

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203567Orig1s000

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: 203567 / 000 (Resubmission)
Drug Name: Jublia (efinaconazole) solution 10%
Indication(s): Onychomycosis
Applicant: Dow
Dates: Submitted: 12/20/2013
PDUFA: 6/20/2014

Review Priority: Resubmission (Class 2)

Biometrics Division: Division of Biometrics III
Statistics Reviewer: Kathleen Fritsch, Ph.D.
Concurring Reviewer: Mohamed Alosch, Ph.D.

Medical Division: Division of Dermatology and Dental Products
Clinical Team: Gary Chiang, M.D. / David Kettl /M.D.
Project Manager: Strother Dixon

Keywords: Labeling review

1 Regulatory Background

NDA 203567 for Jublia (efinaconazole) solution 10% for the treatment of onychomycosis was originally submitted on 7/26/2012. The NDA received a Complete Response due to Product Quality issues. These issues were:

1. Inadequate manufacturing process and control information of the filling/capping/
(b) (4) operation.
2. Inadequate specification for the drug product.
3. Inadequate integrity of the container closure system.
4. Inadequate stability data to assure the expiration dating period.

With this submission, the applicant has submitted information to address the Product Quality issues. A complete biostatistical review was conducted during the initial review cycle. There were no biostatistical issues raised in the initial review that would preclude the conclusion that efficacy had been established in the clinical trials. The team has determined that the changes in the manufacturing and control will not necessitate any new clinical trials. Thus the conclusions from the initial biostatistical review are still applicable. The remaining biostatistical issue that was not addressed in the initial review cycle was product labeling. This review will provide biostatistical recommendations on the product labeling.

2 Biostatistical Conclusions from the Original Review Cycle

The following is the Executive Summary from the biostatistical review for the original review cycle for Jublia. (Reviewer Kathleen Fritsch, dated 3/5/2013).

Executive Summary

Efinaconazole solution 10% was superior to vehicle in the treatment of onychomycosis in two studies. Studies P3-01 and P3-02 enrolled subjects age 18 to 65 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 specified in the protocol were: (1) clinical efficacy rate at Week 52 (<10% affected target nail area), (2) mycological cure rate at Week 52 (negative KOH and culture), and (3) unaffected new nail growth at Week 52 (change from baseline in healthy target nail measurement). 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 (SAP 1)

	Study P3-01			Study P3-02		
	Efinacon. N = 656	Vehicle N = 214	p-value	Efinacon. N = 580	Vehicle N = 201	p-value
Complete Cure	117 (17.8%)	7 (3.3%)	<0.001	88 (15.2%)	11 (5.5%)	<0.001
Clinical Efficacy	234 (36%)	25 (12%)	<0.001	180 (31%)	24 (12%)	<0.001
Mycologic Cure	362 (55%)	36 (17%)	<0.001	310 (53%)	34 (17%)	<0.001
Unaffected new growth (mm)	5.0 (0.2)	1.6 (0.4)	<0.001	3.8 (0.2)	0.9 (0.4)	<0.001

The applicant created two versions of the Statistical Analysis Plan (SAP). The first version of the SAP was signed off about a week after the last subject completed Study P3-01 and the proposed analyses were consistent with the endpoints and analyses specified in the protocol. However, the applicant then revised the SAP about 5 weeks later. The second version of the SAP redefined the sets of secondary and supportive endpoints, and the order in which they were to be analyzed. The primary endpoint remained the same in both versions of the SAP, and thus the primary conclusions of the study are not affected by the changes to the SAP. This review will focus on the endpoints pre-specified in the protocol (and the first version of the SAP), rather than those specified only in the second version of the SAP. The secondary endpoints specified in the second version of the SAP were only proposed after the studies were completed. Although the applicant maintains that the studies were still blinded at that time the second SAP was written, changing endpoints after the studies are completed raises the concern that the Type I error rate could be inflated. Note that because all of the proposed secondary endpoints from either version of the SAP had p-values <0.001, the analyses from the second version of the SAP would lead to the same conclusions of efficacy as those from the original protocol/first version of the SAP.

3 Applicant's Proposed Labeling

The following is the applicant's proposed labeling for the Clinical Studies Section (submission dated 1/16/2014).

14 CLINICAL STUDIES

The safety and efficacy of once daily use of JUBLIA for the treatment of onychomycosis of the toenail were assessed in two (b) (4) 52-week prospective, multi-center, randomized, (b) (4) studies in patients 18 years and older (18 to 70 years of age) with 20% to 50% clinical involvement of the area of the target toenail, without dermatophytomas or lunula (matrix) involvement. (b) (4)

(b) (4) The (b) (4) compared 48-weeks of treatment with JUBLIA to the vehicle solution. (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

4 Recommendations Regarding the Applicant's Proposed Labeling

The key biostatistical recommendations regarding the applicant's proposed labeling are:

1. Present data from the two studies (b) (4) because efficacy is established in the individual studies.
2. Do not include the proposed (b) (4)
3. Present (b) (4) together in one table, selecting the clinically relevant and statistically supported secondary endpoints.

The following is this reviewer's recommended wording for the Clinical Studies section of labeling. Note that the final wording is not final, and may change.

14 CLINICAL STUDIES

The safety and efficacy of once daily use of JUBLIA for the treatment of onychomycosis of the toenail were assessed in two 52-week prospective, multi-center, randomized, double-blind clinical trials in patients 18 years and older (18 to 70 years of age) with 20% to 50% clinical involvement of the area of the target toenail. The trials compared 48-weeks of treatment with JUBLIA to the vehicle solution. The Complete Cure rate was assessed at Week 52 (4-weeks after completion of therapy). Complete cure is defined as 0% involvement of the target nail (no clinical evidence of onychomycosis of the target toenail) in addition to Mycologic Cure, defined as both negative fungal culture and negative KOH. Table 2 lists the efficacy results for trials 1 and 2.

Table 2: Efficacy Endpoints

	Trial 1		Trial 2	
	JUBLIA	Vehicle	JUBLIA	Vehicle
	N = 656	N = 214	N = 580	N = 201
Complete Cure ^a	117 17.8%	7 3.3%	88 15.2%	11 5.5%
Complete or Almost Complete Cure ^b	173 26.4%	17 7.9%	136 23.4%	15 7.4%
Mycologic Cure ^c	362 55.2%	36 16.8%	310 53.4%	34 16.9%

a. Complete cure is defined as 0% clinical involvement of the target toenail plus negative KOH and negative culture.

b. Complete or almost complete is defined as $\leq 5\%$ affected target toenail area involved and negative KOH and culture.

c. Mycologic cure is defined as negative KOH and negative culture.

Signatures/Distribution List

Primary Statistical Reviewer: Kathleen Fritsch, Ph.D.
Date: 3/5/2014

Statistical Team Leader: Mohamed Alosch, Ph.D.

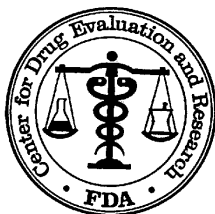
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/s/

KATHLEEN S FRITSCH
05/05/2014

MOHAMED A ALOSH
05/05/2014



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: 203567 / 000
Drug Name: TRADENAME (efinaconazole) solution 10%
Indication(s): Onychomycosis
Applicant: Dow
Dates: Submitted: 7/26/2012
PDUFA: 5/26/2013

Review Priority: Standard review

Biometrics Division: Division of Biometrics III
Statistics Reviewer: Kathleen Fritsch, Ph.D.
Concurring Reviewer: Mohamed Alosch, Ph.D.

Medical Division: Division of Dermatology and Dental Products
Clinical Team: Gary Chiang, M.D. / David Kettl, M.D.
Project Manager: Strother Dixon

Keywords: Onychomycosis, secondary endpoints, SAP

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1 Executive Summary

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2 Introduction

2.1 Overview

2.1.1 Clinical Studies

Efinaconazole solution 10% is a new molecular entity antifungal intended for the treatment of onychomycosis. This product was submitted as a 505(b)(1) application. Efinaconazole solution was evaluated in one Phase 2 and two Phase 3 studies. The Phase 2 study evaluated three treatment regimens (10% solution, 10% solution with occlusion, and 5% solution) and vehicle over a 36-week treatment period. The 10% solution (without occlusion) regimen was selected for Phase 3 development. The first Phase 3 study (P3-01) enrolled 870 subjects (656 efinaconazole/214 vehicle) and the second Phase 3 study (P3-02) enrolled 785 subjects (781 in the ITT: 580 efinaconazole/201 vehicle). Four subjects in Study P3-02 were randomized in error (3 efinaconazole and 1 vehicle), did not receive study medication, and were not included in the ITT population. Both studies enrolled subjects age 18 and older with 20-50% involvement of the target toenail. Treatment was applied once daily at bedtime to all affected toenails for 48 weeks. An overview of the studies is presented in Table 2 and Table 3. This review will focus primarily on the two Phase 3 studies.

Table 2 – Clinical Studies Overview – Phase 3 Studies

Study Numbers	DPSI-IDP-108-P3-01 and DPSI-IDP-108-P3-02		
Study Design	Randomized, double-blind, vehicle-controlled		
Inclusion criteria	Age 18 - 70, clinical diagnosis of onychomycosis, 20-50% involvement of target nail without dermatophytomas or lunula involvement, uninfected length \geq 3mm, thickness \leq 3mm, positive KOH, and positive culture (dermatophyte or mixed dermatophyte/Candida)		
Treatment regimen	Once daily at bedtime to all affected nails for 48 weeks. Solution applied to nail folds, nail bed, hyponychium, and undersurface of the nail plate.		
Primary endpoint	Complete cure at Week 52 (0% clinical involvement of the target nail, negative KOH, and negative culture)		
Treatment arms and sample size		P3-01	P3-02
	Efinaconazole, 10%	656	583*
	Vehicle	214	202*
Study location	P3-01: US – 510 subjects (34 centers), Canada – 117 subjects (7 centers), Japan – 243 subjects (33 centers) P3-02: US – 649 subjects (36 centers), Canada – 132 subjects (8 centers)		

*Four subjects in Study P3-02 were randomized in error (3 efinaconazole and 1 vehicle) and did not receive medication and were not included in the ITT population.

Table 3 – Clinical Studies Overview – Phase 2 Study

Study Number	DPSI-IDP-108-P2-01	
Study Design	Randomized, dose-ranging, vehicle-controlled	
Inclusion criteria	Age 18 - 65, clinical diagnosis of onychomycosis, 20-50% involvement of target nail without dermatophytomas or lunula involvement, uninfected length \geq 3mm, thickness \leq 3mm, positive KOH, and positive culture (dermatophyte or mixed dermatophyte/Candida)	
Treatment regimen	Once daily at bedtime to all affected nails for 36 weeks. The 10% solution was applied with or without overnight semi-occlusion. Solution applied to nail folds, nail bed, hyponychium, and undersurface of the nail plate.	
Primary endpoint	Various visual and mycological assessments	
Treatment arms and Sample Size	Efinaconazole, 10%	39
	Efinaconazole, 10% (with semi-occlusion)	36
	Efinaconazole, 5%	38
	Vehicle	22
Study location	Mexico – 135 subjects (11 centers)	

2.1.2 Regulatory History

The IND for efinaconazole was opened in 2007 with a cumulative irritation safety study. The Phase 3 clinical studies plan was discussed at an End-of-Phase 2 meeting on 8/4/2009. The protocols were amended three times. The protocols were *not* submitted as Special Protocol Assessments. The dates that the versions of the protocols were signed and submitted to the Agency are listed below.

- Original – protocol date 9/14/2009; submitted 11/6/2009
- Amendment 1 – amendment date 11/23/2009; submitted 12/28/2009
- Amendment 2 – amendment date 2/22/2010; submitted 3/3/2010
- Amendment 3 – amendment date 5/3/2010; submitted 5/19/2010

Subjects were first enrolled under Amendment 1 of the Phase 3 protocols. The first subject was screened on 12/3/2009 and the last subject visit was 10/14/2011. The Phase 3 protocols (Amendment 1) were reviewed by the Agency and an Advice Letter was sent to the sponsor on 4/14/2010. The Advice Letter contained two comments on the efficacy assessment: advising the sponsor to clarify how the investigator calculates percent nail involvement, and noting that the proposed supportive efficacy endpoints would have limited regulatory utility. The primary and secondary endpoints and proposed statistical analysis plan were the same across all four versions of the protocol. None of the amendments modified the efficacy evaluations or analyses (with the exception that Amendment 1 added a quality of life questionnaire). The amendments made changes to exclusion criteria, clarified clinical procedures, and added ECG assessments.

The sponsor also submitted two versions of the Statistical Analysis Plan (SAP). Version 2 of the SAP was actually submitted to the Agency first (SAP date 11/9/2011 with

submission date 11/14/2011). Although the definition of the primary endpoint was identical to that in the protocol, the set of secondary endpoints in Version 2 of the SAP differed from those defined in the protocol (one secondary endpoint was reclassified as supportive, one new secondary endpoint was added, and the analysis order was changed). The Agency sent an Advice Letter on 2/27/2012 noting that changing the planned analysis when the studies are nearly completed raises concerns about unblinding, and could affect the Type I error and the interpretation of the results. Subsequently, on 3/23/2012, the sponsor submitted the original version of the SAP (dated 9/29/2011), along with a proposal to include analyses from both versions of the SAP in the final clinical study reports.

The sponsor requested a Pre-NDA meeting, but canceled the meeting after receiving the pre-meeting communication and determining that no face-to-face discussion was required (final minutes dated 5/14/2012).

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\NDA203567\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 P3-01 and P3-02 were identically-designed, randomized, double-blind, vehicle-controlled studies of the efficacy and safety of efinaconazole solution 10% in the treatment of onychomycosis. The studies enrolled subjects aged 18 – 70 with a clinical diagnosis of onychomycosis, including 20-50% involvement of target nail without dermatophytomas or lunula involvement, uninfected length \geq 3mm, thickness \leq 3mm, positive KOH, and a positive culture (dermatophyte or mixed dermatophyte/Candida). Subjects were randomized in a 3:1 ratio to efinaconazole or vehicle. Treatment was applied once daily at bedtime to all affected toenails for 48 weeks. Subjects were evaluated at screening, baseline, and then every four weeks through Week 52.

Efficacy assessments included percent involvement of the target toenail, length of the unaffected part of the target toenail, KOH examination, fungal culturing, and assessment of presence/absence of onychomycosis in non-target toenails. These assessments were conducted every 12 weeks and end of study (screening, baseline, and Weeks 12, 24, 36,

48, and 52). In addition, an onychomycosis quality of life questionnaire was administered to native-English speaking subjects at baseline, Week 24, and Week 52. Localized skin reactions were recorded at each visit. Burning, itching, and vesiculation were recorded as present or absent. Redness and swelling were recorded on a 4-point scale (none, mild, moderate, severe).

The primary efficacy endpoint was complete cure (0% clinical involvement of target toenail plus negative KOH and negative culture) at Week 52 (4 weeks post-treatment). Complete cure was analyzed using a Cochran-Mantel-Haenszel test stratified on analysis center. The applicant wrote two statistical analysis plans (SAPs) for the studies. The primary efficacy endpoint and analysis were identical in both versions and consistent with the protocol. The two SAPs differed in the definition and ordering of the secondary and supportive endpoints. According to the applicant, both SAPs were approved prior to database lock. The two versions of the SAP are dated 9/29/2011 (Version 1) and 11/9/2011 (Version 2). The database locks occurred on 11/21/2011 for Study P3-01 and 12/6/2011 for Study P3-02.

The first version of the SAP listed the secondary and supportive endpoints as they were presented in the protocol. This list included three secondary endpoints as follows:

- Clinical efficacy rate at Week 52 (<10% affected target nail area)
- Mycological cure rate at Week 52 (negative KOH and culture)
- Unaffected new nail growth at Week 52 (change from baseline in healthy target nail measurement)

The second version of the SAP and removed one secondary endpoint, added one secondary endpoint, and re-ordered the list as follows:

- Complete or almost complete cure rate at Week 52 ($\leq 5\%$ affected target nail area and negative KOH and culture)
- Unaffected new nail growth at Week 52 (change from baseline in healthy target nail measurement)
- Mycological cure rate at Week 52 (negative KOH and culture)

Each SAP proposed to test the hypotheses for the secondary endpoints in sequential order (in the order listed). The applicant states that the motivation for revising the SAP was primarily to provide a “more statistically robust and clinically relevant evaluation for the secondary endpoint.” (page 55 of the clinical study report for Study P3-01 and page 52 of the clinical study report for Study P3-02) The Agency advised the sponsor in an Advice Letter dated 2/27/2012 that changing the secondary endpoints and their ordering after the studies were complete or nearly complete could impact the Type I error and would make the results of the study difficult to interpret. Subsequently, the sponsor proposed including analyses from both versions of the SAP in the clinical study report. (b) (4)

Response rate endpoints were analyzed using a Cochran-Mantel-Haenszel test stratified on analysis center. Unaffected new toenail growth was analyzed using ANOVA with factors for treatment and analysis center.

The two SAPs also differed in the list of supportive efficacy analyses. All supportive efficacy endpoints were to be summarized by descriptive statistics. The first SAP included the following list of supportive endpoints:

- Change from baseline in number of affected toenails
- Target nail growth from baseline
- Change from baseline to Week 24 and Week 52 in onychomycosis quality of life (OnyCOE-t)

The second SAP added three new supportive endpoints to those listed in the first SAP so that the list included:

- Clear nail (0% affected nail)
- Almost clear nail ($\leq 5\%$ affected nail)
- Clinical efficacy ($\leq 10\%$ affected nail)
- Change from baseline in number of affected toenails
- Target nail growth from baseline
- Change from baseline to Week 24 and Week 52 in onychomycosis quality of life (OnyCOE-t)

Note that the definition of clinical efficacy ($\leq 10\%$ affected nail) in the second SAP is slightly different from the definition of clinical efficacy ($< 10\%$ affected nail) in the first SAP. Because many investigators reported affected nail area to the nearest 5%, whether or not subjects are included who have 10% affected nail affects the response rates.

Small centers were combined into analysis centers for the CMH and ANOVA analyses. Centers with fewer than 9 efinaconazole and 3 vehicle subjects were pooled into analysis centers. Among the centers with fewer than 9 efinaconazole or 3 vehicle subjects, the smallest center was pooled with the 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
- missed no more than 20% of the total number of expected doses during the treatment period
- did not miss more than 14 cumulative doses in the 28 days leading up to the date of the last dose

- did not miss 28 or more consecutive doses during the treatment period
- were not out of the visit window (± 5 days) for the Week 52 visit

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.

3.2.2 Subject Disposition

Study P3-01 randomized 656 subjects to efinaconazole and 214 to vehicle, and all subjects were included in the ITT population. Study P3-02 randomized 583 subjects to efinaconazole and 202 to vehicle, however, 3 efinaconazole subjects and 1 vehicle subject were not included in the ITT population, so the ITT population includes 580 efinaconazole and 201 vehicle subjects. All four subjects were noted as having been randomized in error and none of the four were dispensed medication. The four subjects were enrolled at three different centers and all of them failed at least one of the inclusion/exclusion criteria which defined the extent or clinical characteristics of the onychomycosis.

Similar proportions of efinaconazole and vehicle subjects discontinued the study early in Study P3-01 (around 12% per arm), while a slightly higher proportion of vehicle subjects discontinued early in Study P3-02 (15% for efinaconazole and 21% for vehicle). The disposition and reasons for discontinuation are presented in Table 4 and Table 5. The most common reasons for discontinuation were subject request and loss-to-follow-up, and the rates for these categories were slightly higher on the vehicle arm than the efinaconazole arm in each study. However, discontinuation due to adverse events was higher on the efinaconazole arm than the vehicle arm in each study. One center in Study P3-01 (Site 121) closed down before the study was completed and 8 subjects were discontinued due to the site closing.

Table 4 – Disposition of Subjects (Study P3-01)

	Efinaconazole	Vehicle
Subjects Randomized	656	214
Discontinued study	81 (12.3%)	27 (12.6%)
<i>Reasons for discontinuation</i>		
Adverse event	21 (3.2%)	1 (0.5%)
<i>Application site</i>	19 (2.9%)	0 (0.0%)
<i>Other</i>	2 (0.3%)	1 (0.5%)
Subject request	31 (4.7%)	12 (5.6%)
<i>Moved or couldn't make visits</i>	16 (2.4%)	5 (2.3%)
<i>Withdrew consent</i>	10 (1.5%)	4 (1.9%)
<i>Lack of Efficacy</i>	4 (0.6%)	3 (1.4%)
<i>Adverse event</i>	1 (0.2%)	0 (0.0%)

--Table continues on next page.--

Table 4 continued - Disposition of Subjects (Study P3-01)

	Efinaconazole	Vehicle
Subjects Randomized	656	214
Lost to follow-up	20 (3.0%)	11 (5.1%)
Protocol violation	0 (0.0%)	1 (0.5%)
Other	9 (1.4%)	2 (0.9%)
<i>Clinic Closing</i>	<i>6 (0.9%)</i>	<i>2 (0.9%)</i>
<i>Lack of Efficacy</i>	<i>1 (0.2%)</i>	<i>0 (0.0%)</i>
<i>Moved</i>	<i>1 (0.2%)</i>	<i>0 (0.0%)</i>
<i>Can't asses nail growth</i>	<i>1 (0.2%)</i>	<i>0 (0.0%)</i>

Note: The bolded terms are the categories from the CRFs. The Adverse event, Subject request, and Other classifications required the investigator to specify additional details. The italicized categories were created by this reviewer for convenience based on similar terms used in the verbatim specifications in the CRFs.

Source: pg. 57 of dps-iidp-108-p3-01-body.pdf and reviewer analysis

Table 5 – Disposition of Subjects (Study P3-02)

	Efinaconazole	Vehicle
Subjects Randomized	583	202
Discontinued study	85 (14.6%)	42 (20.8%)
<i>Reasons for discontinuation</i>		
Adverse event	11 (1.9%)	0 (0.0%)
<i>Application site</i>	<i>8 (1.4%)</i>	<i>0 (0.0%)</i>
<i>Other</i>	<i>3 (0.5%)</i>	<i>0 (0.0%)</i>
Subject request	36 (6.2%)	19 (9.4%)
<i>Moved or couldn't make visits</i>	<i>20 (3.4%)</i>	<i>12 (5.9%)</i>
<i>Withdrew consent</i>	<i>10 (1.7%)</i>	<i>5 (2.5%)</i>
<i>Lack of efficacy</i>	<i>3 (0.5%)</i>	<i>2 (1.0%)</i>
<i>Adverse event</i>	<i>3 (0.5%)</i>	<i>0 (0.0%)</i>
Lost to follow-up	29 (4.9%)	18 (8.9%)
Protocol violation	3 (0.5%)	3 (1.5%)
Pregnancy	0 (0.0%)	1 (0.5%)
Worsening of condition	1 (0.2%)	0 (0.0%)
Other	5 (0.9%)	1 (0.5%)
<i>Randomized in error</i>	<i>3 (0.5%)</i>	<i>1 (0.5%)</i>
<i>Withdrew consent</i>	<i>1 (0.2%)</i>	<i>0 (0.0%)</i>
<i>Non-compliance</i>	<i>1 (0.2%)</i>	<i>0 (0.0%)</i>

Note: The bolded terms are the categories from the CRFs. The Adverse event, Subject request, and Other classifications required the investigator to specify additional details. The italicized categories were created by this reviewer for convenience based on similar terms used in the verbatim specifications in the CRFs.

Source: pg. 55 of dps-iidp-108-p3-02-body.pdf and reviewer analysis

3.2.3 Baseline Characteristics

Baseline demographics were generally balanced across the treatment groups in the two studies. The mean age of subjects was about 51 years with approximately 13% of

subjects aged 65 or older. The majority of subjects were male (75-80%). Approximately 65% of subjects in Study P3-01 and 88% of subjects in Study P3-02 were white, and approximately 6% of subjects were black. Because Study P3-01 enrolled subjects in Japan, approximately 29% of subjects in that study were Asian, while only 2% of subjects in Study P3-02 were Asian. In addition, approximately 12% of subjects in Study P3-01 and 22% of subjects in Study P3-02 were Hispanic or Latino. See Table 6.

Table 6 - Demographics

	Study P3-01		Study P3-02	
	Efinaconazole N=656	Vehicle N=214	Efinaconazole N=580	Vehicle N=201
<i>Age (years)</i>				
Mean	52.4	51.9	50.6	50.7
Range	20 - 71	18 - 70	18 - 71	18 - 70
18 to 64 years	570 (87%)	179 (84%)	504 (87%)	180 (90%)
65 + years	86 (13%)	35 (16%)	76 (13%)	21 (10%)
<i>Gender</i>				
Male	489 (75%)	158 (74%)	464 (80%)	164 (82%)
Female	167 (25%)	56 (26%)	116 (20%)	37 (18%)
<i>Race</i>				
White	425 (65%)	140 (65%)	522 (90%)	164 (82%)
Black or Afric.-Amer.	36 (5%)	7 (3%)	34 (6%)	21 (10%)
Asian	189 (29%)	63 (29%)	11 (2%)	6 (3%)
Other	6 (1%)	4 (2%)	13 (2%)	10 (5%)
<i>Ethnicity</i>				
Hispanic or Latino	71 (11%)	31 (14%)	122 (21%)	46 (23%)
Not Hispanic or Latino	585 (89%)	183 (86%)	457 (79%)	155 (77%)

Source: pg 61 of dpsl-idp-108-p3-01-body.pdf and pg 59 of dpsl-idp-108-p3-02-body.pdf

The mean percentage of affected toenail and the mean number of non-target toenails was similar across both treatment groups in both studies with subjects having an average 37% affected area of the target toenail at baseline and an average of 2.8 affected non-target toenails at baseline. The majority of subjects had screening cultures of *T. rubrum* (93%), while the remaining cultured organisms were *T. mentagrophytes*, *E. floccosum*, and *T. tonsurans*. Three subjects did not have positive fungal cultures (an inclusion criteria violation) but were randomized and dispensed medication anyway. See Table 7.

Table 7 – Baseline Disease Characteristics

	Study P3-01		Study P3-02	
	Efinaconazole N=656	Vehicle N=214	Efinaconazole N=580	Vehicle N=201
Mean percent (SD) of affected toenail	36.7 (10.4)	36.8 (10.6)	36.2 (10.7)	36.7 (10.5)
Mean number (SD) of affected non-target toenails	2.8 (1.7)	2.8 (1.7)	2.7 (1.6)	2.8 (1.7)
Screening Culture				
<i>T. rubrum</i>	604 (92%)	191 (89%)	540 (93%)	193 (96%)
<i>T. mentagrophytes</i>	47 (7%)	22 (10%)	33 (6%)	8 (4%)
<i>E. floccosum</i>	5 (1%)	0 (0%)	4 (1%)	0 (0%)
<i>T. tonsurans</i>	0 (0%)	0 (0%)	1 (<1%)	0 (0%)
No dermatophyte	0 (0%)	1 (<1%)	2 (<1%)	0 (0%)

Source: pg 62 of dpsidp-108-p3-01-body.pdf and pg 60 of dpsidp-108-p3-02-body.pdf and reviewer analysis

3.2.4 Primary Efficacy Endpoint

Efinaconazole foam was superior to vehicle foam on the primary efficacy endpoint of complete cure at Week 52 in both studies ($p < 0.001$). Complete cure is defined as 0% clinical involvement of the target toenail plus negative KOH and negative culture. The complete cure rate was analyzed with a CMH test stratified on analysis center. For the ITT analysis, the primary method of handling missing data was LOCF. The results of the ITT and per protocol analyses were similar. The ITT results are presented in Table 8 and the per protocol results are presented in Table 9.

