CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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/BLA #:	204708
Drug Name:	Mirvaso (brimonidine tartrate) Gel, 0.5%
Indication(s):	Erythema of Rosacea
Applicant:	Galderma
Date(s):	Letter Date: 10/26/2012
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Keywords:

Erythema, rosacea, superiority trials, repeated measures, generalized estimating equations, multiple imputation

Table of Contents

1 EXECUTIVE SUMMARY

The applicant, Galderma, is seeking approval of Mirvaso (brimonidine tartrate) gel, 0.5% for the indication of topical treatment of facial erythema of rosacea in adults 18 years of age or older.

The applicant submitted data from two identically designed, randomized, multicenter, vehicle-controlled, parallel-group, pivotal Phase 3 trials (Studies 18140 and 18141). The trials evaluated the safety and efficacy of Mirvaso gel compared to vehicle gel. The trials enrolled subjects age 18 years or older with a clinical diagnosis of facial rosacea that had a Clinical Erythema Assessment (CEA) score of 3 (moderate erythema) or greater and a Patient Self-Assessment (PSA) score 3 (moderate redness) or greater. The protocol-specified primary efficacy endpoint was the proportion of subjects with composite success (defined as a 2-grade reduction in both CEA and PSA) measured at hours 3, 6, 9 and 12 on Day 29, then on Day 15, and lastly on Day 1. The applicant analyzed the primary endpoint using the Generalized Estimating Equation (GEE) method to account for the repeated measures on each subject (hours 3, 6, 9, and 12) and used a conditional stepwise approach to control multiplicity for evaluating the primary endpoint on three days, where the applicant would first test on Day 29, and if significant would then test Day 15, followed by Day 1. The results presented in Table 1 show that Mirvaso gel were statistically ($p<0.001$) superior to vehicle on Day 29, Day 15, and Day 1 in both trials. Table 2 presents the day response rates (average over hours 3, 6, 9, and 12) for Days 29, 15 and 1 in both trials.

Table 1: Composite Success Rates[(1)] by Hours and Days (ITT)

	Study 18140			**Study 18141**		
	Mirvaso Gel (N=129)	**Vehicle Gel (N=131)**	**p-value[(3)]**	**Mirvaso Gel (N=148)**	**Vehicle Gel (N=145)**	**p-value[(3)]**
Day 29						
Hour 3	31.2%	11.0%	<0.001	25.3%	9.1%	<0.001
Hour 6	30.2%	9.6%		25.3%	9.0%	
Hour 9	25.6%	10.2%		17.7%	10.5%	
Hour 12	22.5%	8.9%		21.5%	9.7%	
Day 15						
Hour 3	24.8%	3.4%	<0.001	25.0%	3.4%	<0.001
Hour 6	27.1%	7.2%		25.5%	4.1%	
Hour 9	19.4%	5.5%		21.6%	4.8%	
Hour 12	16.3%	2.6%		15.7%	6.9%	
Day 1						
Hour 3	16.3%	3.1%	<0.001	19.6%	0%	<0.001
Hour 6	23.3%	2.3%		29.7%	2.1%	
Hour 9	19.4%	3.8%		18.2%	0.7%	
Hour 12	13.2%	3.2%		13.5%	1.4%	

Source: Reviewer's Analysis

(1) Composite success is defined as 2-grade improvement on both CEA and PSA. Multiple Imputation (MI) was used to impute missing data. The rates displayed are the averages over the 5 imputed datasets.

(2) P-value calculated using imputed data and based on a GEE model with treatment, analysis center and time point. For Study 18141 and Day 1, as no missing data in the Mirvaso arm and only 1 subject with missing data in the vehicle arm, MI produced the same 5 datasets; therefore the p-value is based on one imputed dataset.

Table 2: Average Composite Success Rates(1) on Days 29, 15, and 1 (ITT)

	Study 18140		Study 18141	
	Mirvaso Gel (N=129)	**Vehicle Gel (N=131)**	**Mirvaso Gel (N=148)**	**Vehicle Gel (N=145)**
Day 29	27.4%	9.9%	22.4%	9.6%
Day 15	21.9%	4.7%	22.0%	4.8%
Day 1	18.0%	3.1%	20.3%	1.0%

Source: Reviewer's Analysis

(1) Composite success is defined as 2-grade improvement on both CEA and PSA. Multiple Imputation (MI) was used to impute missing data. The rates displayed are the averages over hours 3, 6, 9, and 12, and over the 5 imputed datasets.

2 INTRODUCTION

2.1 Overview

The applicant, Galderma, is seeking approval of Mirvaso (brimonidine tartrate) gel, 0.5% for the indication of topical treatment of (b) (4) erythema of rosacea in adults 18 years of age or older. The active ingredient in Mirvaso gel, brimonidine tartrate, is a highly selective alpha-2 adrenergic agonist and was approved in 1996 for the treatment of open angle glaucoma and elevated intraocular pressure (IOP) [Alphagan®; NDA 020613].

2.1.1 Regulatory History

The regulatory history for this application under IND 74,841 is as follows:

- Pre-IND Meeting (August 9, 2006)
- Guidance Meeting (October 31, 2007)
- End of Phase 2 Meeting (March 10, 2008)
- Guidance Meeting (December 3, 2008)
- Guidance Meeting (April 27, 2010)
- Special Protocol Assessment (SPA) Letter (March 30, 2011)
- Pre-NDA Meeting (May 16, 2012)

On September 10, 2012, the Agency accepted the proprietary name Mirvaso.

2.1.1.1 Special Protocol Assessment (SPA)

On February 11, 2011, the sponsor submitted a Phase 3 protocol (Study 18140) for Special Protocol Assessment (SPA) and the SPA letter was sent to the sponsor on March 30, 2011. For the SPA, the sponsor asked for concurrence on the primary and secondary endpoints, and the proposed statistical analysis.

The Agency stated that the proposed definition of the primary endpoints, a composite success at Hours 3, 5, 9 and 12 on Days 29, 15 and 1 where success is defined as a 2-grade improvement on

both the Clinician Erythema Assessment (CEA) scale and Patient Self Assessment (PSA) scale is acceptable. In addition, the sponsor's proposal to sequentially test the primary endpoint at hours 3, 6, 9 and 12 on Day 29 first, and if statistically significant, to test responses for Day 15, and if statistically significant, test for Day 1 was acceptable. For secondary endpoints, the Agency commented that a secondary endpoint where success is defined as 1-grade improvement on the CEA or on the PSA scale might not be clinically meaningful.

The sponsor proposed to develop the statistical analysis plan (SAP) during the conduct of the study, and finalize prior to database lock and unblinding. The Agency stated that the validity of the statistical inference depends on a detailed SAP set at the design stage and that while the sponsor might consider developing the format and tabulation during the conduct of study, the SAP for a Phase 3 trial is expected to be part of, or developed separately during the development of, the study protocol.

The SPA letter had non-agreements for randomization and the primary imputation method for missing data. For randomization, the sponsor proposed to randomize subjects in a 1:1 ratio and use block randomization. The Agency commented that the sponsor did not provide details about the randomization in the protocol including the block size. In addition, the Agency stated that the study should be designed to have a minimum number of subjects per treatment arm per center (e.g. 8 subjects) to investigate the site-to-site variability. For the primary imputation method for missing data, the sponsor proposed to use the last observation carried forward (LOCF) approach. The Agency noted that proposed statistical analysis methodology (Generalized Estimating Equations (GEE) approach) is only valid under Missing Completely at Random (MCAR). The Agency commented that the sponsor should consider other approaches, including weighting the observations by the propensity to dropout and/or considering Multiple Imputation as the primary imputation method for missing data. In addition, the Agency stated that the sponsor should prespecify how missing data will be handled for subjects who might miss some but not all 4 assessments (hours 3, 6, 9 and 12).

Per the Agency's comments in the SPA letter, the sponsor submitted amended Phase 3 protocols and SAP on May 10, 2011 (SDN 77 & 78). The protocols for the two proposed Phase 3 trials appeared to be identical. The sponsor proposed to develop and finalize the SAP prior to study initiation. For randomization, the sponsor stated that a block size of 4 will be used; however, the block size would not be specified in the protocol. The sponsor revised the primary imputation method for missing data to multiple imputation. The sponsor also amended the secondary endpoints to a single secondary endpoint of 30 minute effect (1-grade improvement from baseline on CEA and PSA at 30 minutes on Day 1).

On February 16, 2012, the sponsor submitted an amended SAP for Study 18141 (SDN 98). The sponsor proposed to conduct a supportive analysis using a modified intent-to-treat (MITT) population, defined as the ITT population excluding all subjects from Dr. Baumann's site (site # 8283). The sponsor included this analysis population due to "site specific data validity concern". In particular, the study coordinator at site #8283 admitted to falsification of vital sign data for 1 subject.

2.1.1.2 Pre-NDA Meeting

On May 16, 2012, there was a Pre-NDA meeting between the Agency and the sponsor. During the meeting, the Agency stated that the sponsor's proposal for the Integrated Summary of Efficacy (ISE) and for the Integrated Summary of Safety (ISS) was acceptable. The Agency provided general comments regarding format of dataset submission for the NDA. In addition, the Agency stated that the sponsor's proposal to provide all SAS programs used to generate efficacy and disposition analyses for the pivotal Phase 3 studies would be acceptable and very helpful. The Agency asked the sponsor to provide the code to implement Multiple Imputation (MI) instead of submitting the multiple imputed datasets.

2.1.2 Clinical Studies Overview

The sponsor submitted data from two pivotal Phase 3 trials (Studies 18140 and 18141). An overview of the studies is presented in Table 3.

Table 3: Clinical Study Overview

Study	Location	Study Population	Treatment Arms	Number of Subjects	Dates
18140	US (12 centers) & Canada (3 centers)	Male and female subjects ≥18 years with CEA ≥ 3 (at least moderate erythema) and PSA ≥ 3 (at least moderate redness)	Mirvaso Gel 0.5%	129	5/16/2011 – 9/23/2011
			Vehicle Gel	131	
18141	US (12 centers) & Canada (3 centers)		Mirvaso Gel 0.5%	148	5/16/2011 – 11/22/2011
			Vehicle Gel	145	

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 entirely electronic. The datasets in this review are archived at the following locations:
\\cdsesub1\evsprod\NDA204708\0000\m5\datasets\18140\
\\cdsesub1\evsprod\NDA204708\0000\m5\datasets\18141\

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The databases for the study required minimal data management prior to performing analyses and no request for additional datasets were made to the sponsor.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Studies 18140 and 18141 were identically designed, randomized, multicenter, vehicle-controlled, double-blind, Phase 3 trials evaluating the safety and efficacy of Mirvaso (brimonidine tartrate) gel, 0.5% in the treatment of moderate to severe facial erythema associated with rosacea. Study 18140 enrolled a total of 260 subjects (129 Mirvaso; 131 vehicle) from 15 centers (12 in the U.S. and 3 in Canada) and Study 18141 enrolled a total of 293 subjects (148 Mirvaso; 145 vehicle) from 15 centers (12 in the U.S. and 3 in Canada). The trials enrolled subjects age 18 years and older with a clinical diagnosis of facial rosacea, a Clinical Erythema Assessment (CEA) score of 3 or greater and a Patient Self-Assessment (PSA) score 3 or greater. The CEA scale is presented in Table 4 and the PSA scale is presented in Table 5. Subjects with more than 3 inflammatory lesions were excluded.

Table 4: Clinical Erythema Assessment (CEA) Scale

Grade	Description
0	Clear skin with no signs of erythema
1	Almost clear, slight redness
2	Mild erythema; definite redness
3	Moderate erythema; marked redness
4	Severe erythema; fiery redness

Table 5: Patient Self Assessment (PSA) Scale

Grade	Description
0	No redness
1	Very mild redness
2	Mild redness
3	Moderate redness
4	Severe redness

Subjects applied study product once daily for 4 weeks, with a 4 week follow-up period. Subject assessments were performed at the investigational centers during a 12-hour post dose evaluation period (at 30 min, 3, 6, 9, and 12 hours) at baseline (Day 1), Day 15, and Day 29.

The protocol-specified primary efficacy endpoint was the proportion of subjects with composite success at hours 3, 6, 9, and 12 on Day 29, Day 15 and Day 1, where composite success is defined as 2-grade improvement on both CEA and PSA.

The protocol specified the following two secondary endpoints:

1. "CEA Initial Effect" defined as 1-grade improvement on CEA at 30 minutes on Day 1
2. "PSA Initial Effect" defined as 1-grade improvement on PSA at 30 minutes on Day 1

It should be noted that the statistical analysis plans (SAP) and the study reports for both studies do not have the two above secondary endpoints but had a single secondary endpoint of 30-

minute effect, defined as 1-grade composite success (1-grade improvement on CEA and PSA) at 30 minutes on Day 1.

3.2.2 Statistical Methodologies

The intent-to-treat (ITT) population was defined as all subjects who were randomized and to whom study drug was administered. The per-protocol (PP) population was defined as the ITT subjects who have met all major protocol criteria. The major protocol deviations include:

1. Entrance Criteria Deviations: subjects who do not meet one or more major Inclusion criteria/Exclusion Criteria such as insufficient washouts for prohibited therapies usage prior to Baseline.
2. Prohibited Medication: subjects who have taken interfering concomitant therapies during the post-baseline period.
3. Primary endpoint is incomplete on Day 29: subjects who do not have Composite Success available at least one time points (hours 3, 6, 9 and 12) on Day 29.
4. Administrative error: subjects who have administrative error such as unblinding or drug dispensing errors.

