | 43.8 | 44.7 | | | |
| SARCOMA, HISTIOCYTIC | 0 | 0 | 0 | 1 | .2543 | .4889 | . | . |
| lymph node, iliac | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | |
| Adj. # at Risk | 46.1 | 40.9 | 43.9 | 44.3 | | | |
| LYMPHOMA | 0 | 1 | 1 | 1 | .3102 | .4889 | .4831 | .4651 |
| lymph node, mandibular | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | |
| Adj. # at Risk | 47.6 | 41.2 | 45.2 | 44.3 | | | |
| LYMPHOMA | 3 | 2 | 5 | 1 | .6918 | .9333 | .3327 | .7742 |
| Adj. # at Risk | 46.1 | 40.9 | 43.8 | 44.7 | | | |
| SARCOMA, HISTIOCYTIC | 0 | 0 | 0 | 1 | .2543 | .4889 | . | . |
| lymph node, mediastinal | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | |
| Adj. # at Risk | 46.3 | 40.9 | 43.8 | 44.3 | | | |
| CARCINOMA, BRONCHIOLAR ALVEOL | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 46.1 | 41.8 | 43.8 | 44.3 | | | |
| LYMPHOMA | 0 | 1 | 0 | 0 | .7356 | . | . | .4713 |
| lymph node, mesenteric | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | |
| Adj. # at Risk | 46.1 | 41.5 | 43.8 | 44.3 | | | |
| CARCINOMA, SQUAMOUS CELL | 0 | 1 | 0 | 0 | .7356 | . | . | .4713 |
| Adj. # at Risk | 47.6 | 41.8 | 45.2 | 45.4 | | | |
| LYMPHOMA | 3 | 2 | 4 | 3 | .4415 | .6405 | .4754 | .7742 |
| Adj. # at Risk | 46.1 | 41.8 | 43.8 | 44.7 | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 0 | 1 | .3684 | .4889 | . | .4713 |
| lymph node, renal | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | |
| Adj. # at Risk | 46.1 | 40.9 | 43.8 | 44.4 | | | |
| LYMPHOMA | 0 | 0 | 0 | 1 | .2543 | .4889 | . | . |
| lymph node, tracheobronch | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | |
| Adj. # at Risk | 46.6 | 40.9 | 43.8 | 44.3 | | | |
| LYMPHOMA | 1 | 1 | 0 | 0 | .9304 | 1 | 1 | .7168 |
| meibomian gland | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | |
| Adj. # at Risk | 46.1 | 40.9 | 43.8 | 44.9 | | | |
| CARCINOMA | 0 | 0 | 0 | 1 | .2543 | .4889 | . | . |
| mesentery/peritoneum | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | |
| Adj. # at Risk | 46.1 | 41.5 | 43.8 | 44.3 | | | |
| CARCINOMA, SQUAMOUS CELL | 0 | 1 | 0 | 0 | .7356 | . | . | .4713 |
| Adj. # at Risk | 46.1 | 40.9 | 43.8 | 44.3 | | | |
| LIPOMA | 0 | 0 | 1 | 0 | .5029 | . | .4831 | . |
| Adj. # at Risk | 46.2 | 40.9 | 43.8 | 44.3 | | | |
| LYMPHOMA | 1 | 1 | 0 | 0 | .9304 | 1 | 1 | .7168 |

**Table A.2.5. (cont.) Overall Results for Organ-Tumor Combinations in Male Mice**

| Organ/ | Overall Results Veh | Low | Med | High | ptrend | phigh | pmed | plow |
|---|---|---|---|---|---|---|---|---|

| Tumor | | | | | | vsVeh | vsVeh | vsVeh |
|---|---|---|---|---|---|---|---|---|
| multicentric neoplasm | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.1 | 41.4 | 43.8 | 44.3 | | | | |
| HEMANGIOMA | 0 | 1 | 1 | 0 | .6200 | . | .4831 | .4713 |
| Adj. # at Risk | 46.7 | 41.2 | 46.0 | 45.9 | | | | |
| HEMANGIOSARCOMA | 2 | 3 | 7 | 4 | .1546 | .3279 | .0789 | .4450 |
| Adj. # at Risk | 46.5 | 40.9 | 43.8 | 44.3 | | | | |
| LEUKEMIA, GRANULOCYTIC | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 47.6 | 42.1 | 45.2 | 45.6 | | | | |
| LYMPHOMA | 4 | 3 | 5 | 4 | .4423 | .6182 | .4720 | .7337 |
| Adj. # at Risk | 46.4 | 40.9 | 43.8 | 44.3 | | | | |
| MAST CELL TUMOR | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 46.1 | 41.8 | 43.8 | 44.9 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 0 | 2 | .1535 | .2362 | . | .4713 |
| nerve, sciatic | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.1 | 40.9 | 43.9 | 44.3 | | | | |
| LYMPHOMA | 0 | 0 | 1 | 0 | .5029 | . | .4831 | . |
| nose, level a | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.5 | 40.9 | 43.8 | 44.3 | | | | |
| LEUKEMIA, GRANULOCYTIC | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 46.1 | 40.9 | 44.0 | 44.3 | | | | |
| OSTEOSARCOMA | 0 | 0 | 1 | 0 | .5057 | . | .4889 | . |
| Adj. # at Risk | 46.1 | 40.9 | 44.7 | 44.3 | | | | |
| SARCOMA, UNDIFFERENTIATED | 0 | 0 | 1 | 0 | .5057 | . | .4889 | . |
| nose, level b | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.5 | 40.9 | 43.8 | 44.3 | | | | |
| LEUKEMIA, GRANULOCYTIC | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 46.9 | 40.9 | 44.3 | 44.3 | | | | |
| LYMPHOMA | 1 | 0 | 1 | 0 | .8090 | 1 | .7416 | 1 |
| Adj. # at Risk | 46.1 | 40.9 | 44.0 | 44.3 | | | | |
| OSTEOSARCOMA | 0 | 0 | 1 | 0 | .5057 | . | .4889 | . |
| Adj. # at Risk | 46.1 | 40.9 | 44.7 | 44.3 | | | | |
| SARCOMA, UNDIFFERENTIATED | 0 | 0 | 1 | 0 | .5057 | . | .4889 | . |
| nose, level c | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.9 | 40.9 | 44.3 | 44.3 | | | | |
| LYMPHOMA | 1 | 0 | 1 | 0 | .8090 | 1 | .7416 | 1 |
| nose, level d | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.9 | 40.9 | 44.3 | 44.3 | | | | |
| LYMPHOMA | 1 | 0 | 1 | 0 | .8090 | 1 | .7416 | 1 |
| pancreas | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.3 | 40.9 | 43.8 | 44.3 | | | | |
| CARCINOMA, BRONCHIOLAR ALVEOL | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 46.1 | 41.5 | 43.8 | 44.3 | | | | |
| CARCINOMA, SQUAMOUS CELL | 0 | 1 | 0 | 0 | .7356 | . | . | .4713 |
| Adj. # at Risk | 47.6 | 41.8 | 44.7 | 44.3 | | | | |
| LYMPHOMA | 3 | 2 | 2 | 0 | .9517 | 1 | .7983 | .7742 |
| Adj. # at Risk | 46.1 | 41.8 | 43.8 | 44.7 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 0 | 1 | .3684 | .4889 | . | .4713 |
| peyers patch | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.9 | 40.9 | 43.8 | 44.3 | | | | |
| LYMPHOMA | 1 | 0 | 0 | 1 | .6214 | .7416 | 1 | 1 |