Table 8 – Complete Cure at Week 52 (ITT analysis)

Study P3-01		Study P3-02	
Efinaconazole N = 656	Vehicle N = 214	Efinaconazole N = 580	Vehicle N = 201
117 (17.8%)	7 (3.3%)	88 (15.2%)	11 (5.5%)
$p < 0.001$		$p < 0.001$	

Source: pg 64 of dpsidp-108-p3-01-body.pdf and pg 61 of dpsidp-108-p3-02-body.pdf

Table 9 – Complete Cure at Week 52 (PP analysis)

Study P3-01		Study P3-02	
Efinaconazole N = 533	Vehicle N = 173	Efinaconazole N = 473	Vehicle N = 146
102 (19.1%)	7 (4.0%)	78 (16.5%)	7 (4.8%)
$p < 0.001$		$p < 0.001$	

Source: pg 235 of dpsidp-108-p3-01-body.pdf and pg 60 of dpsidp-108-p3-02-body.pdf

3.2.5 Missing Data Handling

The primary method of handling missing data was LOCF, which was used in the analyses above. Study P3-01 had 84 (13%) efinaconazole and 29 (14%) vehicle subjects that did not have complete efficacy assessments at Week 52, and therefore had at least one component of the complete cure endpoint imputed for the primary analysis. The timing of dropout was similar on both arms in Study P3-01 with 70% (59/84) of efinaconazole subjects and 72% (21/29) vehicle subjects with imputed responses having their last efficacy assessments before Week 36. Of the subjects with imputed efficacy assessments, only 2 subjects, both on the efinaconazole arm, were imputed as complete cures. Both of these subjects had an affected area assessment of 0% at Week 52 or later (one subject had a visit coded as an ‘unscheduled visit after the Week 40 visit’ but the timing of the assessment was nominally Week 56), but both had mycology assessments imputed from earlier visits.

Study P3-02 had 90 (16%) efinaconazole and 43 (21%) vehicle subjects that did not have complete efficacy assessments at Week 52. The vehicle arm had a higher rate of imputed data (21% vs. 16%) and also had a higher proportion of subjects who discontinued at a relatively early timepoint in the study, with 74% (32/43) of vehicle subjects and 63% (57/29) of efinaconazole subjects with imputed responses having their last efficacy assessments before Week 36. In Study P3-02, 9 subjects, 7 on the efinaconazole arm and 2 on the vehicle arm with incomplete assessments were imputed as complete cures. Of these subjects, 4 efinaconazole and 1 vehicle subject had affected area assessment of 0% at Week 52, but had mycology assessments imputed from earlier visits. An additional two efinaconazole subjects had complete cure imputed from the Week 48 visit. The remaining subjects imputed as complete cure had their response imputed from the Week 32 (efinaconazole subject) or Week 36 (vehicle subject). Thus the majority of subjects imputed as complete cures had at least partial efficacy assessments close to the end of the study at either Week 48 or 52.

The protocol included two sensitivity analyses for handling missing data: (1) treating all missing data as failures and (2) treating all missing data as successes. Treating missing data as failures yields conclusions similar to LOCF because few subjects were imputed as successes (2 efinaconazole and 0 vehicle subjects in Study P3-01 and 7 efinaconazole and 2 vehicle subjects in Study P3-02). See Table 10. On the other hand, the second sensitivity analysis of treating missing observations as successes is highly influenced by any differences in the proportion of subjects with missing data between the two arms. For example, in Study P3-01 the imputation rates were similar across both arms (13% vs 14%) and so the conclusions are similar whether all subjects with missing data are imputed as failures or successes, as the treatment effect remains about the same. However, in Study P3-02, the proportion of subjects with missing data on the vehicle arm was about 5% higher than on the efinaconazole arm. Thus the treatment effect (efinaconazole – vehicle) drops from about 10% when all missing values are imputed as failures to about 4% when all missing values are imputed as successes, and the ‘missing as successes’ sensitivity analysis does not exhibit statistical significance. See Table 10.

Table 10 – Sensitivity Analyses for Handling Missing Data

	Study P3-01			Study P3-02		
Impute Missing as:	Efinacon. N = 656	Vehicle N = 214	P-value	Efinacon. N = 580	Vehicle N = 201	P-value
Failures	115 (18%)	7 (3%)	<0.001	81 (14%)	9 (4%)	<0.001
Successes	199 (30%)	36 (17%)	<0.001	171 (30%)	52 (26%)	0.319

Source: pg 71 of dps-i-idp-108-p3-01-body.pdf and pg 69 of dps-i-idp-108-p3-02-body.pdf

However, both of these proposed analyses treat all missing values the same way—they are imputed as either successes or failures in both arms. There is no guarantee that either of these analyses is conservative. A preferable sensitivity analysis to check robustness of study findings would reduce the estimated treatment effect (and/or increase the variability of the estimate). An extreme way to reduce the treatment effect would be to treat all efinaconazole missing data as failures and all vehicle missing data as responders. Due to the relatively low overall response rates, relatively high proportion of responders, and imbalance in the proportion of missing data between arms (particularly in Study P3-02), such an analysis is not very informative in this case. In Study P3-01 the estimated complete cure rate for efinaconazole vs. vehicle would be 18% vs. 17% (a 1% treatment effect), while in Study P3-02 the estimated complete cure rate for efinaconazole vs. vehicle would be 14% vs. 26% (-12% treatment effect favoring vehicle).

Another type of sensitivity analysis would be to reduce the estimated treatment effect by imputing missing efinaconazole subjects as failures (0% response rate for these subjects), while imputing missing vehicle subjects at conservative yet more plausible level than 100% response, say 2 or 3 times the observed rate in completing subjects. The response rate for vehicle ‘completers’ (observed cases) was about 4% (7/185) in Study P3-01 and 6% (9/158) in Study P3-02. As an additional post-hoc sensitivity analysis, this reviewer proposes to impute approximately 15% of vehicle subjects with missing data as responders (roughly three times the average rate observed in completers from the two studies). In this analysis statistical significance is maintained in both studies. Although this analysis is post-hoc, the conclusion of efficacy is maintained under the assumption that none of the missing efinaconazole subjects responded while the missing vehicle subjects responded at a rate about 3 times that observed in completing vehicle subjects. See Table 11.

Table 11 – Additional Reviewer’s Sensitivity Analysis for Missing Data (Post-Hoc)

Study P3-01			Study P3-02		
Efinacon. N = 656	Vehicle N = 214	P-value	Efinacon. N = 580	Vehicle N = 201	P-value
115 (18%)	11 (5%)	<0.001	81 (14%)	16 (8%)	<0.026

Note: Missing data from efinaconazole subjects is imputed as failure (0/84 successes in Study P3-01 and 0/90 successes in Study P3-02) and approximately 15% of vehicle subjects are imputed as success (4/26 successes in Study P3-01 and 7/43 successes in Study P3-02). P-values are computed from the chi-square distribution.

Source: Reviewer analysis

3.2.6 Secondary Efficacy Endpoints

The applicant wrote two statistical analysis plans (SAPs) for the studies, which differed in the definition and ordering of the secondary and supportive endpoints. The first version of the SAP reflected the way the secondary endpoints had been defined in the protocol. The three secondary endpoints were originally specified as follows:

- Clinical efficacy rate at Week 52 (<10% affected target nail area)
- Mycological cure rate at Week 52 (negative KOH and culture)
- Unaffected new nail growth at Week 52 (change from baseline in healthy target nail measurement)

The second version of the SAP introduced a new secondary endpoint, removed one secondary endpoint, and rearranged the ordering of the secondary endpoints. The new list of secondary endpoints was as follows:

- Complete or almost complete cure rate at Week 52 ($\leq 5\%$ affected target nail area and negative KOH and culture)
- Unaffected new nail growth at Week 52 (change from baseline in healthy target nail measurement)
- Mycological cure rate at Week 52 (negative KOH and culture)

In both versions of the SAP, the secondary efficacy endpoints were to be analyzed sequentially in the order listed to control Type I error. According to the applicant, both SAPs were approved prior to database lock. The final subject visit in Study P3-01 was 9/20/2011 and the final subject visit in Study P3-02 was 10/14/2011. The first SAP is dated 9/29/2011. The second version of the SAP is dated 11/9/2011. The database for Study P3-01 was locked on 11/21/2011 and for Study P3-02 on 12/6/2011. The applicant states that the motivation for revising the SAP was primarily to provide a “more statistically robust and clinically relevant evaluation for the secondary endpoint.” (page 55 of the clinical study report for Study P3-01 and page 52 of the clinical study report for Study P3-02). The protocols themselves were not changed. However, changing the list of secondary endpoints and the ordering of the analyses after the studies are complete is not in fact ‘statistically robust’, as post-hoc changes to the analysis plan can inflate the Type I error rate, particularly if the changes are made based on any knowledge of the data. Although the protocols were not reviewed under a Special Protocol Assessment, the Agency had expressed no disagreement with the applicant’s original list of secondary endpoints when the protocols were reviewed. The fact that the applicant may have decided at the last moment that ‘complete or almost complete cure rate’ is more clinically meaningful than ‘clinical efficacy’ is not a sufficient reason to completely revise the SAP for the secondary endpoints after the trial was completed. This review will focus on the secondary endpoints as specified in the protocol and the first version of the SAP and treat ‘complete or almost complete cure’ as a supportive endpoint.

The difference between the ‘clinical efficacy’ endpoint (specified in the protocol) and the ‘complete or almost complete cure rate’ endpoint is that clinical efficacy requires only that a subject have <10% of affected target nail area, while complete or almost complete cure requires $\leq 5\%$ affected target nail area and negative KOH and culture. The ‘stricter’ definition of the endpoint specified in the second SAP reduces the response rate about 8-10% in the efinaconazole arm and about 5% in the vehicle arm. All four endpoints that

appear in the two lists of secondary endpoints have p-values <0.001 in both studies. See Table 12. Thus all secondary endpoints meet the statistical significance criteria specified in the two SAPs. However, because of the concerns regarding the late proposal to modify the secondary endpoints, ‘complete or almost complete cure’ is not suitable for (b) (4) efficacy (b) (4), as we cannot be assured that the Type I error is adequately controlled for this endpoint.

Table 12 – Secondary Efficacy Endpoints

	Study P3-01			Study P3-02		
	Efinacon. N = 656	Vehicle N = 214	p-value	Efinacon. N = 580	Vehicle N = 201	p-value
Clinical Efficacy	(b) (4)					
Mycologic Cure						
Unaffected new growth (mm)						
Complete or almost complete cure*						

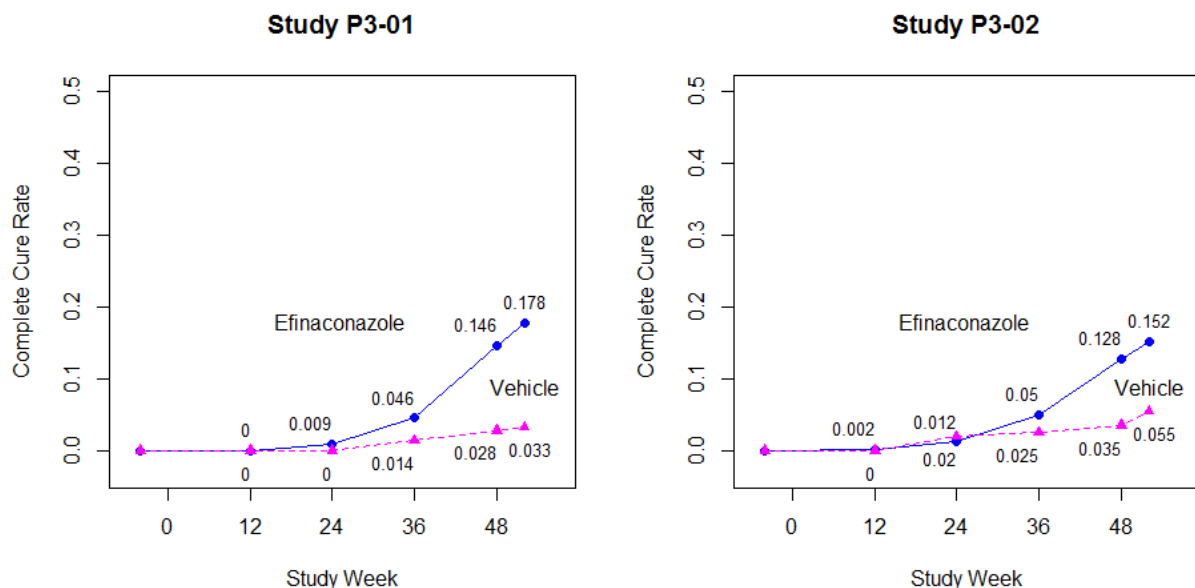
*Endpoint specified in SAP version 2

Source: pg 65-66 of dpsi-idp-108-p3-01-body.pdf and pg 63-64 of dpsi-idp-108-p3-02-body.pdf

3.2.7 Efficacy over Time

Complete cure rates (the primary efficacy endpoint) increased over time through Week 52, and the curves for the two arms began to separate around 36 weeks. The results were similar for the two studies. See Figure 1.

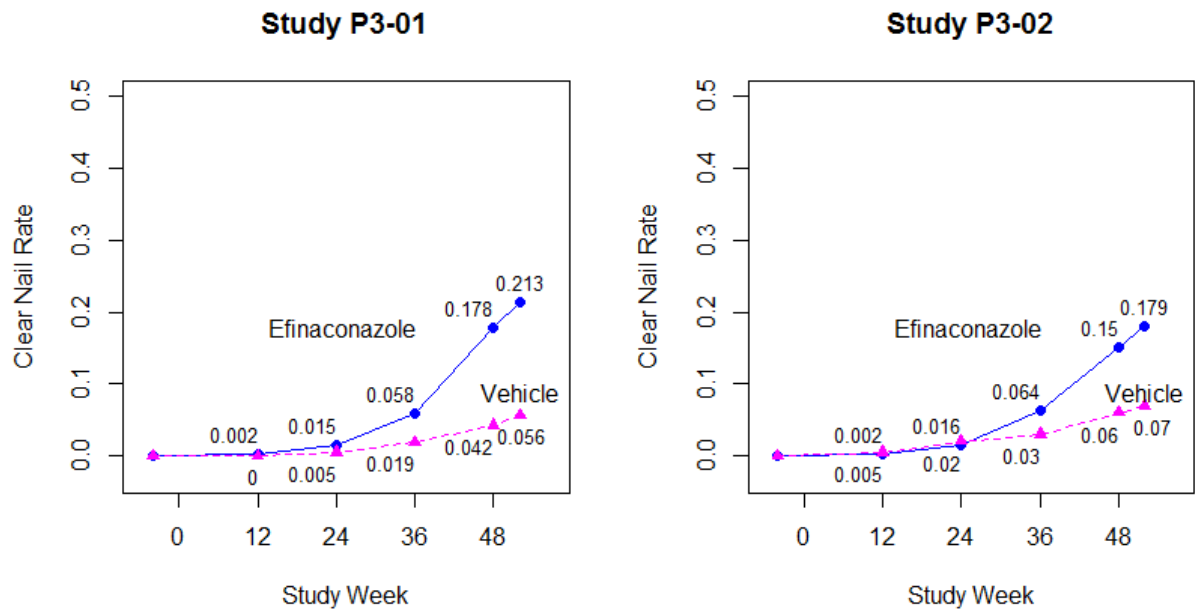
Figure 1 – Complete Cure Rates over Time (LOCF)



Source: Reviewer analysis

Assessment of complete cure involves three components: total area affected, KOH results and culture results. The clear nail rate (0% affected area) has similar trends to the complete cure rate (clear nail plus negative mycology), with the curves separating around Week 36 and rates increasing through Week 52. See Figure 2.

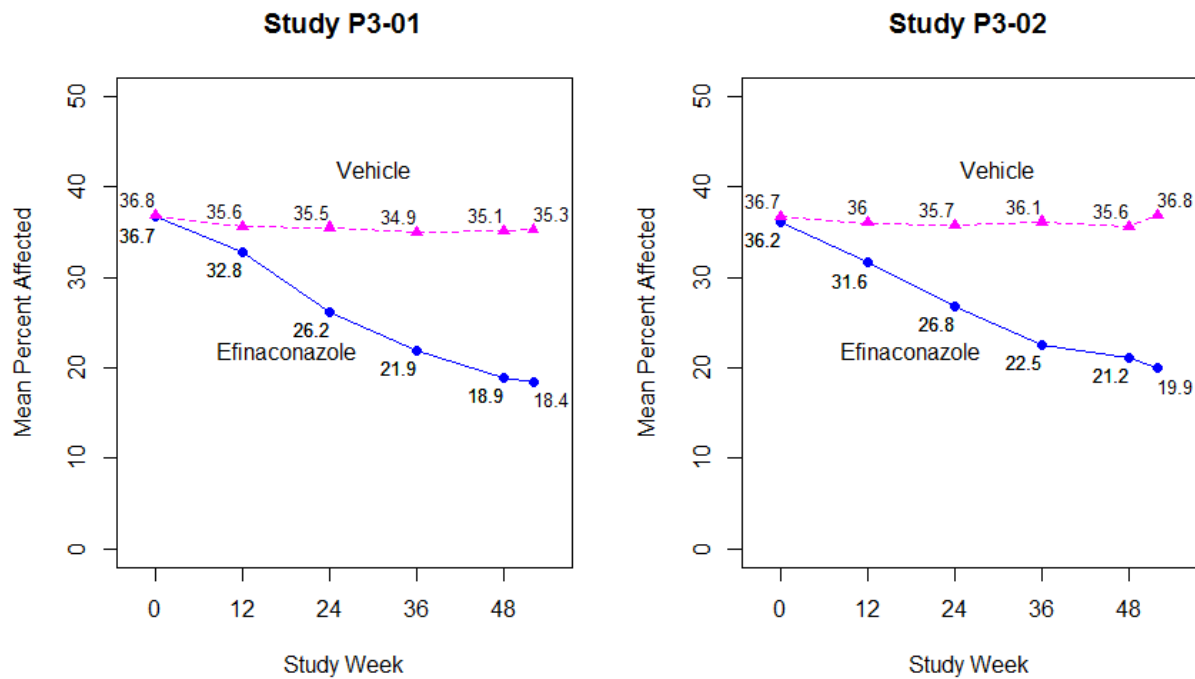
Figure 2 – Clear Nail Rate over Time (LOCF)



Source: Reviewer analysis

Besides looking at the proportion of subjects that achieve a completely clear nail (0% involvement), it may also be of interest to look at the mean percent of area affected over time. Subjects on the efinaconazole arm showed a steady decrease in the mean affected area over the course of the study, while the mean for the vehicle subjects was relatively constant. See Figure 3.

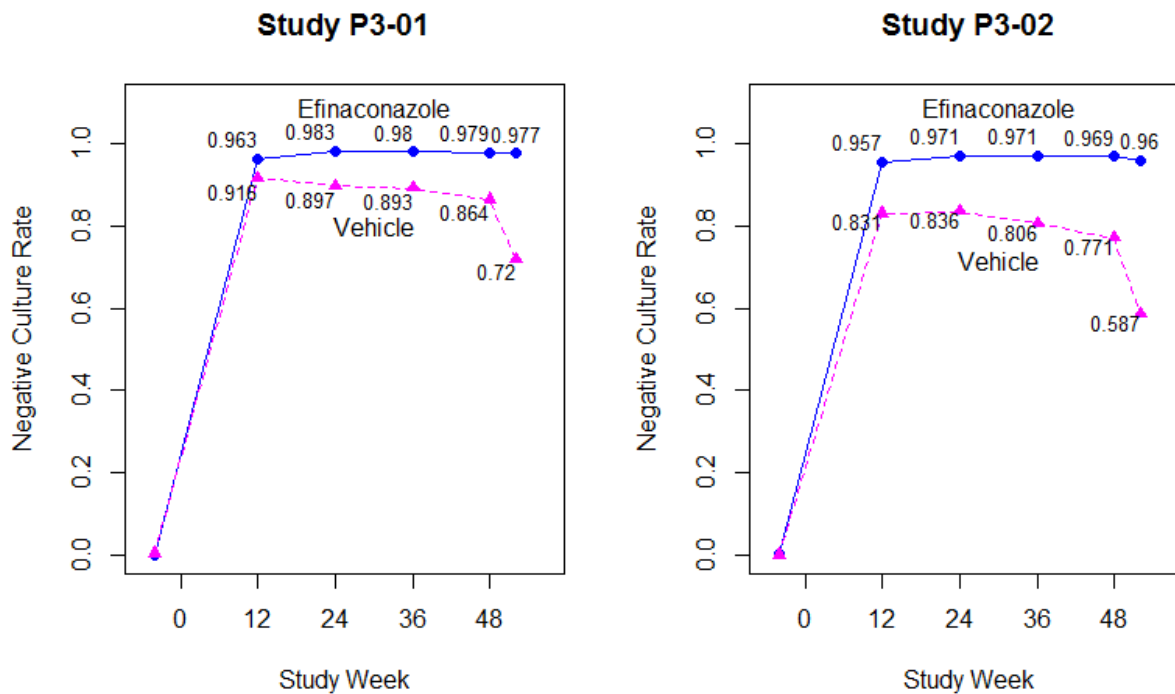
Figure 3 – Mean Percent Affected Area over Time (LOCF)



Source: Reviewer analysis

The majority of subjects had negative cultures starting with the Week 12 visit, though the rate was still slightly higher in the efinaconazole arm. One feature of note, however, is that the negative culture rate dropped on the vehicle arm between the Week 48 (end of treatment) and Week 52 (4 weeks post-treatment) visits, possibly suggesting that the vehicle may hinder the ability to detect positive cultures.

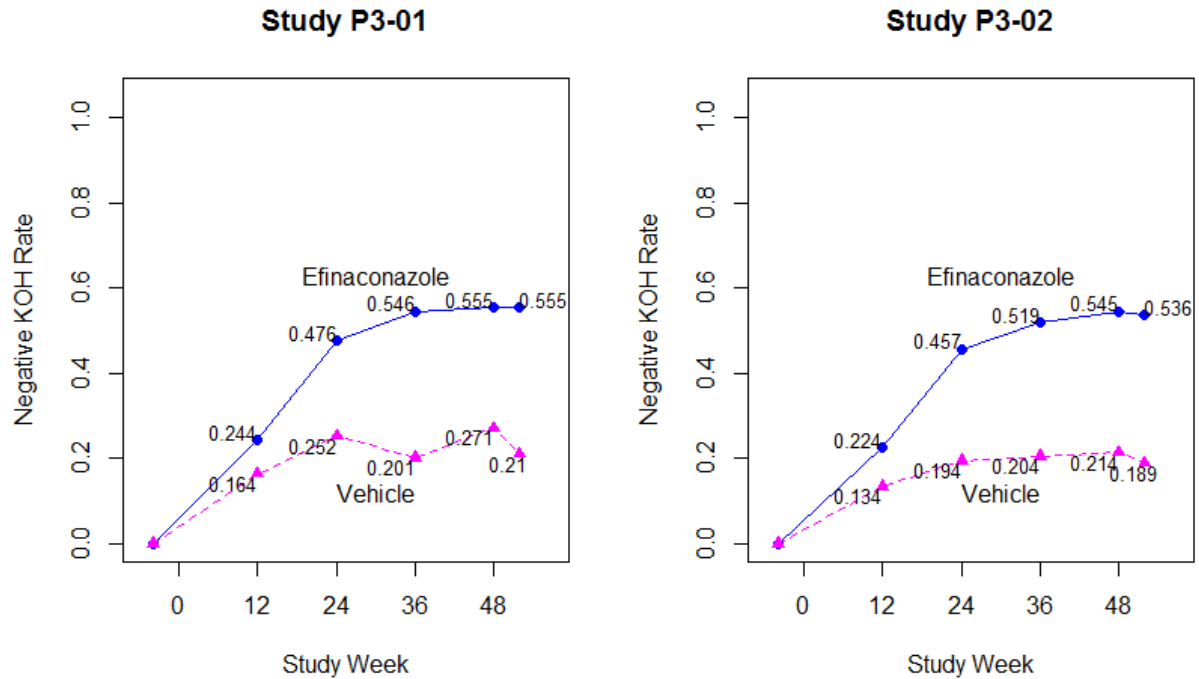
Figure 4 – Negative Culture Rate over Time (LOCF)



Source: Reviewer analysis

The negative KOH rate did not increase as rapidly as the negative culture rate. Both the efinaconazole arm and the vehicle arm reached a plateau between weeks 24 and 36. The negative KOH rate was about 54% for efinaconazole and 20% for vehicle at Week 52 in both studies.

Figure 5 – Negative KOH rate over Time

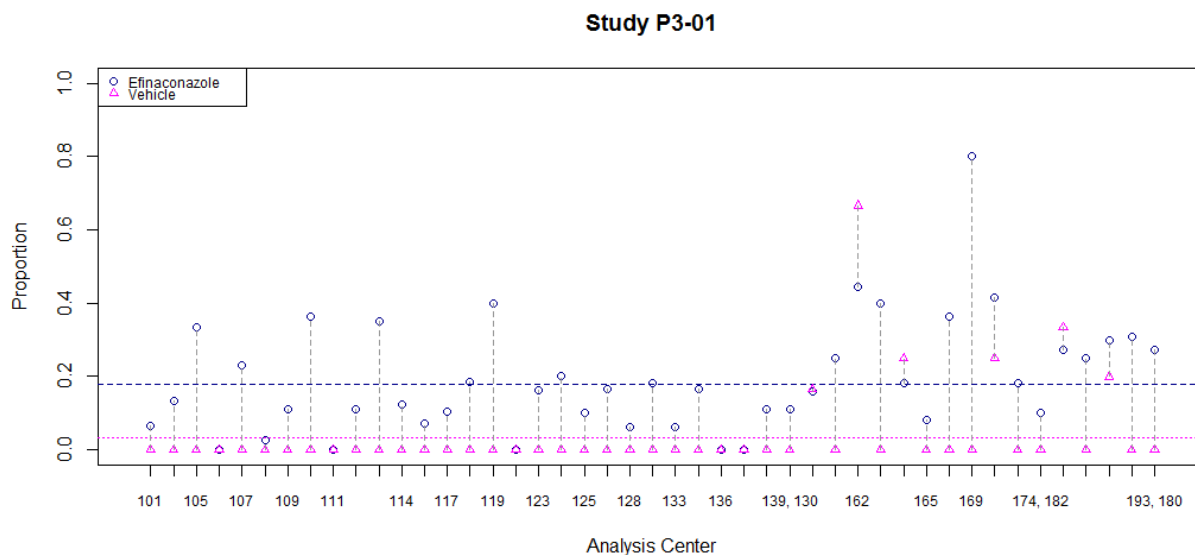


Source: Reviewer analysis

3.2.8 Efficacy by Center

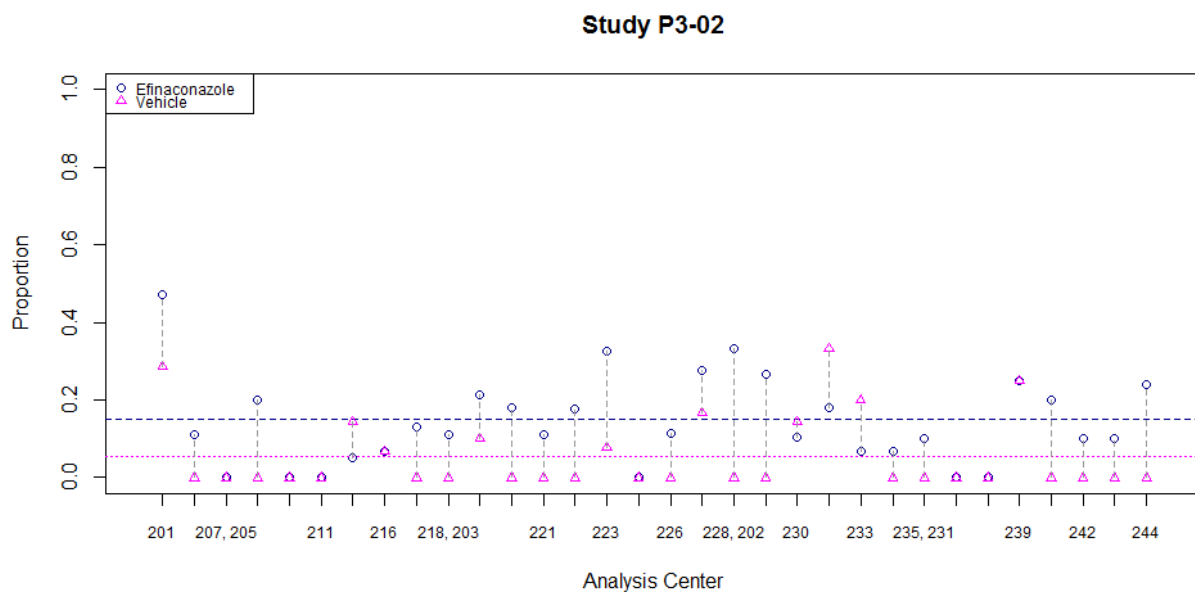
Study P3-01 was conducted at 74 centers in the United States (34), Canada (7), and Japan (33). Small centers were pooled within country to ensure a minimum of 9 efinaconazole and 3 vehicle subjects per analysis center. After the pooling algorithm was applied, Study P3-01 had 45 analysis centers (25 US, 4 Canadian, and 16 Japanese). Study P3-02 was conducted at 44 centers in the United States (36) and Canada (8). A similar pooling algorithm was applied leading to 32 analysis centers (26 US, 6 Canadian) in Study P3-02. 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. The p-values from the Breslow-Day test for homogeneity were 0.935 in Study P3-01 and 0.774 in Study P3-02, and neither test identified significant heterogeneity. See Figure 6 and Figure 7.