The protocol specified that analysis of the ITT population will be primary and analysis of the PP population will be used to confirm the results from the ITT population.

For Study 18141, the applicant also analyzed a modified intent-to-treat (mITT) population, defined as "the ITT population excluding all subjects from Dr. Baumann's site. The data validity issue for Dr. Baumann site is documented in the Blind Review Meeting Minutes." The Blind Review Minutes states that "all subjects at site #8283 (L.Baumann) will be considered major deviations due to study coordinator admission of falsification of vital sign data for 1 subject." It should be noted that as all subjects at this site were classified as major deviators and these subjects were excluded from the PP population.

The protocol specified a pooling strategy for centers that enrolled less than 18 subjects. These centers were pooled by ordering and combining the smallest with the largest. The process repeated until all pooled centers had at least 18 subjects. For Study 18140, 8 of the 15 centers enrolled less than 16 subjects and the pooling strategy yielded a total of 11 analysis centers. For Study 18141, 7 of the 15 centers enrolled less than 16 subjects and the pooling strategy yielded a total of 11 analysis centers.

For the primary analysis, the applicant used the Generalized Estimating Equation (GEE) methodology to test for a treatment differences between Mirvaso and vehicle on the correlated composite successes measured at hours 3, 6, 9, and 12. The protocol specified a conditional stepwise testing approach for the different days (Days 29, 15, and 1). The applicant will first test Day 29 and if the result is statistically significant (α =0.05), the testing will continue to Day 15 and Day 1 accordingly. The logit link function was used to model the marginal expectation. The independent variables in the model were treatment, analysis center and time-point (hours 3, 6, 9 and 12). The protocol specified that the treatment by analysis center interaction would be examined in a separate GEE model and if the interaction was significant at α =0.10 level, the

results will be further explored to examine the magnitude, direction, and potential impact of the interaction.

For the analysis of the secondary efficacy endpoint of 30-minute effect (1-grade improvement from baseline on CEA and PSA at 30 minutes on Day 1), the protocol-specified method was the Cochran-Mantel-Haenszel (CMH) test stratified by analysis center.

The primary imputation method for missing data was the Multiple Imputation (MI) procedure. The applicant imputed the missing data 5 times using Markov Chain Monte Carlo (MCMC) method with a single chain. Three sensitivity analyses for handling of missing data were specified in the protocol as follows:

1. Imputing all missing data as failures
2. Imputing all missing data as successes
3. Using the average score for the complete data at Hours 3, 6, 9, 12 on CEA and PSA to impute success or failure accordingly.

While not specified in the protocol, the sponsor also imputed missing data using last observation carried forward (LOCF) approach in the study reports.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Study 18140 enrolled 260 subjects (129 to Mirvaso, 131 to vehicle) and Study 18141 enrolled 293 subjects (148 to Mirvaso, 145 to vehicle). For Study 18140, 2 subjects (1.6%) in the Mirvaso arm and 4 subjects (3.1%) in the vehicle arm discontinued prior to the end trial. For Study 18141, 7 subjects (4.7%) in the Mirvaso arm and 3 subjects (2.1%) in the vehicle arm discontinued prior to the end of the trial. Table 6 displays the study duration for those subjects who prematurely discontinued from the trial and Table 7 provides the reasons for discontinuation.

Table 6: Study Duration for Discontinued Subjects (ITT)

	Study 18140		**Study 18141**	
	Mirvaso Gel (N=129)	**Vehicle Gel (N=131)**	**Mirvaso Gel (N=148)**	**Vehicle Gel (N=145)**
Discontinued	2 (1.6%)	4 (3.1%)	7 (4.7%)	3 (2.1%)
1-14 Days	1	0	0	0
15-28 Days	0	3	4	2
29-35 Days	1	1	3	1
36-49 Days	0	0	0	0
> 50 Days	0	0	0	0

Source: Table 14.1.2.3 in Study Reports for Studies 18140 and 18141

Table 7: Reasons for Discontinuations (ITT)

	Study 18140		Study 18141	
	Mirvaso Gel (N=129)	**Vehicle Gel (N=131)**	**Mirvaso Gel (N=148)**	**Vehicle Gel (N=145)**
Discontinued	2 (1.6%)	4 (3.1%)	7 (4.7%)	3 (2.1%)
Adverse Event	2	1	1	1
Subject's Request	0	1	2	0
Lost to Follow-Up	0	1	0	0
Protocol Violation	0	1	3	2
Other	0	0	1	0

Source: Reviewer's Analysis

The demographics were generally balanced across the treatment arms in Studies 18140 and 18141. The demographics are presented in Table 8.

Table 8: Demographics

	Study 18140		Study 18141	
	Mirvaso Gel (N=129)	**Vehicle Gel (N=131)**	**Mirvaso Gel (N=148)**	**Vehicle Gel (N=145)**
Age				
Mean (SD)	49.5 (11.8)	48.1 (12.8)	48.5 (11.9)	46.5 (12.1)
Range	20 - 76	18 - 87	22 - 77	19 - 78
Gender				
Male	25 (19.4%)	29 (22.1%)	43 (29.1%)	37 (25.5%)
Female	104 (80.6%)	102 (77.9%)	105 (70.9%)	108 (74.5%)
Race				
White	127 (98.4%)	129 (98.5%)	145 (98.0%)	144 (99.3%)
Black	2 (1.6%)	1 (0.8%)	2 (1.3%)	1 (0.7%)
Asian	0	1 (0.8%)	1 (0.7%)	0
Ethnicity				
Hispanic or Latino	7 (5.4%)	11 (8.4%)	8 (5.4%)	10 (6.9%)
Not Hispanic or Latino	122 (94.6%)	120 (91.6%)	140 (94.6%)	135 (93.1%)

SD: Standard Deviation
Source: Reviewer's Analysis

The baseline disease characteristics are presented in Table 9. Approximately 86% and 76% of the subjects had moderate CEA at baseline in Studies 18140 and 18141, respectively, and approximately 85% and 86% of subjects had moderate PSA at baseline in Studies 18140 and 18141, respectively. In Study 18140, one subject (8303-001) in the vehicle arm had a baseline PSA score of 1 (very mild) and therefore did not meet the baseline inclusion criteria.

Table 9: Baseline Disease Characteristics (ITT)

	Study 18140		Study 18141	
	Mirvaso Gel (N=129)	**Vehicle Gel (N=131)**	**Mirvaso Gel (N=148)**	**Vehicle Gel (N=145)**
CEA				
3 - Moderate	111 (86.0%)	113 (86.3%)	108 (73.0%)	115 (79.3%)
4 - Severe	18 (14.0%)	18 (13.7%)	40 (27.0%)	30 (20.7%)
PSA				
1 - Very Mild	0	1 (0.8%)	0	0
3 - Moderate	107 (82.9%)	114 (87.0%)	129 (87.2%)	122 (84.1%)
4 - Severe	22 (17.1%)	16 (12.2%)	19 (12.8%)	23 (15.9%)
Skin Class				
I	19 (14.7%)	8 (6.1%)	12 (8.1%)	13 (9.0%)
II	65 (50.4%)	74 (56.5%)	88 (59.5%)	84 (57.9%)
III	38 (29.4%)	37 (28.2%)	36 (24.3%)	38 (26.2%)
IV	6 (4.7%)	11 (8.4%)	11 (7.4%)	9 (6.2%)
V	1 (0.8%)	1 (0.8%)	1 (0.7%)	1 (0.7%)

Source: Reviewer's Analysis

3.2.4 Primary Efficacy Endpoints Results

Tables 10 and 11 present the analysis results for composite success (2-grade improvement on both CEA and PSA) at hours 3, 6, 9, and 12 on Day 29, Day 15 and Day 1 based on the ITT population for Studies 18140 and 18141, respectively. The tables display the observed results and the results when missing data are imputed using Multiple Imputation (MI). The statistical analyses were based on the imputed data. Mirvaso gel was statistically ($p<0.001$) superior to vehicle gel for Day 29, Day 15 and Day 1 in both trials. The results for the PP population were similar to those based on the ITT population for both trials; see Appendix A.1 for the PP population results.

Table 10: Composite Success[(1)] Rates by Hours and Days for Study 18140 (ITT)

	Observed Data		Imputed Data[(2)]		
	Mirvaso Gel (N=129)	**Vehicle Gel (N=131)**	**Mirvaso Gel (N=129)**	**Vehicle Gel (N=131)**	**p-value[(3)]**
Day 29					
Hour 3	40/127 (31.5%)	14/128 (10.9%)	40.2 (31.2%)	14.4 (11.0%)	<0.001
Hour 6	39/127 (30.7%)	12/128 (9.4%)	39 (30.2%)	12.6 (9.6%)	
Hour 9	33/127 (26.0%)	13/128 (10.2%)	33 (25.6%)	13.4 (10.2%)	
Hour 12	29/127 (22.8%)	11/128 (8.6%)	29 (22.5%)	11.6 (8.9%)	
Day 15					
Hour 3	32/128 (25.0%)	4/128 (3.1%)	32 (24.8%)	4.4 (3.4%)	<0.001
Hour 6	35/128 (27.3%)	8/128 (6.3%)	35 (27.1%)	9.4 (7.2%)	
Hour 9	25/128 (19.5%)	7/128 (5.5%)	25 (19.4%)	7.2 (5.5%)	
Hour 12	21/128 (16.4%)	3/128 (2.3%)	21 (16.3%)	3.4 (2.6%)	
Day 1					
Hour 3	21/129 (16.3%)	4/131 (3.1%)	*	*	<0.001
Hour 6	30/129 (23.3%)	3/131 (2.3%)	*	*	
Hour 9	25/129 (19.4%)	5/131 (3.8%)	*	*	
Hour 12	17/129 (13.2%)	4/130 (3.1%)	*	4.2 (3.2%)	

Source: Reviewer's Analysis
(1) Composite success is defined as 2-grade improvement on both CEA and PSA.
(2) Multiple Imputation (MI) was used to impute missing data. The rates displayed are the averages over the 5 imputed datasets.
(3) P-value calculated using imputed data and based on a GEE model with treatment, analysis center and time point.
(*) No missing data, therefore no imputation of missing data.

Table 11: Composite Success[(1)] Rates by Hours and Days for Study 18141 (ITT)

	Observed Data		Imputed Data[(2)]		
	Mirvaso Gel (N=148)	**Vehicle Gel (N=145)**	**Mirvaso Gel (N=148)**	**Vehicle Gel (N=145)**	**p-value[(3)]**
Day 29					
Hour 3	36/142 (25.4%)	13/142 (9.2%)	37.4 (25.3%)	13.2 (9.1%)	<0.001
Hour 6	36/142 (25.4%)	13/142 (9.2%)	37.4 (25.3%)	13 (9.0%)	
Hour 9	25/142 (17.6%)	15/142 (10.6%)	26.2 (17.7%)	15.2 (10.5%)	
Hour 12	30/142 (21.1%)	14/142 (9.9%)	31.8 (21.5%)	14 (9.7%)	
Day 15					
Hour 3	36/143 (25.2%)	5/141 (3.5%)	37 (25.0%)	5 (3.4%)	<0.001
Hour 6	37/143 (25.9%)	6/141 (4.3%)	37.8 (25.5%)	6 (4.1%)	
Hour 9	31/143 (21.7%)	7/141 (5.0%)	32 (21.6%)	7 (4.8%)	
Hour 12	22/143 (15.4%)	10/141 (7.1%)	23.2 (15.7%)	10 (6.9%)	
Day 1					
Hour 3	29/148 (19.6%)	0/145 (0%)	*	*	<0.001
Hour 6	44/148 (29.7%)	3/145 (2.1%)	*	*	
Hour 9	27/148 (18.2%)	1/144 (0.7%)	*	1 (0.7%)	
Hour 12	20/148 (13.5%)	2/144 (1.4%)	*	2 (1.4%)	

Source: Reviewer's Analysis
(1) Composite success is defined as 2-grade improvement on both CEA and PSA.
(2) Multiple Imputation (MI) was used to impute missing data. The rates displayed are the averages over the 5 imputed datasets.
(3) P-value calculated using imputed data and based on a GEE model with treatment, analysis center and time point. For Day 1, as no missing data in the Mirvaso arm and only 1 subject with missing data in the vehicle arm, MI produced the same 5 datasets; therefore the p-value is based on one imputed dataset (i.e. not based on all five identical datasets).
(*) No missing data, therefore no imputation of missing data.

This reviewer also considered the day response rates (average over hours 3, 6, 9, and 12) for Day 29, Day 15, and Day 1. These results for both trials are presented in Table 12.

Table 12: Average Composite Success Rates[(1)] on Days 29, 15, and 1 (ITT)

	Study 18140		Study 18141	
	Mirvaso Gel (N=129)	**Vehicle Gel (N=131)**	**Mirvaso Gel (N=148)**	**Vehicle Gel (N=145)**
Day 29	27.4%	9.9%	22.4%	9.6%
Day 15	21.9%	4.7%	22.0%	4.8%
Day 1	18.0%	3.1%	20.3%	1.0%

Source: Reviewer's Analysis

(1) Composite success is defined as 2-grade improvement on both CEA and PSA. Multiple Imputation (MI) was used to impute missing data. The rates displayed are the averages over hours 3, 6, 9, and 12, and over the 5 imputed datasets.