**Table A.2.5. (cont.) Overall Results for Organ-Tumor Combinations in Male Mice**

| | Overall Results | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Organ/ | Veh | Low | Med | High | ptrend | phigh | pmed | plow |

| Tumor | | | | | vsVeh | vsVeh | vsVeh |
|---|---|---|---|---|---|---|---|
| pharynx | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | |
| Adj. # at Risk | 46.1 | 40.9 | 44.3 | 44.3 | | | |
| PAPILLOMA | 0 | 0 | 1 | 0 | .5057 | . | .4889 | . |
| pituitary gland | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | |
| Adj. # at Risk | 46.1 | 40.9 | 44.2 | 44.3 | | | |
| ADENOMA, PARS DISTALIS | 0 | 0 | 1 | 0 | .5057 | . | .4889 | . |
| Adj. # at Risk | 46.1 | 41.7 | 43.8 | 44.3 | | | |
| CARCINOMA, PARS DISTALIS | 0 | 1 | 0 | 0 | .7356 | . | . | .4713 |
| Adj. # at Risk | 46.6 | 40.9 | 43.8 | 45.2 | | | |
| LYMPHOMA | 1 | 0 | 0 | 1 | .6257 | .7473 | 1 | 1 |
| Adj. # at Risk | 46.1 | 41.7 | 44.2 | 44.3 | | | |
| Pars Dist.Adenoma/Carc. | 0 | 1 | 1 | 0 | .6213 | . | .4889 | .4713 |
| preputial glands | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | |
| Adj. # at Risk | 46.1 | 40.9 | 43.9 | 44.3 | | | |
| LYMPHOMA | 0 | 0 | 1 | 0 | .5029 | . | .4831 | . |
| prostate gland | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | |
| Adj. # at Risk | 46.2 | 40.9 | 44.7 | 44.3 | | | |
| LYMPHOMA | 1 | 0 | 2 | 0 | .6820 | 1 | .4831 | 1 |
| salivary gland, mandibula | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | |
| Adj. # at Risk | 46.5 | 40.9 | 43.8 | 44.3 | | | |
| LEUKEMIA, GRANULOCYTIC | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 47.1 | 40.9 | 44.7 | 44.3 | | | |
| LYMPHOMA | 2 | 0 | 2 | 1 | .6402 | .8665 | .6663 | 1 |
| salivary gland, parotid | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | |
| Adj. # at Risk | 46.2 | 40.9 | 44.4 | 44.3 | | | |
| LYMPHOMA | 1 | 0 | 2 | 0 | .6820 | 1 | .4831 | 1 |
| seminal vesicles | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | |
| Adj. # at Risk | 46.1 | 41.5 | 43.8 | 44.3 | | | |
| CARCINOMA, SQUAMOUS CELL | 0 | 1 | 0 | 0 | .7356 | . | . | .4713 |
| Adj. # at Risk | 47.1 | 40.9 | 44.4 | 44.3 | | | |
| LYMPHOMA | 2 | 0 | 3 | 0 | .7739 | 1 | .4684 | 1 |
| skeletal muscle | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | |
| Adj. # at Risk | 46.5 | 40.9 | 43.8 | 44.3 | | | |
| LEUKEMIA, GRANULOCYTIC | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| skeletal muscle, biceps f | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | |
| Adj. # at Risk | 46.1 | 41.8 | 43.8 | 44.3 | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 0 | 0 | .7356 | . | . | .4713 |

**Table A.2.5. (cont.) Overall Results for Organ-Tumor Combinations in Male Mice**

| Organ/ | Overall Results Veh | Low | Med | High | ptrend | phigh | pmed | plow |
|---|---|---|---|---|---|---|---|---|

| Tumor | | | | | | vsVeh | | vsVeh | vsVeh |
|---|---|---|---|---|---|---|---|---|---|
| skin, subcutis | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | | |
| Adj. # at Risk | 46.1 | 40.9 | 44.0 | 44.3 | | | | | |
| CARCINOMA, SQUAMOUS CELL | 0 | 0 | 1 | 0 | .5057 | . | | .4889 | . |
| Adj. # at Risk | 46.1 | 41.3 | 43.8 | 44.3 | | | | | |
| FIBROSARCOMA | 0 | 1 | 0 | 0 | .7356 | . | | . | .4713 |
| Adj. # at Risk | 46.1 | 40.9 | 44.2 | 44.3 | | | | | |
| FIBROUS HISTIOCYTOMA | 0 | 0 | 1 | 0 | .5057 | . | | .4889 | . |
| Adj. # at Risk | 47.1 | 40.9 | 45.2 | 44.3 | | | | | |
| LYMPHOMA | 2 | 0 | 4 | 0 | .6959 | 1 | | .3178 | 1 |
| Adj. # at Risk | 46.1 | 41.8 | 43.8 | 44.3 | | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 0 | 0 | .7356 | . | | . | .4713 |
| Adj. # at Risk | 46.1 | 41.7 | 43.8 | 44.3 | | | | | |
| SARCOMA, UNDIFFERENTIATED | 0 | 1 | 0 | 0 | .7356 | . | | . | .4713 |
| skin, treated | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | | |
| Adj. # at Risk | 46.1 | 41.6 | 44.5 | 44.3 | | | | | |
| CARCINOMA, SQUAMOUS CELL | 0 | 1 | 1 | 0 | .6213 | . | | .4889 | .4713 |
| Adj. # at Risk | 46.2 | 40.9 | 43.8 | 44.3 | | | | | |
| LYMPHOMA | 1 | 0 | 1 | 0 | .8068 | 1 | | .7357 | 1 |
| skin, untreated | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | | |
| Adj. # at Risk | 46.1 | 40.9 | 43.8 | 44.3 | | | | | |
| LYMPHOMA | 0 | 0 | 1 | 0 | .5029 | . | | .4831 | . |
| Adj. # at Risk | 46.1 | 41.8 | 43.8 | 44.3 | | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 0 | 0 | .7356 | . | | . | .4713 |
| small intestine, duodenum | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | | |
| Adj. # at Risk | 47.4 | 41.8 | 43.8 | 45.2 | | | | | |
| LYMPHOMA | 2 | 1 | 0 | 1 | .8560 | .8709 | 1 | | .8522 |
| Adj. # at Risk | 46.1 | 40.9 | 43.8 | 44.7 | | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 0 | 0 | 1 | .2543 | .4889 | . | | . |
| small intestine, ileum | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | | |
| Adj. # at Risk | 46.1 | 40.9 | 43.8 | 44.3 | | | | | |
| ADENOCARCINOMA | 0 | 1 | 0 | 0 | .7341 | . | | . | .4651 |
| Adj. # at Risk | 46.9 | 40.9 | 44.4 | 45.2 | | | | | |
| LYMPHOMA | 1 | 0 | 2 | 1 | .4168 | .7473 | | .4831 | 1 |
| Adj. # at Risk | 46.1 | 40.9 | 43.8 | 44.7 | | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 0 | 0 | 1 | .2543 | .4889 | . | | . |
| small intestine, jejunum | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | | |
| Adj. # at Risk | 46.9 | 41.8 | 43.9 | 44.3 | | | | | |
| LYMPHOMA | 1 | 1 | 1 | 0 | .8379 | 1 | | .7357 | .7233 |
| spinal cord, lumbar | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | | |
| Adj. # at Risk | 46.1 | 40.9 | 43.8 | 44.3 | | | | | |
| LYMPHOMA | 0 | 1 | 0 | 0 | .7341 | . | | . | .4651 |
| spinal cord, thoracic | | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | | |
| Adj. # at Risk | 46.1 | 40.9 | 44.3 | 44.3 | | | | | |
| LYMPHOMA | 0 | 1 | 1 | 0 | .6227 | . | | .4889 | .4651 |

**Table A.2.5. (cont.) Overall Results for Organ-Tumor Combinations in Male Mice**

| | Overall Results | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Organ/ | Veh | Low | Med | High | ptrend | phigh | pmed | plow |