Figure 6 – Complete Cure Rate by Analysis Center (Study P3-01)



Source: Reviewer analysis

Figure 7 – Complete Cure Rate by Analysis Center (Study P3-02)



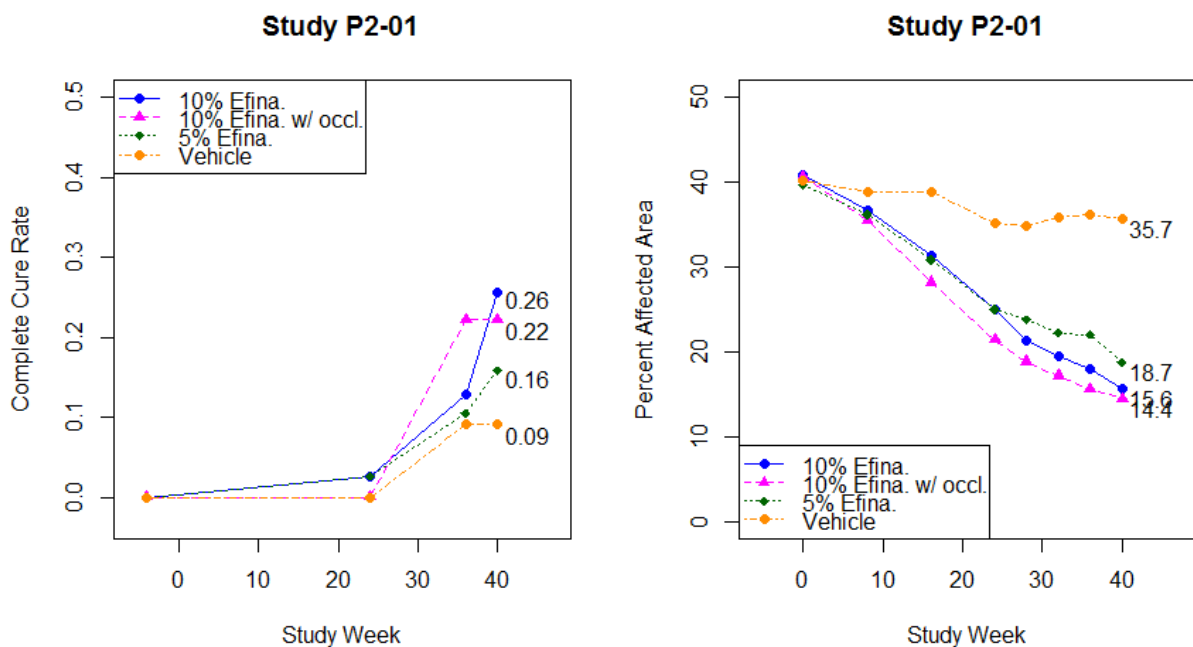
Source: Reviewer analysis

3.2.9 Phase 2 Dose-Ranging Study

Prior to conducting the Phase 3 studies, the applicant conducted a Phase 2 dose-ranging study (P2-01). The study enrolled 135 subjects randomized to efinaconazole 10% (39), efinaconazole 10% with semi-occlusion (36), efinaconazole 5% (38), and vehicle (22). The inclusion criteria were similar to those used in the Phase 3 studies: subjects age 18-65 with 20-50% toenail involvement, without dermatophytomas or lunula involvement,

an uninfected length $\geq 3\text{mm}$, evidence of toenail growth, and positive KOH and positive culture or mixed dermatophyte/Candida culture. The study was shorter than the Phase 3 studies and involved 36 weeks of treatment and 30 days of follow-up. The study did not have a pre-defined primary efficacy endpoint, but evaluated various clinical and mycology assessments. However, the assessments included complete cure and percent area affected. The results of these endpoints are presented in Figure 8. The three active arms had similar results, with a slight trend favoring the 10% efinaconazole arms, and all active arms trending better than vehicle. These findings are generally consistent with those observed in the Phase 3 studies. After completing this study, the applicant selected 10% efinaconazole without occlusion to evaluate in the Phase 3 studies.

Figure 8 – Efficacy Results in Study P2-01 (LOCF)



Source: Reviewer analysis

3.3 Evaluation of Safety

3.3.1 Extent of Exposure

Subjects on the efinaconazole and vehicle arms used similar amounts of study treatment in the Studies P3-01 and P3-02. The planned number of study product applications was 336 and the mean number of applications was around 315 and 318 for the efinaconazole arms in the two studies and 317 and 310 for the vehicle arms in the two studies. Similarly the mean amount of study product used in the two studies was around 49 g in the two efinaconazole arms, and 49 g and 53 g in the two vehicle arms. These calculations were computed in subjects with available data. See Table 13.

Table 13 – Extent of Exposure (Safety Population)

	Study P3-01		Study P3-02	
	Efinacon. N = 653	Vehicle N = 213	Efinacon. N = 574	Vehicle N = 200
<i>Number of Applications</i>	<i>N=633</i>	<i>N=204</i>	<i>N=547</i>	<i>N=182</i>
Mean (SD)	314.5 (51.2)	317.1 (52.0)	317.7 (54.6)	310.0 (68.4)
Range	2 - 357	1 - 378	1 - 365	1 - 351
<i>Amount used (g)</i>	<i>N=576</i>	<i>N=189</i>	<i>N=493</i>	<i>N=164</i>
Mean (SD)	49.3 (24.1)	53.2 (24.0)	49.4 (23.5)	49.0 (23.2)
Range	0.5 – 150.5	6.2 – 119.6	0.4 – 104.5	0.3 – 121.5

Source: pg 76 of dps-i-idp-108-p3-01-body.pdf and pg 74 of dps-i-idp-108-p3-02-body.pdf

3.3.2 Adverse Events

Approximately 65% of efinaconazole and 60% of vehicle subjects experienced at least one adverse event, and approximately 4% of efinaconazole and 2% of vehicle subjects experienced a serious adverse event. See Table 14.

Table 14 – Adverse Events (Safety Population)

	Study P3-01		Study P3-02	
	Efinaconazole N=653	Vehicle N=213	Efinaconazole N=574	Vehicle N=200
Any Adverse Event	431 (66.0%)	130 (61.0%)	370 (64.5%)	117 (58.5%)
Serious Adverse Event	25 (3.8%)	6 (2.8%)	21 (3.7%)	1 (0.5%)
Discontinued due to AEs	21 (3.2%)	1 (0.5%)	11 (1.9%)	0 (0.0%)

Source: pg 78 of dps-i-idp-108-p3-01-body.pdf and pg 76 of dps-i-idp-108-p3-02-body.pdf

Subjects on the efinaconazole arm had a higher rate of administration site adverse reactions than subjects on the vehicle arm, including application site dermatitis (2.2% vs. 0.2%), application site vesicles (1.6% vs. 0%), and application site pain (1.1% vs. 0.2%). Other administration site conditions and skin and subcutaneous tissues disorders observed in at least 0.5% of efinaconazole subjects are presented in Table 15. Other adverse events observed in at least 1.5% of efinaconazole subjects are presented in Table 16.

Table 15 – Administration Site Conditions and Skin and Subcutaneous Tissue Disorders Observed in > 0.5% of Efinaconazole Subjects (Based on Combined Studies P3-01 and P3-02, Safety Population)

	Study P3-01		Study P3-02		Combined	
	Efinacon. N=653	Vehicle N=213	Efinacon. N=574	Vehicle N=200	Efinacon. N=1227	Vehicle N=413
Appl. site dermatitis	23 (3.5%)	0 (0.0%)	4 (0.7%)	1 (0.5%)	27 (2.2%)	1 (0.2%)
Appl. site vesicles	13 (2.0%)	0 (0.0%)	7 (1.2%)	0 (0.0%)	20 (1.6%)	0 (0.0%)
Appl. site pain	7 (1.1%)	0 (0.0%)	6 (1.0%)	1 (0.5%)	13 (1.1%)	1 (0.2%)
Appl. site erythema	5 (0.8%)	0 (0.0%)	6 (1.0%)	0 (0.0%)	11 (0.9%)	0 (0.0%)
Appl. site swelling	3 (0.5%)	0 (0.0%)	5 (0.9%)	0 (0.0%)	8 (0.7%)	0 (0.0%)
Appl. site exfoliation	3 (0.5%)	1 (0.5%)	4 (0.7%)	0 (0.0%)	7 (0.6%)	1 (0.2%)
Appl. site pruritus	4 (0.6%)	0 (0.0%)	2 (0.3%)	0 (0.0%)	6 (0.5%)	0 (0.0%)
Ingrowing nail	17 (2.6%)	1 (0.5%)	11 (1.9%)	2 (1.0%)	28 (2.3%)	3 (0.7%)
Contact dermatitis	19 (2.9%)	4 (1.9%)	8 (1.4%)	2 (1.0%)	27 (2.2%)	6 (1.5%)
Eczema	22 (3.4%)	7 (3.3%)	3 (0.5%)	0 (0.0%)	25 (2.0%)	7 (1.7%)
Rash	5 (0.8%)	1 (0.5%)	8 (1.4%)	0 (0.0%)	13 (1.1%)	1 (0.2%)
Dermatitis	7 (1.1%)	0 (0.0%)	2 (0.3%)	1 (0.5%)	9 (0.7%)	1 (0.2%)
Blister	5 (0.8%)	2 (0.9%)	4 (0.7%)	1 (0.5%)	9 (0.7%)	3 (0.7%)
Hyperkeratosis	6 (0.9%)	2 (0.9%)	0 (0.0%)	0 (0.0%)	6 (0.5%)	2 (0.5%)

Source: pg 257- 278 of dpsidp-108-p3-01-body.pdf and pg 224-242 of dpsidp-108-p3-02-body.pdf

Table 16 – Other Adverse Events Observed in > 1.5% of Efinaconazole Subjects (Based on Combined Studies P3-01 and P3-02)

	Study P3-01		Study P3-02		Combined	
	Efinacon. N=653	Vehicle N=213	Efinacon. N=574	Vehicle N=200	Efinacon. N=1227	Vehicle N=413
Nasopharyngitis	84 (12.9%)	28 (13.1%)	66 (11.5%)	17 (8.5%)	150 (12.2%)	45 (10.9%)
Upper Resp. Tr. Inf.	39 (6.0%)	13 (6.1%)	37 (6.4%)	11 (5.5%)	76 (6.2%)	24 (5.8%)
Sinusitis	31 (4.7%)	4 (1.9%)	18 (3.1%)	5 (2.5%)	49 (4.0%)	9 (2.2%)
Headache	16 (2.5%)	5 (2.3%)	25 (4.3%)	7 (3.5%)	41 (3.3%)	12 (2.9%)
Back pain	18 (2.8%)	6 (2.8%)	21 (3.7%)	7 (3.5%)	39 (3.2%)	13 (3.1%)
Arthralgia	15 (2.3%)	7 (3.3%)	19 (3.3%)	2 (1.0%)	34 (2.8%)	9 (2.2%)
Hypertension	17 (2.6%)	10 (4.7%)	11 (1.9%)	5 (2.5%)	28 (2.3%)	15 (3.6%)
Influenza	17 (2.6%)	9 (4.2%)	10 (1.7%)	1 (0.5%)	27 (2.2%)	10 (2.4%)
Urinary Tract Inf.	13 (2.0%)	8 (3.8%)	13 (2.3%)	2 (1.0%)	26 (2.1%)	10 (2.4%)
Bronchitis	8 (1.2%)	4 (1.9%)	14 (2.4%)	3 (1.5%)	22 (1.8%)	7 (1.7%)
Cough	11 (1.7%)	2 (0.9%)	10 (1.7%)	2 (1.0%)	21 (1.7%)	4 (1.0%)
Gastroenteritis	8 (1.2%)	1 (0.5%)	11 (1.9%)	1 (0.5%)	19 (1.5%)	2 (0.5%)
Pain in extremity	9 (1.4%)	3 (1.4%)	10 (1.7%)	3 (1.5%)	19 (1.5%)	6 (1.5%)

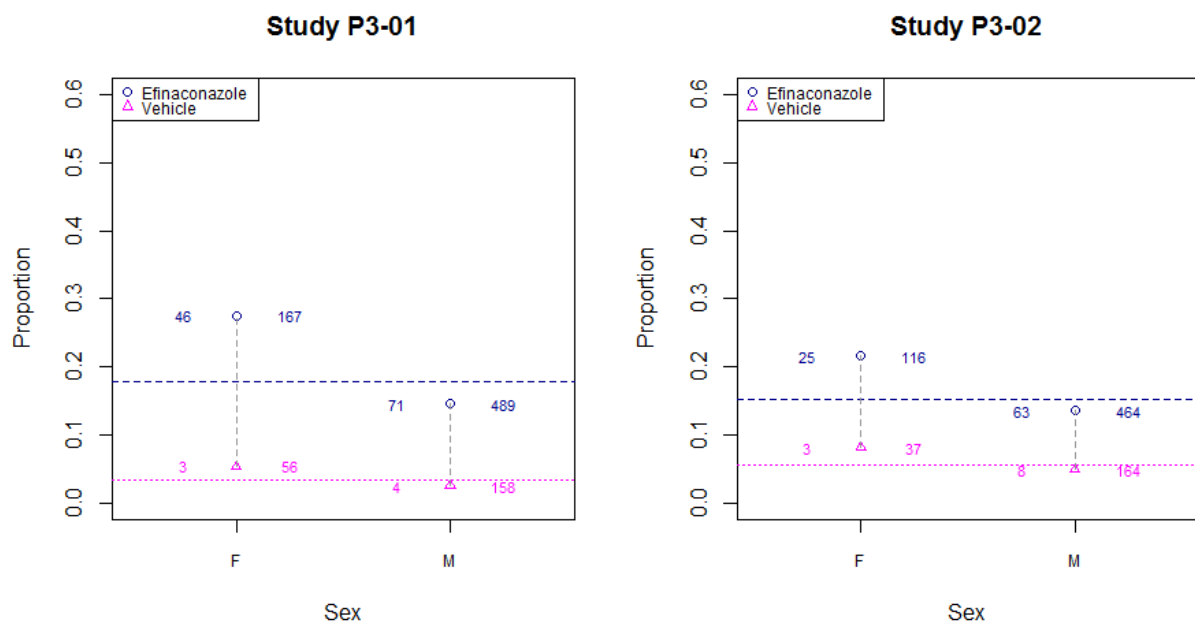
Source: pg 257- 278 of dpsidp-108-p3-01-body.pdf and pg 224-242 of dpsidp-108-p3-02-body.pdf

4 Findings in Special/Subgroup Populations

4.1 Gender, Race, Age, and Geographic Region

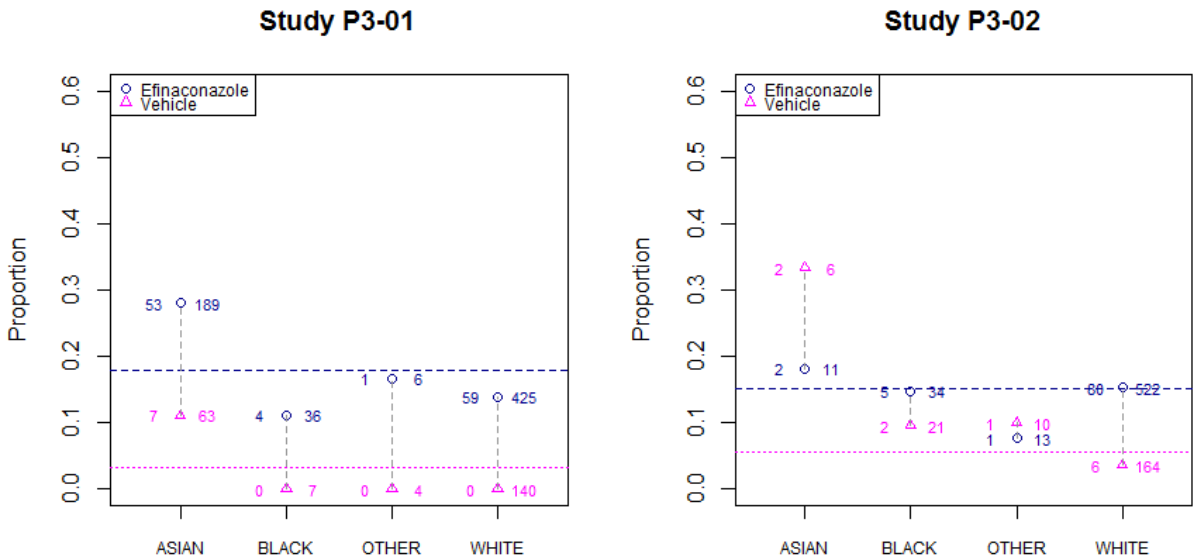
Treatment effects were generally consistent across gender, race, age, and country subgroups in Studies P3-01 and P3-02. The subjects in the Japanese centers in Study P3-01 had higher complete cure rates on both the efinaconazole and vehicle arms than subjects in the U.S. and Canada, though the treatment effect was similar to the other countries. The Japanese subjects also made up the majority of subjects in the ‘Asian’ category for this study as well, leading to the corresponding higher response rates observed in the Asian race group in Study P3-01. See Figure 9 through Figure 12.

Figure 9 – Complete Cure Rate by Gender



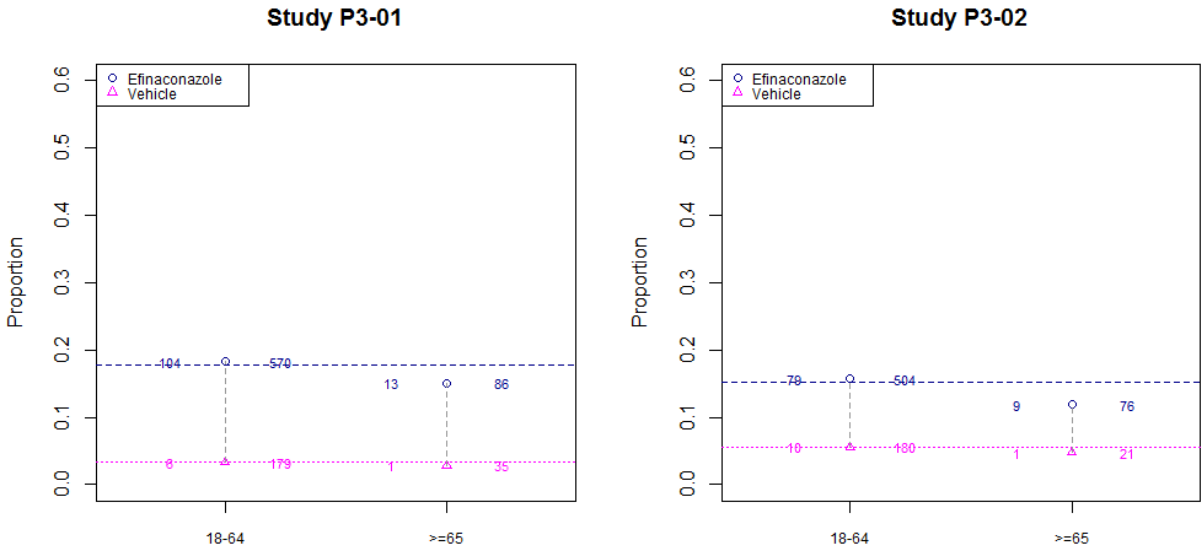
Source: Reviewer analysis

Figure 10 – Complete Cure Rate by Race



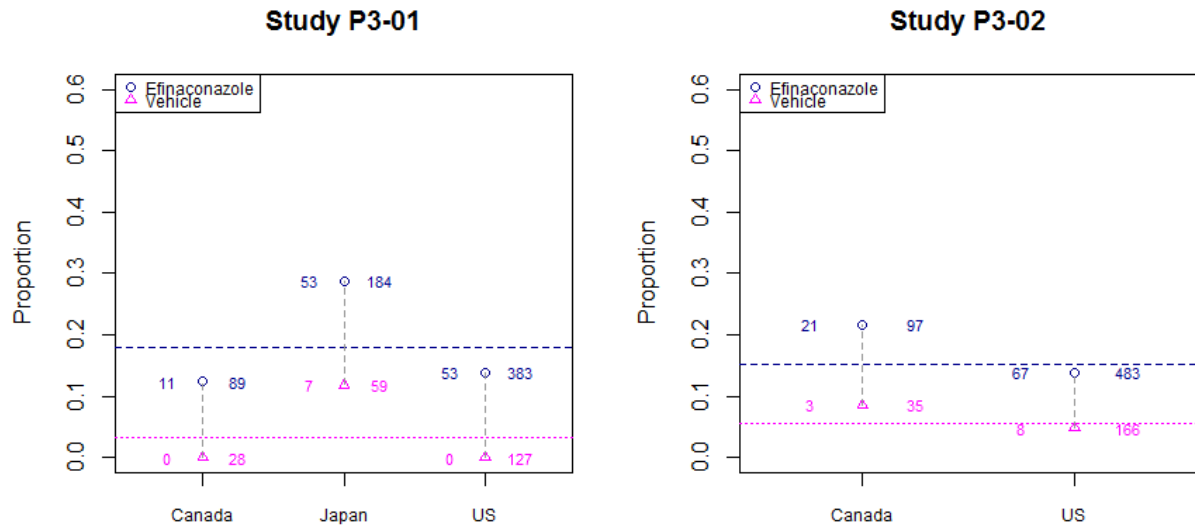
Source: Reviewer analysis

Figure 11 – Complete Cure Rate by Age Group



Source: Reviewer analysis

Figure 12 – Complete Cure Rate by Country



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 efinaconazole solution 10% 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 ($p < 0.001$). Treatment effects were generally consistent across subgroups and centers, and the conclusions were consistent across various assumptions regarding missing data.

However, the applicant modified the list of secondary endpoints and the order in which they were to be analyzed in their final version of the Statistical Analysis Plan (SAP). The final (second) version of the SAP was finalized on 11/9/2011, which falls between the date of the last study subject visit (10/14/2011) and the earlier of the two database locks/unblinding (11/21/2011). The secondary efficacy endpoints, as specified in the protocol and the first version of the SAP (dated 9/29/2011), were: (1) clinical efficacy rate at Week 52 ($< 10\%$ affected target nail area), (2) mycological cure rate at Week 52 (negative KOH and culture), and (3) unaffected new nail growth at Week 52 (change from baseline in healthy target nail measurement). Secondary endpoints were analyzed in sequential order. The second version of the SAP redefined the set of secondary and supportive endpoints, and the order in which they were to be analyzed. The secondary endpoints in the second version of the SAP were: (1) complete or almost complete cure

rate at Week 52 ($\leq 5\%$ affected target nail area and negative KOH and culture), (2) unaffected new nail growth at Week 52 (change from baseline in healthy target nail measurement), and (3) mycological cure rate at Week 52 (negative KOH and culture). The primary endpoint remained the same in both versions of the protocol. The applicant states that the motivation for revising the SAP was primarily to provide a “more statistically robust and clinically relevant evaluation for the secondary endpoint.” This reviewer does not agree with the applicant’s contention that defining new secondary endpoints at the end of the data collection period would lead to ‘more statistically robust’ conclusions, as there is no guarantee that the Type I error is adequately controlled with the post-hoc redefinition of the endpoints. The endpoints defined in the second version of the SAP would not be suitable (b) (4) due to the fact that they were not adequately pre-specified in the protocol.

5.2 Conclusions and Recommendations

Efinaconazole solution 10% was superior to vehicle in the treatment of onychomycosis in two studies. The studies enrolled subjects age 18 to 65 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 efinaconazole vs. vehicle was 18% vs. 3% in Study P3-01 and 15% vs. 5% in Study P3-02. The secondary efficacy endpoints defined in the protocol were supportive of the primary endpoint. The primary and secondary efficacy endpoints were all statistically significant ($p < 0.001$).

Signatures/Distribution List

Primary Statistical Reviewer: Kathleen Fritsch, Ph.D.

Date: 3/5/2013

Statistical Team Leader: Mohamed Alosch, Ph.D.

cc:

DDDP/Walker

DDDP/Ketttl

DDDP/Chiang

DDDP/Dixon

OBIO/Patricia

DBIII/Wilson

DBIII/Alosch

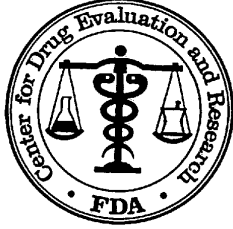
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/s/

KATHLEEN S FRITSCH
03/05/2013

MOHAMED A ALOSH
03/05/2013



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

Statistical Review and Evaluation
CARCINOGENICITY STUDY

IND/NDA Number:	NDA 203-567
Drug Name:	IDP-108
Indication(s):	104 Week Carcinogenicity Study in Mice
Applicant:	Sponsor: Dow Pharmaceuticals Sciences 1330 Redwood Way, Petaluma, California, 94954-1169 Testing Facility: MPI Research, Inc. 54943 North Main Street Mattawan, MI 49071
Documents Reviewed:	Electronic report submission: Submitted on 7/26/2012 Electronic data submission: Submitted on 8/6/2012
Review Priority:	Standard
Biometrics Division:	Division of Biometrics -6
Statistical Reviewer:	Mohammad Atiar Rahman, Ph.D.
Concurring Reviewer:	Karl Lin, Ph.D.
Medical Division:	Division of Neurological Products
Reviewing Pharmacologist:	Linda Pellicore, Ph.D.
Project Manager:	Strother D. Dixon
Keywords:	Carcinogenicity, Dose response

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1. Background

In this submission the sponsor included a report of an animal carcinogenicity study in mice. This study was intended to assess the carcinogenic potential of IDP-108 in mice after once daily dermal administration at appropriate drug levels for about 104 weeks. Results of this review have been discussed with the reviewing pharmacologist Dr. Pellicore.

In this review the phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases.

2. Design

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups, one placebo control, and one untreated control group. Three hundred Crl:CD1®(Icr) mice of each sex were assigned to treated and control groups in equal size of 60 animals per group. The dose levels for treated groups were 3%, 10%, and 30% (changed to 10% beginning in Week 31) of test article. In this review these dose groups were referred to as the low, medium, and high dose groups, respectively. The placebo control received the placebo of IDP-108 topically.

A detailed clinical examination of each animal was performed prior to randomization and weekly during the study. Observations included evaluation of the skin, fur, eyes, ears, nose, oral cavity, thorax, abdomen, external genitalia, limbs and feet, respiratory and circulatory effects, autonomic effects such as salivation, and nervous system effects including tremors, convulsions, reactivity to handling, bizarre behavior, and palpation of tissue masses.

Beginning of Months 5 and 6 of the study, it was noted that some animals had abrasions, scabbing, and swelling apparently as a result of self-mutilation caused by persistent scratching at the cervical region. Application of the higher strengths of test article appeared to exacerbate the scratching as the incidence of skin lesions was higher in the 10% and 30% dose groups. As a result all mice were placed on a dosing holiday from Days 168 to 214 (Weeks 24-30). Dosing was resumed in Week 31 for all mice in the two control groups and at 3% and 10% that did not have scabbing or abrasions. Beginning on Week 31, the dose volume was decreased from 0.1 to 0.05 mL. Beginning on Week 31, the application site was moved just caudal to the previous site but still included the scapular region of the dorsal surface. During Week 33, the dose site was moved further caudal, to the mid-dorsum, to reduce the potential for test material to migrate and pool in the cervical region of the mice. Beginning on Week 31, the dose for all mice in high dose group without scabbing or abrasions was reduced from 30% to 10% and dosing was resumed. Scratching was recorded as a routine detailed clinical observation criteria beginning in Week 28. Mice that did not resume dosing, due to the presence of significant scabbing and/or abrasions, were terminated during Week 34. The number of such termination per group is shown in the following table.

Number of Animals Terminated During Week 34

Sex	Dose Concentration	Number of Animals Terminated
Male	Placebo	3
	3%	4
	10%	13
	30%	30
		Total = 50
Female	10%	12
	30%	19
		Total = 31

The data from high dose group were not further discussed in the submitted report. This group was not processed for the end of the study microscopic evaluation and was removed from the study analysis based upon the severe skin reactions, the need to terminate many of these mice after the dose holiday and the Food and Drug Administration correspondence and advice to not change the dose level to 10% and to not include this group in the study.