For Study 18141, the applicant analyzed the mITT population (the ITT population excluding all subjects from site #8283) to address a data validity concern due to study coordinator admission of falsification of vital sign data for 1 subject. Site #8283 enrolled and randomized 33 subjects (17 to Mirvaso and 16 to vehicle). For the mITT population, Mirvaso gel was statistically (α = 0.05) superior to vehicle gel for Day 29, Day 15 and Day 1 and the results were similar to those based on the ITT population. The results are presented in Table 13.

Table 13: Composite Success[(1)] Rates by Hours and Days for Study 18141 (mITT)

	Observed Data		Imputed Data[(2)]		
	Mirvaso Gel (N=131)	**Vehicle Gel (N=129)**	**Mirvaso Gel (N=131)**	**Vehicle Gel (N=129)**	**p-value[(3)]**
Day 29					
Hour 3	27/125 (21.6%)	13/127 (10.2%)	28.4 (21.7%)	13.2 (10.2%)	<0.001
Hour 6	29/125 (23.2%)	13/127 (10.2%)	30.4 (23.2%)	13 (10.1%)	
Hour 9	23/125 (18.4%)	15/127 (11.8%)	24.2 (18.5%)	15.2 (11.8%)	
Hour 12	24/125 (19.2%)	14/127 (11.0%)	25.8 (19.7%)	14 (10.9%)	
Day 15					
Hour 3	30/126 (23.8%)	5/126 (4.0%)	31 (23.7%)	5 (3.9%)	<0.001
Hour 6	30/126 (23.8%)	6/126 (4.8%)	30.8 (23.5%)	6 (4.7%)	
Hour 9	28/126 (22.2%)	7/126 (5.6%)	29 (22.1%)	7 (5.4%)	
Hour 12	19/126 (15.1%)	10/126 (7.9%)	20.2 (15.4%)	10 (7.8%)	
Day 1					
Hour 3	23/131 (17.6%)	0/129 (0%)	*	*	0.004
Hour 6	36/131 (27.5%)	3/129 (2.3%)	*	*	
Hour 9	24/131 (18.3%)	1/128 (0.8%)	*	1 (0.8%)	
Hour 12	15/131 (11.5%)	2/128 (1.6%)	*	2 (1.6%)	

Source: Reviewer's Analysis

(1) Composite success is defined as 2-grade improvement on both CEA and PSA.

(2) Multiple Imputation (MI) was used to impute missing data. The rates displayed are the averages over the 5 imputed datasets.

(3) P-value calculated using imputed data and based on a GEE model with treatment, analysis center and time point. For Day 1, as no missing data in the Mirvaso arm and only 1 subject with missing data in the vehicle arm, MI produced the same 5 datasets; therefore the p-value is based on one imputed dataset (i.e. not based on all five identical datasets).

(*) No missing data, therefore no imputation of missing data.

3.2.5 Missing Data Sensitivity Analyses

The applicant conducted the following sensitivity analyses for missing data:

1. Imputing all missing data as failures
2. Imputing all missing data as successes
3. Using the average score for the complete data at Hours 3, 6, 9, 12 on CEA and PSA to impute success or failure accordingly.
4. Imputing missing data using LOCF

It should be noted the imputing missing data using LOCF was not prespecified in the protocol. As the amount of missing data was relatively low, the results were very similar between the sensitivity analyses and the primary imputation method of MI. The results are presented in Appendix A.2.

This reviewer conducted an additional sensitivity analysis where missing data for Mirvaso gel was imputed as failures and missing data for vehicle gel was imputed as successes. In this most extreme case, Mirvaso gel was still significantly superior to vehicle gel in both trials. The results for the ITT population are presented in Table 14. The results for the PP and MITT populations were similar to those of the ITT population.

Table 14: Reviewer's Sensitivity Analysis[(1)] for Composite Success[(2)] Rates by Hours and Days (ITT)

	Study 18140			Study 18141		
	Mirvaso Gel (N=129)	**Vehicle Gel (N=131)**	**p-value[(2)]**	**Mirvaso Gel (N=148)**	**Vehicle Gel (N=145)**	**p-value[(2)]**
Day 29						
Hour 3	40 (31.0%)	17 (13.0%)	<0.001	36 (24.3%)	16 (11.0%)	<0.001
Hour 6	39 (30.23%)	15 (11.5%)		36 (24.3%)	16 (11.0%)	
Hour 9	33 (25.6%)	16 (12.2%)		25 (16.9%)	18 (12.4%)	
Hour 12	29 (22.5%)	14 (10.7%)		30 (20.3%)	17 (11.7%)	
Day 15						
Hour 3	32 (24.8%)	7 (5.3%)	<0.001	36 (24.3%)	9 (6.2%)	<0.001
Hour 6	35 (27.1%)	11 (8.4%)		37 (25.0%)	10 (6.9%)	
Hour 9	25 (19.4%)	10 (7.6%)		31 (20.9%)	11 (7.6%)	
Hour 12	21 (16.3%)	6 (4.6%)		22 (14.9%)	14 (9.7%)	
Day 1						
Hour 3	21 (16.3%)	4 (3.1%)	<0.001	29 (19.6%)	0 (0%)	0.002
Hour 6	30 (23.3%)	3 (2.3%)		44 (29.7%)	3 (2.1%)	
Hour 9	25 (19.4%)	5 (3.8%)		27 (18.2%)	2 (1.4%)	
Hour 12	17 (13.2%)	5 (3.8%)		20 (13.5%)	3 (2.1%)	

Source: Reviewer's Analysis
(1) Missing data for Mirvaso gel imputed as failures and missing data for vehicle gel was imputed as successes.
(2) Composite success is defined as 2-grade improvement on both CEA and PSA.
(2) P-value calculated using a GEE model with treatment, analysis center and time point.

3.2.6 Secondary Efficacy Endpoints Results

Table 15 provides the analysis results for the secondary endpoint (1-grade improvement on CEA and PSA at 30 minutes on Day 1) defined in the SAP and study reports. Mirvaso gel was statistically ($\alpha = 0.05$) superior to vehicle gel. The results were similar between the ITT, mITT, and PP populations.

Table 15: 30 Minute Effect[(1)] on Day 1

	Study 18140			Study 18141		
Population	**Mirvaso Gel**	**Vehicle Gel**	**p-value[(2)]**	**Mirvaso Gel**	**Vehicle Gel**	**p-value[(2)]**
ITT	36/129 (27.9%)	9/131 (6.9%)	<0.001	42/148 (28.4%)	7/145 (4.8%)	<0.001
MITT	--	--	--	37/131 (28.2%)	6/129 (4.7%)	<0.001
PP	32/113 (28.3%)	8/118 (6.8%)	<0.001	33/119 (27.7%)	4/120 (3.3%)	<0.001

Source: Reviewer's Analysis
(1) 30 minute effect is defined as a 1-grade improvement on CEA and PSA at 30 minutes on Day 1.
(2) P-value based on a CMH test stratified by analysis center.

3.3 Evaluation of Safety

For Study 18140, a total of 103 adverse events (AE) were reported during the trial by 71 subjects: 61 AEs by 38 subjects (29.5%) in the Mirvaso gel arm and 42 AEs by 33 subjects (25.2%) in the vehicle gel arm. For Study 18141, a total 107 AEs were reported during the trial by 85 subjects: 60 AEs by 50 subjects (33.8%) in the Mirvaso gel arm and 47 AEs by 35 subjects (24.1%) in the vehicle gel arm. The AE rates for events occurring in at least 1% of subjects per treatment arm are presented in Table 16.

Table 16: Adverse Events in >1% of Subjects by System Organ Class and Preferred Term

	Study 18140		Study 18141	
	Mirvaso Gel (N=129)	Vehicle Gel (N=131)	Mirvaso Gel (N=148)	Vehicle Gel (N=145)
Gastrointestinal disorders				
Dental caries	0	0	0	2 (1.4%)
General disorders and administration site conditions				
Application site papules	0	0	0	2 (1.4%)
Infections and infestations				
Nasopharyngitis	2 (1.6%)	0	6 (4.1%)	5 (3.4%)
Upper respirator tract infection	0	0	2 (1.4%)	0
Injury, poisoning and procedural complications				
Joint sprain	0	0	2 (1.4%)	1 (0.7%)
Nervous system disorders				
Headache	4 (3.1%)	6 (4.6%)	7 (4.7%)	5 (3.4%)
Skin and subcutaneous tissue disorders				
Dermatitis contact	2 (1.6%)	1 (0.8%)	0	0
Erythema	6 (4.7%)	2 (1.5%)	5 (3.4%)	0
Pruritus	4 (3.1%)	1 (0.8%)	1 (0.7%)	2 (1.4%)
Rosacea	1 (0.8%)	2 (1.5%)	2 (1.4%)	3 (2.1%)
Skin irritation	3 (2.3%)	4 (3.1%)	0	2 (1.4%)
Vascular disorders				
Flushing	4 (3.1%)	0	2 (1.4%)	0
Hypertension	0	0	2 (1.4%)	2 (1.4%)

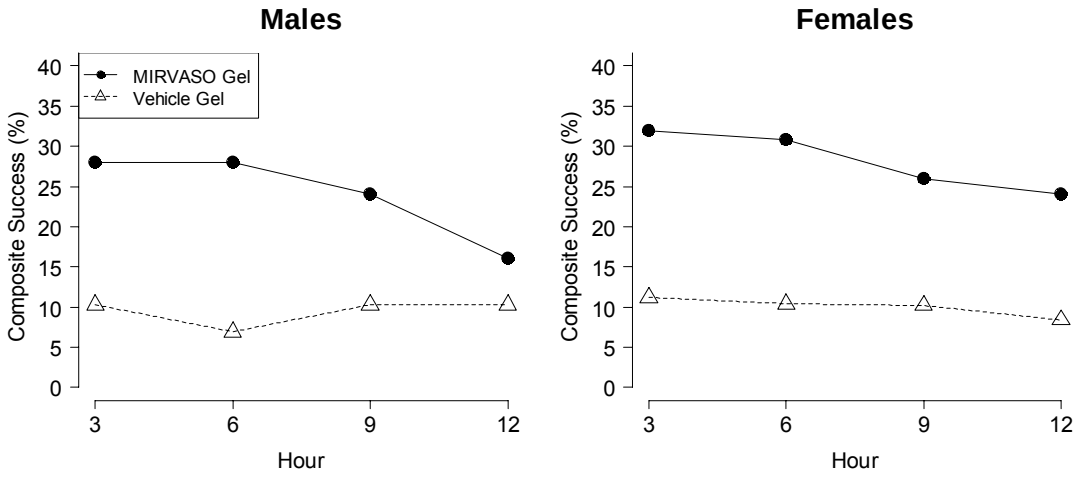
Source: Applicant's Tables 46 and 48, Study Report

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Age, and Race

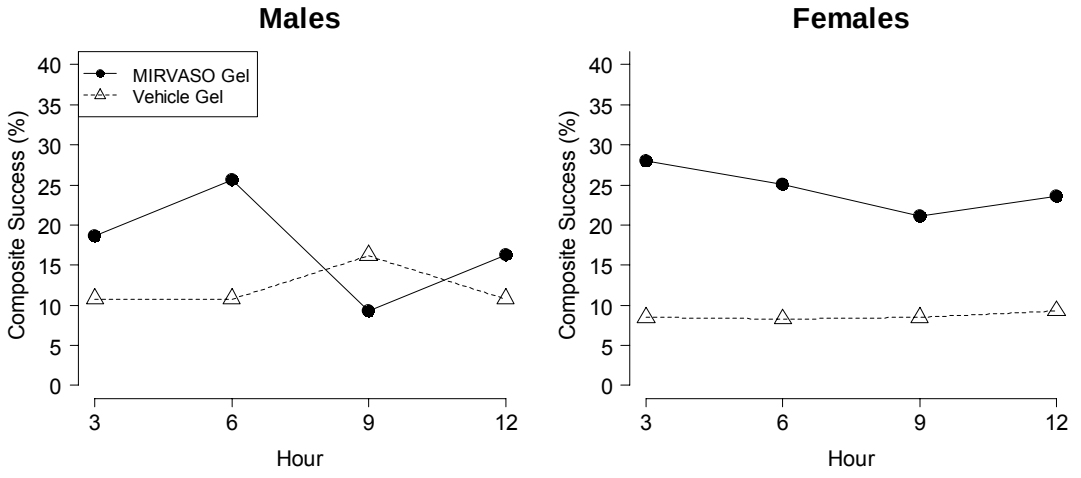
Figures 1 and 2 display the composite success rates by hours and gender on Day 29 for Studies 18140 and 18141, respectively. For Study 18140, the success rates for females were slightly higher than males. For Study 18141, the success rate for males in the Mirvaso gel arm was less than the success rate for males in the vehicle gel arm. However, it should be noted that the number of male subjects is small in both trials. Age was dichotomized by this reviewer into two groups (18-64 and ≥65) and the composite success rates by hours and dichotomized age on Day 29 for Studies 18140 and 18141 are displayed in Figures 3 and 4, respectively. In both trials, there did not appear to be a treatment effect in subject ≥ 65 years of age; however, Studies 18140 and 18141 enrolled 26 subjects (10%) and 23 subjects (7.8%) with ages ≥ 65 years, respectively. Approximately 98% and 99% of the subjects were white in Studies 18140 and 18141, respectively, thus subgroup analyses by race is not feasible.