| Tumor | | | | | vsVeh | vsVeh | vsVeh |
|---|---|---|---|---|---|---|---|
| spleen | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | |
| Adj. # at Risk | 46.1 | 41.1 | 44.2 | 44.3 | | | |
| HEMANGIOSARCOMA | 0 | 2 | 1 | 1 | .4084 | .4889 | .4889 | .2192 |
| Adj. # at Risk | 47.6 | 41.2 | 45.2 | 45.4 | | | |
| LYMPHOMA | 4 | 2 | 5 | 3 | .5409 | .7643 | .4720 | .8641 |
| Adj. # at Risk | 46.4 | 40.9 | 43.8 | 44.3 | | | |
| MAST CELL TUMOR | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 46.1 | 40.9 | 43.8 | 44.7 | | | |
| SARCOMA, HISTIOCYTIC | 0 | 0 | 0 | 1 | .2543 | .4889 | . | . |
| stomach, glandular | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | |
| Adj. # at Risk | 46.1 | 41.8 | 45.1 | 44.3 | | | |
| LYMPHOMA | 0 | 1 | 2 | 0 | .4980 | . | .2418 | .4713 |
| Adj. # at Risk | 46.1 | 41.8 | 43.8 | 44.7 | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 0 | 1 | .3684 | .4889 | . | .4713 |
| stomach, nonglandular | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | |
| Adj. # at Risk | 46.1 | 41.5 | 43.8 | 44.3 | | | |
| CARCINOMA, SQUAMOUS CELL | 0 | 1 | 0 | 0 | .7356 | . | . | .4713 |
| Adj. # at Risk | 46.1 | 40.9 | 44.6 | 44.3 | | | |
| LYMPHOMA | 0 | 0 | 1 | 0 | .5057 | . | .4889 | . |
| Adj. # at Risk | 46.1 | 41.8 | 43.8 | 44.3 | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 0 | 0 | .7356 | . | . | .4713 |
| testes | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | |
| Adj. # at Risk | 46.1 | 41.1 | 43.8 | 45.0 | | | |
| ADENOMA, INTERSTITIAL CELL | 0 | 1 | 1 | 2 | .1334 | .2362 | .4831 | .4713 |
| Adj. # at Risk | 46.1 | 40.9 | 43.8 | 44.3 | | | |
| HEMANGIOMA | 0 | 0 | 1 | 0 | .5029 | . | .4831 | . |
| Adj. # at Risk | 46.1 | 40.9 | 43.8 | 44.5 | | | |
| SARCOMA, HISTIOCYTIC | 0 | 0 | 0 | 1 | .2543 | .4889 | . | . |
| thymus gland | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | |
| Adj. # at Risk | 47.6 | 42.1 | 44.7 | 45.5 | | | |
| LYMPHOMA | 4 | 3 | 4 | 2 | .7635 | .8881 | .6052 | .7337 |
| Adj. # at Risk | 46.1 | 40.9 | 43.8 | 44.7 | | | |
| SARCOMA, HISTIOCYTIC | 0 | 0 | 0 | 1 | .2543 | .4889 | . | . |
| Adj. # at Risk | 46.1 | 41.1 | 43.8 | 44.3 | | | |
| THYMOMA | 0 | 1 | 0 | 0 | .7356 | . | . | .4713 |
| thyroid gland | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | |
| Adj. # at Risk | 46.1 | 40.9 | 44.4 | 44.5 | | | |
| LYMPHOMA | 0 | 0 | 2 | 1 | .1557 | .4889 | .2362 | . |
| tongue | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | |
| Adj. # at Risk | 46.9 | 40.9 | 43.9 | 44.3 | | | |
| LYMPHOMA | 1 | 0 | 1 | 0 | .8068 | 1 | .7357 | 1 |
| trachea | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | |
| Adj. # at Risk | 46.1 | 40.9 | 43.9 | 44.5 | | | |
| LYMPHOMA | 0 | 0 | 2 | 1 | .1551 | .4889 | .2306 | . |
| ureters | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | |
| Adj. # at Risk | 46.1 | 40.9 | 44.4 | 44.3 | | | |
| LYMPHOMA | 0 | 0 | 2 | 0 | .3713 | . | .2362 | . |
| Adj. # at Risk | 46.1 | 41.8 | 43.8 | 44.7 | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 0 | 1 | .3684 | .4889 | . | .4713 |

**Table A.2.5. (cont.) Overall Results for Organ-Tumor Combinations in Male Mice**

| | Overall Results | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Organ/ | Veh | Low | Med | High | ptrend | phigh | pmed | plow |

| Tumor | | | | | | vsVeh | vsVeh | vsVeh |
|---|---|---|---|---|---|---|---|---|
| urinary bladder | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.3 | 40.9 | 43.8 | 44.3 | | | | |
| CARCINOMA, BRONCHIOLAR ALVEOL | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 46.5 | 40.9 | 43.8 | 44.3 | | | | |
| CARCINOMA, TRANSITIONAL CELL | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 47.4 | 40.9 | 43.9 | 44.3 | | | | |
| LYMPHOMA | 2 | 0 | 2 | 0 | .8535 | 1 | .6573 | 1 |
| zymbal`s gland | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 46.9 | 40.9 | 44.4 | 44.3 | | | | |
| LYMPHOMA | 1 | 0 | 2 | 0 | .6820 | 1 | .4831 | 1 |

## Table A.2.6. Overall Results for Organ-Tumor Combinations in Female Mice

| Organ/ Tumor | Overall Results Veh | Low | Med | High | ptrend | phigh vsVeh | pmed vsVeh | plow vsVeh |
|---|---|---|---|---|---|---|---|---|
| Systemic | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 44.4 | 47.0 | 46.0 | 45.4 | | | | |
| ADENOCARCINOMA | 6 | 1 | 2 | 2 | .9555 | .9731 | .9750 | .9953 |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.4 | | | | |
| GRANULOSA CELL TUMOR | 0 | 0 | 0 | 2 | .0628 | .2646 | . | . |
| Adj. # at Risk | 42.7 | 46.8 | 45.9 | 45.1 | | | | |
| HEMANGIOMA | 0 | 0 | 2 | 1 | .1610 | .5172 | .2646 | . |
| Adj. # at Risk | 42.7 | 48.9 | 46.3 | 46.6 | | | | |
| HEMANGIOSARCOMA | 2 | 6 | 4 | 5 | .2812 | .2563 | .3828 | .1811 |
| Adj. # at Risk | 42.7 | 48.9 | 46.9 | 46.6 | | | | |
| Hemangioma/Hemangiosacroma | 2 | 6 | 6 | 6 | .1451 | .1645 | .1645 | .1811 |
| Adj. # at Risk | 45.1 | 51.3 | 47.7 | 50.9 | | | | |
| LYMPHOMA | 9 | 10 | 9 | 14 | .2035 | .2524 | .6427 | .6205 |
| Adj. # at Risk | 43.2 | 47.3 | 47.9 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 2 | 2 | 5 | 1 | .5768 | .8875 | .2556 | .7247 |
| adrenal glands | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.3 | | | | |
| ADENOCARCINOMA | 0 | 0 | 0 | 1 | .2528 | .5172 | . | . |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.1 | | | | |
| ADENOMA, CORTICAL | 0 | 1 | 0 | 0 | .7640 | . | . | .5227 |
| Adj. # at Risk | 42.7 | 46.8 | 46.0 | 45.1 | | | | |
| CARCINOMA, SQUAMOUS CELL | 0 | 0 | 1 | 0 | .5056 | . | .5172 | . |
| Adj. # at Risk | 44.0 | 49.2 | 47.7 | 47.3 | | | | |
| LYMPHOMA | 5 | 4 | 7 | 4 | .5876 | .8003 | .4441 | .8183 |
| Adj. # at Risk | 42.7 | 47.3 | 45.7 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 2 | 0 | .5117 | . | .2646 | .5281 |
| aorta | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.3 | | | | |
| ADENOCARCINOMA | 0 | 0 | 0 | 1 | .2528 | .5172 | . | . |
| Adj. # at Risk | 42.7 | 46.8 | 46.0 | 45.1 | | | | |
| CARCINOMA, SQUAMOUS CELL | 0 | 0 | 1 | 0 | .5056 | . | .5172 | . |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.4 | | | | |
| GRANULOSA CELL TUMOR | 0 | 0 | 0 | 1 | .2528 | .5172 | . | . |
| Adj. # at Risk | 43.4 | 48.8 | 46.2 | 47.4 | | | | |
| LYMPHOMA | 3 | 4 | 1 | 5 | .4345 | .4082 | .9495 | .5620 |

## Table A.2.6. (cont.) Overall Results for Organ-Tumor Combinations in Female Mice

| Organ/ Tumor | Overall Results Veh | Low | Med | High | ptrend | phigh vsVeh | pmed vsVeh | plow vsVeh |
|---|---|---|---|---|---|---|---|---|

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| bone marrow, femur | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 47.4 | 45.3 | 45.1 | | | | |
| HEMANGIOSARCOMA | 0 | 1 | 0 | 0 | .7654 | . | . | .5281 |
| Adj. # at Risk | 43.4 | 46.8 | 45.3 | 45.7 | | | | |
| LYMPHOMA | 1 | 1 | 0 | 1 | .6980 | .7641 | 1 | .7694 |
| Adj. # at Risk | 42.7 | 46.8 | 46.0 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 0 | 1 | 0 | .5056 | . | .5172 | . |
| bone marrow, sternum | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.3 | | | | |
| ADENOCARCINOMA | 0 | 0 | 0 | 1 | .2528 | .5172 | . | . |
| Adj. # at Risk | 42.7 | 47.4 | 45.8 | 45.1 | | | | |
| HEMANGIOSARCOMA | 0 | 1 | 1 | 0 | .6356 | . | .5172 | .5281 |
| Adj. # at Risk | 43.4 | 48.0 | 45.3 | 45.7 | | | | |
| LYMPHOMA | 1 | 3 | 0 | 1 | .7947 | .7641 | 1 | .3427 |
| Adj. # at Risk | 42.7 | 46.8 | 46.0 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 0 | 1 | 0 | .5056 | . | .5172 | . |
| bone marrow, tibia | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 45.8 | 45.1 | | | | |
| HEMANGIOSARCOMA | 0 | 0 | 1 | 0 | .5056 | . | .5172 | . |
| bone, femur | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 43.0 | 46.8 | 45.3 | 46.4 | | | | |
| LYMPHOMA | 1 | 0 | 0 | 3 | .1451 | .3434 | 1 | 1 |
| bone, sternum | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 46.0 | 45.1 | | | | |
| CARCINOMA, SQUAMOUS CELL | 0 | 0 | 1 | 0 | .5056 | . | .5172 | . |
| Adj. # at Risk | 43.7 | 47.8 | 45.3 | 45.2 | | | | |
| LYMPHOMA | 2 | 2 | 0 | 1 | .8913 | .8875 | 1 | .7247 |
| brain | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.9 | 48.9 | 45.3 | 47.5 | | | | |
| LYMPHOMA | 1 | 3 | 0 | 6 | .0649 | .0746 | 1 | .3604 |
| cavity, abdominal | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 46.0 | 45.1 | | | | |
| CARCINOMA, SQUAMOUS CELL | 0 | 0 | 1 | 0 | .5056 | . | .5172 | . |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.4 | | | | |
| GRANULOSA CELL TUMOR | 0 | 0 | 0 | 1 | .2528 | .5172 | . | . |
| Adj. # at Risk | 43.4 | 46.8 | 46.2 | 45.2 | | | | |
| LYMPHOMA | 4 | 0 | 2 | 2 | .8016 | .9088 | .9133 | 1 |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 0 | 1 | .3856 | .5172 | . | .5227 |
| cavity, thoracic | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 43.1 | 46.8 | 45.3 | 45.1 | | | | |
| MESOTHELIOMA | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 0 | 0 | .7640 | . | . | .5227 |
| clitoral glands | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 43.7 | 47.5 | 45.5 | 46.2 | | | | |
| LYMPHOMA | 2 | 1 | 2 | 3 | .3337 | .5323 | .7089 | .8950 |