Observations for morbidity, mortality, injury, and the availability of food and water were conducted at least two times daily for all animals. Observations for clinical signs and masses were conducted weekly.

All male groups were terminated in Week 102 when the total survivors in the placebo control group reached 20 mice. All females at 10% were terminated in Week 100 when the total survivors in the group reached 17 mice and the remaining groups were terminated in Week 102 when the total survivors in the placebo control group were reduced to ≤ 20 mice.

All animals had a complete list of tissues collected. Microscopic examination of fixed hematoxylin and eosin-stained paraffin sections was performed on protocol-designated sections of tissues of untreated controls, placebo animals and animals at 3% and 10% as well as animals euthanized in extremis and animals found dead. All animals had a complete list of tissues collected. The treated skin and thyroid gland were determined to be potential target organs.

The applications sites (treated skin) of three placebo control males, three males at 3%, and three animals/sex at 10% and 30%/10% of mice that were sacrificed at Week 34 containing abrasions or scabbing were examined microscopically.

2.1. Sponsor's analyses

As mentioned above the sponsor presented the data of the high dose group (in Appendix I) but did not further discuss in this report. Therefore, the sponsor's data analyses involved data from placebo control, untreated control, 3% and 10% treated groups only.

2.1.1. Survival analysis

The sponsor analyzed the intercurrent mortality data using the Kaplan-Meier product-limit method. An overall test comparing all groups was conducted using the log-rank test. If this overall test was significant ($p < 0.05$) a follow up analysis was done where each treatment group was compared to the placebo group using the log-rank test. Results of all pair-wise comparisons were reported at the 0.05 and 0.01 significance levels. All endpoints were analyzed using two-tailed tests.

Sponsor's findings: Sponsor's analysis showed 33.3%, 56.7%, 41.7%, and 33.3% survival in the placebo control, untreated control, 3% and 10% dosage levels, respectively in male mice, and . 30.0%, 45.0%, 35.0%, and 28.3% (Week 100), in the placebo control, untreated control, 3%, and 10% dosage levels, respectively in female mice. The sponsor considered the overall survival as acceptable for this strain and source of mice.

2.1.2. Tumor data analysis

The sponsor analyzed the tumor incidence data using both the survival unadjusted and survival adjusted tests. The survival unadjusted dose response relationship (trend) tests were performed using the Cochran-Armitage test and the corresponding pairwise comparisons of each treatment group with the placebo groups were performed using the Fisher's exact test. The survival adjusted tests were conducted using the methods described by Peto et al (1980).

Adjustment for multiple testing: Evaluation of p-values (p-values of significance) was done according to the FDA guidance as described below.

Evaluation Criteria for Common and Rare Tumors	
Test for Positive Trends	Placebo-High Pair-wise Comparisons
Common and rare tumors will be tested at 0.005 and 0.025 significance levels, respectively	Common and rare tumors will be tested at 0.01 and 0.05 significance levels, respectively

Reviewer's comment: For the adjustment of multiple testing the FDA guidance advises to use a test level of $\alpha=0.005$ for common tumors (with prevalence $\geq 1\%$) and a test level of $\alpha=.025$ for rare tumors (with prevalence $< 1\%$) for trend tests for a submission with two species (rat and mouse). However, the guidance advises to use a test level of $\alpha=0.01$ for common tumors and a test level of $\alpha=.05$ for rare tumors for trend tests for a submission with only one species.

Sponsor's findings:

Week 34: The treated skin of a limited number of animals that were euthanized on Week 34 of the study was examined microscopically. The sponsor's analysis of this data showed that the changes were similar across groups and there were no discernible test article effects.

Terminal: The sponsor's analysis showed no significant test article-related microscopic neoplastic findings. The analysis showed that the benign follicular cell adenomas were present in the thyroid glands (2/47, 4.3%) of males in 10% group. The sponsor mentioned that this incident was higher than those recorded in historical control data [up to 1.7%, (b) (4) CD-1 Mouse – (b) (4)]

2 Year Studies 10/99 to 10/09 (Reviewer's comment: In the report it says 10/09. This looks like a typing mistake. The real value may be 10/109]. The sponsor considered this finding as incidental based on the very low

incidence of follicular cell hyperplasia in this study (1/60 males and 1/60 females in the untreated group, 1/60 females at 3%, and 1/47 males at 10%).

2.2. Reviewer's analyses

To verify sponsor's analyses and to perform additional analysis suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically.

2.2.1. Survival analysis

The survival distributions of animals in placebo control, untreated control, low, and medium dose groups were estimated by the Kaplan-Meier product limit method. The dose response relationship was tested using the likelihood ratio test and the homogeneity of survival distributions was tested using the log-rank test. The intercurrent mortality data are given in Tables 1A and 1B in the appendix for male and female mice, respectively. The Kaplan-Meier curves for survival rates are given in Figures 1A and 1B in the appendix for male and female mice, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A and 2B in the appendix for male and female mice, respectively.

Reviewer's findings: This reviewer's analysis showed 35.09%, 55.17%, 44.64%, and 42.55% overall survival of male mice and 30.00%, 44.07%, 35.00%, and 31.25% overall survival of female mice in placebo control, untreated control, low, and medium dose groups, respectively. This reviewer's analysis showed no statistically significant dose response relationship in mortality across treatment groups in either sex. The pairwise comparisons did not show statistically significant increased mortality in any of the treated groups compared to the placebo control in either sex. The pairwise comparison also did not show statistically significant difference in mortality between the animals in placebo and untreated control groups.

Reviewer's comment: *There are some differences between the overall survival rates calculated by the sponsor and this reviewer. These differences are due to the fact that there were two mice in male untreated control group (#3039 and #3040), one female mouse in untreated control group (#3525), and two female mice in medium dose group (#2515 and #2552) that died due to natural causes during the terminal sacrifice weeks. The sponsor did not count them with the terminally sacrificed mice, while this reviewer counted them with the terminally sacrificed mice. Also the sponsor calculated the percentages out of the original group size (60 mice per group), while this reviewer calculated the percentages out of the number of mice after excluding the mice that were interim sacrificed at week 34. The used group sizes were 57, 58, 56 and 47 for males, and 60, 59, 60, and 48 for females.*

2.2.2. Tumor data analysis

The tumor data were analyzed for dose response relationships and pairwise comparisons of control group with each of the treated groups. Both the dose response relationship tests and pairwise comparisons were performed using the Poly-K method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). In this method an animal that lives the full study period (w_{\max}) or dies before the terminal sacrifice but develops the tumor type being tested gets a score of $s_h = 1$. An animal that dies at week w_h without a tumor before the end of

the study gets a score of $s_h = \left(\frac{w_h}{w_{\max}} \right)^k < 1$. The adjusted group size is defined as $N^* = \sum s_h$. As an interpretation,

an animal with score $s_h = 1$ can be considered as a whole animal while an animal with score $s_h < 1$ can be considered as a partial animal. The adjusted group size N^* is equal to N (the original group size) if all animals live

up to the end of the study or if each animal that dies before the terminal sacrifice develops at least one tumor being tested, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. One critical point for Poly-K test is the choice of the appropriate value of K, which depends on the tumor incidence pattern with the increased dose. For long term 104 week standard rat and mouse studies, a value of K=3 is suggested in the literature. Hence, this reviewer used K=3 for the analysis of this data. For the calculation of p-values the exact permutation method was used.

Multiple testing adjustment: For the adjustment of multiple testing of dose response relationship, the FDA guidance for the carcinogenicity study design and data analysis suggests the use of test levels of $\alpha=0.005$ for common tumors and $\alpha=0.025$ for rare tumors for a submission with two species, and a significance level of $\alpha=0.01$ for common tumors and $\alpha=0.05$ for rare tumors for a submission with one species in order to keep the false-positive rate at the nominal level of approximately 10%. A rare tumor is defined as one in which the published spontaneous tumor rate is less than 1%. For multiple pairwise comparisons of treated group with control the FDA guidance suggests the use of test levels $\alpha=0.01$ for common tumors and $\alpha=0.05$ for rare tumors, in order to keep the false-positive rate at the nominal level of approximately 10% for both submissions with two or one species.

It should be noted that the FDA guidance for multiple testing for dose response relationship is based on a publication by Lin and Rahman (1998). In this work the authors investigated the use of this rule for Peto analysis. However, in a later work Lin and Rahman (2008) showed that this rule for multiple testing for dose response relationship is also suitable for Poly-K tests.

Since the mice sacrificed at Week 34 might not have enough exposure to the drug to develop tumors, an analysis of tumor data excluding them seems more reasonable. However, since all animals sacrificed at Week 34 had complete microscopic examination, a further analysis including these animals may also be important. Based on advice of the reviewing pharmacologist this reviewer analyzed the data twice, once excluding the interim sacrifice animals and once including them. An exploratory analysis of the tumor data was also performed using the untreated control excluding the interim sacrificed mice.

The tumor rates and the p-values of the tested tumor types using the placebo control group and excluding the interim sacrificed mice are given in Tables 3A and 3B in the appendix for male and female mice, respectively. The tumor rates and the p-values of the tested tumor types using the placebo control group and including the interim sacrificed mice are given in Tables 4A and 4B in the appendix for male and female mice, respectively. A pairwise comparison of placebo and untreated control excluding the interim sacrificed mice are given in Tables 5A and 5B in the appendix for male and female mice, respectively. A pairwise comparison of placebo and untreated control including the interim sacrificed mice are given in Tables 6A and 6B in the appendix for male and female mice, respectively.

Reviewer's findings: Based on the criteria of adjustment for multiple testing discussed above, the dose response relationship for the incidences of none of the observed tumor types was considered to be statistically significant in either sex. The pairwise comparisons also did not show statistically significant increased incidences in the treated groups in any of the observed tumor types compared to the placebo control in either sex.

2.2.3. Exploratory analysis

For the purpose of exploratory analysis this reviewer analyzed the tumor data using the untreated control after

excluding the interim sacrificed animals. The results are shown in Tables 7A and 7B in the appendix for male and female mice, respectively. The analysis showed statistically significant dose response relationships for the incidences of lymphomas in sternum bone marrow, and brain in female mice. The pairwise comparisons did not show statistically significant increased incidence of these tumor types in any of the treated groups.

3. Evaluation of validity of the design of the mouse study

As has been noted, the tumor data analyses showed no statistically significant dose-response relationship in any of the observed tumor types. However, before drawing any conclusion regarding the carcinogenic or non-carcinogenic potential of the drug in mice, it is important to look into the following two issues, as have been pointed out in the paper by Haseman (1984).

- (i) Were enough animals exposed, for a sustained amount of time, to the risk of late developing tumors?
- (ii) Were dose levels high enough to pose a reasonable tumor challenge to the animals?

There is no consensus among experts regarding the number of animals and length of time at risk, although most carcinogenicity studies are designed to run for two years with about fifty to seventy animals per treatment group. The following are some rules of thumb regarding these two issues as suggested by experts in this field.

Haseman (1985) has done an investigation on the first issue. He gathered data from 21 studies using Fischer 344 rats and B6C3F1 mice conducted at the National Toxicology Program (NTP). It was found that, on the average, approximately 50% of the animals in the high dose group survived the two-year study period. Also, in a personal communication with Dr. Karl Lin of Division of Biometrics-6, Haseman suggested that, as a rule of thumb, a 50% survival of 50 initial animals or 20 to 30 animals still alive in the high dose group, between weeks 80-90, would be considered as a sufficient number and adequate exposure. In addition Chu, Cueto and Ward (1981), suggested that "to be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50% survival at one-year."

It appears, from these three sources that the proportions of survival at 52 weeks, 80-90 weeks, and two years are of interest in determining the adequacy of exposure and number of animals at risk.

Regarding the question of adequate dose levels, it is generally accepted that the high dose should be close to the maximum tolerated dose (MTD). In the paper of Chu, Cueto and Ward (1981), the following criteria are mentioned for dose adequacy. A high dose is considered as close to MTD if any of the criteria is met.

- (i) "A dose is considered adequate if there is a detectable loss in weight gain of up to 10% in a dosed group relative to the controls."
- (ii) "The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."
- (iii) "In addition, doses are considered adequate if the dosed animals show a slight increased mortality compared to the controls."

We will now investigate the validity of the IDP-108 mouse carcinogenicity study, in the light of the above guidelines.

It should be noted that, in this study the high dose group (30%) were abandoned due to high rate of scabbing and

the highest dose that was carried up to the end of the study was the medium dose. Hence, in this review this reviewer evaluated the adequacy of the medium dose group.

The following is the summary of survival data of rats in the high dose groups:

Percentage of survival in the medium dose group at the end of Weeks 52, 78, and 91

	End of 52 weeks	End of 91 weeks	End of 102 weeks
Male	85%	64%	43%
Female	94%	48%	31%

Based on the survival criterion Haseman, and Chu, Cueto and Ward proposed and looking at the survival rate at the end of Weeks 2 and 91, it may be concluded that enough mice were exposed to the medium dose for a sufficient amount of time in both sexes.

The following table shows the percent difference in mean body weight gain in mice from the concurrent control,

**Percent Difference in Mean body Weight Gain
from Controls**

Male		Female	
3%	10%	3%	10%
-9.74	-15.32	-9.95	-5.13

Source: Tables given in section 8.1.5 of sponsor's submission

Therefore, relative to placebo control the animals in medium dose group had 15.32% decreased body weight gain in male mice and 5.13% decreased body weight gain in female mice. Similarly, relative to placebo control the animals in low dose group had 9.74% decreased body weight gain in male mice and 9.95% decreased body weight gain in female mice.

The mortality rates at the end of the experiment were as follows:

Mortality Rates at the End of the Experiment

	Placebo Control	3% (Difference)	10% (Difference)
Male	64.91%	55.36% (9.55)	57.45% (7.46)
Female	70.00%	65.00% (5.00)	68.75% (1.25)

This shows that the mortality rates of in medium dose group are 7.46% and 1.25% lower than the placebo control in male and female mice, respectively. Also, the mortality rates of in low dose group are 9.55% and 5.00% lower than the placebo control in male and female mice, respectively.

Thus, from the body weight gain and mortality data it can be concluded that the used medium dose level might have reached the MTD in both sexes. Similar consideration shows that even the low dose might be adequate.

However, for a final determination of the adequacy of the doses used for both male and female mice, other clinical signs and histopathological toxic effects must be considered

4. Summary

In this submission the sponsor included a report of an animal carcinogenicity study in mice. This study was intended to assess the carcinogenic potential of IDP-108 in mice after once daily dermal administration at appropriate drug levels for about 104 weeks.

In this review the phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases.

Design: Two separate experiments were conducted, one in male and one in female mice. In each of these two experiments there were three treated groups, one placebo control, and one untreated control group. Three hundred CrI:CD1®(Icr) mice of each sex were assigned to treated and control groups in equal size of 60 animals per group. The dose levels for treated groups were 3%, 10%, and 30% (changed to 10% beginning in Week 31) concentration of test article. In this review these dose groups were referred to as the low, medium, and high dose groups, respectively. The placebo control received the placebo of IDP-108 topically.

A detailed clinical examination of each animal was performed prior to randomization and weekly during the study. Beginning in the 5th and 6th month of the study, it was noted that some animals had abrasions, scabbing, and swelling apparently as a result of self-mutilation caused by persistent scratching at the cervical region. Application of the higher strengths of test article appeared to exacerbate the scratching as the incidence of skin lesions was higher in the 10% and 30% dose groups. As a result all mice were placed on a dosing holiday from Days 168 to 214 (Week 24-30). Dosing was resumed in Week 31 for all mice in the two control groups and at 3% and 10% that did not have scabbing or abrasions. Beginning on Week 31, the dose volume was decreased from 0.1 to 0.05 mL. Beginning on Week 31, the application site was moved just caudal to the previous site but still included the scapular region of the dorsal surface. During Week 33, the dose site was moved further caudal, to the mid-dorsum, to reduce the potential for test material to migrate and pool in the cervical region of the mice. Beginning on Week 31, the dose for all mice in Group 5 without scabbing or abrasions was reduced from 30% to 10% and dosing was resumed. Scratching was recorded as a routine detailed clinical observation criteria beginning in Week 28. Mice that did not resume dosing, due to the presence of significant scabbing and/or abrasions, were terminated during Week 34. The number of such termination were 3, 4, 13 and 30 male mice in placebo control, 3%, 10% and 30% concentration groups respectively, and 12 and 19 female mice in 10% and 30% concentration groups, respectively.

The data for high dose group were not processed for the Week 102 (male) or 100 (female) microscopic evaluation and was removed from the study analysis based upon the severe skin reactions, the need to terminate many of these mice after the dose holiday and the Food and Drug Administration correspondence and advice to not change the dose level to 10% and to not include this group in the study.

All male groups were terminated in Week 102 when the total survivors in the placebo control group reached 20 mice. All females at 10% were terminated in Week 100 when the total survivors in the group reached 17 mice and the remaining groups were terminated in Week 102 when the total survivors in the placebo control group were reduced to ≤ 20 mice. All animals had a complete list of tissues collected. The treated skin and thyroid gland were determined to be potential target organs.

The tests showed no statistically significant dose response relationship in mortality across treatment groups in

either sex using the Placebo control in either sex. The pairwise comparisons did not showed statistically significant increased mortality in any of the treated groups compared to the Placebo control in either sex. The pairwise comparison also did not show statistically significant difference in mortality between the animals in Placebo and untreated control groups.

The tests did not show statistically significant dose response relationship for the incidences of any of the observed tumor types in either sex. The pairwise comparisons also did not show statistically significant increased incidences in the treated groups in any of the observed tumor types compared to the Placebo control in either sex.

From the body weight gain and mortality data it can be concluded that the used medium dose level might have reached the MTD in both sexes. Similar consideration shows that even the low dose might be adequate. However, For a final determination of the adequacy of the doses used for both male and female mice, other clinical signs and histopathological toxic effects must be considered

Mohammad Atiar Rahman, Ph.D.
Mathematical Statistician

Concur: Karl Lin, Ph.D.
Team Leader, Biometrics-6

cc:
Archival NDA 203-567

Dr. Pellicore
Ms. Dixon

Dr. Machado
Dr. Lin
Dr. Rahman
MS. Patrician

5. Appendix

**Table 1A: Intercurrent Mortality Rate
Male Mice Excluding data of Interim Sacrifice Animals**

Week	Placebo Cont.		Untreated Cont.		_____3 %_____		_____10 %_____	
	No. of	Cum. %	No. of	Cum. %	No. of	Cum. %	No. of	Cum. %
Death	Death	Cum. %	Death	Cum. %	Death	Cum. %	Death	Cum. %
~~~~~								
0 - 52	4	7.02	1	1.72	.	.	7	14.89
53 - 78	8	21.05	11	20.69	9	16.07	2	19.15
79 - 91	15	47.37	9	36.21	10	33.93	8	36.17
92 - 102	10	64.91	5	44.83	12	55.36	10	57.45
Ter. Sac.	20	35.09	32	55.17	25	44.64	20	42.55
-----								
Total	N=57		N=58		N=56		N=47	

**Table 1B: Intercurrent Mortality Rate  
Female Mice Excluding data of Interim Sacrifice Animals**

Week	Placebo Cont.		Untreated Cont.		_____3 %_____		_____10 %_____	
	No. of	Cum. %	No. of	Cum. %	No. of	Cum. %	No. of	Cum. %
Death	Death	Cum. %	Death	Cum. %	Death	Cum. %	Death	Cum. %
~~~~~								
0 - 52	1	1.67	2	3.39	4	6.67	3	6.25
53 - 78	11	20.00	16	30.51	8	20.00	13	33.33
79 - 91	12	40.00	3	35.59	15	45.00	7	47.92
92 - 102	18	70.00	12	55.93	12	65.00	10	68.75
Ter. Sac.	18	30.00	26	44.07	21	35.00	15	31.25

Total	N=60		N=59		N=60		N=48	

**Table 2A: Intercurrent Mortality Comparison
Male Mice**

Test	Statistic	P_Value*
~~~~~		
Dose-Response	Likelihood Ratio	0.4888
Homogeneity	Log-Rank	0.5562

* The p-values were calculated using data from Placebo control, low, and medium dose groups excluding the data from interim sacrifice.

**Table 2B: Intercurrent Mortality Comparison  
Female Mice**

Test	Statistic	P_Value*
~~~~~		
Dose-Response	Likelihood Ratio	0.2822
Homogeneity	Log-Rank	0.4744

* The p-values were calculated using data from Placebo control, low, and medium dose groups excluding the data from interim sacrifice.

Male Mice

~~~~~

### Male Mice

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |            | Untrtd       | Placeb       | 3 %         | 10 %        | P-Value   |         |         |
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| Organ Name                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             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| ))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))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|            |              |              |             |             |           |         |         |

### Male Mice

[illegible]

**Table 3A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons  
Using Placebo Control Excluding Interim Sacrifice  
Male Mice**

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |            | Untrtd | Placeb | 3 %  | 10 % |           |         |         |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|--------|--------|------|------|-----------|---------|---------|
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |            | Cont   | Cont   | Low  | Med  | P-Val ue  |         |         |
| Organ Name                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Tumor Name | N=58   | N=57   | N=56 | N=47 | Dose Resp | PC vs L | PC vs M |
| %%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%% |            |        |        |      |      |           |         |         |

**Table 3B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons  
Using Placebo Control Excluding Interim Sacrifice  
Female Mice**

| Organ Name           | Tumor Name             | Untreated | Placebo | 3 %  | 10 % | P-Value   |         |         |
|----------------------|------------------------|-----------|---------|------|------|-----------|---------|---------|
|                      |                        | N=59      | N=60    | N=60 | N=48 | Dose Resp | PC vs L | PC vs M |
| ~~~~~                |                        |           |         |      |      |           |         |         |
| adipose tissue       | LYMPHOMA               | 1         | 0       | 0    | 1    | 0.2627    | .       | 0.4133  |
|                      | SARCOMA, ENDOMETRIAL   | 0         | 0       | 0    | 1    | 0.2627    | .       | 0.4133  |
| adrenal glands       | ADENOMA, SUBCAPSULAR   | 2         | 1       | 0    | 1    | 0.4581    | 1.0000  | 0.6591  |
|                      | LYMPHOMA               | 4         | 5       | 3    | 3    | 0.5735    | 0.8668  | 0.7288  |
|                      | PHEOCHROMOCYTOMA       | 1         | 1       | 0    | 0    | 1.0000    | 1.0000  | 1.0000  |
|                      | SARCOMA, HISTIOCYTIC   | 0         | 0       | 0    | 1    | 0.2627    | .       | 0.4133  |
| aorta                | CARCINOMA, BRONCHIOLO  | 0         | 2       | 0    | 0    | 1.0000    | 1.0000  | 1.0000  |
|                      | LYMPHOMA               | 3         | 5       | 5    | 7    | 0.1120    | 0.6305  | 0.1985  |
|                      | SARCOMA, HISTIOCYTIC   | 0         | 1       | 0    | 0    | 1.0000    | 1.0000  | 1.0000  |
| bone                 | OSTEOSARCOMA           | 0         | 0       | 1    | 0    | 0.6271    | 0.4943  | .       |
| bone marrow, femur   | FIBROSARCOMA           | 0         | 0       | 1    | 0    | 0.6303    | 0.5000  | .       |
|                      | LYMPHOMA               | 1         | 4       | 2    | 2    | 0.6550    | 0.8935  | 0.8007  |
|                      | SARCOMA, HISTIOCYTIC   | 0         | 2       | 0    | 2    | 0.2817    | 1.0000  | 0.5505  |
| bone marrow, sternum | LYMPHOMA               | 0         | 3       | 2    | 3    | 0.3171    | 0.8126  | 0.4891  |
|                      | SARCOMA, HISTIOCYTIC   | 0         | 2       | 0    | 2    | 0.2817    | 1.0000  | 0.5505  |
| bone, femur          | LYMPHOMA               | 1         | 2       | 1    | 1    | 0.6546    | 0.8793  | 0.8039  |
|                      | OSTEOMA                | 0         | 1       | 0    | 0    | 1.0000    | 1.0000  | 1.0000  |
| bone, sternum        | LYMPHOMA               | 2         | 5       | 3    | 6    | 0.1501    | 0.8596  | 0.3055  |
|                      | SARCOMA, HISTIOCYTIC   | 0         | 1       | 0    | 0    | 1.0000    | 1.0000  | 1.0000  |
| brain                | LYMPHOMA               | 0         | 2       | 2    | 3    | 0.2152    | 0.6919  | 0.3505  |
| cavity, abdominal    | SEX-CORD/STROMAL TUMOR | 0         | 0       | 1    | 0    | 0.6271    | 0.4943  | .       |
| cavity, thoracic     | LYMPHOMA               | 0         | 0       | 1    | 0    | 0.6271    | 0.4943  | .       |
| esophagus            | LYMPHOMA               | 0         | 2       | 0    | 1    | 0.5992    | 1.0000  | 0.7982  |
| eyes                 | LYMPHOMA               | 2         | 1       | 2    | 0    | 0.7996    | 0.5000  | 1.0000  |
| eyes, optic nerve    | LYMPHOMA               | 0         | 1       | 0    | 1    | 0.4581    | 1.0000  | 0.6591  |
| gallbladder          | FIBROMA                | 0         | 1       | 0    | 0    | 1.0000    | 1.0000  | 1.0000  |
|                      | LYMPHOMA               | 1         | 4       | 6    | 1    | 0.8663    | 0.3985  | 0.9371  |
|                      | SARCOMA, HISTIOCYTIC   | 0         | 0       | 0    | 1    | 0.2627    | .       | 0.4133  |
| harderian gland      | ADENOMA                | 2         | 1       | 0    | 0    | 1.0000    | 1.0000  | 1.0000  |
| heart                | CARCINOMA, BRONCHIOLO  | 1         | 1       | 0    | 1    | 0.4672    | 1.0000  | 0.6681  |
|                      | LYMPHOMA               | 3         | 8       | 3    | 7    | 0.2463    | 0.9728  | 0.4676  |
|                      | SARCOMA, HISTIOCYTIC   | 1         | 0       | 1    | 1    | 0.2605    | 0.5000  | 0.4133  |
| joint, tibiofemoral  | LYMPHOMA               | 0         | 1       | 1    | 1    | 0.4921    | 0.7529  | 0.6591  |

**Table 3B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Using Placebo Control Excluding Interim Sacrifice Female Mice**

|                    |                         | Untrtd | Placeb | 3 %  | 10 % | P-Val ue  |         |         |
|--------------------|-------------------------|--------|--------|------|------|-----------|---------|---------|
| Organ Name         | Tumor Name              | N=59   | N=60   | N=60 | N=48 | Dose Resp | PC vs L | PC vs M |
|                    |                         |        |        |      |      |           |         |         |
| J oint, tibi ofem  | SARCOMA, HI STI OCYTI C | 0      | 1      | 0    | 0    | 1. 0000   | 1. 0000 | 1. 0000 |
| ki dneys           | LYMPHOMA                | 5      | 10     | 6    | 7    | 0. 4803   | 0. 9161 | 0. 6527 |
|                    | SARCOMA, HI STI OCYTI C | 2      | 2      | 0    | 2    | 0. 2779   | 1. 0000 | 0. 5410 |
|                    | SEX-CORD/STROMAL TUM    | 0      | 0      | 1    | 0    | 0. 6271   | 0. 4943 | .       |
| l acri mal gl ands | LYMPHOMA                | 3      | 5      | 6    | 4    | 0. 4628   | 0. 5158 | 0. 5618 |
|                    | SARCOMA, HI STI OCYTI C | 0      | 1      | 0    | 1    | 0. 4581   | 1. 0000 | 0. 6591 |
| l arge i ntestine  | LYMPHOMA                | 1      | 0      | 1    | 0    | 0. 6303   | 0. 5000 | .       |
|                    |                         | 2      | 1      | 2    | 0    | 0. 8013   | 0. 5085 | 1. 0000 |
|                    |                         | 3      | 1      | 0    | 0    | 1. 0000   | 1. 0000 | 1. 0000 |
| l ary nx           | LYMPHOMA                | 2      | 3      | 1    | 2    | 0. 4789   | 0. 9390 | 0. 6839 |
|                    | SARCOMA, HI STI OCYTI C | 0      | 1      | 0    | 0    | 1. 0000   | 1. 0000 | 1. 0000 |
| l iv er            | ADENOMA, HEPATOCELLU    | 0      | 1      | 3    | 3    | 0. 1321   | 0. 3081 | 0. 1886 |
|                    | CARCI NOMA, HEPATOCCEL  | 0      | 2      | 0    | 0    | 1. 0000   | 1. 0000 | 1. 0000 |
|                    | ADEN+CAR, HEPATOCELL    | 0      | 3      | 3    | 3    | 0. 3379   | 0. 6509 | 0. 4726 |
|                    | HEMANGI OMA             | 0      | 0      | 1    | 0    | 0. 6271   | 0. 4943 | .       |
|                    | HEMANGI OSARCOMA        | 3      | 2      | 1    | 1    | 0. 6492   | 0. 8750 | 0. 7982 |
|                    | LYMPHOMA                | 3      | 9      | 6    | 4    | 0. 8019   | 0. 8707 | 0. 8838 |
|                    | SARCOMA, HI STI OCYTI C | 2      | 5      | 1    | 3    | 0. 4752   | 0. 9850 | 0. 7018 |
| l ung              | ADENOCARCI NOMA         | 0      | 0      | 0    | 1    | 0. 2627   | .       | 0. 4133 |
|                    | ADENOMA, BRONCHI OLAR   | 3      | 7      | 4    | 1    | 0. 9698   | 0. 8948 | 0. 9886 |
|                    | CARCI NOMA, BRONCHI OL  | 7      | 6      | 3    | 6    | 0. 2068   | 0. 9105 | 0. 3904 |
|                    | ADEN+CAR, BRONCHI OLA   | 9      | 12     | 7    | 7    | 0. 6415   | 0. 9260 | 0. 7771 |
|                    | LYMPHOMA                | 3      | 11     | 5    | 7    | 0. 5319   | 0. 9678 | 0. 7138 |
|                    | SARCOMA, HI STI OCYTI C | 1      | 5      | 0    | 0    | 1. 0000   | 1. 0000 | 1. 0000 |
| l ymph node, axi   | FIBROSARCOMA            | 0      | 0      | 1    | 0    | 0. 6271   | 0. 4943 | .       |
|                    | LYMPHOMA                | 0      | 1      | 1    | 1    | 0. 4921   | 0. 7529 | 0. 6591 |
| l ymph node, hep   | LYMPHOMA                | 0      | 1      | 2    | 2    | 0. 2500   | 0. 5000 | 0. 3696 |
|                    | SARCOMA, HI STI OCYTI C | 0      | 0      | 0    | 1    | 0. 2627   | .       | 0. 4133 |
| l ymph node, ili   | LYMPHOMA                | 1      | 0      | 3    | 0    | 0. 6462   | 0. 1250 | .       |
|                    | SARCOMA, ENDOMETRI AL   | 0      | 0      | 0    | 1    | 0. 2627   | .       | 0. 4133 |
| l ymph node, ing   | HEMANGI OSARCOMA        | 0      | 0      | 1    | 0    | 0. 6271   | 0. 4943 | .       |
|                    | LYMPHOMA                | 0      | 1      | 1    | 0    | 0. 8653   | 0. 7529 | 1. 0000 |
| l ymph node, man   | LYMPHOMA                | 3      | 7      | 6    | 6    | 0. 3458   | 0. 7245 | 0. 4783 |
|                    | SARCOMA, HI STI OCYTI C | 0      | 1      | 0    | 1    | 0. 4581   | 1. 0000 | 0. 6591 |
| l ymph node, med   | CARCI NOMA, BRONCHI OL  | 1      | 1      | 0    | 0    | 1. 0000   | 1. 0000 | 1. 0000 |
|                    | LYMPHOMA                | 1      | 2      | 1    | 1    | 0. 6645   | 0. 8793 | 0. 8116 |
| l ymph node, mes   | LYMPHOMA                | 4      | 8      | 6    | 5    | 0. 5854   | 0. 8077 | 0. 7130 |
|                    | SARCOMA, HI STI OCYTI C | 1      | 3      | 0    | 2    | 0. 4106   | 1. 0000 | 0. 6839 |
|                    | SEX-CORD/STROMAL TUM    | 0      | 0      | 1    | 0    | 0. 6271   | 0. 4943 | .       |

**Table 3B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Using Placebo Control Excluding Interim Sacrifice Female Mice**

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |            | Untrtd       | Placeb       | 3 %         | 10 %        | P-Val ue  |         |         |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|--------------|--------------|-------------|-------------|-----------|---------|---------|
| Organ Name                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Tumor Name | Cont<br>N=59 | Cont<br>N=60 | Low<br>N=60 | Med<br>N=48 | Dose Resp | PC vs L | PC vs M |
| %%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%% |            |              |              |             |             |           |         |         |

## Female Mice

[illegible]



## Female Mice

[illegible]

### Male Mice

[illegible]

### Male Mice

[illegible]

**Table 4A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons  
Using Placebo Control Including Interim Sacrifice  
Male Mice**

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |            | Untrtd       | Placeb       | 3 %         | 10 %        | P-Val ue  |         |         |
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| Organ Name                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Tumor Name | Cont<br>N=58 | Cont<br>N=59 | Low<br>N=59 | Med<br>N=50 | Dose Resp | PC vs L | PC vs M |
| ))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))))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|            |              |              |             |             |           |         |         |

**Table 4A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons  
Using Placebo Control Including Interim Sacrifice  
Male Mice**

|                   |                       | Untrtd       | Placeb       | 3 %         | 10 %        | P-Val ue  |         |         |
|-------------------|-----------------------|--------------|--------------|-------------|-------------|-----------|---------|---------|
| Organ Name        | Tumor Name            | Cont<br>N=58 | Cont<br>N=59 | Low<br>N=59 | Med<br>N=50 | Dose Resp | PC vs L | PC vs M |
| trachea           | LYMPHOMA              | 0            | 0            | 3           | 1           | 0.3931    | 0.1437  | 0.4667  |
| ureters           | LEUKEMI A, GRANULOCYT | 0            | 0            | 1           | 0           | 0.6610    | 0.5238  | .       |
|                   | LYMPHOMA              | 1            | 3            | 5           | 0           | 0.9511    | 0.4093  | 1.0000  |
| uri nary bl adder | LYMPHOMA              | 0            | 2            | 4           | 1           | 0.7464    | 0.3948  | 0.8484  |

## Female Mice

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Female Mice