Figure 1: Composite Success[(1)] Rates by Hours and Gender on Day 29 for Study 18140 (ITT)



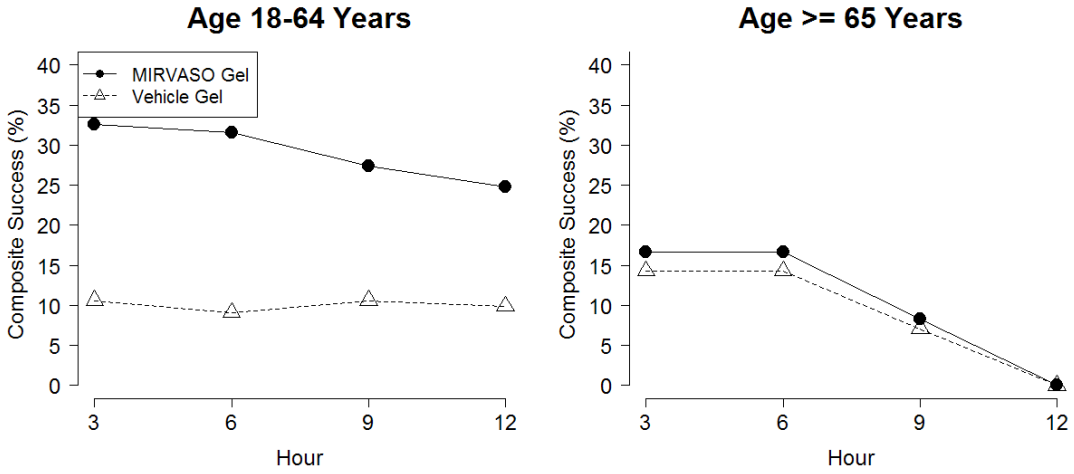
Source: Reviewer's Analysis
(1) Composite success is defined as 2-grade improvement on both CEA and PSA.
(2) Multiple Imputation (MI) was used to impute missing data. The rates displayed are the averages over the 5 imputed datasets.

Figure 2: Composite Success[(1)] Rates by Hours and Gender on Day 29 for Study 18141 (ITT)



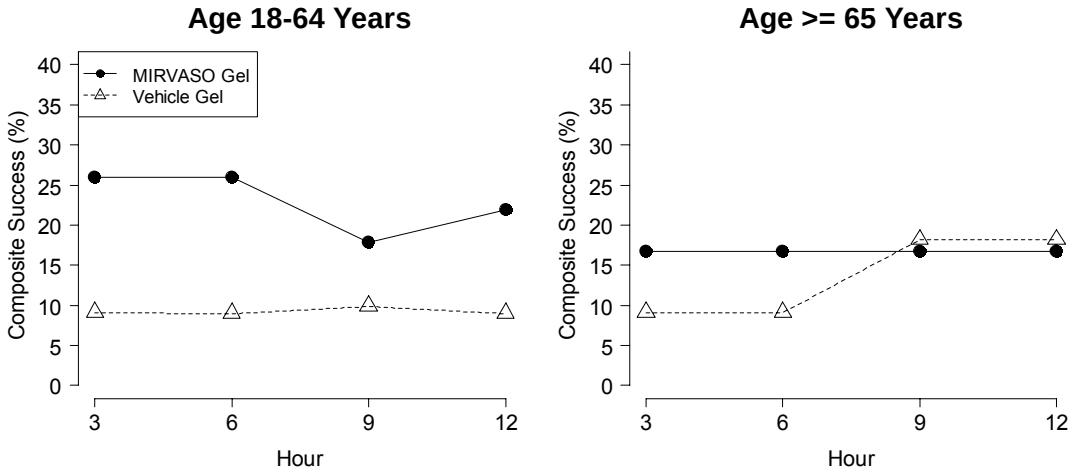
Source: Reviewer's Analysis
(1) Composite success is defined as 2-grade improvement on both CEA and PSA.
(2) Multiple Imputation (MI) was used to impute missing data. The rates displayed are the averages over the 5 imputed datasets.

Figure 3: Composite Success[(1)] Rates by Hours and Age on Day 29 for Study 18140 (ITT)



Source: Reviewer's Analysis
(1) Composite success is defined as 2-grade improvement on both CEA and PSA.
(2) Multiple Imputation (MI) was used to impute missing data. The rates displayed are the averages over the 5 imputed datasets.

Figure 4: Composite Success[(1)] Rates by Hours and Age on Day 29 for Study 18141 (ITT)



Source: Reviewer's Analysis
(1) Composite success is defined as 2-grade improvement on both CEA and PSA.
(2) Multiple Imputation (MI) was used to impute missing data. The rates displayed are the averages over the 5 imputed datasets.

4.2 Efficacy by Center

Treatment effects varied somewhat across centers. The average day results for Day 29 and both trials are presented in Appendix A.3. For Study 18140, 8 of the 15 centers enrolled less than 16 subjects and the pooling strategy yielded a total of 11 pooled analysis centers. For Study 18141, 7 of the 15 centers enrolled less than 16 subjects and the pooling strategy yielded a total of 11 pooled analysis centers. This reviewer conducted a sensitivity analysis where each analysis center was systematically removed to explore the possible effect each analysis center had on the efficacy results. For both studies, the removal of any one analysis center had little impact on the efficacy results.

Three centers (#8026, #8303, and #8060) in Study 18140 and two centers (#8069 and #8226) in Study 18141 had investigators file financial disclosures. This reviewer conducted a sensitivity analyses were analysis centers that had financial disclosures were removed. For both studies, the removal of analysis centers that had financial disclosures had little impact of the efficacy results.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There were no major statistical issues affecting overall conclusions. In Study 18141, a study coordinator admitted to the falsification of vital sign data for 1 subject. The applicant conducted a sensitivity analysis by excluding this center and the results showed that this center did not impact the efficacy findings. This reviewer conducted a sensitivity analysis where each analysis center was systematically removed to determine if any single analysis center dominated the efficacy results. For both studies, the removal of any one analysis center had little impact on the efficacy results.

Since the amount of missing data was relatively small, the results were very similar between the applicant's prespecified sensitivity analyses and the primary imputation method of MI. This reviewer conducted an additional sensitivity analysis where missing data for Mirvaso gel was imputed as failures and missing data for vehicle gel was imputed as successes. In this most extreme case, Mirvaso gel was still significantly superior to vehicle gel in both trials.

5.2 Collective Evidence

The applicant submitted data from two identically designed, randomized, multicenter, vehicle-controlled, parallel-grouped, pivotal Phase 3 trials (Studies 18140 and 18141). The trials evaluated the safety and efficacy of Mirvaso gel compared to vehicle gel. The trials enrolled subjects age 18 years or older with a clinical diagnosis of facial rosacea that had a Clinical Erythema Assessment (CEA) score of 3 (moderate erythema) or greater and a Patient Self-Assessment (PSA) score 3 (moderate redness) or greater. The protocol-specified primary

efficacy endpoint was the proportion of subjects with composite success (defined as a 2-grade reduction in both CEA and PSA) measured at hours 3, 6, 9 and 12 on Day 29, then on Day 15, and lastly on Day 1. The results presented in Tables 10 and 11 (pg. 12) show that Mirvaso gel was statistically ($p<0.001$) superior to vehicle on Day 29, Day 15, and Day 1.

5.3 Conclusions

Efficacy findings from the two pivotal trials (Studies 18140 and 18141) established that Mirvaso gel was superior to vehicle gel in the treatment of facial erythema of rosacea in adults 18 years of age or older.

5.4 Labeling Recommendations

Table 17 is presented in Section 14 (Clinical Studies) of the applicant's proposed label. The values displayed are based on only subjects with evaluations on Day 29 (observed data), which is why they differ from those found in Table 1. This reviewer recommends including those subjects with missing evaluations by using the averages over the 5 imputed datasets generated by the Multiple Imputation (MI) approach, as efficacy results are usually presented for all randomized subjects enrolled in the trial (ITT) and not for observed cases only.

Table 17: Efficacy Table in the Sponsor's Proposed Label

Success	**Study 1**		**Study 2**	
	MIRVASO Gel	**Vehicle Gel**	**MIRVASO Gel**	**Vehicle Gel**
	(b) (4)			
Hour 3				
Hour 6				
Hour 9				
Hour 12				
Day 29 p-value				

Source: The sponsor's proposed label

APPENDIX

A.1 Per-Protocol Results

Table A.1.1: Composite Success[(1)] Rates by Hours and Days for Study 18140 (PP)

	Observed Data		Imputed Data[(2)]		
	Mirvaso Gel (N=113)	**Vehicle Gel (N=118)**	**Mirvaso Gel (N=113)**	**Vehicle Gel (N=118)**	**p-value[(3)]**
Day 29					
Hour 3	35/113 (31.0%)	13/118 (11.0%)	*	*	<0.001
Hour 6	35/113 (31.0%)	11/118 (9.3%)	*	*	
Hour 9	30/113 (26.5%)	12/118 (10.2%)	*	*	
Hour 12	24/113 (21.2%)	9/118 (7.6%)	*	*	
Day 15					
Hour 3	30/113 (26.5%)	4/117 (3.4%)	*	4 (3.4%)	<0.001
Hour 6	33/113 (29.2%)	7/117 (6.0%)	*	7.4 (6.3%)	
Hour 9	23/113 (20.4%)	6/117 (5.1%)	*	6 (5.1%)	
Hour 12	18/113 (15.9%)	2/117 (1.7%)	*	2 (1.7%)	
Day 1					
Hour 3	16/113 (14.2%)	4/118 (3.4%)	*	*	<0.001
Hour 6	22/113 (19.5%)	2/118 (1.7%)	*	*	
Hour 9	22/113 (19.5%)	5/118 (4.2%)	*	*	
Hour 12	15/113 (13.3%)	4/117 (3.4%)	*	4.2 (3.6%)	

Source: Reviewer's Analysis
(1) Composite success is defined as 2-grade improvement on both CEA and PSA.
(2) Multiple Imputation (MI) was used to impute missing data. The rates displayed are the averages over the 5 imputed datasets.
(3) P-value calculated based on a GEE model with treatment, analysis center and time point.
(*) No missing data, therefore no imputation of missing data.

Table A.1.2: Composite Success[(1)] Rates by Hours and Days for Study 18141 (PP)

	Observed Data		Imputed Data[(2)]		
	Mirvaso Gel (N=119)	**Vehicle Gel (N=120)**	**Mirvaso Gel (N=119)**	**Vehicle Gel (N=120)**	**p-value[(3)]**
Day 29					
Hour 3	26/119 (21.8%)	11/120 (9.2%)	*	*	0.003
Hour 6	29/119 (24.4%)	12/120 (10.0%)	*	*	
Hour 9	23/119 (19.3%)	14/120 (11.7%)	*	*	
Hour 12	23/119 (19.3%)	13/120 (10.8%)	*	*	
Day 15					
Hour 3	29/118 (24.6%)	4/119 (3.4%)	29.8 (25.0%)	4 (3.3%)	<0.001
Hour 6	29/118 (24.6%)	5/119 (4.2%)	29.6 (24.9%)	5 (4.2%)	
Hour 9	28/118 (23.7%)	6/119 (5.0%)	28.8 (24.2%)	6 (5.0%)	
Hour 12	19/118 (16.1%)	9/119 (7.6%)	19.6 (16.5%)	9 (7.6%)	
Day 1					
Hour 3	21/119 (17.6%)	0/120 (0%)	*	*	<0.001
Hour 6	32/119 (26.9%)	2/120 (1.7%)	*	*	
Hour 9	21/119 (17.6%)	1/120 (0.8%)	*	*	
Hour 12	13/119 (10.9%)	2/120 (1.7%)	*	*	

Source: Reviewer's Analysis
(1) Composite success is defined as 2-grade improvement on both CEA and PSA.
(2) Multiple Imputation (MI) was used to impute missing data. The rates displayed are the averages over the 5 imputed datasets.
(3) P-value calculated based on a GEE model with treatment, analysis center and time point.
(*) No missing data, therefore no imputation of missing data.