## Table A.2.6. (cont.) Overall Results for Organ-Tumor Combinations in Female Mice

| Organ/ Tumor | Overall Results Veh | Low | Med | High | ptrend | phigh vsVeh | pmed vsVeh | plow vsVeh |
|---|---|---|---|---|---|---|---|---|

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| esophagus | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 43.4 | 46.8 | 45.4 | 45.5 | | | | |
| LYMPHOMA | 1 | 0 | 1 | 1 | .5085 | .7641 | .7641 | 1 |
| eyes | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 43.9 | 47.5 | 45.3 | 46.2 | | | | |
| LYMPHOMA | 3 | 1 | 0 | 3 | .6505 | .6935 | 1 | .9517 |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 0 | 0 | .7640 | . | . | .5227 |
| eyes, optic nerves | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 43.4 | 46.8 | 45.3 | 45.2 | | | | |
| LYMPHOMA | 1 | 0 | 0 | 1 | .6327 | .7641 | 1 | 1 |
| gallbladder | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.3 | | | | |
| ADENOCARCINOMA | 0 | 0 | 0 | 1 | .2528 | .5172 | . | . |
| Adj. # at Risk | 43.4 | 48.0 | 45.6 | 46.7 | | | | |
| LYMPHOMA | 1 | 3 | 2 | 3 | .2870 | .3342 | .5172 | .3511 |
| Adj. # at Risk | 42.7 | 46.8 | 46.0 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 0 | 1 | 0 | .5056 | . | .5172 | . |
| harderian glands | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 46.3 | 45.4 | | | | |
| ADENOMA | 1 | 0 | 3 | 1 | .3644 | .7698 | .3434 | 1 |
| Adj. # at Risk | 43.4 | 47.5 | 46.7 | 45.8 | | | | |
| LYMPHOMA | 1 | 1 | 3 | 2 | .2575 | .5172 | .3342 | .7745 |
| Adj. # at Risk | 42.7 | 47.3 | 45.3 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 0 | 0 | .7654 | . | . | .5281 |
| heart | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.3 | | | | |
| ADENOCARCINOMA | 0 | 0 | 0 | 1 | .2528 | .5172 | . | . |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.1 | | | | |
| CARCINOMA, BRONCHIOLAR ALVEOL | 0 | 0 | 0 | 1 | .2528 | .5172 | . | . |
| Adj. # at Risk | 42.7 | 46.8 | 46.0 | 45.1 | | | | |
| CARCINOMA, SQUAMOUS CELL | 0 | 0 | 1 | 0 | .5056 | . | .5172 | . |
| Adj. # at Risk | 44.0 | 48.9 | 46.2 | 47.3 | | | | |
| LYMPHOMA | 4 | 4 | 5 | 7 | .2006 | .3152 | .5434 | .7033 |
| Adj. # at Risk | 42.7 | 46.8 | 45.6 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 1 | 0 | .6370 | . | .5172 | .5227 |
| kidneys | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.4 | | | | |
| GRANULOSA CELL TUMOR | 0 | 0 | 0 | 1 | .2528 | .5172 | . | . |
| Adj. # at Risk | 42.7 | 47.2 | 45.3 | 45.1 | | | | |
| LIPOSARCOMA | 0 | 1 | 0 | 0 | .7654 | . | . | .5281 |
| Adj. # at Risk | 44.6 | 50.4 | 47.1 | 50.0 | | | | |
| LYMPHOMA | 5 | 8 | 4 | 10 | .2320 | .1960 | .7896 | .3653 |
| Adj. # at Risk | 42.7 | 47.3 | 46.3 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 2 | 1 | .2659 | .5172 | .2704 | .5281 |
| lacrimal glands, exorbita | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 44.0 | 48.4 | 47.1 | 48.8 | | | | |
| LYMPHOMA | 4 | 5 | 5 | 7 | .2528 | .3288 | .5572 | .5705 |
| Adj. # at Risk | 42.7 | 46.8 | 45.6 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 1 | 0 | .6370 | . | .5172 | .5227 |

**Table A.2.6. (cont.) Overall Results for Organ-Tumor Combinations in Female Mice**

| Organ/ Tumor | Overall Results Veh | Low | Med | High | ptrend | phigh vsVeh | pmed vsVeh | plow vsVeh |
|---|---|---|---|---|---|---|---|---|

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| large intestine, cecum | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 46.4 | | | | |
| LYMPHOMA | 0 | 0 | 0 | 2 | .0650 | .2704 | . | . |
| large intestine, colon | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 43.0 | 46.8 | 45.3 | 45.5 | | | | |
| LYMPHOMA | 1 | 0 | 0 | 1 | .6370 | .7698 | 1 | 1 |
| Adj. # at Risk | 42.7 | 47.3 | 45.3 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 0 | 0 | .7654 | . | . | .5281 |
| large intestine, rectum | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 43.4 | 47.5 | 45.3 | 45.7 | | | | |
| LYMPHOMA | 1 | 1 | 0 | 1 | .6969 | .7641 | 1 | .7745 |
| larynx | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 43.2 | 47.8 | 45.6 | 45.6 | | | | |
| LYMPHOMA | 3 | 2 | 3 | 2 | .6795 | .8337 | .6834 | .8461 |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 0 | 0 | .7640 | . | . | .5227 |
| liver | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.3 | | | | |
| ADENOCARCINOMA | 0 | 0 | 0 | 1 | .2528 | .5172 | . | . |
| Adj. # at Risk | 43.2 | 46.8 | 45.3 | 45.7 | | | | |
| ADENOMA, HEPATOCELLULAR | 3 | 0 | 0 | 2 | .7958 | .8337 | 1 | 1 |
| Adj. # at Risk | 42.7 | 47.5 | 45.3 | 45.4 | | | | |
| CARCINOMA, HEPATOCELLULAR | 0 | 1 | 0 | 2 | .1594 | .2646 | . | .5281 |
| Adj. # at Risk | 42.7 | 46.8 | 46.0 | 45.1 | | | | |
| CARCINOMA, SQUAMOUS CELL | 0 | 0 | 1 | 0 | .5056 | . | .5172 | . |
| Adj. # at Risk | 42.7 | 46.9 | 45.3 | 45.1 | | | | |
| FIBROSARCOMA | 0 | 1 | 0 | 0 | .7640 | . | . | .5227 |
| Adj. # at Risk | 42.7 | 47.8 | 45.8 | 46.3 | | | | |
| HEMANGIOSARCOMA | 2 | 3 | 2 | 4 | .3196 | .3828 | .7176 | .5538 |
| Adj. # at Risk | 43.2 | 47.5 | 45.3 | 46.1 | | | | |
| Hepato.Adenoma/Carcinoma | 3 | 1 | 0 | 4 | .4564 | .5381 | 1 | .9517 |
| Adj. # at Risk | 44.6 | 48.9 | 46.9 | 47.9 | | | | |
| LYMPHOMA | 5 | 5 | 3 | 6 | .5311 | .5472 | .8807 | .6848 |
| Adj. # at Risk | 43.0 | 47.3 | 47.8 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 1 | 1 | 4 | 1 | .3814 | .7641 | .2094 | .7745 |