~~~~~

## Female Mice

[illegible]



**Table 4B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Using Placebo Control Including Interim Sacrifice Female Mice**

|                 |                      | Untrt'd | Placebo | 3 %  | 10 % | P-Value   |         |         |
|-----------------|----------------------|---------|---------|------|------|-----------|---------|---------|
| Organ Name      | Tumor Name           | N=59    | N=60    | N=60 | N=51 | Dose Resp | PC vs L | PC vs M |
|                 |                      |         |         |      |      |           |         |         |
| skin, treated   | LYMPHOMA             | 2       | 4       | 3    | 2    | 0.6787    | 0.7830  | 0.8007  |
|                 | SARCOMA, HISTIOCYTIC | 0       | 1       | 0    | 0    | 1.0000    | 1.0000  | 1.0000  |
|                 |                      |         |         |      |      |           |         |         |
| skin, untreated | CARCINOMA, SQUAMOUS  | 1       | 0       | 1    | 0    | 0.6271    | 0.4943  | .       |
|                 | KERATOACANTHOMA      | 0       | 1       | 0    | 0    | 1.0000    | 1.0000  | 1.0000  |
|                 | LYMPHOMA             | 1       | 2       | 3    | 0    | 0.8895    | 0.5000  | 1.0000  |
|                 |                      |         |         |      |      |           |         |         |
| small intestine | LYMPHOMA             | 1       | 0       | 1    | 0    | 0.6303    | 0.5000  | .       |
|                 |                      |         | 1       | 0    | 1    | 0.4548    | 1.0000  | 0.6526  |
|                 |                      | 2       | 1       | 0    | 0    | 1.0000    | 1.0000  | 1.0000  |
|                 | POLYP, GLANDULAR     | 0       | 0       | 1    | 0    | 0.6271    | 0.4943  | .       |
|                 | SCHWANNOMA           | 0       | 0       | 1    | 0    | 0.6303    | 0.5000  | .       |
|                 |                      |         |         |      |      |           |         |         |
| spinal cord, ce | LYMPHOMA             | 0       | 1       | 2    | 0    | 0.7996    | 0.5000  | 1.0000  |
|                 |                      |         |         |      |      |           |         |         |
| spinal cord, lu | LYMPHOMA             | 0       | 1       | 0    | 1    | 0.4581    | 1.0000  | 0.6591  |
|                 |                      |         |         |      |      |           |         |         |
| spinal cord, th | LYMPHOMA             | 0       | 1       | 1    | 0    | 0.8630    | 0.7471  | 1.0000  |
|                 |                      |         |         |      |      |           |         |         |
| spleen          | HEMANGIOSARCOMA      | 1       | 0       | 2    | 0    | 0.5889    | 0.2414  | .       |
|                 | LYMPHOMA             | 4       | 10      | 6    | 6    | 0.6241    | 0.9161  | 0.7671  |
|                 | SARCOMA, HISTIOCYTIC | 0       | 1       | 0    | 2    | 0.1684    | 1.0000  | 0.3696  |
|                 |                      |         |         |      |      |           |         |         |
| stomach, glandu | LYMPHOMA             | 3       | 3       | 4    | 2    | 0.5938    | 0.5127  | 0.7061  |
|                 | SARCOMA, HISTIOCYTIC | 0       | 1       | 0    | 1    | 0.4548    | 1.0000  | 0.6526  |
|                 | SEX-CORD/STROMAL TUM | 0       | 0       | 1    | 0    | 0.6271    | 0.4943  | .       |
|                 |                      |         |         |      |      |           |         |         |
| stomach, nongla | LYMPHOMA             | 0       | 2       | 3    | 0    | 0.8934    | 0.5108  | 1.0000  |
|                 | SARCOMA, HISTIOCYTIC | 0       | 1       | 0    | 1    | 0.4581    | 1.0000  | 0.6591  |
|                 |                      |         |         |      |      |           |         |         |
| tail            | HEMANGIOSARCOMA      | 0       | 0       | 1    | 0    | 0.6303    | 0.5000  | .       |
|                 |                      |         |         |      |      |           |         |         |
| thymus          | CARCINOMA, BRONCHIOL | 2       | 1       | 0    | 0    | 1.0000    | 1.0000  | 1.0000  |
|                 | LYMPHOMA             | 5       | 12      | 4    | 9    | 0.3980    | 0.9935  | 0.6411  |
|                 | SARCOMA, HISTIOCYTIC | 1       | 1       | 0    | 1    | 0.4581    | 1.0000  | 0.6591  |
|                 |                      |         |         |      |      |           |         |         |
| thyroid gland   | ADENOMA, FOLLICULAR  | 0       | 0       | 0    | 1    | 0.2689    | .       | 0.4211  |
|                 | LYMPHOMA             | 2       | 4       | 2    | 2    | 0.6550    | 0.8935  | 0.8007  |
|                 | SARCOMA, HISTIOCYTIC | 0       | 1       | 0    | 0    | 1.0000    | 1.0000  | 1.0000  |
|                 |                      |         |         |      |      |           |         |         |
| tongue          | LYMPHOMA             | 1       | 3       | 3    | 2    | 0.5642    | 0.6617  | 0.6968  |
|                 |                      |         |         |      |      |           |         |         |
| trachea         | LYMPHOMA             | 1       | 2       | 1    | 1    | 0.6492    | 0.8750  | 0.7982  |
|                 | SARCOMA, HISTIOCYTIC | 0       | 1       | 0    | 0    | 1.0000    | 1.0000  | 1.0000  |
|                 |                      |         |         |      |      |           |         |         |
| ureters         | LYMPHOMA             | 5       | 8       | 5    | 5    | 0.5421    | 0.8764  | 0.6925  |
|                 | SARCOMA, HISTIOCYTIC | 0       | 0       | 0    | 1    | 0.2627    | .       | 0.4133  |
|                 |                      |         |         |      |      |           |         |         |
| urinary bladder | LYMPHOMA             | 3       | 5       | 6    | 2    | 0.8001    | 0.5158  | 0.8727  |
|                 | SARCOMA, ENDOMETRIAL | 0       | 0       | 0    | 1    | 0.2627    | .       | 0.4133  |

## Female Mice

[illegible]

**Table 5A: Comparison of Placebo and Untreated Controls  
Male Mice Excluding Interim Sacrifice**

|                                                                  |                        | Untreat      | Placeb       |                      |
|------------------------------------------------------------------|------------------------|--------------|--------------|----------------------|
| Organ Name                                                       | Tumor Name             | Cont<br>N=57 | Cont<br>N=58 | P_Val ue<br>PC vs UC |
| ffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffff |                        |              |              |                      |
| adrenal glands                                                   | LEI OMYOSARCOMA        | 1            | 0            | 0. 5294              |
|                                                                  | LEUKEMI A, GRANULOCYT  | 0            | 0            | .                    |
|                                                                  | LYMPHOMA               | 3            | 2            | 0. 5652              |
| aorta                                                            | CARCI NOMA, BRONCHI OL | 1            | 0            | 0. 5294              |
|                                                                  | LEI OMYOSARCOMA        | 1            | 0            | 0. 5294              |
|                                                                  | LYMPHOMA               | 2            | 3            | 0. 8469              |
| bone marrow, fe                                                  | HEMANGI OMA            | 1            | 0            | 0. 5294              |
|                                                                  | HEMANGI OSARCOMA       | 1            | 0            | 0. 5294              |
|                                                                  | LEUKEMI A, GRANULOCYT  | 0            | 0            | .                    |
|                                                                  | LYMPHOMA               | 3            | 2            | 0. 5652              |
| bone marrow, st                                                  | LEUKEMI A, GRANULOCYT  | 0            | 0            | .                    |
|                                                                  | LYMPHOMA               | 3            | 2            | 0. 5652              |
| bone, femur                                                      | LYMPHOMA               | 1            | 0            | 0. 5349              |
| bone, sternum                                                    | LYMPHOMA               | 3            | 2            | 0. 5538              |
| brain                                                            | ASTROCYTOMA            | 1            | 0            | 0. 5294              |
|                                                                  | LYMPHOMA               | 0            | 0            | .                    |
| cavi ty, abdomi n                                                | CARCI NOMA, BRONCHI OL | 1            | 0            | 0. 5294              |
|                                                                  | LYMPHOMA               | 0            | 1            | 1. 0000              |
| cavi ty, thoraci                                                 | CARCI NOMA, BRONCHI OL | 1            | 0            | 0. 5294              |
| epi di dymi des                                                  | LEI OMYOSARCOMA        | 1            | 0            | 0. 5294              |
|                                                                  | LYMPHOMA               | 2            | 2            | 0. 7342              |
| esophagus                                                        | LYMPHOMA               | 0            | 0            | .                    |
| eyes                                                             | LYMPHOMA               | 1            | 2            | 0. 8958              |
| gal l bl adder                                                   | LYMPHOMA               | 1            | 0            | 0. 5294              |
| harder ian gland                                                 | ADENOMA                | 0            | 0            | .                    |
| heart                                                            | CARCI NOMA, BRONCHI OL | 1            | 0            | 0. 5294              |
|                                                                  | HEMANGI OMA            | 0            | 0            | .                    |
|                                                                  | HEMANGI OSARCOMA       | 1            | 0            | 0. 5294              |
|                                                                  | LYMPHOMA               | 3            | 3            | 0. 7140              |
| ki dneys                                                         | ADENOMA, TUBULAR CEL   | 1            | 0            | 0. 5294              |
|                                                                  | CARCI NOMA, TUBULAR C  | 1            | 0            | 0. 5294              |
|                                                                  | HEMANGI OMA            | 0            | 1            | 1. 0000              |
|                                                                  | LEI OMYOSARCOMA        | 1            | 0            | 0. 5294              |
|                                                                  | LEUKEMI A, GRANULOCYT  | 0            | 0            | .                    |
|                                                                  | LYMPHOMA               | 4            | 2            | 0. 4057              |

**Table 5A: Comparison of Placebo and Untreated Controls**  
**Male Mice Excluding Interim Sacrifice**

| Organ Name         | Tumor Name              | Untreat   | Placeb    | P_Val ue |
|--------------------|-------------------------|-----------|-----------|----------|
|                    |                         | Cont N=58 | Cont N=57 |          |
| l acri mal gl ands | LEUKEMI A, GRANULOCYT   | 0         | 0         | .        |
|                    | LYMPHOMA                | 3         | 3         | 0. 7140  |
| l arge i ntesti ne | LEI OMYOSARCOMA         | 1         | 0         | 0. 5294  |
|                    | LYMPHOMA                | 0         | 1         | 1. 0000  |
|                    |                         | 1         | 1         | 0. 7756  |
| l arynx            | LYMPHOMA                | 1         | 1         | 0. 7756  |
|                    |                         |           |           |          |
| l i ver            | ADENOMA, HEPATOCELLU    | 11        | 14        | 0. 8266  |
|                    | CARCI NOMA, HEPATOCEL   | 1         | 0         | 0. 5294  |
|                    | ADEN+CAR, HEPATOCELL    | 12        | 14        | 0. 7571  |
|                    | HEMANGI OSARCOMA        | 2         | 5         | 0. 9608  |
|                    | LEI OMYOSARCOMA         | 1         | 0         | 0. 5294  |
|                    | LEUKEMI A, GRANULOCYT   | 0         | 0         | .        |
|                    | LYMPHOMA                | 3         | 2         | 0. 5652  |
|                    | SARCOMA, HI STI OCYTI C | 0         | 0         | .        |
| l ung              | ADENOMA, BRONCHI OLAR   | 5         | 5         | 0. 7291  |
|                    | CARCI NOMA, BRONCHI OL  | 8         | 7         | 0. 5775  |
|                    | ADEN+CAR, BRONCHI OLA   | 11        | 12        | 0. 8040  |
|                    | CARCI NOMA, HEPATOCEL   | 0         | 0         | .        |
|                    | LEI OMYOSARCOMA         | 1         | 0         | 0. 5294  |
|                    | LEUKEMI A, GRANULOCYT   | 0         | 0         | .        |
|                    | LYMPHOMA                | 3         | 4         | 0. 8268  |
|                    | SARCOMA, HI STI OCYTI C | 0         | 0         | .        |
| l ymph node, axi   | LYMPHOMA                | 1         | 0         | 0. 5294  |
|                    |                         |           |           |          |
| l ymph node, hep   | LEUKEMI A, GRANULOCYT   | 0         | 0         | .        |
|                    | LYMPHOMA                | 1         | 0         | 0. 5294  |
|                    | SARCOMA, HI STI OCYTI C | 0         | 0         | .        |
| l ymph node, ili   | LYMPHOMA                | 1         | 1         | 0. 7756  |
|                    |                         |           |           |          |
| l ymph node, man   | LEUKEMI A, GRANULOCYT   | 0         | 0         | .        |
|                    | LYMPHOMA                | 3         | 3         | 0. 7140  |
| l ymph node, med   | CARCI NOMA, BRONCHI OL  | 1         | 0         | 0. 5294  |
|                    | LYMPHOMA                | 1         | 0         | 0. 5294  |
| l ymph node, mes   | LEUKEMI A, GRANULOCYT   | 0         | 0         | .        |
|                    | LYMPHOMA                | 3         | 3         | 0. 7140  |
|                    | SARCOMA, HI STI OCYTI C | 0         | 0         | .        |
| l ymph node, ren   | LYMPHOMA                | 2         | 0         | 0. 2832  |
|                    |                         |           |           |          |
| mul ti centric ne  | HEMANGI OMA             | 1         | 1         | 0. 7815  |
|                    | HEMANGI OSARCOMA        | 3         | 5         | 0. 9010  |
|                    | LEUKEMI A, GRANULOCYT   | 0         | 0         | .        |
|                    | LYMPHOMA                | 4         | 5         | 0. 8003  |
|                    | SARCOMA, HI STI OCYTI C | 0         | 0         | .        |

**Table 5A: Comparison of Placebo and Untreated Controls**  
**Male Mice Excluding Interim Sacrifice**

| Organ Name      | Tumor Name             | Untreat      | Placeb       | P_Val ue<br>PC vs UC |
|-----------------|------------------------|--------------|--------------|----------------------|
|                 |                        | Cont<br>N=58 | Cont<br>N=57 |                      |
| nerve, sciatic  | LYMPHOMA               | 0            | 1            | 1.0000               |
| pancreas        | HEMANGI OSARCOMA       | 1            | 0            | 0.5294               |
|                 | LEI OMYOSARCOMA        | 1            | 0            | 0.5294               |
|                 | LEUKEMI A, GRANULOCYTO | 0            | 0            | .                    |
|                 | LYMPHOMA               | 2            | 2            | 0.7342               |
|                 | SARCOMA, HISTIOCYTIC   | 0            | 0            | .                    |
| peyers patch    | LYMPHOMA               | 0            | 1            | 1.0000               |
| pituitary gland | LYMPHOMA               | 1            | 1            | 0.7808               |
| preputial gland | LEUKEMI A, GRANULOCYTO | 0            | 0            | .                    |
| prostate gland  | LYMPHOMA               | 0            | 1            | 1.0000               |
| salivary gland, | LYMPHOMA               | 0            | 1            | 1.0000               |
|                 |                        | 1            | 1            | 0.7756               |
|                 |                        | 2            | 2            | 0.7342               |
| seminal vesicle | LEI OMYOSARCOMA        | 1            | 0            | 0.5294               |
|                 | LYMPHOMA               | 0            | 2            | 1.0000               |
| skeletal muscle | LYMPHOMA               | 0            | 1            | 1.0000               |
| skin, subcutis  | FIBROUS HISTIOCYTOMA   | 0            | 1            | 1.0000               |
| skin, treated   | HIBERNOMA              | 0            | 1            | 1.0000               |
|                 | LYMPHOMA               | 1            | 2            | 0.8994               |
| skin, untreated | LEI OMYOSARCOMA        | 1            | 0            | 0.5294               |
|                 | LYMPHOMA               | 1            | 2            | 0.8958               |
|                 | PAPILLOMA, SQUAMOUS    | 0            | 0            | .                    |
| small intestine | LYMPHOMA               | 0            | 0            | .                    |
|                 |                        |              | 1            | 1.0000               |
| spinal cord, ce | LYMPHOMA               | 0            | 0            | .                    |
| spinal cord, th | LYMPHOMA               | 0            | 0            | .                    |
| spleen          | HEMANGI OSARCOMA       | 1            | 1            | 0.7756               |
|                 | LEUKEMI A, GRANULOCYTO | 0            | 0            | .                    |
|                 | LYMPHOMA               | 3            | 3            | 0.7140               |
| stomach, glandu | LEI OMYOSARCOMA        | 1            | 0            | 0.5294               |
|                 | LEUKEMI A, GRANULOCYTO | 0            | 0            | .                    |
|                 | LYMPHOMA               | 3            | 2            | 0.5652               |
| stomach, nongla | LYMPHOMA               | 1            | 0            | 0.5294               |

**Table 5A: Comparison of Placebo and Untreated Controls**  
**Male Mice Excluding Interim Sacrifice**

|                   |                         | Untreat      | Placeb       |                      |
|-------------------|-------------------------|--------------|--------------|----------------------|
| Organ Name        | Tumor Name              | Cont<br>N=58 | Cont<br>N=57 | P_Val ue<br>PC vs UC |
| testes            | ADENOMA, I NTERSTI TIA  | 2            | 1            | 0.5353               |
|                   | LYMPHOMA                | 1            | 2            | 0.8994               |
| thymus            | LEUKEMI A, GRANULOCYT   | 0            | 0            | .                    |
|                   | LYMPHOMA                | 2            | 3            | 0.8469               |
| thyroi d gland    | LYMPHOMA                | 2            | 1            | 0.5436               |
|                   | SARCOMA, HI STI OCYTI C | 0            | 0            | .                    |
| tongue            | LYMPHOMA                | 1            | 0            | 0.5294               |
| trachea           | LYMPHOMA                | 0            | 0            | .                    |
| ureters           | LEI OMYOSARCOMA         | 1            | 0            | 0.5294               |
|                   | LEUKEMI A, GRANULOCYT   | 0            | 0            | .                    |
|                   | LYMPHOMA                | 1            | 3            | 0.9497               |
| uri nary bl adder | LYMPHOMA                | 0            | 2            | 1.0000               |

**Table 5B: Comparison of Placebo and Untreated Controls**  
**Female Mice Excluding Interim Sacrifice**

| Organ Name       | Tumor Name            | Untreat      | Placeb       | P_Val ue<br>PC vs UC |
|------------------|-----------------------|--------------|--------------|----------------------|
|                  |                       | Cont<br>N=59 | Cont<br>N=60 |                      |
| adipose tissue   | LYMPHOMA              | 1            | 0            | 0.5000               |
| adrenal glands   | ADENOMA, SUBCAPSULAR  | 2            | 1            | 0.5000               |
|                  | CARCINOMA, YOLK SAC   | 1            | 0            | 0.4943               |
|                  | LYMPHOMA              | 4            | 5            | 0.7685               |
|                  | PHEOCHROMOCYTOMA      | 1            | 1            | 0.7471               |
| aorta            | CARCINOMA, BRONCHIOLO | 0            | 2            | 1.0000               |
|                  | CARCINOMA, YOLK SAC   | 1            | 0            | 0.4943               |
|                  | LYMPHOMA              | 3            | 5            | 0.8737               |
|                  | SARCOMA, HISTIOCYTIC  | 0            | 1            | 1.0000               |
| bone             | OSTEOSARCOMA          | 0            | 0            | .                    |
| bone marrow, fem | FIBROSARCOMA          | 0            | 0            | .                    |
|                  | HEMANGIOSARCOMA       | 1            | 0            | 0.5000               |
|                  | LYMPHOMA              | 1            | 4            | 0.9706               |
|                  | SARCOMA, HISTIOCYTIC  | 0            | 2            | 1.0000               |
| bone marrow, st  | LYMPHOMA              | 0            | 3            | 1.0000               |
|                  | SARCOMA, HISTIOCYTIC  | 0            | 2            | 1.0000               |
| bone, femur      | LYMPHOMA              | 1            | 2            | 0.8793               |
|                  | OSTEOMA               | 0            | 1            | 1.0000               |
| bone, mandible   | OSTEOSARCOMA          | 1            | 0            | 0.4943               |
| bone, sternum    | LYMPHOMA              | 2            | 5            | 0.9449               |
|                  | SARCOMA, HISTIOCYTIC  | 0            | 1            | 1.0000               |
| brain            | LYMPHOMA              | 0            | 2            | 1.0000               |
| cavity, abdomin  | FIBROSARCOMA          | 1            | 0            | 0.5000               |
|                  | HEMANGIOSARCOMA       | 1            | 0            | 0.5000               |
|                  | LYMPHOMA              | 1            | 0            | 0.5000               |
|                  | SEX-CORD/STROMAL TUM  | 0            | 0            | .                    |
| cavity, thoraci  | LYMPHOMA              | 0            | 0            | .                    |
| esophagus        | LYMPHOMA              | 0            | 2            | 1.0000               |
| eyes             | LYMPHOMA              | 2            | 1            | 0.5085               |
| eyes, optic ner  | LYMPHOMA              | 0            | 1            | 1.0000               |
| gallbladder      | FIBROMA               | 0            | 1            | 1.0000               |
|                  | LYMPHOMA              | 1            | 4            | 0.9723               |
| harderian gland  | ADENOMA               | 2            | 1            | 0.5000               |
| heart            | CARCINOMA, BRONCHIOLO | 1            | 1            | 0.7471               |