A.2 Missing Data Sensitivity Analyses Results

Table A.2.1: Composite Success[(1)] Rates by Hours and Days when Missing Data Imputed as Failures (ITT)

	Study 18140			Study 18141		
	Mirvaso Gel (N=129)	Vehicle Gel (N=131)	p-value[(2)]	Mirvaso Gel (N=148)	Vehicle Gel (N=145)	p-value[(2)]
Day 29						
Hour 3	40 (31.0%)	14 (10.7%)	<0.001	36 (24.3%)	13 (9.0%)	<0.001
Hour 6	39 (30.2%)	12 (9.2%)		36 (24.3%)	13 (9.0%)	
Hour 9	33 (25.6%)	13 (9.9%)		25 (16.9%)	15 (10.3%)	
Hour 12	29 (22.5%)	11 (8.4%)		30 (20.3%)	14 (9.7%)	
Day 15						
Hour 3	32 (24.8%)	4 (3.1%)	<0.001	36 (24.3%)	5 (3.4%)	<0.001
Hour 6	35 (27.1%)	8 (6.1%)		37 (25.0%)	6 (4.1%)	
Hour 9	25 (19.4%)	7 (5.3%)		31 (20.9%)	7 (4.8%)	
Hour 12	21 (16.3%)	3 (2.3%)		22 (14.9%)	10 (6.9%)	
Day 1						
Hour 3	21 (16.3%)	4 (3.1%)	<0.001	29 (19.6%)	0 (0%)	<0.001
Hour 6	30 (23.3%)	3 (2.3%)		44 (29.7%)	3 (2.1%)	
Hour 9	25 (19.4%)	5 (3.8%)		27 (18.2%)	1 (0.7%)	
Hour 12	17 (13.2%)	4 (3.1%)		20 (13.5%)	2 (1.4%)	

Source: Reviewer's Analysis
(1) Composite success is defined as 2-grade improvement on both CEA and PSA.
(2) P-value calculated based on a GEE model with treatment, analysis center and time point.

Table A.2.2: Composite Success[(1)] Rates by Hours and Days when Missing Data Imputed as Successes (ITT)

	Study 18140			Study 18141		
	Mirvaso Gel (N=129)	Vehicle Gel (N=131)	p-value[(2)]	Mirvaso Gel (N=148)	Vehicle Gel (N=145)	p-value[(2)]
Day 29						
Hour 3	42 (32.6%)	17 (13.0%)	<0.001	42 (28.4%)	16 (11.0%)	<0.001
Hour 6	41 (31.8%)	15 (11.5%)		42 (28.4%)	16 (11.0%)	
Hour 9	35 (27.1%)	16 (12.2%)		31 (20.9%)	18 (12.4%)	
Hour 12	31 (24.0%)	14 (10.7%)		36 (24.3%)	17 (11.7%)	
Day 15						
Hour 3	33 (25.6%)	7 (5.3%)	<0.001	41 (27.7%)	9 (6.2%)	<0.001
Hour 6	36 (27.9%)	11 (8.4%)		42 (28.4%)	10 (6.9%)	
Hour 9	26 (20.2%)	10 (7.6%)		36 (24.3%)	11 (7.6%)	
Hour 12	22 (17.1%)	6 (4.6%)		27 (18.2%)	14 (9.7%)	
Day 1						
Hour 3	21 (16.3%)	4 (3.1%)	<0.001	29 (19.6%)	0 (0%)	<0.001
Hour 6	30 (23.3%)	3 (2.3%)		44 (29.7%)	3 (2.1%)	
Hour 9	25 (19.4%)	5 (3.8%)		27 (18.2%)	2 (1.4%)	
Hour 12	17 (13.2%)	5 (3.8%)		20 (13.5%)	3 (2.1%)	

Source: Reviewer's Analysis
(1) Composite success is defined as 2-grade improvement on both CEA and PSA.
(2) P-value calculated based on a GEE model with treatment, analysis center and time point.

Table A.2.3: Composite Success[(1)] Rates by Hours and Days when Missing Data Imputed as Average Score (ITT)

	Study 18140			Study 18141		
	Mirvaso Gel (N=129)	Vehicle Gel (N=131)	p-value[(2)]	Mirvaso Gel (N=148)	Vehicle Gel (N=145)	p-value[(2)]
Day 29						
Hour 3	40/127 (31.5%)	14/128 (10.9%)	<0.001	36/142 (25.4%)	13/142 (9.2%)	<0.001
Hour 6	39/127 (30.7%)	12/128 (9.4%)		36/142 (25.4%)	13/142 (9.2%)	
Hour 9	33/127 (26.0%)	13/128 (10.2%)		25/142 (17.6%)	15/142 (10.6%)	
Hour 12	29/127 (22.8%)	11/128 (8.6%)		30/142 (21.1%)	14/142 (9.9%)	
Day 15						
Hour 3	32/128 (25.0%)	4/128 (3.1%)	<0.001	36/143 (25.2%)	5/141 (3.5%)	<0.001
Hour 6	35/128 (27.3%)	8/128 (6.5%)		37/143 (25.9%)	6/141 (4.3%)	
Hour 9	25/128 (19.5%)	7/128 (5.5%)		31/143 (21.7%)	7/141 (5.0%)	
Hour 12	21/128 (16.4%)	3/128 (2.3%)		22/143 (15.4%)	10/141 (7.1%)	
Day 1						
Hour 3	21/129 (16.3%)	4/131 (3.1%)	<0.001	29/148 (19.6%)	0/145 (0%)	<0.001
Hour 6	30/129 (23.3%)	3/131 (2.3%)		44/148 (29.7%)	3/145 (2.1%)	
Hour 9	25/129 (19.4%)	5/131 (3.8%)		27/148 (18.2%)	1/145 (0.7%)	
Hour 12	17/129 (13.2%)	4/131 (3.1%)		20/148 (13.5%)	2/145 (1.4%)	

Source: Reviewer's Analysis
(1) Composite success is defined as 2-grade improvement on both CEA and PSA.
(2) P-value calculated based on a GEE model with treatment, analysis center and time point.

Table A.2.4: Composite Success[(1)] Rates by Hours and Days when Missing Data Imputed using LOCF (ITT)

	Study 18140			Study 18141		
	Mirvaso Gel (N=129)	Vehicle Gel (N=131)	p-value[(2)]	Mirvaso Gel (N=148)	Vehicle Gel (N=145)	p-value[(2)]
Day 29						
Hour 3	40 (31.0%)	14 (10.7%)	<0.001	36 (24.3%)	13 (9.0%)	<0.001
Hour 6	39 (30.2%)	13 (9.9%)		37 (25.0%)	13 (9.0%)	
Hour 9	33 (25.6%)	13 (9.9%)		27 (18.2%)	15 (10.3%)	
Hour 12	29 (22.5%)	11 (8.4%)		31 (20.9%)	14 (9.7%)	
Day 15						
Hour 3	32 (24.8%)	4 (3.1%)	<0.001	37 (25.0%)	5 (3.4%)	<0.001
Hour 6	35 (27.1%)	9 (6.9%)		39 (26.4%)	6 (4.1%)	
Hour 9	25 (19.4%)	7 (5.3%)		33 (22.3%)	7 (4.9%)	
Hour 12	21 (16.3%)	3 (2.3%)		23 (15.5%)	10 (6.9%)	
Day 1						
Hour 3	21 (16.3%)	4 (3.1%)	<0.001	29 (19.6%)	0 (0%)	<0.001
Hour 6	30 (23.3%)	3 (2.3%)		44 (29.7%)	3 (2.1%)	
Hour 9	25 (19.4%)	5 (3.8%)		27 (18.2%)	1 (0.7%)	
Hour 12	17 (13.2%)	4 (3.1%)		20 (13.5%)	2 (1.4%)	

Source: Reviewer's Analysis
(1) Composite success is defined as 2-grade improvement on both CEA and PSA.
(2) P-value calculated based on a GEE model with treatment, analysis center and time point.

A.3 Efficacy by Center

Table A.3.1: Average Observed Composite Success Rates[(1)] by Center on Day 29 for Study 18140 (ITT)

Center	Analysis Center	Total # of Subjects	# of Subject with Missing Data	Mirvaso Gel (N=129)	Vehicle Gel (N=129)
8133	1	36	0	34.7%	16.7%
8017	2	28	1 (M)	32.7%	8.9%
8076	3	27	0	37.5%	9.6%
8130	4	24	0	27.1%	6.3%
8057	5	21	1 (V)	32.5%	2.5%
8089	6	18	0	19.4%	0%
8228	7	18	1 (V)	30.6%	0%
8033	8	16	0	18.8%	0%
8060	8	5	0	0%	0%
8149	9	6	0	12.5%	6.3%
8303	9	16	1 (V)	28.1%	0%
8007	10	15	0	25.0%	28.6%
8026	10	6	0	12.5%	25.0%
8110	11	14	0	7.1%	28.6%
8238	11	10	1 (M)	43.8%	15.0%

Source: Reviewer's Analysis
(1) Composite success is defined as 2-grade improvement on both CEA and PSA.

Table A.3.2: Average Observed Composite Success Rates[(1)] by Center on Day 29 for Study 18141 (ITT)

Center	Analysis Center	Total # of Subjects	# of Subject with Missing Data	Mirvaso Gel (N=148)	Vehicle Gel (N=145)
8039	1	44	0	18.2%	2.3%
8056	2	35	0	13.9%	14.7%
8198	3	34	0	35.3%	20.6%
8283	4	33	1 (V)	35.3%	0.0%
8069	5	25	1 (M)	31.8%	15.4%
8139	6	21	0	7.5%	11.4%
8145	7	19	0	13.9%	17.5%
8195	8	18	1 (M)	12.5%	11.1%
8009	9	15	0	18.8%	0.0%
8085	9	2	0	0.0%	0.0%
8147	9	5	1	50.0%	0.0%
8000	10	8	0	43.8%	0.0%
8227	10	15	0	21.9%	17.9%
8212	11	10	1 (M), 1 (V)	15.0%	0.0%
8226	11	9	2 (M), 1(V)	0.0%	0.0%

Source: Reviewer's Analysis
(1) Composite success is defined as 2-grade improvement on both CEA and PSA.

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Matthew Guerra, Ph.D.
Date: June 11, 2013

Statistical Team Leader: Mohamed Alosh, Ph.D.
Date: June 11, 2013

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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 STUDIES

IND/NDA Number:	NDA 204-708
Drug Name:	CD07805/47
Applicant:	Sponosor: Galderma Research and Development, Inc. 2400 route des Colles Les Templiers, BP 87 06902 Sophia Antipolis Cedex France Test Facility: (b) (4) (b) (4)
Documents Reviewed:	Electronic data submitted on November 26, 2012
Review Priority:	Standard
Biometrics Division:	Division of Biometrics -6
Statistical Reviewer:	Min Min, Ph.D.
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Project Manager:	
Keywords:	Carcinogenicity, Dose response

Table of Contents

1. Background

In this submission the sponsor included reports of one animal carcinogenicity study in rats. The purpose of rat study was to assess the carcinogenic potential of the test article, CD07805/47 (brimonidine tartrate) gel, in rats following daily dermal application (60/sex/group) for at least 104 weeks. Three treatment groups of 60 male and 60 female Wistar Han [Crl:WI(Han)] rats were administered the test article at respective dose concentrations of 0.03%, 0.06%, and 0.18% for male animals during the study, 0.18%, 1%, and 2% for female animals from Days 1 through 343 (Week 49). Due to decreasing survival at 1% and 2% in females, these initial mid and high doses were reduced to 0.36% and 0.72% respectively, from Days 344 (Week 50) through 728 (end of study, Week 104), following FDA recommendation. The dose volume was 3 mL/kg/dose. Dose levels corresponded to 0.9, 1.8 and 5.4 mg/kg/day in males and to 5.4, 30 and 60 mg/kg/day in females until day 343 and to 5.4, 10.8 and 21.6 mg/kg/day in females from day 344 until the end of the study. Two additional groups of 60 animals/sex/group served as the control and received 0% (water control) or 0% (placebo gel control). The controls or test article were administered to all groups via dermal application once per day for up to 104 consecutive weeks. Results of this review have been discussed with the reviewing pharmacologist Dr. Wang.

2. Rat Study

Two separate experiments were conducted, one in males and one in females. Male and female Crl:WI(Han)] rats were assigned to 5 groups (60/sex/group) and received two controls (water control and placebo gel control), or at a dose level of 0.9, 1.8 and 5.4 mg/kg/day for males and 5.4, 30 and 60 mg/kg/day in females until day 343 and to 5.4, 10.8 and 21.6 mg/kg/day in females from day 344 until the end of the study, respectively. The dose volume was 3 mL/kg/dose. The following table contains the information about the study design:

Group Assignments				
Group Number	Male (% concentration)	Female (% concentration)	Number of Animals	
			Male	Female
Main Study				
1	0 (water control)	0 (water control)	60	60
2	0 (placebo control)	0 (placebo control)	60	60
3	0.03	0.18	60	60
4	0.06	1/0.36[c]	60	60
5	0.18	2/0.72[c]	60	60
Toxicokinetic				
6	0 (water control)	0 (water control)	4[a]	4[a]
7	0 (placebo control)	0 (placebo control)	4[a]	4[a]
8	0.03	0.18	12[b]	12[b]
9	0.06	1/0.36[c]	12[b]	12[b]
10	0.18	2/0.72[c]	12[b]	12[b]
	Sentinels		25	25

[a]One additional animal included as a possible replacement animal.
[b]Three additional animals included as possible replacement animals.
[c]Dose concentrations were reduced beginning on Day 344.

Observations for morbidity, mortality, injury, and the availability of food and water were conducted twice daily for all animals. Beginning on Week 53, a third mortality check was conducted. Detailed clinical observations for clinical signs and masses as well as evaluation of skin reaction were conducted on main study animals weekly. Body weights were measured and recorded and body weight change was calculated. Food consumption was measured and recorded and food efficiency was calculated. At study termination, necropsy examinations were performed and tissues were microscopically examined.