**Table A.2.6. (cont.) Overall Results for Organ-Tumor Combinations in Female Mice**

| Organ/ Tumor | Overall Results Veh | Low | Med | High | ptrend | phigh vsVeh | pmed vsVeh | plow vsVeh |
|---|---|---|---|---|---|---|---|---|

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| lung | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 46.0 | 45.3 | | | | |
| ADENOCARCINOMA | 0 | 0 | 1 | 1 | .1914 | .5172 | .5172 | . |
| Adj. # at Risk | 44.4 | 47.2 | 45.9 | 45.2 | | | | |
| ADENOMA, BRONCHIOLAR ALVEOLAR | 4 | 1 | 4 | 2 | .7127 | .9038 | .6559 | .9766 |
| Adj. # at Risk | 44.5 | 47.9 | 46.2 | 45.2 | | | | |
| Bronch.Alv.Adenoma/Carc. | 5 | 5 | 7 | 4 | .5916 | .7691 | .4112 | .6720 |
| Adj. # at Risk | 42.8 | 47.5 | 45.6 | 45.1 | | | | |
| CARCINOMA, BRONCHIOLAR ALVEOL | 1 | 4 | 3 | 2 | .4651 | .5262 | .3347 | .2174 |
| Adj. # at Risk | 42.7 | 46.8 | 46.0 | 45.1 | | | | |
| CARCINOMA, SQUAMOUS CELL | 0 | 0 | 1 | 0 | .5056 | . | .5172 | . |
| Adj. # at Risk | 43.7 | 46.9 | 45.3 | 45.1 | | | | |
| FIBROSARCOMA | 2 | 1 | 0 | 0 | .9869 | 1 | 1 | .8913 |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.4 | | | | |
| GRANULOSA CELL TUMOR | 0 | 0 | 0 | 1 | .2528 | .5172 | . | . |
| Adj. # at Risk | 42.7 | 47.2 | 45.3 | 45.1 | | | | |
| LIPOSARCOMA | 0 | 1 | 0 | 0 | .7654 | . | . | .5281 |
| Adj. # at Risk | 44.4 | 50.7 | 47.6 | 49.2 | | | | |
| LYMPHOMA | 6 | 8 | 6 | 9 | .3533 | .3698 | .6673 | .4895 |
| Adj. # at Risk | 42.7 | 47.3 | 47.0 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 3 | 0 | .4282 | . | .1383 | .5281 |
| Adj. # at Risk | 43.3 | 46.8 | 45.3 | 45.1 | | | | |
| SARCOMA, UNDIFFERENTIATED | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| lymph node, axillary | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.3 | | | | |
| ADENOCARCINOMA | 0 | 0 | 0 | 1 | .2528 | .5172 | . | . |
| Adj. # at Risk | 42.7 | 47.2 | 45.3 | 45.1 | | | | |
| LIPOSARCOMA | 0 | 1 | 0 | 0 | .7654 | . | . | .5281 |
| lymph node, hepatic | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.3 | | | | |
| ADENOCARCINOMA | 0 | 0 | 0 | 1 | .2528 | .5172 | . | . |
| Adj. # at Risk | 42.7 | 46.8 | 45.8 | 45.1 | | | | |
| HEMANGIOSARCOMA | 0 | 0 | 1 | 0 | .5056 | . | .5172 | . |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.1 | | | | |
| LYMPHOMA | 0 | 0 | 0 | 1 | .2528 | .5172 | . | . |
| lymph node, iliac | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.9 | 46.8 | 45.3 | 45.3 | | | | |
| ADENOCARCINOMA | 1 | 0 | 0 | 1 | .6370 | .7698 | 1 | 1 |
| Adj. # at Risk | 42.7 | 47.3 | 45.6 | 45.1 | | | | |
| LYMPHOMA | 1 | 1 | 1 | 0 | .8552 | 1 | .7698 | .7801 |
| Adj. # at Risk | 42.7 | 47.3 | 46.8 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 2 | 1 | .2659 | .5172 | .2704 | .5281 |
| lymph node, mandibular | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.9 | 45.3 | 45.1 | | | | |
| FIBROSARCOMA | 0 | 1 | 0 | 0 | .7640 | . | . | .5227 |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.4 | | | | |
| GRANULOSA CELL TUMOR | 0 | 0 | 0 | 1 | .2528 | .5172 | . | . |
| Adj. # at Risk | 45.1 | 49.3 | 46.8 | 47.8 | | | | |
| LYMPHOMA | 7 | 6 | 5 | 6 | .7006 | .7524 | .8338 | .7772 |
| Adj. # at Risk | 42.7 | 46.8 | 46.0 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 1 | 0 | .6370 | . | .5172 | .5227 |

## Table A.2.6. (cont.) Overall Results for Organ-Tumor Combinations in Female Mice

| Organ/ Tumor | Overall Results Veh | Low | Med | High | ptrend | phigh vsVeh | pmed vsVeh | plow vsVeh |
|---|---|---|---|---|---|---|---|---|

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| lymph node, mesenteric | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.3 | | | | |
| ADENOCARCINOMA | 0 | 0 | 0 | 1 | .2528 | .5172 | . | . |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.4 | | | | |
| GRANULOSA CELL TUMOR | 0 | 0 | 0 | 1 | .2528 | .5172 | . | . |
| Adj. # at Risk | 45.1 | 49.8 | 47.6 | 49.5 | | | | |
| LYMPHOMA | 7 | 7 | 6 | 12 | .1634 | .2065 | .7524 | .6784 |
| Adj. # at Risk | 42.7 | 47.3 | 46.0 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 2 | 1 | 0 | .7022 | . | .5172 | .2760 |
| lymph node, renal | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 48.2 | 45.6 | 45.6 | | | | |
| LYMPHOMA | 0 | 3 | 1 | 1 | .5133 | .5172 | .5172 | .1472 |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 0 | 0 | 1 | .2528 | .5172 | . | . |
| mammary gland | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 43.5 | 47.0 | 46.0 | 45.4 | | | | |
| ADENOCARCINOMA | 4 | 1 | 2 | 2 | .8302 | .9088 | .9133 | .9781 |
| Adj. # at Risk | 43.4 | 46.8 | 45.3 | 45.1 | | | | |
| FIBROSARCOMA | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 42.7 | 46.8 | 46.2 | 45.1 | | | | |
| LYMPHOMA | 0 | 0 | 1 | 0 | .5084 | . | .5227 | . |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 0 | 0 | .7640 | . | . | .5227 |
| mesentery/peritoneum | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 43.1 | 46.8 | 45.5 | 45.3 | | | | |
| LYMPHOMA | 2 | 0 | 1 | 1 | .7537 | .8875 | .8875 | 1 |
| multicentric neoplasm | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 45.9 | 45.1 | | | | |
| HEMANGIOMA | 0 | 0 | 2 | 1 | .1610 | .5172 | .2646 | . |
| Adj. # at Risk | 42.7 | 48.9 | 46.3 | 46.6 | | | | |
| HEMANGIOSARCOMA | 2 | 6 | 4 | 5 | .2812 | .2563 | .3828 | .1811 |
| Adj. # at Risk | 45.1 | 51.3 | 47.7 | 50.9 | | | | |
| LYMPHOMA | 9 | 10 | 9 | 14 | .2035 | .2524 | .6427 | .6205 |
| Adj. # at Risk | 43.2 | 47.3 | 47.9 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 2 | 2 | 5 | 1 | .5768 | .8875 | .2556 | .7247 |
| nerve, sciatic | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 43.7 | 48.0 | 45.4 | 45.6 | | | | |
| LYMPHOMA | 2 | 2 | 1 | 2 | .6433 | .7089 | .8875 | .7247 |
| nose, level a | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 43.0 | 46.8 | 45.3 | 45.6 | | | | |
| LYMPHOMA | 1 | 0 | 0 | 1 | .6370 | .7698 | 1 | 1 |
| Adj. # at Risk | 43.0 | 46.8 | 45.3 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| nose, level b | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 43.0 | 46.8 | 45.3 | 45.8 | | | | |
| LYMPHOMA | 1 | 0 | 0 | 2 | .3222 | .5262 | 1 | 1 |
| Adj. # at Risk | 43.0 | 47.3 | 45.3 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 1 | 1 | 0 | 0 | .9439 | 1 | 1 | .7745 |

## Table A.2.6. (cont.) Overall Results for Organ-Tumor Combinations in Female Mice

| Organ/ Tumor | Overall Results Veh | Low | Med | High | ptrend | phigh vsVeh | pmed vsVeh | plow vsVeh |
|---|---|---|---|---|---|---|---|---|