**Table 5B: Comparison of Placebo and Untreated Controls**  
**Female Mice Excluding Interim Sacrifice**

|                  |                         | Untreat   | Placeb    |                   |
|------------------|-------------------------|-----------|-----------|-------------------|
| Organ Name       | Tumor Name              | Cont N=59 | Cont N=60 | P_Val ue PC vs UC |
| heart            | CARCI NOMA, YOLK SAC    | 1         | 0         | 0.4943            |
|                  | LYMPHOMA                | 3         | 8         | 0.9728            |
|                  | SARCOMA, HI STI OCYTI C | 1         | 0         | 0.5000            |
| joint, tibi ofem | LYMPHOMA                | 0         | 1         | 1.0000            |
|                  | SARCOMA, HI STI OCYTI C | 0         | 1         | 1.0000            |
| ki dneys         | LYMPHOMA                | 5         | 10        | 0.9599            |
|                  | SARCOMA, HI STI OCYTI C | 2         | 2         | 0.6833            |
|                  | SEX-CORD/STROMAL TUM    | 0         | 0         | .                 |
| lacri mal glands | LYMPHOMA                | 3         | 5         | 0.8668            |
|                  | SARCOMA, HI STI OCYTI C | 0         | 1         | 1.0000            |
| large intestine  | LYMPHOMA                | 1         | 0         | 0.5000            |
|                  |                         | 2         | 1         | 0.5085            |
|                  |                         | 3         | 1         | 0.3167            |
| larynx           | LYMPHOMA                | 2         | 3         | 0.8196            |
|                  | SARCOMA, HI STI OCYTI C | 0         | 1         | 1.0000            |
| liver            | ADENOMA, HEPATOCELLU    | 0         | 1         | 1.0000            |
|                  | CARCI NOMA, HEPATOCEL   | 0         | 2         | 1.0000            |
|                  | ADEN+CAR, HEPATOCELL    | 0         | 3         | 1.0000            |
|                  | HEMANGI OMA             | 0         | 0         | .                 |
|                  | HEMANGI OSARCOMA        | 3         | 2         | 0.4892            |
|                  | LYMPHOMA                | 3         | 9         | 0.9852            |
|                  | SARCOMA, HI STI OCYTI C | 2         | 5         | 0.9377            |
| lung             | ADENOMA, BRONCHI OLAR   | 3         | 7         | 0.9477            |
|                  | CARCI NOMA, BRONCHI OL  | 7         | 6         | 0.4823            |
|                  | ADEN+CAR, BRONCHI OLA   | 9         | 12        | 0.8105            |
|                  | CARCI NOMA, YOLK SAC    | 1         | 0         | 0.4943            |
|                  | LYMPHOMA                | 3         | 11        | 0.9959            |
|                  | SARCOMA, HI STI OCYTI C | 1         | 5         | 0.9850            |
| lymph node, axi  | FIBROSARCOMA            | 0         | 0         | .                 |
|                  | LYMPHOMA                | 0         | 1         | 1.0000            |
| lymph node, hep  | LYMPHOMA                | 0         | 1         | 1.0000            |
| lymph node, ili  | LYMPHOMA                | 1         | 0         | 0.5000            |
| lymph node, ing  | HEMANGI OSARCOMA        | 0         | 0         | .                 |
|                  | LYMPHOMA                | 0         | 1         | 1.0000            |
| lymph node, man  | LYMPHOMA                | 3         | 7         | 0.9515            |
|                  | SARCOMA, HI STI OCYTI C | 0         | 1         | 1.0000            |
| lymph node, med  | CARCI NOMA, BRONCHI OL  | 1         | 1         | 0.7529            |
|                  | LYMPHOMA                | 1         | 2         | 0.8793            |
| lymph node, mes  | LYMPHOMA                | 4         | 8         | 0.9405            |



| Organ Name        | Tumor Name             | Untreated | Placebo | P-Value          |
|-------------------|------------------------|-----------|---------|------------------|
|                   |                        | N=59      | N=60    | PC vs UC         |
| <i>ffffffffff</i> |                        |           |         |                  |
| lymph node, mes   | SARCOMA, HI STI OCYTIC | 1         | 3       | 0.9390           |
|                   | SEX-CORD/STROMAL TUM   | 0         | 0       | .                |
| lymph node, ren   | LYMPHOMA               | 1         | 1       | 0.7529           |
| lymph node, tra   | LYMPHOMA               | 0         | 1       | 1.0000           |
| mammary gland     | ADENOCARCINOMA         | 1         | 0       | 0.5000           |
|                   | LYMPHOMA               | 4         | 4       | 0.6555           |
|                   | SARCOMA, HI STI OCYTIC | 0         | 1       | 1.0000           |
| mesentery/perit   | LYMPHOMA               | 0         | 0       | .                |
| multicentric ne   | HEMANGIOMA             | 1         | 2       | 0.8750           |
|                   | HEMANGIOSARCOMA        | 3         | 4       | 0.7641           |
|                   | LYMPHOMA               | 5         | 13      | 0.9917           |
|                   | SARCOMA, HI STI OCYTIC | 2         | 5       | 0.9377           |
| nerve, sciatic    | LYMPHOMA               | 2         | 6       | 0.9686           |
|                   | SARCOMA, HI STI OCYTIC | 0         | 1       | 1.0000           |
| ovaries           | ADENOMA, TUBULOSTROM   | 1         | 0       | 0.4943           |
|                   | CARCINOMA, YOLK SAC    | 1         | 0       | 0.4943           |
|                   | CHORIOCARCINOMA        | 0         | 1       | 1.0000           |
|                   | CYSTADENOMA            | 0         | 2       | 1.0000           |
|                   | LYMPHOMA               | 5         | 9       | 0.9272           |
|                   | SARCOMA, HI STI OCYTIC | 1         | 2       | 0.8793           |
|                   | SEX-CORD/STROMAL TUM   | 1         | 1       | 0.7472           |
| oviducts          | LYMPHOMA               | 1         | 1       | 0.7529           |
| pancreas          | CARCINOMA, YOLK SAC    | 1         | 0       | 0.4943           |
|                   | HEMANGIOMA             | 1         | 0       | 0.5000           |
|                   | LYMPHOMA               | 5         | 7       | 0.8332           |
|                   | SARCOMA, HI STI OCYTIC | 1         | 1       | 0.7529           |
|                   | SCHWANNOMA             | 0         | 0       | .                |
| peyers patch      | LYMPHOMA               | 1         | 1       | 0.7472           |
|                   | SARCOMA, HI STI OCYTIC | 0         | 1       | 1.0000           |
| pituitary gland   | ADENOMA, PARASITIAL    | 1         | 1       | 0.7471           |
|                   | ADENOMA, PARSINTERM    | 0         | 2       | 1.0000           |
|                   | LYMPHOMA               | 0         | 0       | .                |
| salivary gland,   | LYMPHOMA               | 2         | 1       | 0.5085           |
|                   |                        | 3         | 3       | 0.6617           |
|                   | SARCOMA, HI STI OCYTIC | 0         | 1       | 0.6725<br>1.0000 |
| skeletal muscle   | LYMPHOMA               | 1         | 2       | 0.8750           |

**Table 5B: Comparison of Placebo and Untreated Controls**  
**Female Mice Excluding Interim Sacrifice**

|                 |                      | Untreat      | P laceb      |                      |
|-----------------|----------------------|--------------|--------------|----------------------|
| Organ Name      | Tumor Name           | N=59<br>Cont | N=60<br>Cont | P_Val ue<br>PC vs UC |
| skin, subcutis  | FIBROSARCOMA         | 0            | 0            | .                    |
|                 | HEMANGIOSARCOMA      | 0            | 0            | .                    |
|                 | OSTEOSARCOMA         | 0            | 0            | .                    |
|                 | SCHWANNOMA           | 0            | 0            | .                    |
| skin, treated   | CARCINOMA, YOLK SAC  | 1            | 0            | 0.4943               |
|                 | LYMPHOMA             | 2            | 4            | 0.8986               |
|                 | SARCOMA, HISTIOCYTIC | 0            | 1            | 1.0000               |
| skin, untreated | CARCINOMA, SQUAMOUS  | 1            | 0            | 0.5000               |
|                 | KERATOACANTHOMA      | 0            | 1            | 1.0000               |
|                 | LYMPHOMA             | 1            | 2            | 0.8750               |
| small intestine | LYMPHOMA             | 1            | 0            | 0.5000               |
|                 |                      |              | 1            | 0.7472               |
|                 |                      | 2            | 1            | 0.5000               |
|                 | POLYP, GLANDULAR     | 0            | 0            | .                    |
|                 | SCHWANNOMA           | 0            | 0            | .                    |
| spinal cord, ce | LYMPHOMA             | 0            | 1            | 1.0000               |
| spinal cord, lu | LYMPHOMA             | 0            | 1            | 1.0000               |
| spinal cord, th | LYMPHOMA             | 0            | 1            | 1.0000               |
| spleen          | HEMANGIOSARCOMA      | 1            | 0            | 0.5000               |
|                 | LYMPHOMA             | 4            | 10           | 0.9803               |
|                 | SARCOMA, HISTIOCYTIC | 0            | 1            | 1.0000               |
| stomach, glandu | CARCINOMA, YOLK SAC  | 1            | 0            | 0.4943               |
|                 | LYMPHOMA             | 3            | 3            | 0.6725               |
|                 | SARCOMA, HISTIOCYTIC | 0            | 1            | 1.0000               |
|                 | SEX-CORD/STROMAL TUM | 0            | 0            | .                    |
| stomach, nongla | LYMPHOMA             | 0            | 2            | 1.0000               |
|                 | SARCOMA, HISTIOCYTIC | 0            | 1            | 1.0000               |
| tail            | HEMANGIOSARCOMA      | 0            | 0            | .                    |
| thymus          | CARCINOMA, BRONCHIOL | 2            | 1            | 0.5000               |
|                 | CARCINOMA, YOLK SAC  | 1            | 0            | 0.4943               |
|                 | LYMPHOMA             | 5            | 12           | 0.9869               |
|                 | SARCOMA, HISTIOCYTIC | 1            | 1            | 0.7529               |
| thyroid gland   | LYMPHOMA             | 2            | 4            | 0.8986               |
|                 | SARCOMA, HISTIOCYTIC | 0            | 1            | 1.0000               |
| tongue          | LYMPHOMA             | 1            | 3            | 0.9390               |
| trachea         | LYMPHOMA             | 1            | 2            | 0.8750               |
|                 | SARCOMA, HISTIOCYTIC | 0            | 1            | 1.0000               |

**Table 5B: Comparison of Placebo and Untreated Controls**  
**Female Mice Excluding Interim Sacrifice**

|                  |                         | Untreat      | Placeb       |                      |
|------------------|-------------------------|--------------|--------------|----------------------|
| Organ Name       | Tumor Name              | Cont<br>N=59 | Cont<br>N=60 | P_Val ue<br>PC vs UC |
| ureters          | LYMPHOMA                | 5            | 8            | 0.8925               |
| uri nary bladder | CARCI NOMA, YOLK SAC    | 1            | 0            | 0.4943               |
|                  | LYMPHOMA                | 3            | 5            | 0.8668               |
|                  | SARCOMA, HI STI OCYTI C | 0            | 1            | 1.0000               |
| uterus wi th cer | ADENOCARCI NOMA         | 0            | 1            | 1.0000               |
|                  | CARCI NOMA, YOLK SAC    | 1            | 0            | 0.4943               |
|                  | FIBROSARCOMA            | 0            | 0            | .                    |
|                  | HEMANGI OMA             | 0            | 2            | 1.0000               |
|                  | HEMANGI OSARCOMA        | 0            | 2            | 1.0000               |
|                  | LEI OMYOMA              | 0            | 1            | 1.0000               |
|                  | LEI OMYOSARCOMA         | 0            | 0            | .                    |
|                  | LYMPHOMA                | 5            | 4            | 0.5280               |
|                  | POLYP, ENDOMETRI AL S   | 8            | 3            | 0.0914               |
|                  | SARCOMA, ENDOMETRI AL   | 2            | 3            | 0.8053               |
|                  | SARCOMA, HI STI OCYTI C | 2            | 2            | 0.6833               |
|                  | SCHWANNOMA              | 0            | 0            | .                    |
|                  | SEX-CORD/STROMAL TUM    | 0            | 0            | .                    |
| vagi na          | LYMPHOMA                | 2            | 3            | 0.8267               |
|                  | POLYP                   | 0            | 1            | 1.0000               |

**Table 6A: Comparison of Placebo and Untreated Controls  
Male Mice Including Interim Sacrifice**

|                                                                  |                        | Untreat      | Placeb       |                      |
|------------------------------------------------------------------|------------------------|--------------|--------------|----------------------|
| Organ Name                                                       | Tumor Name             | Cont<br>N=58 | Cont<br>N=59 | P_Val ue<br>PC vs UC |
| ffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffff |                        |              |              |                      |
| adrenal glands                                                   | LEI OMYOSARCOMA        | 1            | 0            | 0. 5294              |
|                                                                  | LEUKEMI A, GRANULOCYT  | 0            | 0            | .                    |
|                                                                  | LYMPHOMA               | 3            | 2            | 0. 5652              |
| aorta                                                            | CARCI NOMA, BRONCHI OL | 1            | 0            | 0. 5294              |
|                                                                  | LEI OMYOSARCOMA        | 1            | 0            | 0. 5294              |
|                                                                  | LYMPHOMA               | 2            | 3            | 0. 8469              |
| bone marrow, fe                                                  | HEMANGI OMA            | 1            | 0            | 0. 5294              |
|                                                                  | HEMANGI OSARCOMA       | 1            | 0            | 0. 5294              |
|                                                                  | LEUKEMI A, GRANULOCYT  | 0            | 0            | .                    |
|                                                                  | LYMPHOMA               | 3            | 2            | 0. 5652              |
| bone marrow, st                                                  | LEUKEMI A, GRANULOCYT  | 0            | 0            | .                    |
|                                                                  | LYMPHOMA               | 3            | 2            | 0. 5652              |
| bone, femur                                                      | LYMPHOMA               | 1            | 0            | 0. 5349              |
| bone, sternum                                                    | LYMPHOMA               | 3            | 2            | 0. 5538              |
| brai n                                                           | ASTROCYTOMA            | 1            | 0            | 0. 5294              |
|                                                                  | LYMPHOMA               | 0            | 0            | .                    |
| cavi ty, abdomi n                                                | CARCI NOMA, BRONCHI OL | 1            | 0            | 0. 5294              |
|                                                                  | LYMPHOMA               | 0            | 1            | 1. 0000              |
| cavi ty, thoraci                                                 | CARCI NOMA, BRONCHI OL | 1            | 0            | 0. 5294              |
| epi di dymi des                                                  | LEI OMYOSARCOMA        | 1            | 0            | 0. 5294              |
|                                                                  | LYMPHOMA               | 2            | 2            | 0. 7342              |
| esophagus                                                        | LYMPHOMA               | 0            | 0            | .                    |
| eyes                                                             | LYMPHOMA               | 1            | 2            | 0. 8958              |
| gal l bl adder                                                   | LYMPHOMA               | 1            | 0            | 0. 5294              |
| harder ian gland                                                 | ADENOMA                | 0            | 0            | .                    |
| heart                                                            | CARCI NOMA, BRONCHI OL | 1            | 0            | 0. 5294              |
|                                                                  | HEMANGI OMA            | 0            | 0            | .                    |
|                                                                  | HEMANGI OSARCOMA       | 1            | 0            | 0. 5294              |
|                                                                  | LYMPHOMA               | 3            | 3            | 0. 7140              |
| ki dneys                                                         | ADENOMA, TUBULAR CEL   | 1            | 0            | 0. 5294              |
|                                                                  | CARCI NOMA, TUBULAR C  | 1            | 0            | 0. 5294              |
|                                                                  | HEMANGI OMA            | 0            | 1            | 1. 0000              |
|                                                                  | LEI OMYOSARCOMA        | 1            | 0            | 0. 5294              |
|                                                                  | LEUKEMI A, GRANULOCYT  | 0            | 0            | .                    |
|                                                                  | LYMPHOMA               | 4            | 2            | 0. 4057              |

**Table 6A: Comparison of Placebo and Untreated Controls  
Male Mice Including Interim Sacrifice**

|                                                                  |                         | Untreat      | Placeb       |                      |
|------------------------------------------------------------------|-------------------------|--------------|--------------|----------------------|
| Organ Name                                                       | Tumor Name              | Cont<br>N=58 | Cont<br>N=59 | P_Val ue<br>PC vs UC |
| ffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffff |                         |              |              |                      |
| Lacrimal glands                                                  | LEUKEMI A, GRANULOCYT   | 0            | 0            | .                    |
|                                                                  | LYMPHOMA                | 3            | 3            | 0. 7140              |
| Large intestine                                                  | LEI OMYOSARCOMA         | 1            | 0            | 0. 5294              |
|                                                                  | LYMPHOMA                | 0            | 1            | 1. 0000              |
|                                                                  |                         | 1            | 1            | 0. 7756              |
| Larynx                                                           | LYMPHOMA                | 1            | 1            | 0. 7756              |
| Liver                                                            | ADENOMA, HEPATOCELLU    | 11           | 14           | 0. 8266              |
|                                                                  | CARCI NOMA, HEPATOCEL   | 1            | 0            | 0. 5294              |
|                                                                  | ADEN+CAR, HEPATOCELL    | 12           | 14           | 0. 7571              |
|                                                                  | HEMANGI OSARCOMA        | 2            | 5            | 0. 9608              |
|                                                                  | LEI OMYOSARCOMA         | 1            | 0            | 0. 5294              |
|                                                                  | LEUKEMI A, GRANULOCYT   | 0            | 0            | .                    |
|                                                                  | LYMPHOMA                | 3            | 2            | 0. 5652              |
|                                                                  | SARCOMA, HI STI OCYTI C | 0            | 0            | .                    |
| Lung                                                             | ADENOMA, BRONCHI OLAR   | 5            | 5            | 0. 7291              |
|                                                                  | CARCI NOMA, BRONCHI OL  | 8            | 7            | 0. 5775              |
|                                                                  | ADEN+CAR, BRONCHI OLA   | 11           | 12           | 0. 8040              |
|                                                                  | CARCI NOMA, HEPATOCEL   | 0            | 0            | .                    |
|                                                                  | LEI OMYOSARCOMA         | 1            | 0            | 0. 5294              |
|                                                                  | LEUKEMI A, GRANULOCYT   | 0            | 0            | .                    |
|                                                                  | LYMPHOMA                | 3            | 4            | 0. 8268              |
|                                                                  | SARCOMA, HI STI OCYTI C | 0            | 0            | .                    |
| Lymph node, axi                                                  | LYMPHOMA                | 1            | 0            | 0. 5294              |
| Lymph node, hep                                                  | LEUKEMI A, GRANULOCYT   | 0            | 0            | .                    |
|                                                                  | LYMPHOMA                | 1            | 0            | 0. 5294              |
|                                                                  | SARCOMA, HI STI OCYTI C | 0            | 0            | .                    |
| Lymph node, ili                                                  | LYMPHOMA                | 1            | 1            | 0. 7756              |
| Lymph node, man                                                  | LEUKEMI A, GRANULOCYT   | 0            | 0            | .                    |
|                                                                  | LYMPHOMA                | 3            | 3            | 0. 7140              |
| Lymph node, med                                                  | CARCI NOMA, BRONCHI OL  | 1            | 0            | 0. 5294              |
|                                                                  | LYMPHOMA                | 1            | 0            | 0. 5294              |
| Lymph node, mes                                                  | LEUKEMI A, GRANULOCYT   | 0            | 0            | .                    |
|                                                                  | LYMPHOMA                | 3            | 3            | 0. 7140              |
|                                                                  | SARCOMA, HI STI OCYTI C | 0            | 0            | .                    |
| Lymph node, ren                                                  | LYMPHOMA                | 2            | 0            | 0. 2832              |
| multicentric ne                                                  | HEMANGI OMA             | 1            | 1            | 0. 7815              |
|                                                                  | HEMANGI OSARCOMA        | 3            | 5            | 0. 9010              |
|                                                                  | LEUKEMI A, GRANULOCYT   | 0            | 0            | .                    |
|                                                                  | LYMPHOMA                | 4            | 5            | 0. 8003              |
|                                                                  | SARCOMA, HI STI OCYTI C | 0            | 0            | .                    |

**Table 6A: Comparison of Placebo and Untreated Controls  
Male Mice Including Interim Sacrifice**

| Organ Name                                                               | Tumor Name            | Untreat Placeb |      | P_Val ue |
|--------------------------------------------------------------------------|-----------------------|----------------|------|----------|
|                                                                          |                       | Cont           | Cont |          |
|                                                                          |                       | N=58           | N=59 | PC vs UC |
| ffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffff |                       |                |      |          |
| nerve, sciatic                                                           | LYMPHOMA              | 0              | 1    | 1.0000   |
| pancreas                                                                 | HEMANGI OSARCOMA      | 1              | 0    | 0.5294   |
|                                                                          | LEI OMYOSARCOMA       | 1              | 0    | 0.5294   |
|                                                                          | LEUKEMI A, GRANULOCYT | 0              | 0    | .        |
|                                                                          | LYMPHOMA              | 2              | 2    | 0.7342   |
|                                                                          | SARCOMA, HISTIOCYTIC  | 0              | 0    | .        |
| peyers patch                                                             | LYMPHOMA              | 0              | 1    | 1.0000   |
| pituitary gland                                                          | LYMPHOMA              | 1              | 1    | 0.7808   |
| preputial gland                                                          | LEUKEMI A, GRANULOCYT | 0              | 0    | .        |
| prostate gland                                                           | LYMPHOMA              | 0              | 1    | 1.0000   |
|                                                                          | LYMPHOMA              | 0              | 1    | 1.0000   |
|                                                                          | LYMPHOMA              | 1              | 1    | 0.7756   |
|                                                                          |                       | 2              | 2    | 0.7342   |
| seminal vesicle                                                          | LEI OMYOSARCOMA       | 1              | 0    | 0.5294   |
|                                                                          | LYMPHOMA              | 0              | 2    | 1.0000   |
| skeletal muscle                                                          | LYMPHOMA              | 0              | 1    | 1.0000   |
| skin, subcutis                                                           | FIBROUS HISTIOCYTOMA  | 0              | 1    | 1.0000   |
| skin, treated                                                            | HIBERNOMA             | 0              | 1    | 1.0000   |
|                                                                          | LYMPHOMA              | 1              | 2    | 0.8994   |
| skin, untreated                                                          | LEI OMYOSARCOMA       | 1              | 0    | 0.5294   |
|                                                                          | LYMPHOMA              | 1              | 2    | 0.8958   |
|                                                                          | PAPILLOMA, SQUAMOUS   | 0              | 0    | .        |
| small intestine                                                          | LYMPHOMA              | 0              | 0    | .        |
|                                                                          | LYMPHOMA              |                | 1    | 1.0000   |
| spinal cord, ce                                                          | LYMPHOMA              | 0              | 0    | .        |
| spinal cord, th                                                          | LYMPHOMA              | 0              | 0    | .        |
| spleen                                                                   | HEMANGI OSARCOMA      | 1              | 1    | 0.7756   |
|                                                                          | LEUKEMI A, GRANULOCYT | 0              | 0    | .        |
|                                                                          | LYMPHOMA              | 3              | 3    | 0.7140   |
| stomach, glandu                                                          | LEI OMYOSARCOMA       | 1              | 0    | 0.5294   |
|                                                                          | LEUKEMI A, GRANULOCYT | 0              | 0    | .        |
|                                                                          | LYMPHOMA              | 3              | 2    | 0.5652   |
| stomach, nongla                                                          | LYMPHOMA              | 1              | 0    | 0.5294   |

**Table 6A: Comparison of Placebo and Untreated Controls  
Male Mice Including Interim Sacrifice**

|                   |                         | Untreat      | Placeb       |                      |
|-------------------|-------------------------|--------------|--------------|----------------------|
| Organ Name        | Tumor Name              | Cont<br>N=58 | Cont<br>N=59 | P_Val ue<br>PC vs UC |
| testes            | ADENOMA, I NTERSTI TI A | 2            | 1            | 0.5353               |
|                   | LYMPHOMA                | 1            | 2            | 0.8994               |
| thymus            | LEUKEMI A, GRANULOCYT   | 0            | 0            | .                    |
|                   | LYMPHOMA                | 2            | 3            | 0.8469               |
| thyroi d gland    | LYMPHOMA                | 2            | 1            | 0.5436               |
|                   | SARCOMA, HI STI OCYTI C | 0            | 0            | .                    |
| tongue            | LYMPHOMA                | 1            | 0            | 0.5294               |
| trachea           | LYMPHOMA                | 0            | 0            | .                    |
| ureters           | LEI OMYOSARCOMA         | 1            | 0            | 0.5294               |
|                   | LEUKEMI A, GRANULOCYT   | 0            | 0            | .                    |
|                   | LYMPHOMA                | 1            | 3            | 0.9497               |
| uri nary bl adder | LYMPHOMA                | 0            | 2            | 1.0000               |

**Table 6B: Comparison of Placebo and Untreated Controls  
Female Mice Including Interim Sacrifice**

|                                                                          |                         | Untreat      | Placeb       |                      |
|--------------------------------------------------------------------------|-------------------------|--------------|--------------|----------------------|
| Organ Name                                                               | Tumor Name              | Cont<br>N=59 | Cont<br>N=60 | P_Val ue<br>PC vs UC |
| ffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffff |                         |              |              |                      |
| adi pose ti ssue                                                         | LYMPHOMA                | 1            | 0            | 0. 5000              |
| adrenal gl ands                                                          | ADENOMA, SUBCAPSULAR    | 2            | 1            | 0. 5000              |
|                                                                          | CARCI NOMA, YOLK SAC    | 1            | 0            | 0. 4943              |
|                                                                          | LYMPHOMA                | 4            | 5            | 0. 7685              |
|                                                                          | PHEOCHROMOCYTOMA        | 1            | 1            | 0. 7471              |
| aorta                                                                    | CARCI NOMA, BRONCHI OL  | 0            | 2            | 1. 0000              |
|                                                                          | CARCI NOMA, YOLK SAC    | 1            | 0            | 0. 4943              |
|                                                                          | LYMPHOMA                | 3            | 5            | 0. 8737              |
|                                                                          | SARCOMA, HI STI OCYTI C | 0            | 1            | 1. 0000              |
| bone                                                                     | OSTEOSARCOMA            | 0            | 0            | .                    |
| bone marrow, fe                                                          | FI BROSARCOMA           | 0            | 0            | .                    |
|                                                                          | HEMANGI OSARCOMA        | 1            | 0            | 0. 5000              |
|                                                                          | LYMPHOMA                | 1            | 4            | 0. 9706              |
|                                                                          | SARCOMA, HI STI OCYTI C | 0            | 2            | 1. 0000              |
| bone marrow, st                                                          | LYMPHOMA                | 0            | 3            | 1. 0000              |
|                                                                          | SARCOMA, HI STI OCYTI C | 0            | 2            | 1. 0000              |
| bone, femur                                                              | LYMPHOMA                | 1            | 2            | 0. 8793              |
|                                                                          | OSTEOMA                 | 0            | 1            | 1. 0000              |
| bone, mandi ble                                                          | OSTEOSARCOMA            | 1            | 0            | 0. 4943              |
| bone, sternum                                                            | LYMPHOMA                | 2            | 5            | 0. 9449              |
|                                                                          | SARCOMA, HI STI OCYTI C | 0            | 1            | 1. 0000              |
| brain                                                                    | LYMPHOMA                | 0            | 2            | 1. 0000              |
| cavi ty, abdomi n                                                        | FI BROSARCOMA           | 1            | 0            | 0. 5000              |
|                                                                          | HEMANGI OSARCOMA        | 1            | 0            | 0. 5000              |
|                                                                          | LYMPHOMA                | 1            | 0            | 0. 5000              |
|                                                                          | SEX-CORD/STROMAL TUM    | 0            | 0            | .                    |
| cavi ty, thoraci                                                         | LYMPHOMA                | 0            | 0            | .                    |
| esophagus                                                                | LYMPHOMA                | 0            | 2            | 1. 0000              |
| eyes                                                                     | LYMPHOMA                | 2            | 1            | 0. 5085              |
| eyes, opti c ner                                                         | LYMPHOMA                | 0            | 1            | 1. 0000              |
| gal l bl adder                                                           | FI BROMA                | 0            | 1            | 1. 0000              |
|                                                                          | LYMPHOMA                | 1            | 4            | 0. 9723              |
| harderian gl and                                                         | ADENOMA                 | 2            | 1            | 0. 5000              |
| heart                                                                    | CARCI NOMA, BRONCHI OL  | 1            | 1            | 0. 7471              |