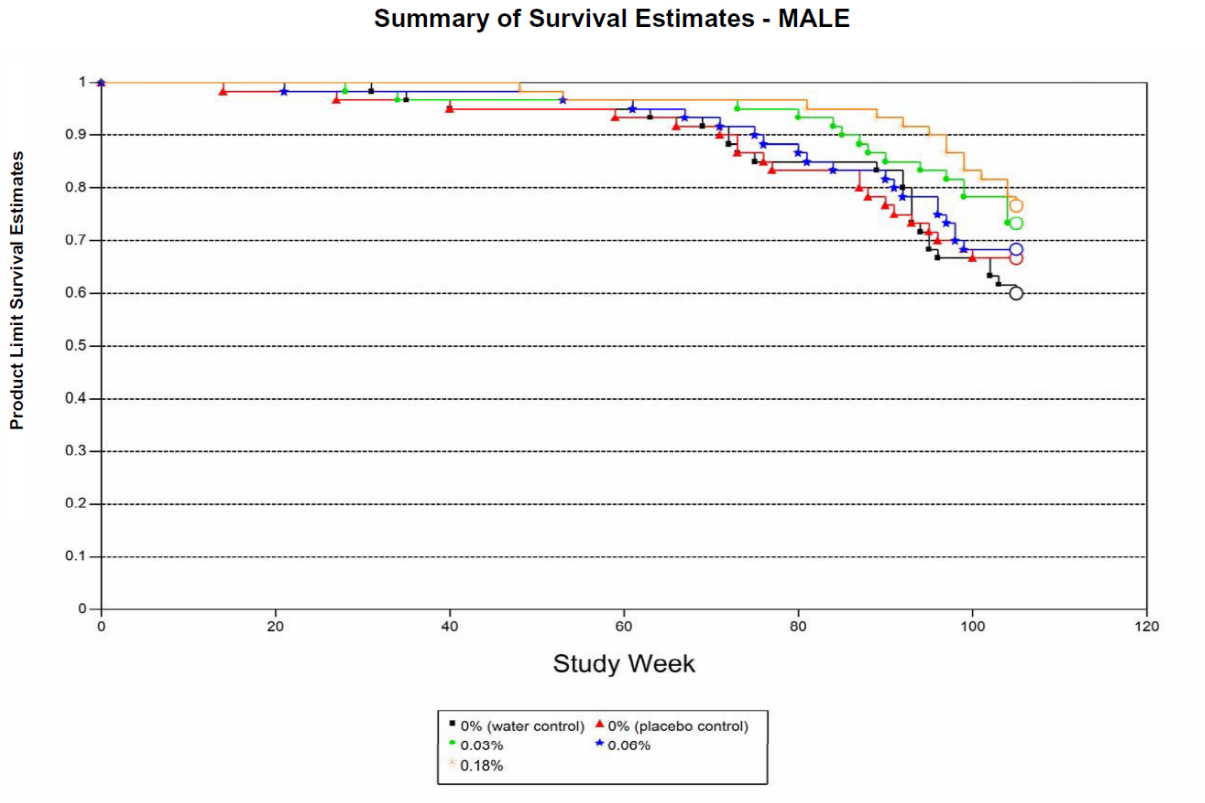
2.1. Sponsor's analyses

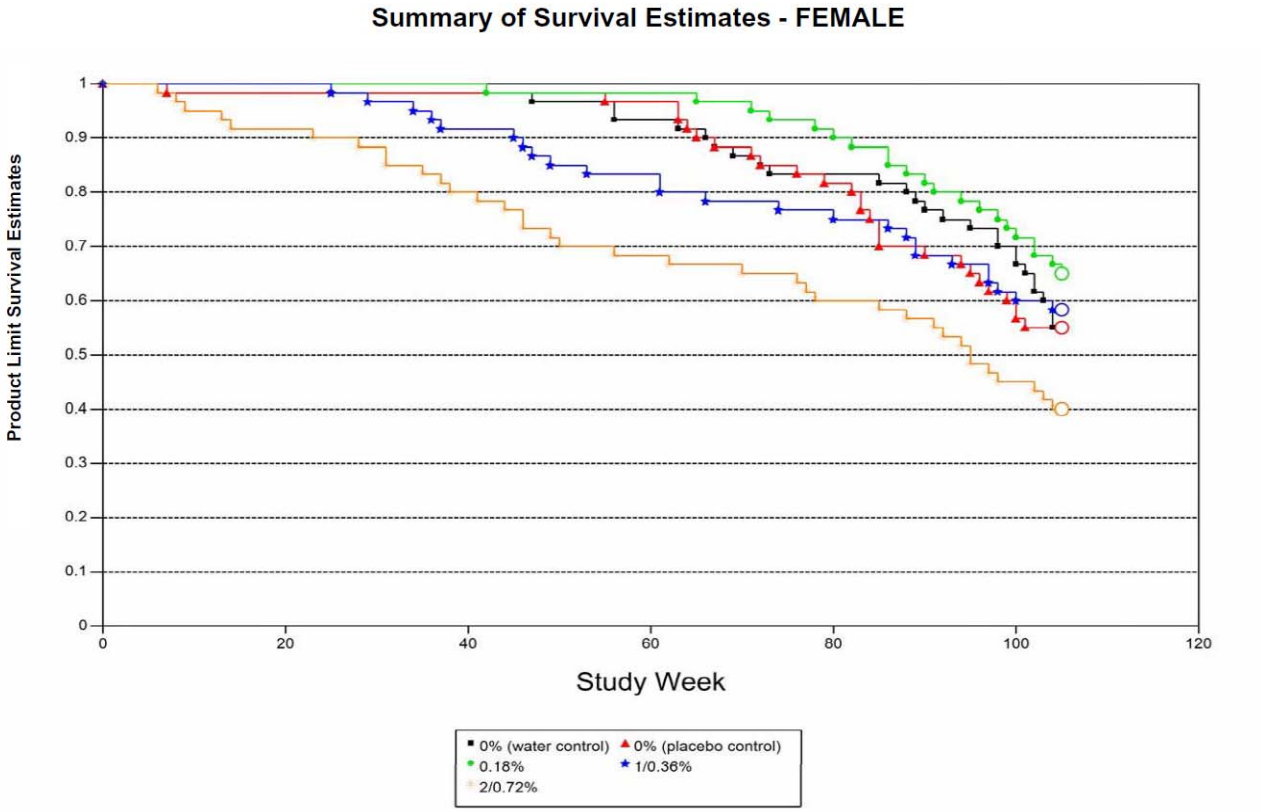
2.1.1. Survival analysis

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

Sponsor's findings: An increased incidence of mortality was noted during the first year of the study among

females at 1 and 2%. Once these doses were reduced to 0.36 and 0.72%, mortality occurred at normal instances. No test article-related causes of death occurred in either sex.





2.1.2. Tumor data analysis

Tumor incidence data were analyzed using both survival adjusted and unadjusted tests. The unadjusted tests were based on the incidence and number of sites examined for each tumor type. The Cochran-Armitage trend test was calculated and Fisher's exact test was used to compare each treatment group with the control group. The survival adjusted test was conducted according to the prevalence/mortality methods described by Peto et al. Evaluation criteria (p-values of significance) was applied differently for rare tumors (background rate of 1% or less) and common tumors (background rate greater than 1%). The evaluation criteria (from the FDA) are given in the following table.

Evaluation Criteria for Common and Rare Tumors	
Test for Positive Trends	**Control-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

Sponsor's findings: No test article-related neoplastic findings occurred in either sex. There were no statistically significant increases in any tumor type in either sex. All tumors noted were of the types typically seen in rats of this strain and age.

2.2. Reviewer's analyses

To verify sponsor's analyses and to perform the additional analysis suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. There are two sets of analysis included: placebo control, water control with three treated groups (survival analysis) and placebo control with three treated groups (tumor analysis). Tumor analysis for placebo and water control group pair-wise comparison is also included. Data used in this reviewer's analyses were provided by the sponsor electronically.

2.2.1. Survival data analysis

The survival distributions of animals in five groups including two controls were estimated by the Kaplan-Meier product limit method. The dose response relationship and homogeneity of survival distributions were tested using the Cox test (Cox, 1972). The inter-current mortality data are given in Tables 1A and 1B in the appendix for five groups (including two controls) in males and females, respectively. The Kaplan-Meier curves for survival rate are given in Figures 1A and 1B with five groups including two control groups in the appendix for males and females, respectively. Results for the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A1, 2A2, 2B1 and 2B2 for two sets groupings (water control, placebo control with three treated groups (Tables 2A1 and 2B1); placebo control with three treated groups (Tables 2A2 and 2B2)) in the appendix for males and females, respectively.

Reviewer's findings: The test results showed no statistically significant dose-response relationship in males and statistically significant difference in mortality in either sex when compared with water control and placebo control, respectively. The test results showed statistically significant dose-response relationship in females when compared with water control and placebo control, respectively. In addition, the test results showed no statistically significant difference in mortality when compared between water control and placebo control in males and females. There were some differences between reviewer's and sponsor's survival rates and the differences may be caused by the different dates of starting the terminal killing.

2.2.2. Tumor data analysis

The tumor data were analyzed for dose response relationships and pair-wise comparisons of the water and placebo control groups; placebo control group with each of the treated groups were performed using the Poly-k method described in the paper of Bailer and Portier (1988), and Bieler and Williams (1993). One critical point for Poly-k test is the choice of the appropriate value of k. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. For the calculation of p-values the exact permutation method was used. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A1 and 3B1 for one set of groupings (placebo control with three treated groups) in the appendix for males and females, respectively.

As suggested by the reviewing pharmacologist Dr. Wang, this reviewer did the analysis of the following combinations of all organ/tumors:

For male rats:
1. combine lymphoma seen in all organs
2. combine hemangioma and hemangiosarcoma seen in all organs

3. adrenal: combine adenoma and carcinoma
4. liver: combine adenoma and carcinoma
5. lymph node: combine same type of tumors seen in different area of lymph nodes in different animals, e.g., combining histiocytic sarcoma seen in different lymph nodes (but if the same tumor was seen in different lymph nodes in the same animal, count as 1)
6. pancreas: combine adenoma and carcinoma
7. skin, subcutis: combine fibroma and fibrosarcoma
8. thyroid gland: combine adenoma and carcinoma originated from the same cell type

For female rats:
In addition to the combinations mentioned above
1. mammary gland: combine adenoma and adenocarcinoma
2. pituitary gland: combine adenoma and carcinoma
3. uterus with cervix: combine adenoma and adenocarcinoma; combine stromal polyp and stromal sarcoma

Multiple testing adjustment: Adjustment for the multiple dose response relationship testing was done using the criteria developed by Lin and Rahman (1998). The criteria recommend the use of a significance level α=0.025 for rare tumors and α=0.005 for common tumors for a submission with two species for 2-year rodent studies, and a significance level α=0.05 for rare tumors and α=0.01 for common tumors for a submission with only one species study 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 spontaneous tumor rate is less than 1%. The adjustment for multiple pair-wise comparisons was done using the criteria developed by Haseman (1983) that recommends the use of a significance level α=0.05 for rare tumors and α=0.01 for common tumors, in order to keep the false-positive rate at the nominal level of approximately 10%. It should be noted that the recommended test levels by Lin and Rahman for the adjustment of multiple testing were originally based on the result of a simulation and an empirical study using the Peto method for dose response relationship analysis. However, some later simulation results by Rahman and Lin (2008) indicate that the criteria apply equally well to the analysis using the poly-3 test.

Reviewer's findings: Following tumor types showed p-values less than or equal to 0.05 either tests for dose response relationship and/or pair-wise comparisons between control and each of individual treated groups. In the following table, p-values in red show significant findings show the significant findings based on the above proposed levels of significance.

Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pair-wise Comparisons

			0 mg	5 mg	20 mg	40 mg				
			Cont	Low	Med	High	P_Value	P_Value	P_Value	P_Value
	Organ Name	Tumor Name	N=60	N=60	N=60	N=60	Dos Resp	C vs. L	C vs. M	C vs. H
Female	cavity, abdomin									
		SCHWANNOMA	0	0	0	2	0.040	.	.	0.185
			[47]	[52]	[44]	[36]	.	.	.	.

For tumor analysis including placebo control and three treated groups:

Based on the criteria of adjustment for multiple testing of trends by Lin and Rahman, the positive dose-response relationship in the incidence of schwannoma from cavity in females was considered to be statistically significant. Also in male rats, the incidence of none of any chosen tested tumor types was considered to have a statistically significant positive dose response relationship and the increased tumor incidences of none of any chosen tested tumor types were considered to be statistically significant when compared to the placebo control group. There are no significant findings in pair-wise comparisons between the water and placebo control groups in either sex.

3. Evaluation of validity of the designs of the male rat study

As having been noted, the tumor data analyses from male rat study showed no statistically significant dose-response relationship in any tested single tumor type. Before drawing any conclusion regarding the carcinogenic or non-carcinogenic potential of the drug in rats and 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 fifty 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 B6C3Fl mice conducted at the (b) (4). 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 consider 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 CD07805/47 rat study, in the light of the above guidelines.