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| nose, level c | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 43.7 | 48.2 | 45.3 | 45.8 | | | | |
| LYMPHOMA | 2 | 2 | 0 | 2 | .7153 | .7089 | 1 | .7322 |
| nose, level d | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 43.7 | 46.8 | 45.3 | 46.7 | | | | |
| LYMPHOMA | 2 | 0 | 0 | 3 | .3631 | .5323 | 1 | 1 |
| ovaries | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.3 | | | | |
| ADENOCARCINOMA | 0 | 0 | 0 | 1 | .2528 | .5172 | . | . |
| Adj. # at Risk | 43.3 | 46.8 | 45.3 | 45.1 | | | | |
| CHORIOCARCINOMA | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 42.7 | 46.8 | 45.4 | 45.1 | | | | |
| CYSTADENOMA | 2 | 1 | 1 | 0 | .9494 | 1 | .8917 | .8954 |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.4 | | | | |
| GRANULOSA CELL TUMOR | 0 | 0 | 0 | 2 | .0628 | .2646 | . | . |
| Adj. # at Risk | 42.7 | 46.8 | 45.8 | 45.1 | | | | |
| HEMANGIOMA | 0 | 0 | 1 | 1 | .1914 | .5172 | .5172 | . |
| Adj. # at Risk | 42.7 | 46.8 | 45.8 | 45.1 | | | | |
| HEMANGIOSARCOMA | 0 | 0 | 1 | 0 | .5056 | . | .5172 | . |
| Adj. # at Risk | 44.4 | 49.2 | 47.7 | 47.7 | | | | |
| LYMPHOMA | 6 | 4 | 7 | 7 | .3438 | .5518 | .5518 | .8822 |
| Adj. # at Risk | 42.7 | 47.3 | 46.0 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 2 | 1 | 1 | .4282 | .5172 | .5227 | .2760 |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.1 | | | | |
| SEX-CORD/STROMAL TUMOR | 0 | 1 | 0 | 1 | .3856 | .5172 | . | .5227 |
| pancreas | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.3 | | | | |
| ADENOCARCINOMA | 0 | 0 | 0 | 1 | .2528 | .5172 | . | . |
| Adj. # at Risk | 42.7 | 46.8 | 46.0 | 45.1 | | | | |
| CARCINOMA, SQUAMOUS CELL | 0 | 0 | 1 | 0 | .5056 | . | .5172 | . |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.4 | | | | |
| GRANULOSA CELL TUMOR | 0 | 0 | 0 | 1 | .2528 | .5172 | . | . |
| Adj. # at Risk | 44.8 | 49.6 | 47.1 | 48.7 | | | | |
| LYMPHOMA | 6 | 6 | 5 | 8 | .3988 | .4561 | .7760 | .6951 |
| Adj. # at Risk | 42.7 | 47.3 | 46.7 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 2 | 2 | 1 | .3618 | .5172 | .2704 | .2760 |
| peyers patch | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.3 | | | | |
| ADENOCARCINOMA | 0 | 0 | 0 | 1 | .2528 | .5172 | . | . |
| Adj. # at Risk | 43.5 | 47.5 | 45.9 | 45.7 | | | | |
| LYMPHOMA | 2 | 1 | 1 | 1 | .7947 | .8875 | .8875 | .8950 |
| Adj. # at Risk | 42.7 | 46.8 | 46.0 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 0 | 1 | 0 | .5056 | . | .5172 | . |
| pituitary gland | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.9 | 45.4 | 45.5 | | | | |
| ADENOMA, PARS DISTALIS | 1 | 1 | 1 | 1 | .6034 | .7698 | .7698 | .7751 |
| Adj. # at Risk | 42.7 | 47.4 | 45.3 | 45.1 | | | | |
| LYMPHOMA | 0 | 1 | 0 | 0 | .7654 | . | . | .5281 |

## Table A.2.6. (cont.) Overall Results for Organ-Tumor Combinations in Female Mice

| Organ/ Tumor | Overall Results Veh | Low | Med | High | ptrend | phigh vsVeh | pmed vsVeh | plow vsVeh |
|---|---|---|---|---|---|---|---|---|

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| salivary gland, mandibula | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.3 | | | | |
| ADENOCARCINOMA | 0 | 0 | 0 | 1 | .2528 | .5172 | . | . |
| Adj. # at Risk | 43.7 | 47.3 | 47.3 | 48.2 | | | | |
| LYMPHOMA | 2 | 1 | 4 | 6 | .0465 | .1721 | .3819 | .8950 |
| Adj. # at Risk | 42.7 | 46.8 | 45.6 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 1 | 0 | .6370 | . | .5172 | .5227 |
| salivary gland, parotid | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.3 | | | | |
| ADENOCARCINOMA | 0 | 0 | 0 | 1 | .2528 | .5172 | . | . |
| Adj. # at Risk | 43.0 | 48.0 | 45.8 | 47.0 | | | | |
| LYMPHOMA | 2 | 2 | 4 | 4 | .1999 | .3819 | .3602 | .7247 |
| Adj. # at Risk | 42.7 | 46.8 | 45.6 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 1 | 0 | .6370 | . | .5172 | .5227 |
| salivary gland, sublingua | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 43.7 | 47.1 | 45.4 | 46.5 | | | | |
| LYMPHOMA | 3 | 1 | 2 | 3 | .5213 | .6935 | .8337 | .9517 |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 0 | 0 | .7640 | . | . | .5227 |
| skeletal muscle | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 47.5 | 45.4 | 46.2 | | | | |
| LYMPHOMA | 0 | 1 | 1 | 2 | .1434 | .2704 | .5172 | .5281 |
| skeletal muscle, biceps f | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 43.0 | 48.4 | 45.5 | 45.7 | | | | |
| LYMPHOMA | 1 | 3 | 1 | 1 | .7222 | .7698 | .7698 | .3604 |
| skin, subcutis | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 46.0 | 45.1 | | | | |
| CARCINOMA, SQUAMOUS CELL | 0 | 0 | 1 | 0 | .5056 | . | .5172 | . |
| Adj. # at Risk | 44.2 | 47.5 | 45.3 | 45.1 | | | | |
| FIBROSARCOMA | 3 | 2 | 0 | 0 | .9951 | 1 | 1 | .8394 |
| Adj. # at Risk | 42.7 | 46.9 | 45.3 | 45.1 | | | | |
| HEMANGIOSARCOMA | 0 | 1 | 0 | 0 | .7640 | . | . | .5227 |
| Adj. # at Risk | 43.0 | 48.6 | 47.1 | 47.7 | | | | |
| LYMPHOMA | 3 | 3 | 6 | 7 | .0799 | .1965 | .2891 | .7127 |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 46.0 | | | | |
| OSTEOSARCOMA | 0 | 0 | 0 | 1 | .2570 | .5227 | . | . |
| Adj. # at Risk | 42.7 | 46.8 | 46.0 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 1 | 0 | .6370 | . | .5172 | .5227 |
| Adj. # at Risk | 43.3 | 46.8 | 45.3 | 45.9 | | | | |
| SARCOMA, UNDIFFERENTIATED | 1 | 0 | 0 | 1 | .6327 | .7641 | 1 | 1 |
| skin, treated | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.4 | | | | |
| CARCINOMA, SQUAMOUS CELL | 0 | 0 | 0 | 1 | .2528 | .5172 | . | . |
| Adj. # at Risk | 42.7 | 47.2 | 45.3 | 45.1 | | | | |
| LIPOSARCOMA | 0 | 1 | 0 | 0 | .7654 | . | . | .5281 |
| Adj. # at Risk | 43.0 | 46.8 | 45.3 | 45.8 | | | | |
| LYMPHOMA | 1 | 0 | 0 | 2 | .3222 | .5262 | 1 | 1 |
| Adj. # at Risk | 42.7 | 46.8 | 45.4 | 45.1 | | | | |
| SARCOMA, UNDIFFERENTIATED | 0 | 0 | 1 | 0 | .5056 | . | .5172 | . |

## Table A.2.6. (cont.) Overall Results for Organ-Tumor Combinations in Female Mice

| Organ/ Tumor | Overall Results Veh | Low | Med | High | ptrend | phigh vsVeh | pmed vsVeh | plow vsVeh |
|---|---|---|---|---|---|---|---|---|