**Table 6B: Comparison of Placebo and Untreated Controls  
Female Mice Including Interim Sacrifice**

|                                                                  |                         | Untreat      | Placeb       |                      |
|------------------------------------------------------------------|-------------------------|--------------|--------------|----------------------|
| Organ Name                                                       | Tumor Name              | Cont<br>N=59 | Cont<br>N=60 | P_Val ue<br>PC vs UC |
| ffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffff |                         |              |              |                      |
| heart                                                            | CARCI NOMA, YOLK SAC    | 1            | 0            | 0.4943               |
|                                                                  | LYMPHOMA                | 3            | 8            | 0.9728               |
|                                                                  | SARCOMA, HI STI OCYTI C | 1            | 0            | 0.5000               |
| joint, tibi ofem                                                 | LYMPHOMA                | 0            | 1            | 1.0000               |
|                                                                  | SARCOMA, HI STI OCYTI C | 0            | 1            | 1.0000               |
| ki dneys                                                         | LYMPHOMA                | 5            | 10           | 0.9599               |
|                                                                  | SARCOMA, HI STI OCYTI C | 2            | 2            | 0.6833               |
|                                                                  | SEX-CORD/STROMAL TUM    | 0            | 0            | .                    |
| l acri mal gl ands                                               | LYMPHOMA                | 3            | 5            | 0.8668               |
|                                                                  | SARCOMA, HI STI OCYTI C | 0            | 1            | 1.0000               |
| l arge i ntesti ne                                               | LYMPHOMA                | 1            | 0            | 0.5000               |
|                                                                  |                         | 2            | 1            | 0.5085               |
|                                                                  |                         | 3            | 1            | 0.3167               |
| l arynx                                                          | LYMPHOMA                | 2            | 3            | 0.8196               |
|                                                                  | SARCOMA, HI STI OCYTI C | 0            | 1            | 1.0000               |
| l i ver                                                          | ADENOMA, HEPATOCELLU    | 0            | 1            | 1.0000               |
|                                                                  | CARCI NOMA, HEPATOCEL   | 0            | 2            | 1.0000               |
|                                                                  | ADEN+CAR, HEPATOCELL    | 0            | 3            | 1.0000               |
|                                                                  | HEMANGI OMA             | 0            | 0            | .                    |
|                                                                  | HEMANGI OSARCOMA        | 3            | 2            | 0.4892               |
|                                                                  | LYMPHOMA                | 3            | 9            | 0.9852               |
|                                                                  | SARCOMA, HI STI OCYTI C | 2            | 5            | 0.9377               |
| l ung                                                            | ADENOMA, BRONCHI OLAR   | 3            | 7            | 0.9477               |
|                                                                  | CARCI NOMA, BRONCHI OL  | 7            | 6            | 0.4823               |
|                                                                  | ADEN+CAR, BRONCHI OLA   | 9            | 12           | 0.8105               |
|                                                                  | CARCI NOMA, YOLK SAC    | 1            | 0            | 0.4943               |
|                                                                  | LYMPHOMA                | 3            | 11           | 0.9959               |
|                                                                  | SARCOMA, HI STI OCYTI C | 1            | 5            | 0.9850               |
| l ymph node, axi                                                 | FI BROSARCOMA           | 0            | 0            | .                    |
|                                                                  | LYMPHOMA                | 0            | 1            | 1.0000               |
| l ymph node, hep                                                 | LYMPHOMA                | 0            | 1            | 1.0000               |
| l ymph node, ili                                                 | LYMPHOMA                | 1            | 0            | 0.5000               |
| l ymph node, ing                                                 | HEMANGI OSARCOMA        | 0            | 0            | .                    |
|                                                                  | LYMPHOMA                | 0            | 1            | 1.0000               |
| l ymph node, man                                                 | LYMPHOMA                | 3            | 7            | 0.9515               |
|                                                                  | SARCOMA, HI STI OCYTI C | 0            | 1            | 1.0000               |
| l ymph node, med                                                 | CARCI NOMA, BRONCHI OL  | 1            | 1            | 0.7529               |
|                                                                  | LYMPHOMA                | 1            | 2            | 0.8793               |
| l ymph node, mes                                                 | LYMPHOMA                | 4            | 8            | 0.9405               |

**Table 6B: Comparison of Placebo and Untreated Controls  
Female Mice Including Interim Sacrifice**

| Organ Name                                                       | Tumor Name              | Untreat      | Placeb       | P_Val ue<br>PC vs UC |
|------------------------------------------------------------------|-------------------------|--------------|--------------|----------------------|
|                                                                  |                         | Cont<br>N=59 | Cont<br>N=60 |                      |
| ffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffff |                         |              |              |                      |
| lymph node, mes                                                  | SARCOMA, HI STI OCYTI C | 1            | 3            | 0.9390               |
|                                                                  | SEX-CORD/STROMAL TUM    | 0            | 0            | .                    |
| lymph node, ren                                                  | LYMPHOMA                | 1            | 1            | 0.7529               |
| lymph node, tra                                                  | LYMPHOMA                | 0            | 1            | 1.0000               |
| mammary gland                                                    | ADENOCARCI NOMA         | 1            | 0            | 0.5000               |
|                                                                  | LYMPHOMA                | 4            | 4            | 0.6555               |
|                                                                  | SARCOMA, HI STI OCYTI C | 0            | 1            | 1.0000               |
| mesentery/perit                                                  | LYMPHOMA                | 0            | 0            | .                    |
| mul ti centri c ne                                               | HEMANGI OMA             | 1            | 2            | 0.8750               |
|                                                                  | HEMANGI OSARCOMA        | 3            | 4            | 0.7641               |
|                                                                  | LYMPHOMA                | 5            | 13           | 0.9917               |
|                                                                  | SARCOMA, HI STI OCYTI C | 2            | 5            | 0.9377               |
| nerve, sciatic                                                   | LYMPHOMA                | 2            | 6            | 0.9686               |
|                                                                  | SARCOMA, HI STI OCYTI C | 0            | 1            | 1.0000               |
| ovaries                                                          | ADENOMA, TUBULOSTROM    | 1            | 0            | 0.4943               |
|                                                                  | CARCI NOMA, YOLK SAC    | 1            | 0            | 0.4943               |
|                                                                  | CHORI OCARCI NOMA       | 0            | 1            | 1.0000               |
|                                                                  | CYSTADENOMA             | 0            | 2            | 1.0000               |
|                                                                  | LYMPHOMA                | 5            | 9            | 0.9272               |
|                                                                  | SARCOMA, HI STI OCYTI C | 1            | 2            | 0.8793               |
|                                                                  | SEX-CORD/STROMAL TUM    | 1            | 1            | 0.7472               |
| ovi ducts                                                        | LYMPHOMA                | 1            | 1            | 0.7529               |
| pancreas                                                         | CARCI NOMA, YOLK SAC    | 1            | 0            | 0.4943               |
|                                                                  | HEMANGI OMA             | 1            | 0            | 0.5000               |
|                                                                  | LYMPHOMA                | 5            | 7            | 0.8332               |
|                                                                  | SARCOMA, HI STI OCYTI C | 1            | 1            | 0.7529               |
|                                                                  | SCHWANNOMA              | 0            | 0            | .                    |
| peyers patch                                                     | LYMPHOMA                | 1            | 1            | 0.7472               |
|                                                                  | SARCOMA, HI STI OCYTI C | 0            | 1            | 1.0000               |
| pi tui tary gland                                                | ADENOMA, PARS DI STAL   | 1            | 1            | 0.7471               |
|                                                                  | ADENOMA, PARS I NTERM   | 0            | 2            | 1.0000               |
|                                                                  | LYMPHOMA                | 0            | 0            | .                    |
| sal i vary gl and,                                               | LYMPHOMA                | 2            | 1            | 0.5085               |
|                                                                  |                         | 3            | 3            | 0.6617               |
|                                                                  |                         |              |              | 0.6725               |
|                                                                  | SARCOMA, HI STI OCYTI C | 0            | 1            | 1.0000               |
| skel etal muscle                                                 | LYMPHOMA                | 1            | 2            | 0.8750               |

**Table 6B: Comparison of Placebo and Untreated Controls  
Female Mice Including Interim Sacrifice**

|                                                                  |                         | Untreat      | Placeb       |                      |
|------------------------------------------------------------------|-------------------------|--------------|--------------|----------------------|
| Organ Name                                                       | Tumor Name              | Cont<br>N=59 | Cont<br>N=60 | P_Val ue<br>PC vs UC |
| ffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffff |                         |              |              |                      |
| skin, subcutis                                                   | FIBROSARCOMA            | 0            | 0            | .                    |
|                                                                  | HEMANGI OSARCOMA        | 0            | 0            | .                    |
|                                                                  | OSTEOSARCOMA            | 0            | 0            | .                    |
|                                                                  | SCHWANNOMA              | 0            | 0            | .                    |
| skin, treated                                                    | CARCI NOMA, YOLK SAC    | 1            | 0            | 0.4943               |
|                                                                  | LYMPHOMA                | 2            | 4            | 0.8986               |
|                                                                  | SARCOMA, HI STI OCYTI C | 0            | 1            | 1.0000               |
| skin, untreated                                                  | CARCI NOMA, SQUAMOUS    | 1            | 0            | 0.5000               |
|                                                                  | KERATOACANTHOMA         | 0            | 1            | 1.0000               |
|                                                                  | LYMPHOMA                | 1            | 2            | 0.8750               |
| small intestine                                                  | LYMPHOMA                | 1            | 0            | 0.5000               |
|                                                                  |                         |              | 1            | 0.7472               |
|                                                                  |                         | 2            | 1            | 0.5000               |
|                                                                  | POLYP, GLANDULAR        | 0            | 0            | .                    |
|                                                                  | SCHWANNOMA              | 0            | 0            | .                    |
| spinal cord, ce                                                  | LYMPHOMA                | 0            | 1            | 1.0000               |
| spinal cord, lu                                                  | LYMPHOMA                | 0            | 1            | 1.0000               |
| spinal cord, th                                                  | LYMPHOMA                | 0            | 1            | 1.0000               |
| spleen                                                           | HEMANGI OSARCOMA        | 1            | 0            | 0.5000               |
|                                                                  | LYMPHOMA                | 4            | 10           | 0.9803               |
|                                                                  | SARCOMA, HI STI OCYTI C | 0            | 1            | 1.0000               |
| stomach, glandu                                                  | CARCI NOMA, YOLK SAC    | 1            | 0            | 0.4943               |
|                                                                  | LYMPHOMA                | 3            | 3            | 0.6725               |
|                                                                  | SARCOMA, HI STI OCYTI C | 0            | 1            | 1.0000               |
|                                                                  | SEX-CORD/STROMAL TUM    | 0            | 0            | .                    |
| stomach, nongla                                                  | LYMPHOMA                | 0            | 2            | 1.0000               |
|                                                                  | SARCOMA, HI STI OCYTI C | 0            | 1            | 1.0000               |
| tail                                                             | HEMANGI OSARCOMA        | 0            | 0            | .                    |
| thymus                                                           | CARCI NOMA, BRONCHI OL  | 2            | 1            | 0.5000               |
|                                                                  | CARCI NOMA, YOLK SAC    | 1            | 0            | 0.4943               |
|                                                                  | LYMPHOMA                | 5            | 12           | 0.9869               |
|                                                                  | SARCOMA, HI STI OCYTI C | 1            | 1            | 0.7529               |
| thyroid gland                                                    | LYMPHOMA                | 2            | 4            | 0.8986               |
|                                                                  | SARCOMA, HI STI OCYTI C | 0            | 1            | 1.0000               |
| tongue                                                           | LYMPHOMA                | 1            | 3            | 0.9390               |
| trachea                                                          | LYMPHOMA                | 1            | 2            | 0.8750               |
|                                                                  | SARCOMA, HI STI OCYTI C | 0            | 1            | 1.0000               |

**Table 6B: Comparison of Placebo and Untreated Controls**  
**Female Mice Including Interim Sacrifice**

|                  |                         | Untreat      | Placeb       |                      |
|------------------|-------------------------|--------------|--------------|----------------------|
| Organ Name       | Tumor Name              | Cont<br>N=59 | Cont<br>N=60 | P_Val ue<br>PC vs UC |
| ureters          | LYMPHOMA                | 5            | 8            | 0.8925               |
| uri nary bladder | CARCI NOMA, YOLK SAC    | 1            | 0            | 0.4943               |
|                  | LYMPHOMA                | 3            | 5            | 0.8668               |
|                  | SARCOMA, HI STI OCYTI C | 0            | 1            | 1.0000               |
| uterus with cer  | ADENOCARCI NOMA         | 0            | 1            | 1.0000               |
|                  | CARCI NOMA, YOLK SAC    | 1            | 0            | 0.4943               |
|                  | FIBROSARCOMA            | 0            | 0            | .                    |
|                  | HEMANGI OMA             | 0            | 2            | 1.0000               |
|                  | HEMANGI OSARCOMA        | 0            | 2            | 1.0000               |
|                  | LEI OMYOMA              | 0            | 1            | 1.0000               |
|                  | LEI OMYOSARCOMA         | 0            | 0            | .                    |
|                  | LYMPHOMA                | 5            | 4            | 0.5280               |
|                  | POLYP, ENDOMETRI AL S   | 8            | 3            | 0.0914               |
|                  | SARCOMA, ENDOMETRI AL   | 2            | 3            | 0.8053               |
|                  | SARCOMA, HI STI OCYTI C | 2            | 2            | 0.6833               |
|                  | SCHWANNOMA              | 0            | 0            | .                    |
|                  | SEX-CORD/STROMAL TUM    | 0            | 0            | .                    |
| vagi na          | LYMPHOMA                | 2            | 3            | 0.8267               |
|                  | POLYP                   | 0            | 1            | 1.0000               |

Table 7A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons  
Using Untreated Control Excluding Interim Sacrifice  
Male Mice

|                                                                                                                           |                           | Untrtd       | Placeb       | 3 %         | 10 %        | P_Val ue  |        |          |   |
|---------------------------------------------------------------------------------------------------------------------------|---------------------------|--------------|--------------|-------------|-------------|-----------|--------|----------|---|
| Organ Name                                                                                                                | Tumor Name                | Cont<br>N=58 | Cont<br>N=57 | Low<br>N=56 | Med<br>N=47 | Dose Resp | UC vs. | L UC vs. | M |
| %%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%% |                           |              |              |             |             |           |        |          |   |
| adrenal glands                                                                                                            | ADENOMA, CORTICAL         | 0            | 0            | 0           | 1           | 0.2764    | .      | 0.4304   |   |
|                                                                                                                           | LEI OMYOSARCOMA           | 1            | 0            | 0           | 0           | 1.0000    | 1.0000 | 1.0000   |   |
|                                                                                                                           | LEUKEMI A, GRANULOCYT     | 0            | 0            | 1           | 0           | 0.6341    | 0.4944 | .        |   |
|                                                                                                                           | LYMPHOMA                  | 3            | 2            | 3           | 0           | 0.9480    | 0.6405 | 1.0000   |   |
| aorta                                                                                                                     | ADENOCARCINOMA            | 0            | 0            | 0           | 1           | 0.2764    | .      | 0.4304   |   |
|                                                                                                                           | CARCINOMA, BRONCHIAL      | 1            | 0            | 0           | 0           | 1.0000    | 1.0000 | 1.0000   |   |
|                                                                                                                           | LEI OMYOSARCOMA           | 1            | 0            | 0           | 0           | 1.0000    | 1.0000 | 1.0000   |   |
|                                                                                                                           | LYMPHOMA                  | 2            | 3            | 1           | 1           | 0.6815    | 0.8708 | 0.8221   |   |
| bone marrow, femur                                                                                                        | HEMANGIOMA                | 1            | 0            | 0           | 0           | 1.0000    | 1.0000 | 1.0000   |   |
|                                                                                                                           | HEMANGIOSARCOMA           | 1            | 0            | 0           | 0           | 1.0000    | 1.0000 | 1.0000   |   |
|                                                                                                                           | LEUKEMI A, GRANULOCYT     | 0            | 0            | 1           | 0           | 0.6341    | 0.4944 | .        |   |
|                                                                                                                           | LYMPHOMA                  | 3            | 2            | 3           | 1           | 0.8019    | 0.6512 | 0.8980   |   |
| bone marrow, sternum                                                                                                      | LEUKEMI A, GRANULOCYT     | 0            | 0            | 1           | 0           | 0.6341    | 0.4944 | .        |   |
|                                                                                                                           | LYMPHOMA                  | 3            | 2            | 4           | 1           | 0.8057    | 0.4878 | 0.8980   |   |
| bone, femur                                                                                                               | LYMPHOMA                  | 1            | 0            | 3           | 1           | 0.5405    | 0.3083 | 0.6806   |   |
|                                                                                                                           | OSTEOSARCOMA              | 0            | 0            | 0           | 1           | 0.2823    | .      | 0.4375   |   |
| bone, sternum                                                                                                             | LYMPHOMA                  | 3            | 2            | 5           | 1           | 0.8097    | 0.3449 | 0.8980   |   |
|                                                                                                                           |                           |              |              |             |             |           |        |          |   |
| brain                                                                                                                     | ASTROCYTOMA               | 1            | 0            | 0           | 0           | 1.0000    | 1.0000 | 1.0000   |   |
|                                                                                                                           | LYMPHOMA                  | 0            | 0            | 2           | 1           | 0.2982    | 0.2472 | 0.4375   |   |
| cavity, abdominal                                                                                                         | CARCINOMA, BRONCHIAL      | 1            | 0            | 0           | 0           | 1.0000    | 1.0000 | 1.0000   |   |
| cavity, thoracic                                                                                                          | CARCINOMA, BRONCHIAL      | 1            | 0            | 0           | 0           | 1.0000    | 1.0000 | 1.0000   |   |
|                                                                                                                           | FIBROSITIC CYTOMA         | 0            | 0            | 0           | 1           | 0.2823    | .      | 0.4375   |   |
| epididymides                                                                                                              | ADENOMA, INTERSTITIAL     | 0            | 0            | 0           | 1           | 0.2764    | .      | 0.4304   |   |
|                                                                                                                           | LEI OMYOSARCOMA           | 1            | 0            | 0           | 0           | 1.0000    | 1.0000 | 1.0000   |   |
|                                                                                                                           | LYMPHOMA                  | 2            | 2            | 5           | 1           | 0.7193    | 0.2172 | 0.8221   |   |
| esophagus                                                                                                                 | LYMPHOMA                  | 0            | 0            | 2           | 0           | 0.6042    | 0.2416 | .        |   |
|                                                                                                                           | LYMPHOMA                  | 1            | 2            | 1           | 1           | 0.5221    | 0.7472 | 0.6867   |   |
| gallbladder                                                                                                               | LYMPHOMA                  | 1            | 0            | 2           | 1           | 0.5242    | 0.5000 | 0.6867   |   |
| harderian gland                                                                                                           | ADENOMA                   | 0            | 0            | 1           | 0           | 0.6341    | 0.4944 | .        |   |
| heart                                                                                                                     | CARCINOMA, BRONCHIAL      | 1            | 0            | 0           | 0           | 1.0000    | 1.0000 | 1.0000   |   |
|                                                                                                                           | HEMANGIOMA                | 0            | 0            | 1           | 0           | 0.6341    | 0.4944 | .        |   |
|                                                                                                                           | HEMANGIOSARCOMA           | 1            | 0            | 0           | 0           | 1.0000    | 1.0000 | 1.0000   |   |
|                                                                                                                           | LYMPHOMA                  | 3            | 3            | 5           | 1           | 0.8097    | 0.3449 | 0.8980   |   |
| kidneys                                                                                                                   | ADENOCARCINOMA            | 0            | 0            | 0           | 1           | 0.2764    | .      | 0.4304   |   |
|                                                                                                                           | ADENOMA, TUBULAR CELL     | 1            | 0            | 1           | 0           | 0.8681    | 0.7472 | 1.0000   |   |
|                                                                                                                           | CARCINOMA, TUBULAR CELL   | 1            | 0            | 0           | 0           | 1.0000    | 1.0000 | 1.0000   |   |
|                                                                                                                           | LEI OMYOSARCOMA           | 1            | 0            | 0           | 0           | 1.0000    | 1.0000 | 1.0000   |   |
|                                                                                                                           | LEUKEMI A, GRANULOCYT     | 0            | 0            | 1           | 0           | 0.6341    | 0.4944 | .        |   |
| lacrimal glands                                                                                                           | LYMPHOMA                  | 4            | 2            | 5           | 1           | 0.8800    | 0.4862 | 0.9438   |   |
|                                                                                                                           | LEUKEMI A, GRANULOCYT     | 0            | 0            | 1           | 0           | 0.6341    | 0.4944 | .        |   |
|                                                                                                                           | LYMPHOMA                  | 3            | 3            | 5           | 1           | 0.8097    | 0.3449 | 0.8980   |   |
|                                                                                                                           |                           |              |              |             |             |           |        |          |   |
| large intestine                                                                                                           | LEI OMYOSARCOMA           | 1            | 0            | 0           | 0           | 1.0000    | 1.0000 | 1.0000   |   |
|                                                                                                                           | LYMPHOMA                  | 0            | 0            | 0           | 1           | 0.2823    | .      | 0.4375   |   |
| larynx                                                                                                                    |                           | 1            | 1            | 0           | 1           | 0.2800    | 0.4944 | 0.4375   |   |
|                                                                                                                           |                           | 1            | 1            | 0           | 1           | 0.4865    | 1.0000 | 0.6867   |   |
|                                                                                                                           | LYMPHOMA                  | 1            | 1            | 3           | 0           | 0.8116    | 0.3082 | 1.0000   |   |
| liver                                                                                                                     | ADENOCARCINOMA            | 0            | 0            | 0           | 1           | 0.2764    | .      | 0.4304   |   |
|                                                                                                                           | ADENOMA, HEPATOCELLULAR   | 11           | 14           | 9           | 12          | 0.1251    | 0.7923 | 0.2366   |   |
|                                                                                                                           | CARCINOMA, HEPATOCELLULAR | 1            | 0            | 2           | 1           | 0.5243    | 0.4915 | 0.6867   |   |
|                                                                                                                           | ADENOCARCINOMA            | 12           | 14           | 10          | 13          | 0.1365    | 0.7861 | 0.2503   |   |
|                                                                                                                           | HEMANGIOMA                | 0            | 0            | 0           | 1           | 0.2823    | .      | 0.4375   |   |

### Using Untreated Control Excluding Interim Sacrifice Male Mice

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |            | Untrtd | Placeb | 3 %  | 10 % |          |      |        |            |
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                                                                      |            | Cont   | Cont   | Low  | Med  | P_Val ue |      |        |            |
| Organ Name                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Tumor Name | N=58   | N=57   | N=56 | N=47 | Dose     | Resp | UC vs. | L UC vs. M |
| f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f f 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### Using Untreated Control Excluding Interim Sacrifice Male Mice

| Organ Name            | Tumor Name            | Untreated | Placebo | 3 %  | 10 % | P_Value |        |          |
|-----------------------|-----------------------|-----------|---------|------|------|---------|--------|----------|
|                       |                       | N=58      | N=57    | N=56 | N=47 | Dose    | Resp   | UC vs. L |
| skin, untreated       | LEIOMYOSARCOMA        | 1         | 0       | 0    | 0    | 1.0000  | 1.0000 | 1.0000   |
|                       | LYMPHOMA              | 1         | 2       | 3    | 1    | 0.5488  | 0.3082 | 0.6867   |
|                       | PAPILLOMA, SQUAMOUS   | 0         | 0       | 1    | 0    | 0.6341  | 0.4944 | .        |
| small intestine       | LYMPHOMA              | 0         | 0       | 1    | 1    | 0.2800  | 0.4944 | 0.4375   |
|                       |                       |           | 1       | 0    | 1    | 0.2823  | .      | 0.4375   |
|                       |                       |           |         | 1    | 1    | 0.2800  | 0.4944 | 0.4375   |
| spinal cord, cervical | LYMPHOMA              | 0         | 0       | 1    | 0    | 0.6341  | 0.4944 | .        |
| spinal cord, thoracic | LYMPHOMA              | 0         | 0       | 1    | 0    | 0.6341  | 0.4944 | .        |
| spleen                | HEMANGIOSARCOMA       | 1         | 1       | 0    | 0    | 1.0000  | 1.0000 | 1.0000   |
|                       | LEUKEMIA, GRANULOCYT  | 0         | 0       | 1    | 0    | 0.6341  | 0.4944 | .        |
|                       | LYMPHOMA              | 3         | 3       | 6    | 1    | 0.8126  | 0.2428 | 0.8980   |
| stomach, glandular    | ADENOCARCINOMA        | 0         | 0       | 0    | 1    | 0.2764  | .      | 0.4304   |
|                       | LEIOMYOSARCOMA        | 1         | 0       | 0    | 0    | 1.0000  | 1.0000 | 1.0000   |
|                       | LEUKEMIA, GRANULOCYT  | 0         | 0       | 1    | 0    | 0.6341  | 0.4944 | .        |
|                       | LYMPHOMA              | 3         | 2       | 6    | 1    | 0.8129  | 0.2320 | 0.8980   |
| stomach, nonglandular | LYMPHOMA              | 1         | 0       | 2    | 0    | 0.8106  | 0.5000 | 1.0000   |
|                       | ADENOMA, INTERSTITIAL | 2         | 1       | 1    | 0    | 0.9531  | 0.8750 | 1.0000   |
|                       | LYMPHOMA              | 1         | 2       | 2    | 0    | 0.8042  | 0.4831 | 1.0000   |
| thymus                | LEUKEMIA, GRANULOCYT  | 0         | 0       | 1    | 0    | 0.6341  | 0.4944 | .        |
|                       | LYMPHOMA              | 2         | 3       | 5    | 0    | 0.8896  | 0.2172 | 1.0000   |
| thyroid gland         | ADENOMA, FOLLICULAR   | 0         | 0       | 0    | 2    | 0.0748  | .      | 0.1821   |
|                       | LYMPHOMA              | 2         | 1       | 2    | 0    | 0.9114  | 0.6747 | 1.0000   |
|                       | SARCOMA, HISTIOCYTIC  | 0         | 0       | 1    | 0    | 0.6341  | 0.4944 | .        |
| tongue                | LYMPHOMA              | 1         | 0       | 1    | 0    | 0.8681  | 0.7472 | 1.0000   |
| trachea               | LYMPHOMA              | 0         | 0       | 3    | 1    | 0.3633  | 0.1208 | 0.4375   |
| ureters               | LEIOMYOSARCOMA        | 1         | 0       | 0    | 0    | 1.0000  | 1.0000 | 1.0000   |
|                       | LEUKEMIA, GRANULOCYT  | 0         | 0       | 1    | 0    | 0.6341  | 0.4944 | .        |
|                       | LYMPHOMA              | 1         | 3       | 5    | 0    | 0.8145  | 0.1066 | 1.0000   |
| urinary bladder       | LYMPHOMA              | 0         | 2       | 4    | 1    | 0.4154  | 0.0611 | 0.4375   |