3.1. Male Rat Study

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

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

	Percentage of survival		
	End of 52 weeks	End of 78 weeks	End of 91 weeks
Male	98.3%	96.7%	91.7%
Female	70%	60%	53.3%

Based on the survival criterion Haseman proposed, it could be concluded that enough male rats were exposed to the high dose for a sufficient amount of time.

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

$$\text{Percent difference} = \frac{(\text{Final BW} - \text{Baseline BW})_{\text{Treated}} - (\text{Final BW} - \text{Baseline BW})_{\text{Control}}}{(\text{Final BW} - \text{Baseline BW})_{\text{Control}}} \times 100$$

Percent Difference in Mean body Weight Gain from Control

Male		
1mg	2 mg	5 mg
-4.63	-8.13	-19.49

Source: Table 4 (Volume 1) of sponsor's submission

Therefore, relative to the control, there had been more than 10% decrement in body weight gain in high dose groups in males.

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

Mortality Rates at the End of the Experiment

	Cont.	**1 mg**	**2 mg**	**5 mg**
Male	66.7%	73.3%	68.3%	78.3%

This shows that the morality rate of in the high dose group in males is 9.5% higher than the control. Thus, from the body weight gain and mortality data it can be concluded that for males the used high dose level might have reached or exceeded the MTD. For a final determination of the adequacy of the doses used, other clinical signs and histopathological toxic effects must be considered.

4. Summary

In this submission the sponsor included reports of one animal carcinogenicity study in rats. The purpose of rat study was to assess the carcinogenic potential of the test article, CD07805/47 (brimonidine tartrate) gel, in rats following daily dermal application (60/sex/group) for at least 104 weeks. Three treatment groups of 60 male and 60 female Wistar Han [Crl:WI(Han)] rats were administered the test article at respective dose concentrations of 0.03%, 0.06%, and 0.18% for male animals during the study, 0.18%, 1%, and 2% for female animals from Days 1 through 343 (Week 49). Due to decreasing survival at 1% and 2% in females, these initial mid and high doses were reduced to 0.36% and 0.72% respectively, from Days 344 (Week 50) through 728 (end of study, Week 104), following FDA recommendation. The dose volume was 3 mL/kg/dose.

Rat Study: Two separate experiments were conducted, one in males and one in females. Male and female Crl:WI(Han)] rats were assigned to 5 groups (60/sex/group) and received two controls (water control and placebo gel control), or at a dose level of 0.9, 1.8 and 5.4 mg/kg/day for males and 5.4, 30 and 60 mg/kg/day in females until day 343 and to 5.4, 10.8 and 21.6 mg/kg/day in females from day 344 until the end of the study, respectively. The dose volume was 3 mL/kg/dose.

Survival data analysis:

The test results showed no statistically significant dose-response relationship in males and statistically significant difference in mortality in either sex when compared with water control and placebo control, respectively. The test results showed statistically significant dose-response relationship in females when compared with water control and placebo control, respectively. In addition, the test results showed no statistically significant difference in mortality when compared between water control and placebo control in males and females.

Tumor data analysis (placebo control and three treated groups):

Based on the criteria of adjustment for multiple testing of trends by Lin and Rahman, the positive dose-response relationship in the incidence of schwannoma from cavity in females was considered to be statistically significant.

From the body weight gain and mortality data it can be concluded that for males the used high dose level might have reached or exceeded the MTD. For a final determination of the adequacy of the doses used, other clinical signs and histopathological toxic effects must be considered.

Also in male rats, the incidence of none of any chosen tested tumor types was considered to have a statistically significant positive dose response relationship and the increased tumor incidences of none of any chosen tested tumor types were considered to be statistically significant when compared to the placebo control group. There are no significant findings in pair-wise comparisons between the water and placebo control groups in either sex.

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Team Leader, Biometrics-6

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Dr. Tiwari
Dr. Nevius
Dr. Machado
Dr. Lin
Dr. Min

5. Appendix

Table 1A: Intercurrent Mortality Rate
Male Rats

Week	WATER CONTROL1 NO.OF DEATH	PERCENT	PLACEBO CONTROL NO.OF DEATH	PERCENT	1mg NO.OF DEATH	PERCENT	2mg NO.OF DEATH	PERCENT	5mG NO.OF DEATH	PERCENT
0-52	3	5.0%	3	5.0%	2	3.3%	1	1.7%	1	1.7%
53-78	6	15.0%	7	16.7%	1	5.0%	6	11.7%	1	3.3%
79-92	3	20.0%	5	25.0%	6	15.0%	6	21.7%	3	8.3%
93-104	11	38.0%	5	33.3%	7	26.7%	6	31.7%	8	21.7%
Term. Sac.	37	100.0%	40	100.0%	44	100.0%	41	100.0%	47	100.0%

Table 1B: Intercurrent Mortality Rate
Female Rats

Week	WATER CONTROL NO.OF DEATH	PERCENT	PLACEBO CONTROL NO.OF DEATH	PERCENT	1mg NO.OF DEATH	PERCENT	2mg NO.OF DEATH	PERCENT	5mg NO.OF DEATH	PERCENT
0-52	2	3.3%	1	1.7%	1	1.7%	9	15.0%	18	30.0%
53-78	8	16.7%	9	16.7%	4	8.3%	5	23.3%	6	40.0%
79-92	5	25.0%	9	31.7%	7	20.0%	5	31.7%	4	46.7%
93-104	12	45.0%	8	45.0%	8	33.3%	6	41.7%	8	60.0%
Term. Sac.	33	100.0%	33	100.0%	40	100.0%	35	100.0%	24	100.0%

Table 2A1: Intercurrent Mortality Comparison
Male Rats (five groups)

Test	P-Value (across five groups)	P-Value (water control vs placebo control)	P-Value (water control vs low)	P-Value (water control vs medium)	P-Value (water control vs high)
Dose Response	0.2829	0.8065	0.4162	0.6730	0.2446
Homogeneity	0.2505	0.5727	0.1124	0.3840	0.0334

Table 2A2: Intercurrent Mortality Comparison
Male Rats (placebo control)

Test	P-Value (across four groups)	P-Value (placebo control vs low)	P-Value (placebo control vs medium)	P-Value (placebo control vs high)
Dose Response	0.4351	0.6004	0.8757	0.3895
Homogeneity	0.4436	0.3365	0.7831	0.1430

Table 2B1: Intercurrent Mortality Comparison
Female Rats (five groups)

Test	P-Value (across five groups)	P-Value (water control vs placebo control)	P-Value (water control vs low)	P-Value (water control vs medium)	P-Value (water control vs high)
Dose Response	0.0448	0.8621	0.4299	0.9727	0.1010
Homogeneity	0.0103	0.7943	0.2616	0.9584	0.0222

Table 2B2: Intercurrent Mortality Comparison
Female Rats (placebo control)

Test	P-Value (across four groups)	P-Value (placebo control vs low)	P-Value (placebo control vs medium)	P-Value (placebo control vs high)
Dose Response	0.0426	0.3474	0.9364	0.1359
Homogeneity	0.0061	0.1734	0.9031	0.0384

Table 3A1: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Male Rats (Placebo Control)

Organ Name	Tumor Name	0 mg Cont N=60	1 mg Low N=60	2 mg Med N=60	5 mg High N=60	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
ADRENAL_GLAND		(60)	(60)	(60)	(60)	.	.	.	.
	ADENOMA+CARCINOMA	1	0	2	0	0.752	1.000	0.508	1.000
		[50]	[54]	[51]	[56]	.	.	.	.
ALL_SITES		(60)	(60)	(60)	(60)	.	.	.	.
	HEMANGIOMA+HEMANGIOSARCOMA	2	3	1	4	0.259	0.546	0.886	0.405
		[49]	[54]	[51]	[56]	.	.	.	.
	LYMPHOMAS	0	0	1	1	0.200	.	0.510	0.533
		[49]	[54]	[51]	[56]	.	.	.	.
LIVER		(60)	(60)	(60)	(60)	.	.	.	.
	ADENOMA+CARCINOMA	1	1	1	0	0.861	0.776	0.762	1.000
		[49]	[54]	[51]	[56]	.	.	.	.
LYMPH_NODE		(60)	(60)	(60)	(60)	.	.	.	.
	HISTIOCYTIC_SARCOMA	2	3	4	4	0.293	0.546	0.368	0.405
		[49]	[54]	[52]	[56]	.	.	.	.
	LEUKEMIA	2	3	3	4	0.283	0.546	0.528	0.405
		[49]	[54]	[52]	[56]	.	.	.	.
	LYMPHOMAS	2	3	4	5	0.175	0.546	0.368	0.278
		[49]	[54]	[52]	[56]	.	.	.	.
PANCREAS		(60)	(60)	(60)	(60)	.	.	.	.
	ISLET_CELL_ADENOMA+CARCINOMA	7	3	1	6	0.533	0.968	0.998	0.803
		[49]	[54]	[51]	[56]	.	.	.	.
SKIN_SUBCUTS		(60)	(60)	(60)	(60)	.	.	.	.
	FIBROMA+FIBROSARCOMA	0	3	1	1	0.556	0.140	0.510	0.533
		[49]	[54]	[51]	[56]	.	.	.	.
THYROID_GLAND		(60)	(60)	(60)	(60)	.	.	.	.
	FOLLICULAR_CELL_ADENOMA+CARCIN	3	3	3	3	0.576	0.706	0.689	0.722
		[49]	[54]	[52]	[56]	.	.	.	.
adrenal glands		(60)	(60)	(60)	(60)	.	.	.	.
	ADENOMA, CORTICAL	1	0	2	0	0.752	1.000	0.508	1.000
		[50]	[54]	[51]	[56]	.	.	.	.
	GANGLIONEUROMA	2	0	0	0	1.000	1.000	1.000	1.000
		[50]	[54]	[51]	[56]				

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 3A1 (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Rats (Placebo Control)

Organ Name	Tumor Name	0 mg Cont N=60	1 mg Low N=60	2 mg Med N=60	5 mg High N=60	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
adrenal glands	LEUKEMIA, LARGE GRANULAR LYMPH	0	0	0	1	0.267	.	.	0.533
		[49]	[54]	[51]	[56]	.	.	.	.
	PHEOCHROMOCYTOMA	1	4	2	1	0.768	0.206	0.508	0.780
		[50]	[54]	[51]	[56]	.	.	.	.
	PHEOCHROMOCYTOMA, COMPLEX	1	0	0	0	1.000	1.000	1.000	1.000
		[49]	[54]	[51]	[56]	.	.	.	.
bone marrow, fe		(60)	(60)	(60)	(60)	.	.	.	.
	LEUKEMIA, LARGE GRANULAR LYMPH	0	0	0	1	0.267	.	.	0.533
		[49]	[54]	[51]	[56]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.510	.	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
bone marrow, st		(60)	(60)	(60)	(60)	.	.	.	.
	LEUKEMIA, LARGE GRANULAR LYMPH	0	0	0	1	0.267	.	.	0.533
		[49]	[54]	[51]	[56]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.510	.	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
brain		(60)	(60)	(60)	(60)	.	.	.	.
	ASTROCYTOMA	2	2	1	1	0.797	0.734	0.886	0.902
		[49]	[55]	[51]	[56]	.	.	.	.
	GRANULAR CELL TUMOR	0	1	2	0	0.667	0.524	0.258	.
		[49]	[54]	[51]	[56]	.	.	.	.
	MIXED GLIOMA	0	0	1	0	0.510	.	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.510	.	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
cavity, abdomin		(60)	(60)	(60)	(60)	.	.	.	.
	LYMPHOMA	0	0	1	0	0.510	.	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
	SCHWANNOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[50]	[54]	[51]	[56]	.	.	.	.
cavity, thoraci		(60)	(60)	(60)	(60)	.	.	.	.
	LYMPHOMA	0	0	1	0	0.510	.	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.510	.	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 3A1 (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Male Rats (Placebo Control)

Organ Name	Tumor Name	0 mg Cont N=60	1 mg Low N=60	2 mg Med N=60	5 mg High N=60	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
epididymides		(60)	(60)	(60)	(60)	.	.	.	.
	MESOTHELIOMA	0	0	0	2	0.070	.	.	0.282
		[49]	[54]	[51]	[56]	.	.	.	.
harderian gland		(60)	(60)	(60)	(60)	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.510	.	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
heart		(60)	(60)	(60)	(60)	.	.	.	.
	LIPOSARCOMA	0	1	0	0	0.767	0.524	.	.
		[49]	[54]	[51]	[56]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	1	1	0	0.647	0.524	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
	SCHWANNOMA, ENDOCARDIAL	0	0	1	0	0.510	.	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
	SCHWANNOMA, INTRAMURAL	0	1	0	0	0.767	0.524	.	.
		[49]	[54]	[51]	[56]	.	.	.	.
joint, tibiofem		(60)	(60)	(60)	(60)	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.510	.	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
kidneys		(60)	(60)	(60)	(60)	.	.	.	.
	ADENOMA, RENAL TUBULE	1	0	0	0	1.000	1.000	1.000	1.000
		[49]	[54]	[51]	[56]	.	.	.	.
	HEMANGIOSARCOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[49]	[54]	[51]	[56]	.	.	.	.
	LEUKEMIA, LARGE GRANULAR LYMPH	0	0	0	1	0.267	.	.	0.533
		[49]	[54]	[51]	[56]	.	.	.	.
	LIPOSARCOMA	0	0	0	1	0.267	.	.	0.533
		[49]	[54]	[51]	[56]	.	.	.	.
	LYMPHOMA	0	0	1	0	0.510	.	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
	NEPHROBLASTOMA	0	1	0	0	0.768	0.529	.	.
		[49]	[55]	[51]	[56]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	1	2	0	0.667	0.524	0.258	.
		[49]	[54]	[51]	[56]	.	.	.	.
lacrimal glands		(60)	(60)	(60)	(60)	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.510	.	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 3A1 (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Male Rats (Placebo Control)