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| skin, untreated | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 47.5 | 45.4 | 45.5 | | | | |
| LYMPHOMA | 0 | 1 | 2 | 1 | .2647 | .5172 | .2646 | .5281 |
| Adj. # at Risk | 42.7 | 46.8 | 45.4 | 45.1 | | | | |
| PAPILLOMA, SQUAMOUS CELL | 0 | 1 | 1 | 0 | .6370 | . | .5172 | .5227 |
| small intestine, duodenum | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.3 | | | | |
| ADENOCARCINOMA | 0 | 0 | 0 | 1 | .2528 | .5172 | . | . |
| Adj. # at Risk | 44.1 | 47.5 | 46.2 | 45.1 | | | | |
| LYMPHOMA | 4 | 1 | 1 | 0 | .9945 | 1 | .9753 | .9766 |
| small intestine, ileum | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 43.0 | 47.5 | 46.2 | 47.1 | | | | |
| LYMPHOMA | 2 | 1 | 1 | 3 | .3949 | .5426 | .8913 | .8950 |
| small intestine, jejunum | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.3 | | | | |
| ADENOCARCINOMA | 0 | 0 | 0 | 1 | .2528 | .5172 | . | . |
| Adj. # at Risk | 43.1 | 46.8 | 45.3 | 45.1 | | | | |
| LYMPHOMA | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| spinal cord, cervical | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.9 | 47.1 | 45.3 | 45.6 | | | | |
| LYMPHOMA | 1 | 1 | 0 | 1 | .7022 | .7698 | 1 | .7801 |
| spinal cord, lumbar | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.9 | 48.2 | 45.3 | 45.1 | | | | |
| LYMPHOMA | 1 | 3 | 0 | 0 | .9492 | 1 | 1 | .3604 |
| spinal cord, thoracic | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 47.5 | 45.3 | 45.6 | | | | |
| LYMPHOMA | 0 | 1 | 0 | 1 | .3842 | .5172 | . | .5281 |
| spleen | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.3 | | | | |
| ADENOCARCINOMA | 0 | 0 | 0 | 1 | .2528 | .5172 | . | . |
| Adj. # at Risk | 42.7 | 47.4 | 45.8 | 45.1 | | | | |
| HEMANGIOSARCOMA | 0 | 1 | 2 | 0 | .5117 | . | .2646 | .5281 |
| Adj. # at Risk | 44.7 | 49.8 | 47.3 | 48.2 | | | | |
| LYMPHOMA | 8 | 7 | 7 | 9 | .4878 | .5794 | .7595 | .7859 |
| Adj. # at Risk | 42.7 | 47.3 | 46.3 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 2 | 0 | .5138 | . | .2704 | .5281 |
| stomach, glandular | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 43.4 | 46.8 | 45.3 | 45.1 | | | | |
| ADENOCARCINOMA | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 42.7 | 46.8 | 46.0 | 45.1 | | | | |
| CARCINOMA, SQUAMOUS CELL | 0 | 0 | 1 | 0 | .5056 | . | .5172 | . |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.4 | | | | |
| GRANULOSA CELL TUMOR | 0 | 0 | 0 | 1 | .2528 | .5172 | . | . |
| Adj. # at Risk | 43.7 | 49.3 | 46.0 | 48.2 | | | | |
| LYMPHOMA | 2 | 5 | 2 | 5 | .3059 | .2653 | .7170 | .2750 |
| Adj. # at Risk | 42.7 | 47.3 | 45.3 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 0 | 0 | .7654 | . | . | .5281 |

## Table A.2.6. (cont.) Overall Results for Organ-Tumor Combinations in Female Mice

| Organ/ Tumor | Overall Results Veh | Low | Med | High | ptrend | phigh vsVeh | pmed vsVeh | plow vsVeh |
|---|---|---|---|---|---|---|---|---|

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| stomach, nonglandular | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 46.0 | 45.1 | | | | |
| CARCINOMA, SQUAMOUS CELL | 0 | 0 | 1 | 0 | .5056 | . | .5172 | . |
| Adj. # at Risk | 43.4 | 47.5 | 45.3 | 45.8 | | | | |
| LYMPHOMA | 1 | 1 | 0 | 2 | .4203 | .5172 | 1 | .7745 |
| Adj. # at Risk | 42.7 | 46.8 | 45.4 | 45.1 | | | | |
| PAPILLOMA, SQUAMOUS CELL | 0 | 0 | 1 | 0 | .5056 | . | .5172 | . |
| thymus gland | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.3 | | | | |
| ADENOCARCINOMA | 0 | 0 | 0 | 1 | .2528 | .5172 | . | . |
| Adj. # at Risk | 43.6 | 50.9 | 47.7 | 49.7 | | | | |
| LYMPHOMA | 5 | 7 | 8 | 10 | .1289 | .1971 | .3364 | .4905 |
| Adj. # at Risk | 42.7 | 46.8 | 46.3 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 2 | 0 | .5159 | . | .2704 | .5227 |
| thyroid gland | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.1 | | | | |
| ADENOMA, FOLLICULAR CELL | 0 | 1 | 0 | 0 | .7640 | . | . | .5227 |
| Adj. # at Risk | 43.6 | 47.5 | 46.4 | 45.6 | | | | |
| LYMPHOMA | 3 | 1 | 3 | 2 | .6340 | .8337 | .6935 | .9517 |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 0 | 0 | .7640 | . | . | .5227 |
| tongue | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.9 | 47.5 | 45.4 | 45.6 | | | | |
| LYMPHOMA | 1 | 1 | 1 | 2 | .3599 | .5262 | .7698 | .7801 |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 0 | 0 | .7640 | . | . | .5227 |
| trachea | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 43.3 | 47.5 | 45.9 | 45.6 | | | | |
| LYMPHOMA | 2 | 1 | 2 | 2 | .5106 | .7089 | .7089 | .8950 |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 0 | 0 | .7640 | . | . | .5227 |
| ureters | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.3 | | | | |
| ADENOCARCINOMA | 0 | 0 | 0 | 1 | .2528 | .5172 | . | . |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.4 | | | | |
| GRANULOSA CELL TUMOR | 0 | 0 | 0 | 1 | .2528 | .5172 | . | . |
| Adj. # at Risk | 43.4 | 49.4 | 46.6 | 47.2 | | | | |
| LYMPHOMA | 1 | 4 | 3 | 4 | .1957 | .2094 | .3342 | .2240 |
| Adj. # at Risk | 42.7 | 47.3 | 46.0 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 1 | 1 | 0 | .6356 | . | .5172 | .5281 |
| urinary bladder | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| ADENOCARCINOMA | 0 | 0 | 0 | 1 | .2528 | .5172 | . | . |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.4 | | | | |
| GRANULOSA CELL TUMOR | 0 | 0 | 0 | 1 | .2528 | .5172 | . | . |
| Adj. # at Risk | 44.3 | 50.1 | 46.7 | 48.9 | | | | |
| LYMPHOMA | 5 | 7 | 6 | 8 | .2885 | .3353 | .5319 | .4733 |
| Adj. # at Risk | 42.7 | 46.8 | 45.4 | 45.1 | | | | |
| MESENCHYMAL TUMOR | 0 | 0 | 1 | 0 | .5056 | . | .5172 | . |
| Adj. # at Risk | 42.7 | 47.3 | 46.3 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 2 | 2 | 0 | .6037 | . | .2704 | .2760 |

**Table A.2.6. (cont.) Overall Results for Organ-Tumor Combinations in Female Mice**

| Organ/ Tumor | Overall Results Veh | Low | Med | High | ptrend | phigh vsVeh | pmed vsVeh | plow vsVeh |
|---|---|---|---|---|---|---|---|---|