**Table 7B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons  
Using Untreated Control Excluding Interim Sacrifice  
Female Mice**

| Organ Name           | Tumor Name             | Untreated    | Placebo      | 3 %         | 10 %        | P_Value   |          |          |
|----------------------|------------------------|--------------|--------------|-------------|-------------|-----------|----------|----------|
|                      |                        | Cont<br>N=59 | Cont<br>N=60 | Low<br>N=60 | Med<br>N=48 | Dose Resp | UC vs. L | UC vs. M |
| ~~~~~                |                        |              |              |             |             |           |          |          |
| adipose tissue       | LYMPHOMA               | 1            | 0            | 0           | 1           | 0.4581    | 1.0000   | 0.6591   |
|                      | SARCOMA, ENDOMETRIAL   | 0            | 0            | 0           | 1           | 0.2650    | .        | 0.4189   |
| adrenal glands       | ADENOMA, SUBCAPSULAR   | 2            | 1            | 0           | 1           | 0.6029    | 1.0000   | 0.8039   |
|                      | CARCINOMA, YOLK SAC    | 1            | 0            | 0           | 0           | 1.0000    | 1.0000   | 1.0000   |
|                      | LYMPHOMA               | 4            | 5            | 3           | 3           | 0.4384    | 0.7736   | 0.5919   |
|                      | PHEOCHROMOCYTOMA       | 1            | 1            | 0           | 0           | 1.0000    | 1.0000   | 1.0000   |
|                      | SARCOMA, HISTIOCYTIC   | 0            | 0            | 0           | 1           | 0.2650    | .        | 0.4189   |
| aorta                | CARCINOMA, YOLK SAC    | 1            | 0            | 0           | 0           | 1.0000    | 1.0000   | 1.0000   |
|                      | LYMPHOMA               | 3            | 5            | 5           | 7           | 0.0374    | 0.3445   | 0.0626   |
| bone                 | OSTEOSARCOMA           | 0            | 0            | 1           | 0           | 0.6325    | 0.5000   | .        |
| bone marrow, femur   | FIBROSARCOMA           | 0            | 0            | 1           | 0           | 0.6356    | 0.5057   | .        |
|                      | HEMANGIOSARCOMA        | 1            | 0            | 0           | 0           | 1.0000    | 1.0000   | 1.0000   |
|                      | LYMPHOMA               | 1            | 4            | 2           | 2           | 0.2601    | 0.5000   | 0.3810   |
|                      | SARCOMA, HISTIOCYTIC   | 0            | 2            | 0           | 2           | 0.0685    | .        | 0.1722   |
| bone marrow, sternum | LYMPHOMA               | 0            | 3            | 2           | 3           | 0.0439*   | 0.2529   | 0.0735   |
|                      | SARCOMA, HISTIOCYTIC   | 0            | 2            | 0           | 2           | 0.0685    | .        | 0.1722   |
| bone, femur          | LYMPHOMA               | 1            | 2            | 1           | 1           | 0.4921    | 0.7529   | 0.6591   |
| bone, mandible       | OSTEOSARCOMA           | 1            | 0            | 0           | 0           | 1.0000    | 1.0000   | 1.0000   |
| bone, sternum        | LYMPHOMA               | 2            | 5            | 3           | 6           | 0.0277    | 0.4892   | 0.0610   |
| brain                | LYMPHOMA               | 0            | 2            | 2           | 3           | 0.0439*   | 0.2529   | 0.0735   |
| cavity, abdominal    | FIBROSARCOMA           | 1            | 0            | 0           | 0           | 1.0000    | 1.0000   | 1.0000   |
|                      | HEMANGIOSARCOMA        | 1            | 0            | 0           | 0           | 1.0000    | 1.0000   | 1.0000   |
|                      | LYMPHOMA               | 1            | 0            | 0           | 0           | 1.0000    | 1.0000   | 1.0000   |
|                      | SEX-CORD/STROMAL TUMOR | 0            | 0            | 1           | 0           | 0.6325    | 0.5000   | .        |
| cavity, thoracic     | LYMPHOMA               | 0            | 0            | 1           | 0           | 0.6325    | 0.5000   | .        |
| esophagus            | LYMPHOMA               | 0            | 2            | 0           | 1           | 0.2650    | .        | 0.4189   |
| eyes                 | LYMPHOMA               | 2            | 1            | 2           | 0           | 0.9059    | 0.6833   | 1.0000   |
| eyes, optic nerve    | LYMPHOMA               | 0            | 1            | 0           | 1           | 0.2650    | .        | 0.4189   |
| gallbladder          | LYMPHOMA               | 1            | 4            | 6           | 1           | 0.5704    | 0.0623   | 0.6591   |
|                      | SARCOMA, HISTIOCYTIC   | 0            | 0            | 0           | 1           | 0.2650    | .        | 0.4189   |
| harderian gland      | ADENOMA                | 2            | 1            | 0           | 0           | 1.0000    | 1.0000   | 1.0000   |
| heart                | CARCINOMA, BRONCHIOLE  | 1            | 1            | 0           | 1           | 0.4614    | 1.0000   | 0.6657   |
|                      | CARCINOMA, YOLK SAC    | 1            | 0            | 0           | 0           | 1.0000    | 1.0000   | 1.0000   |



**Table 7B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons  
Using Untreated Control Excluding Interim Sacrifice  
Female Mice**

[illegible]

**Table 7B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons  
Using Untreated Control Excluding Interim Sacrifice  
Female Mice**

| Organ Name      | Tumor Name             | Untrtd | Placeb | 3 % | 10 % | P_Val ue  |          |          |
|-----------------|------------------------|--------|--------|-----|------|-----------|----------|----------|
|                 |                        | Cont   | Cont   | Low | Med  | Dose Resp | UC vs. L | UC vs. M |
| N=59            |                        |        |        |     |      |           |          |          |
| N=60            |                        |        |        |     |      |           |          |          |
| N=60            |                        |        |        |     |      |           |          |          |
| N=48            |                        |        |        |     |      |           |          |          |
| P_Val ue        |                        |        |        |     |      |           |          |          |
| Dose Resp       |                        |        |        |     |      |           |          |          |
| UC vs. L        |                        |        |        |     |      |           |          |          |
| UC vs. M        |                        |        |        |     |      |           |          |          |
| P_Val ue        |                        |        |        |     |      |           |          |          |
| lymph node, mes | SARCOMA, HI STIOCYTI C | 1      | 3      | 0   | 2    | 0.1684    | 1.0000   | 0.3696   |
|                 | SEX-CORD/STROMAL TUM   | 0      | 0      | 1   | 0    | 0.6325    | 0.5000   | .        |
| lymph node, ren | LYMPHOMA               | 1      | 1      | 1   | 2    | 0.2225    | 0.7529   | 0.3696   |
| lymph node, tra | LYMPHOMA               | 0      | 1      | 0   | 1    | 0.2650    | .        | 0.4189   |
| mammary gland   | ADENOCARCINOMA         | 1      | 0      | 2   | 1    | 0.4921    | 0.5000   | 0.6591   |
|                 | LYMPHOMA               | 4      | 4      | 3   | 4    | 0.2780    | 0.7641   | 0.4277   |
|                 | SARCOMA, HI STIOCYTI C | 0      | 1      | 0   | 1    | 0.2650    | .        | 0.4189   |
| mesentery/perit | LYMPHOMA               | 0      | 0      | 1   | 1    | 0.2650    | 0.5000   | 0.4189   |
| multicentric ne | HEMANGIOMA             | 1      | 2      | 1   | 0    | 0.8630    | 0.7471   | 1.0000   |
|                 | HEMANGIOSARCOMA        | 3      | 4      | 5   | 1    | 0.7917    | 0.3566   | 0.8883   |
|                 | LYMPHOMA               | 5      | 13     | 8   | 10   | 0.0242    | 0.2617   | 0.0372   |
|                 | SARCOMA, HI STIOCYTI C | 2      | 5      | 1   | 4    | 0.0670    | 0.8793   | 0.1886   |
| nerve, sciatic  | LYMPHOMA               | 2      | 6      | 5   | 2    | 0.4589    | 0.2170   | 0.5410   |
| ovaries         | ADENOMA, TUBULOSTROM   | 1      | 0      | 0   | 0    | 1.0000    | 1.0000   | 1.0000   |
|                 | CARCINOMA, YOLK SAC    | 1      | 0      | 0   | 0    | 1.0000    | 1.0000   | 1.0000   |
|                 | CYSTADENOMA            | 0      | 2      | 0   | 1    | 0.2650    | .        | 0.4189   |
|                 | LYMPHOMA               | 5      | 9      | 8   | 5    | 0.3425    | 0.2617   | 0.3934   |
|                 | SARCOMA, ENDOMETRIAL   | 0      | 0      | 0   | 1    | 0.2650    | .        | 0.4189   |
|                 | SARCOMA, HI STIOCYTI C | 1      | 2      | 0   | 1    | 0.4581    | 1.0000   | 0.6591   |
|                 | SEX-CORD/STROMAL TUM   | 1      | 1      | 4   | 3    | 0.1546    | 0.1874   | 0.1886   |
| oviducts        | LYMPHOMA               | 1      | 1      | 1   | 0    | 0.8630    | 0.7471   | 1.0000   |
| pancreas        | CARCINOMA, YOLK SAC    | 1      | 0      | 0   | 0    | 1.0000    | 1.0000   | 1.0000   |
|                 | HEMANGIOMA             | 1      | 0      | 0   | 0    | 1.0000    | 1.0000   | 1.0000   |
|                 | LYMPHOMA               | 5      | 7      | 6   | 3    | 0.6147    | 0.4846   | 0.7067   |
|                 | SARCOMA, ENDOMETRIAL   | 0      | 0      | 0   | 1    | 0.2650    | .        | 0.4189   |
|                 | SARCOMA, HI STIOCYTI C | 1      | 1      | 0   | 1    | 0.4581    | 1.0000   | 0.6591   |
|                 | SCHWANNOMA             | 0      | 0      | 1   | 0    | 0.6356    | 0.5057   | .        |
| peyers patch    | LYMPHOMA               | 1      | 1      | 1   | 1    | 0.4921    | 0.7529   | 0.6591   |
| pituitary gland | ADENOMA, PARADISTAL    | 1      | 1      | 0   | 0    | 1.0000    | 1.0000   | 1.0000   |
|                 | LYMPHOMA               | 0      | 0      | 2   | 1    | 0.2863    | 0.2529   | 0.4267   |
| salivary gland, | LYMPHOMA               | 2      | 1      | 3   | 2    | 0.4156    | 0.4892   | 0.5410   |
|                 |                        | 3      | 3      | 4   | 3    | 0.3629    | 0.5000   | 0.4726   |
|                 | SARCOMA, HI STIOCYTI C | 0      | 1      | 0   | 1    | 0.2650    | .        | 0.4189   |
| skeletal muscle | LYMPHOMA               | 1      | 2      | 3   | 0    | 0.7969    | 0.3167   | 1.0000   |
| skin, subcutis  | FIBROSARCOMA           | 0      | 0      | 2   | 0    | 0.5951    | 0.2529   | .        |
|                 | HEMANGIOSARCOMA        | 0      | 0      | 1   | 0    | 0.6325    | 0.5000   | .        |

**Table 7B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons  
Using Untreated Control Excluding Interim Sacrifice  
Female Mice**

|                       |                        | Untreated | Placebo | 3 %  | 10 % | P_Value   |          |          |
|-----------------------|------------------------|-----------|---------|------|------|-----------|----------|----------|
| Organ Name            | Tumor Name             | N=59      | N=60    | N=60 | N=48 | Dose Resp | UC vs. L | UC vs. M |
| <i>))))))))))</i>     |                        |           |         |      |      |           |          |          |
| skin, subcutis        | OSTEOSARCOMA           | 0         | 0       | 1    | 0    | 0.6356    | 0.5057   | .        |
|                       | SCHWANNOMA             | 0         | 0       | 1    | 0    | 0.6356    | 0.5057   | .        |
| skin, treated         | CARCINOMA, YOLK SAC    | 1         | 0       | 0    | 0    | 1.0000    | 1.0000   | 1.0000   |
|                       | LYMPHOMA               | 2         | 4       | 3    | 2    | 0.4283    | 0.5000   | 0.5544   |
| skin, untreated       | CARCINOMA, SQUAMOUS    | 1         | 0       | 1    | 0    | 0.8630    | 0.7471   | 1.0000   |
|                       | LYMPHOMA               | 1         | 2       | 3    | 0    | 0.7969    | 0.3167   | 1.0000   |
| small intestine       | LYMPHOMA               | 1         | 0       | 1    | 0    | 0.8653    | 0.7529   | 1.0000   |
|                       |                        |           | 1       | 0    | 1    | 0.4581    | 1.0000   | 0.6591   |
|                       |                        | 2         | 1       | 0    | 0    | 1.0000    | 1.0000   | 1.0000   |
|                       | POLYP, GLANDULAR       | 0         | 0       | 1    | 0    | 0.6325    | 0.5000   | .        |
|                       | SCHWANNOMA             | 0         | 0       | 1    | 0    | 0.6356    | 0.5057   | .        |
| spinal cord, cervical | LYMPHOMA               | 0         | 1       | 2    | 0    | 0.5951    | 0.2529   | .        |
| spinal cord, lumbar   | LYMPHOMA               | 0         | 1       | 0    | 1    | 0.2650    | .        | 0.4189   |
| spinal cord, thoracic | LYMPHOMA               | 0         | 1       | 1    | 0    | 0.6325    | 0.5000   | .        |
| spleen                | HEMANGIOSARCOMA        | 1         | 0       | 2    | 0    | 0.7980    | 0.4913   | 1.0000   |
|                       | LYMPHOMA               | 4         | 10      | 6    | 6    | 0.1430    | 0.3697   | 0.1959   |
|                       | SARCOMA, HISTIOCYTIC   | 0         | 1       | 0    | 2    | 0.0685    | .        | 0.1722   |
| stomach, glandular    | CARCINOMA, YOLK SAC    | 1         | 0       | 0    | 0    | 1.0000    | 1.0000   | 1.0000   |
|                       | LYMPHOMA               | 3         | 3       | 4    | 2    | 0.5684    | 0.5000   | 0.6839   |
|                       | SARCOMA, HISTIOCYTIC   | 0         | 1       | 0    | 1    | 0.2650    | .        | 0.4189   |
|                       | SEX-CORD/STROMAL TUMOR | 0         | 0       | 1    | 0    | 0.6325    | 0.5000   | .        |
| stomach, nonglandular | LYMPHOMA               | 0         | 2       | 3    | 0    | 0.6511    | 0.1293   | .        |
|                       | SARCOMA, HISTIOCYTIC   | 0         | 1       | 0    | 1    | 0.2650    | .        | 0.4189   |
| tail                  | HEMANGIOSARCOMA        | 0         | 0       | 1    | 0    | 0.6356    | 0.5057   | .        |
| thymus                | CARCINOMA, BRONCHIOL   | 2         | 1       | 0    | 0    | 1.0000    | 1.0000   | 1.0000   |
|                       | CARCINOMA, YOLK SAC    | 1         | 0       | 0    | 0    | 1.0000    | 1.0000   | 1.0000   |
|                       | LYMPHOMA               | 5         | 12      | 4    | 9    | 0.0224    | 0.7351   | 0.0677   |
|                       | SARCOMA, HISTIOCYTIC   | 1         | 1       | 0    | 1    | 0.4581    | 1.0000   | 0.6591   |
| thyroid gland         | ADENOMA, FOLLICULAR    | 0         | 0       | 0    | 1    | 0.2712    | .        | 0.4267   |
|                       | LYMPHOMA               | 2         | 4       | 2    | 2    | 0.3902    | 0.6833   | 0.5410   |
| tongue                | LYMPHOMA               | 1         | 3       | 3    | 2    | 0.2763    | 0.3167   | 0.3696   |
| trachea               | LYMPHOMA               | 1         | 2       | 1    | 1    | 0.4921    | 0.7529   | 0.6591   |
| ureters               | LYMPHOMA               | 5         | 8       | 5    | 5    | 0.2653    | 0.6020   | 0.3733   |
|                       | SARCOMA, HISTIOCYTIC   | 0         | 0       | 0    | 1    | 0.2650    | .        | 0.4189   |

**Table 7B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons  
Using Untreated Control Excluding Interim Sacrifice  
Female Mice**

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |            | Untrtd | Placeb | 3 %  | 10 % |           |          |          |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|--------|--------|------|------|-----------|----------|----------|
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |            | Cont   | Cont   | Low  | Med  | P_Val ue  |          |          |
| Organ Name                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Tumor Name | N=59   | N=60   | N=60 | N=48 | Dose Resp | UC vs. L | UC vs. M |
| %%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%% |            |        |        |      |      |           |          |          |

Figure 1A: Kaplan-Meier Survival Functions  
Male Mice All Groups Excluding data of Interim Sacrifice Animals

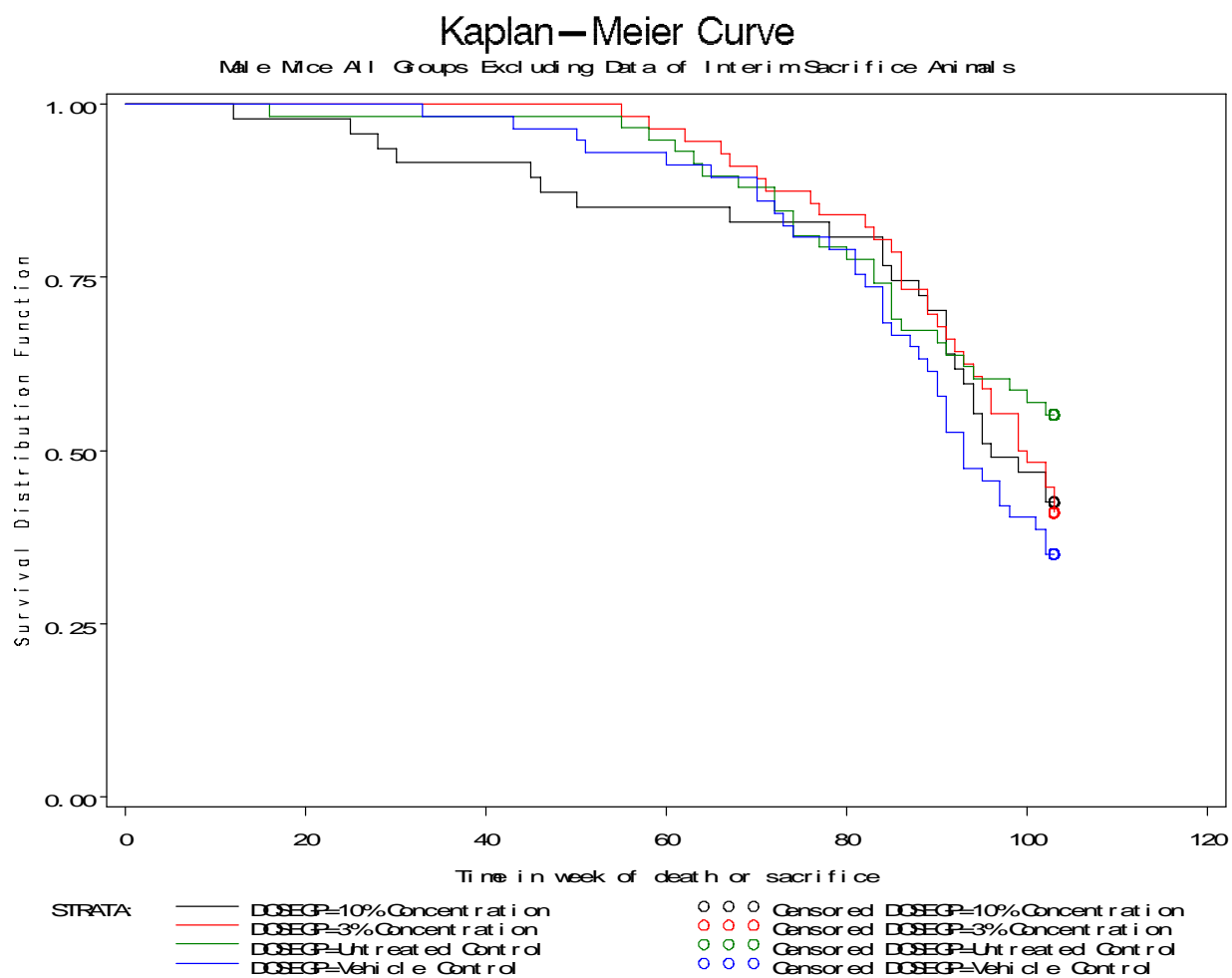
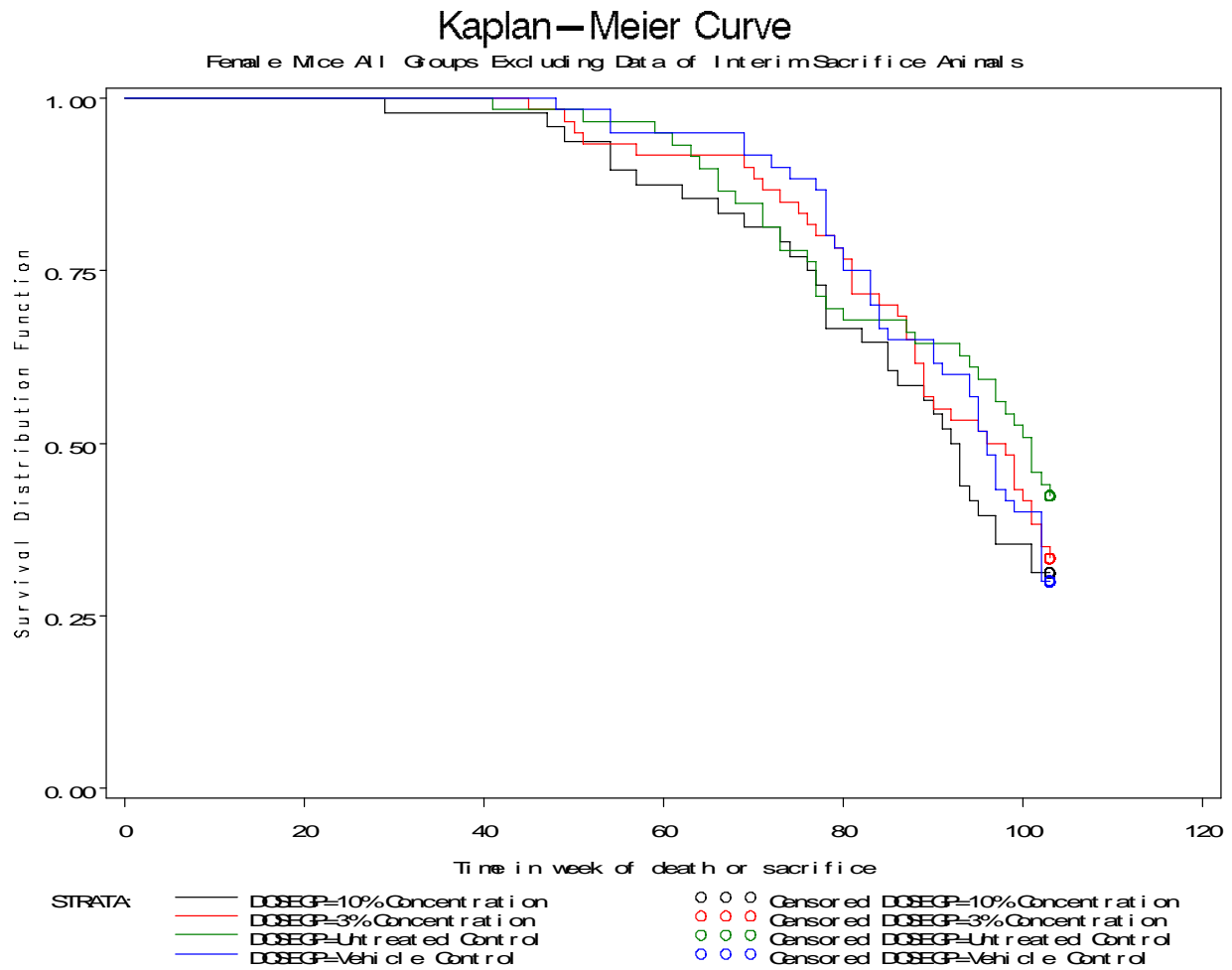


Figure 1B: Kaplan-Meier Survival Functions  
Male Mice All Groups Excluding data of Interim Sacrifice Animals



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/s/  
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MOHAMMAD A RAHMAN  
12/06/2012

KARL K LIN  
12/06/2012  
Concur with review



**Executive CAC****Date of Meeting:** November 27, 2012

**Committee:** David Jacobson-Kram, Ph.D., OND IO, Chair  
Abby Jacobs, Ph.D., OND IO, Member  
Paul Brown, Ph.D., OND IO, Member  
Lynnda Reid, Ph.D., DRUP, Alternate Member  
Barbara Hill, Ph.D., DDDP, Supervisor  
Linda Pellicore, Ph.D., DDDP, Presenting Reviewer

**Author of Draft:** Linda Pellicore, Ph.D.

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

**NDA #:** 203567  
**Drug Name:** Efinaconazole Topical Solution, 10%  
**Sponsor:** Dow Pharmaceutical Sciences

**Background:**

Efinaconazole Topical Solution, 10% is a triazole antifungal agent being developed for the topical treatment of onychomycosis in adults 18 years of age and older. Dose selection for the dermal mouse carcinogenicity study was based on a 13-week dose range finding study. However, the 13-week dose range finding study was not conducted with the to-be-marketed formulation. Therefore, the Executive CAC recommended that another dose range finding study be conducted with the to-be-marketed formulation to support dose selection for the dermal mouse carcinogenicity study. However, the sponsor decided to conduct the dermal mouse carcinogenicity study with the to-be-marketed formulation without conducting another dose range finding study.

**Dermal Mouse Carcinogenicity Study**

CD-1 mice (60 mice/sex/group) were treated with 0% (untreated control), 0% (vehicle control), 3%, 10%, or 30% efinaconazole solution. The initial dose volume was 100 µL of test article applied to an unoccluded treatment site (2 x 3cm<sup>2</sup>). Test article was to be applied once daily, 7 days per week for up to 104 weeks. The clinical vehicle contained cyclomethicone, NF (b) (4), diisopropyl adipate (b) (4), C12-C15 alkyl lactate, (b) (4), purified water (b) (4), butylated hydroxytoluene, NF (b) (4), citric acid, USP (b) (4), edetate disodium (b) (4), alcohol, USP (b) (4).

Severe irritation was noted at the treatment site beginning at week 20 in vehicle, low-, mid- and high-dose groups. The irritation noted at the treatment site appeared to be related to the vehicle and did increase in severity in the high-dose group. All animals were placed on a dosing holiday from week 25 to week 31 due to skin irritation and scabbing in all treatment groups. At week 31, the dose volume was decreased from 100 µL to 50 µL and the high dose group was terminated at week 34 due to severe skin effects. These modifications in the study received Executive CAC concurrence. It appeared that adequate numbers of mid- and low-dose animals survived to the end of the study.

### **Executive CAC Recommendations and Conclusions:**

#### **Dermal Mouse:**

- The Committee concluded that the study was suboptimal due to the mice being very sensitive to severe dermal effects elicited by the vehicle. However, the Committee did not recommend repeating the dermal mouse carcinogenicity study. The Executive CAC noted the results of the chronic dermal mini-pig study conducted with once daily application of up to 30% efinaconazole solution for 9 months. No preneoplastic lesions were observed in that study and the high-dose of 30% efinaconazole was the no-observed-adverse-effect level (NOAEL) for dermal and systemic toxicity in the mini-pig.
- The Committee concurred that there were no drug-related neoplasms in the dermal mouse carcinogenicity study.

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

cc:\

- /Division File, DDDP
- /B. Hill, Pharm/Tox Supervisor, DDDP
- /L. Pellicore, Pharm/Tox reviewer, DDDP
- /S. Dixon, Project Manager, DDDP
- /ASeifried, OND IO

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/s/  
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ADELE S SEIFRIED  
11/30/2012

DAVID JACOBSON KRAM  
11/30/2012

# STATISTICS FILING CHECKLIST FOR A NEW NDA

**NDA Number:** 203567

**Applicant:** Dow

**Stamp Date:** 7/26/2012

**Drug Name:** Efinaconazole  
Solution 10%

**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:

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

**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.

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

**74-DAY LETTER REQUESTS TO THE APPLICANT**

None.

# STATISTICS FILING CHECKLIST FOR A NEW NDA

## SUBMISSION SUMMARY

This submission contains one Phase 2 study and two Phase 3 studies for efinaconazole solution 10% vs. vehicle in the treatment of onychomycosis. The Phase 2 study evaluated three treatment regimens (10% solution, 10% solution with occlusion, and 5% solution) and vehicle over a 36-week treatment period. The 10% solution (without occlusion) regimen was selected for Phase 3 development. Study P3-01 enrolled 870 subjects (656 efinaconazole/214 vehicle) and Study P3-02 enrolled 785 subjects (781 in the ITT: 580 efinaconazole/201 vehicle). Both studies enrolled subjects age 18 and older with 20-50% involvement of the target toenail. Treatment was applied once daily at bedtime to all affected toenails for 48 weeks. The primary efficacy endpoint was complete cure (0% clinical involvement of target toenail plus negative KOH and negative culture) at Week 52. The sponsor wrote two SAPs for the studies. The first SAP matched the definitions in the protocol, but the second included some changes in the definition and ordering of the secondary endpoints. The sponsor states that the motivation for revising the SAP was primarily to provide a “more statistically robust and clinically relevant evaluation.” After the Agency queried the sponsor on the reason for the changes, the sponsor agreed to report both the analyses from both SAPs.

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

| Study P3-01   |          | Study P3-02   |           |
|---------------|----------|---------------|-----------|
| Efinaconazole | Vehicle  | Efinaconazole | Vehicle   |
| N = 656       | N = 214  | N = 580       | N = 201   |
| 117 (17.8%)   | 7 (3.3%) | 88 (15.2%)    | 11 (5.5%) |
| p<0.001       |          | p<0.001       |           |

**ASSOCIATED IND:** IND 77732

**WERE PROTOCOLS REVIEWED UNDER A SPA?** No.

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

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

cc:  
NDA/BLA 203567 / 000  
DDDP/Walker  
DDDP/Kettl  
DDDP/Chiang  
DDDP/Dixon  
OBIO/Patrician  
DBIII/Wilson  
DBIII/Alosch  
DBIII/Fritsch

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/s/  
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KATHLEEN S FRITSCH  
09/12/2012

MOHAMED A ALOSH  
09/12/2012