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| uterus with cervix | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.9 | 46.8 | 45.3 | 45.3 | | | | |
| ADENOCARCINOMA | 1 | 0 | 0 | 1 | .6370 | .7698 | 1 | 1 |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.1 | | | | |
| ADENOMA | 0 | 0 | 0 | 1 | .2528 | .5172 | . | . |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.1 | | | | |
| Adenoma/Adenocarcinoma | 0 | 0 | 0 | 1 | .2528 | .5172 | . | . |
| Adj. # at Risk | 42.7 | 46.8 | 45.4 | 45.1 | | | | |
| CHORIOCARCINOMA | 0 | 0 | 1 | 0 | .5056 | . | .5172 | . |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.1 | | | | |
| GRANULAR CELL TUMOR | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.4 | | | | |
| GRANULOSA CELL TUMOR | 0 | 0 | 0 | 2 | .0628 | .2646 | . | . |
| Adj. # at Risk | 42.7 | 46.8 | 45.5 | 45.1 | | | | |
| HEMANGIOMA | 0 | 0 | 1 | 0 | .5056 | . | .5172 | . |
| Adj. # at Risk | 42.7 | 47.2 | 45.8 | 46.0 | | | | |
| HEMANGIOSARCOMA | 0 | 1 | 1 | 2 | .1434 | .2704 | .5172 | .5281 |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.1 | | | | |
| LEIOMYOMA | 0 | 0 | 0 | 1 | .2528 | .5172 | . | . |
| Adj. # at Risk | 42.7 | 46.8 | 45.4 | 45.5 | | | | |
| LEIOMYOSARCOMA | 1 | 0 | 1 | 2 | .2671 | .5262 | .7698 | 1 |
| Adj. # at Risk | 43.7 | 49.1 | 45.9 | 47.6 | | | | |
| LYMPHOMA | 3 | 4 | 3 | 6 | .2304 | .2891 | .6834 | .5735 |
| Adj. # at Risk | 42.7 | 46.8 | 45.4 | 45.5 | | | | |
| Leiomyoma/Leiomyosarcoma | 1 | 0 | 1 | 3 | .1221 | .3347 | .7698 | 1 |
| Adj. # at Risk | 44.5 | 47.9 | 45.8 | 46.2 | | | | |
| POLYP, STROMAL | 5 | 5 | 8 | 4 | .5598 | .7796 | .2899 | .6720 |
| Adj. # at Risk | 43.2 | 47.3 | 47.2 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 2 | 2 | 3 | 1 | .7007 | .8875 | .5426 | .7247 |
| Adj. # at Risk | 43.6 | 46.9 | 45.3 | 45.4 | | | | |
| SARCOMA, STROMAL | 2 | 2 | 0 | 1 | .8918 | .8875 | 1 | .7170 |
| vagina | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 42.7 | 46.8 | 45.3 | 45.4 | | | | |
| GRANULOSA CELL TUMOR | 0 | 0 | 0 | 1 | .2528 | .5172 | . | . |
| Adj. # at Risk | 43.6 | 47.5 | 45.4 | 47.4 | | | | |
| LYMPHOMA | 4 | 1 | 2 | 5 | .3786 | .5572 | .9088 | .9781 |
| Adj. # at Risk | 42.7 | 47.3 | 45.6 | 45.1 | | | | |
| SARCOMA, HISTIOCYTIC | 0 | 2 | 1 | 0 | .7022 | . | .5172 | .2760 |
| zymbal`s gland | | | | | | | | |
| # Evaluated | 65 | 65 | 65 | 65 | | | | |
| Adj. # at Risk | 44.0 | 47.9 | 45.3 | 45.7 | | | | |
| LYMPHOMA | 3 | 2 | 0 | 1 | .9546 | .9444 | 1 | .8394 |

## Appendix 3. References

Bailer, A. and Portier, C. (1988), "Effects of Treatment-Induced Mortality on Tests for Carcinogenicity in Small Samples", *Biometrics*, **44**, 4, 417-431.

Bieler, G.S., and Williams, R.L. (1993), "Ratio Estimates, the Delta Method, and Quantal Response Tests for Increased Carcinogenicity", *Biometrics*, **49**, 4, 793-801.

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.

Greaves, P. (2007), "Neoplasia of Adrenal Medulla," In: *Histopathology of Preclinical Toxicity Studies.* 3rd edition, pp 819. Oxford, UK: Academic Press, Elsevier Inc.

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

Jara, A. (2007), "Applied Bayesian Non- and Semi-parametric Inference using DPpackage", *Rnews***, 7**, 3, 17-26.

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.

McConnell, E.E., Solleveld, H.A., Swenberg, J.A., and Boorman, G.A. (1986), "Guidelines for Combining Neoplasms for Evaluation of Rodent Carcinogenesis Studies", *Journal of the National Cancer Institute*. **76**, 283-289.

Parola, A, and Jacobs, A. (2010). "Combining Tumors for Statistical Analysis", online FDA handout.

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.

R Development Core Team (2009). *R: A language and environment for statistical computing. R Foundation for Statistical Computing*, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org.

Rahman, M.A. and Lin, K.K. (2008), "A Comparison of False Positive Rates of Peto and Poly-3 Methods for Long Term Carcinogenicity Data Analysis Using Multiple Comparison Adjustment Method Suggested by Lin and Rahman", *Journal of Biopharmaceutical Statistics*. **18**, 949-958.

STP Peto Working Group (2002), "Statistical Methods for Carcinogenicity Studies", *Toxicologic Pathology*. **30** (3), 403-414.

U.S. Department of Health and Human Services (2013), Guidance for Industry Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals (DRAFT GUIDANCE), Center for Drug Evaluation and Research, Food and Drug Administration

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/s/

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STEVEN F THOMSON
01/08/2014
Statistical carcinogenicity review

KARL K LIN
01/08/2014
Concur with review

# STATISTICS FILING CHECKLIST FOR A NEW NDA

**NDA Number:** 204427 **Applicant:** Anacor **Stamp Date:** 7/29/2013

**Drug Name:** Tavaborole Solution 5% **NDA Type:** NME; 505(b)(1) **Indication:** Onychomycosis

I. On **initial** overview of the NDA/BLA application identify and list any potential Refuse to File issues:

| | Content Parameter for RTF | Yes | No | NA | Comments |
|---|---|---|---|---|---|
| 1 | Indexing and reference links within the electronic submission are sufficient to permit navigation through the submission, including access to reports, tables, data, etc. | X | | | |
| 2 | ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.) | X | | | ISS/ISE provided as Clin summaries |
| 3 | Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated. | X | | | |
| 4 | Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets). | X | | | |

**IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE?** Yes.

II. Identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

| Content Parameter (possible review concerns for 74-day letter) | Yes | No | NA | Comment |
|---|---|---|---|---|
| Designs utilized are appropriate for the indications requested. | X | | | |
| Endpoints and methods of analysis are specified in the protocols/statistical analysis plans. | X | | | |
| Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available. | | | X | |
| Appropriate references for novel statistical methodology (if present) are included. | | | X | |
| Safety data organized to permit analyses across clinical trials in the NDA/BLA. | X | | | |
| Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate. | X | | | |

**74-DAY LETTER REQUESTS TO THE APPLICANT**
None.

# STATISTICS FILING CHECKLIST FOR A NEW NDA

**SUBMISSION SUMMARY**

This submission contains two Phase 3 studies (tavaborole solution 5% vs. vehicle) in the treatment of onychomycosis. The applicant also conducted a randomized Phase 2 study that evaluated doses of 2.5%, 5%, 7.5%, and vehicle in a regimen of daily for 90 days followed by three times weekly for 90 days, and two open-label cohort study that evaluated various dosing regimens. A treatment regimen of 5% solution with daily treatment for 48 weeks was selected for Phase 3 development. Study 301 enrolled 399 tavaborole and 194 vehicle subjects. Study 302 enrolled 396 tavaborole and 205 vehicle subjects. Both studies enrolled subjects age 18 and older with 20-60% involvement of the target toenail, positive culture and positive KOH. The primary efficacy endpoint was complete cure (0% clinical involvement of target toenail plus negative KOH and negative culture) at Week 52. Note: the studies were powered at 95% for complete cure estimates of 15% vs. 5%.

**Primary Efficacy Endpoint (Complete Cure) at Week 52 in Phase 3 Studies**

| **Study 301** | | **Study 302** | |
|---|---|---|---|
| **Tavaborole 5%** N = 396 | **Vehicle** N = 214 | **Tavaborole 5%** N = 396 | **Vehicle** N = 205 |
| 26 (6.5%) | 1 (0.5%) | 36 (9.1%) | 3 (1.5%) |
| p=0.001 | | p<0.001 | |

**Treatment Response at Day 360 in Phase 2 Studies**

| **Study** | **Vehicle** | **Tavaborole 2.5%** | **Tavaborole 5%** | **Tavaborole 7.5%** |
|---|---|---|---|---|
| 200/200A | 2/63 (3%) | 2/33 (6%) | 4/31 (13%) | 4/60 (7%) |
| 201 | -- | -- | 2/29 (7%) | -- |
| 203 | | | 4/30 (13%) | |

Note: In Study 200/200A, the treatment regimen was once daily for 90 days/three times weekly for 90 days. Treatment response was defined as complete absence of signs and symptoms, negative KOH and culture. In Study 201 (open-label), the treatment regimen was once daily for 360 days. Treatment response was clinical assessment of clear nail and negative culture. In Study 203 (open-label) the treatment regimen was once daily for 30 days/three times weekly for 150 days. Treatment response was clear nail or at least 5 mm of clear nail growth and negative KOH and culture.

**ASSOCIATED IND:** IND 71206
**WERE PROTOCOLS REVIEWED UNDER A SPA?** Yes.

Reviewing Statistician: Kathleen Fritsch, Ph.D.
Mathematical Statistician, Biometrics III

Supervisor/Team Leader: Mohamed Alosh, Ph.D.
Team Leader, Biometrics III

cc:
NDA/BLA 204467 / 000
DDDP/Walker
DDDP/Kettl
DDDP/Lolic
DDDP/Gould
OBIO/Patrician
DBIII/Wilson
DBIII/Alosh
DBIII/Fritsch

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