Organ Name	Tumor Name	0 mg Cont N=60	1 mg Low N=60	2 mg Med N=60	5 mg High N=60	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
large intestine		(60)	(60)	(60)	(60)	.	.	.	.
	ADENOCARCINOMA	0	1	0	0	0.767	0.524	.	.
		[49]	[54]	[51]	[56]	.	.	.	.
	FIBROMA	1	0	0	1	0.463	1.000	1.000	0.785
		[49]	[54]	[51]	[56]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.510	.	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
liver		(60)	(60)	(60)	(60)	.	.	.	.
	ADENOMA, HEPATOCELLULAR	1	1	1	0	0.861	0.776	0.762	1.000
		[49]	[54]	[51]	[56]	.	.	.	.
	LEUKEMIA, LARGE GRANULAR LYMPH	0	0	0	1	0.267	.	.	0.533
		[49]	[54]	[51]	[56]	.	.	.	.
	LYMPHOMA	0	0	1	0	0.510	.	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	1	2	0	0.667	0.524	0.258	.
		[49]	[54]	[51]	[56]	.	.	.	.
lung		(60)	(60)	(60)	(60)	.	.	.	.
	FIBROSARCOMA	0	1	0	0	0.767	0.524	.	.
		[49]	[54]	[51]	[56]	.	.	.	.
	LEUKEMIA, LARGE GRANULAR LYMPH	0	0	0	1	0.267	.	.	0.533
		[49]	[54]	[51]	[56]	.	.	.	.
	LIPOSARCOMA	0	1	0	0	0.767	0.524	.	.
		[49]	[54]	[51]	[56]	.	.	.	.
	LYMPHOMA	0	0	1	0	0.510	.	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	1	2	0	0.667	0.524	0.258	.
		[49]	[54]	[51]	[56]	.	.	.	.
lymph node, axi		(60)	(60)	(60)	(60)	.	.	.	.
	LEUKEMIA, LARGE GRANULAR LYMPH	0	0	0	1	0.267	.	.	0.533
		[49]	[54]	[51]	[56]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.510	.	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
lymph node, ili		(60)	(60)	(60)	(60)	.	.	.	.
	LEUKEMIA, LARGE GRANULAR LYMPH	0	0	0	1	0.267	.	.	0.533
		[49]	[54]	[51]	[56]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.510	.	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 3A1 (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Male Rats (Placebo Control)

Organ Name	Tumor Name	0 mg Cont N=60	1 mg Low N=60	2 mg Med N=60	5 mg High N=60	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
lymph node, ing		(60)	(60)	(60)	(60)	.	.	.	.
	LEUKEMIA, LARGE GRANULAR LYMPH	0	0	0	1	0.267	.	.	0.533
		[49]	[54]	[51]	[56]	.	.	.	.
	LYMPHOMA	0	0	1	0	0.510	.	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.510	.	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
lymph node, man		(60)	(60)	(60)	(60)	.	.	.	.
	LEUKEMIA, LARGE GRANULAR LYMPH	0	0	0	1	0.267	.	.	0.533
		[49]	[54]	[51]	[56]	.	.	.	.
	LYMPHOMA	0	0	1	0	0.510	.	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.510	.	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
lymph node, med		(60)	(60)	(60)	(60)	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	2	0	0.521	.	0.258	.
		[49]	[54]	[51]	[56]	.	.	.	.
lymph node, mes		(60)	(60)	(60)	(60)	.	.	.	.
	HEMANGIOMA	0	1	0	0	0.767	0.524	.	.
		[49]	[54]	[51]	[56]	.	.	.	.
	HEMANGIOSARCOMA	2	1	1	3	0.272	0.896	0.886	0.564
		[49]	[54]	[51]	[56]	.	.	.	.
	LEUKEMIA, LARGE GRANULAR LYMPH	0	0	0	1	0.267	.	.	0.533
		[49]	[54]	[51]	[56]	.	.	.	.
	LYMPHOMA	0	0	1	0	0.510	.	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	1	1	0	0.647	0.524	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
mammary gland		(60)	(60)	(60)	(60)	.	.	.	.
	ADENOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[49]	[54]	[51]	[56]	.	.	.	.
multicentric ne		(60)	(60)	(60)	(60)	.	.	.	.
	LEUKEMIA, LARGE GRANULAR LYMPH	0	0	0	1	0.267	.	.	0.533
		[49]	[54]	[51]	[56]	.	.	.	.
	LYMPHOMA	0	0	1	1	0.200	.	0.510	0.533
		[49]	[54]	[51]	[56]	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 3A1 (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Male Rats (Placebo Control)

Organ Name	Tumor Name	0 mg Cont N=60	1 mg Low N=60	2 mg Med N=60	5 mg High N=60	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
lymph node, ing		(60)	(60)	(60)	(60)	.	.	.	.
	LEUKEMIA, LARGE GRANULAR LYMPH	0	0	0	1	0.267	.	.	0.533
		[49]	[54]	[51]	[56]	.	.	.	.
	LYMPHOMA	0	0	1	0	0.510	.	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.510	.	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
lymph node, man		(60)	(60)	(60)	(60)	.	.	.	.
	LEUKEMIA, LARGE GRANULAR LYMPH	0	0	0	1	0.267	.	.	0.533
		[49]	[54]	[51]	[56]	.	.	.	.
	LYMPHOMA	0	0	1	0	0.510	.	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.510	.	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
lymph node, med		(60)	(60)	(60)	(60)	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	2	0	0.521	.	0.258	.
		[49]	[54]	[51]	[56]	.	.	.	.
lymph node, mes		(60)	(60)	(60)	(60)	.	.	.	.
	HEMANGIOMA	0	1	0	0	0.767	0.524	.	.
		[49]	[54]	[51]	[56]	.	.	.	.
	HEMANGIOSARCOMA	2	1	1	3	0.272	0.896	0.886	0.564
		[49]	[54]	[51]	[56]	.	.	.	.
	LEUKEMIA, LARGE GRANULAR LYMPH	0	0	0	1	0.267	.	.	0.533
		[49]	[54]	[51]	[56]	.	.	.	.
	LYMPHOMA	0	0	1	0	0.510	.	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	1	1	0	0.647	0.524	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
mammary gland		(60)	(60)	(60)	(60)	.	.	.	.
	ADENOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[49]	[54]	[51]	[56]	.	.	.	.
multicentric ne		(60)	(60)	(60)	(60)	.	.	.	.
	LEUKEMIA, LARGE GRANULAR LYMPH	0	0	0	1	0.267	.	.	0.533
		[49]	[54]	[51]	[56]	.	.	.	.
	LYMPHOMA	0	0	1	1	0.200	.	0.510	0.533
		[49]	[54]	[51]	[56]	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 3A1 (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Male Rats (Placebo Control)

Organ Name	Tumor Name	0 mg Cont N=60	1 mg Low N=60	2 mg Med N=60	5 mg High N=60	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
pituitary gland	LEUKEMIA, LARGE GRANULAR LYMPH	[49]	[54]	[51]	[56]	.	.	.	.
preputial gland		(60)	(60)	(60)	(60)	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.510	.	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
prostate gland		(60)	(60)	(60)	(60)	.	.	.	.
	ADENOMA	0	0	2	1	0.221	.	0.258	0.533
		[49]	[54]	[51]	[56]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	1	1	0	0.647	0.524	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
salivary gland,		(60)	(60)	(60)	(60)	.	.	.	.
	SCHWANNOMA	0	0	1	0	0.510	.	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
skeletal muscle		(60)	(60)	(60)	(60)	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.510	.	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
skin, subcutis		(60)	(60)	(60)	(60)	.	.	.	.
	FIBROMA	0	1	1	1	0.322	0.524	0.510	0.533
		[49]	[54]	[51]	[56]	.	.	.	.
	FIBROSARCOMA	0	2	0	0	0.826	0.272	.	.
		[49]	[54]	[51]	[56]	.	.	.	.
	LIPOSARCOMA	0	1	0	0	0.767	0.524	.	.
		[49]	[54]	[51]	[56]	.	.	.	.
	LYMPHOMA	0	0	1	0	0.510	.	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.510	.	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
	SCHWANNOMA	1	0	1	1	0.463	1.000	0.757	0.780
		[50]	[54]	[51]	[56]	.	.	.	.
skin, treated		(60)	(60)	(60)	(60)	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.510	.	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
skin, untreated		(60)	(60)	(60)	(60)	.	.	.	.
	ADENOMA, BASAL CELL	1	0	0	0	1.000	1.000	1.000	1.000
		[49]	[54]	[51]	[56]	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 3A1 (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Male Rats (Placebo Control)

Organ Name	Tumor Name	0 mg Cont N=60	1 mg Low N=60	2 mg Med N=60	5 mg High N=60	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
skin, untreated	ADENOMA, SEBACEOUS CELL	0	0	1	0	0.510	.	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
	KERATOACANTHOMA	0	3	2	1	0.564	0.140	0.258	0.533
		[49]	[54]	[51]	[56]	.	.	.	.
	PAPILLOMA, SQUAMOUS CELL	0	1	1	0	0.647	0.524	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.510	.	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
small intestine		(60)	(60)	(60)	(60)	.	.	.	.
	LEIOMYOSARCOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[49]	[54]	[51]	[56]	.	.	.	.
spleen		(60)	(60)	(60)	(60)	.	.	.	.
	HEMANGIOMA	0	1	0	0	0.767	0.524	.	.
		[49]	[54]	[51]	[56]	.	.	.	.
	HEMANGIOSARCOMA	0	0	0	1	0.267	.	.	0.533
		[49]	[54]	[51]	[56]	.	.	.	.
	LEUKEMIA, LARGE GRANULAR LYMPH	0	0	0	1	0.267	.	.	0.533
		[49]	[54]	[51]	[56]	.	.	.	.
	LYMPHOMA	0	0	1	0	0.510	.	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	1	1	0	0.647	0.524	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
stomach, glandu		(60)	(60)	(60)	(60)	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.510	.	0.510	.
		[49]	[54]	[51]	[56]	.	.	.	.
testes		(60)	(60)	(60)	(60)	.	.	.	.
	ADENOMA, INTERSTITIAL CELL	4	2	3	0	0.985	0.918	0.798	1.000
		[49]	[54]	[51]	[56]	.	.	.	.
thymus		(60)	(60)	(60)	(60)	.	.	.	.
	LYMPHOMA	0	0	0	1	0.267	.	.	0.533
		[49]	[54]	[51]	[56]	.	.	.	.
	THYMOMA	1	0	2	0	0.756	1.000	0.515	1.000
		[49]	[54]	[51]	[56]	.	.	.	.
thyroid gland		(60)	(60)	(60)	(60)	.	.	.	.
	ADENOMA, C-CELL	11	8	8	11	0.496	0.885	0.867	0.705

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 3A1 (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Male Rats (Placebo Control)

Organ Name	Tumor Name	0 mg Cont N=60	1 mg Low N=60	2 mg Med N=60	5 mg High N=60	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
thyroid gland	ADENOMA, C-CELL	[50]	[54]	[52]	[56]	.	.	.	.
	ADENOMA, FOLLICULAR CELL	2	3	1	3	0.431	0.546	0.889	0.564
		[49]	[54]	[52]	[56]	.	.	.	.
	CARCINOMA, FOLLICULAR CELL	2	0	2	0	0.895	1.000	0.706	1.000
		[49]	[54]	[51]	[56]	.	.	.	.
zymbal`s gland		(60)	(60)	(60)	(60)	.	.	.	.
	CARCINOMA, SEBACEOUS CELL	0	0	0	1	0.267	.	.	0.533
		[49]	[54]	[51]	[56]	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 3B1: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Female Rats (Placebo Control)

Organ Name	Tumor Name	0 mg Cont N=60	5 mg Low N=60	20 mg Med N=60	40 mg High N=60	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
ADRENAL_GLANDS		(60)	(60)	(60)	(60)	.	.	.	.
	ADENOMA+CARCINOMA	0	1	0	0	0.447	0.525	.	.
		[47]	[52]	[44]	[36]	.	.	.	.
ALL_SITES		(60)	(60)	(60)	(60)	.	.	.	.
	LYMPHOMAS	6	0	0	0	1.000	1.000	1.000	1.000
		[48]	[52]	[44]	[36]	.	.	.	.
LYMPH_NODE		(60)	(60)	(60)	(60)	.	.	.	.
	LYMPHOMA	6	3	2	1	0.952	0.941	0.964	0.984
		[48]	[53]	[45]	[36]	.	.	.	.
MAMMARY_GLAND		(60)	(60)	(60)	(60)	.	.	.	.
	ADENOMA+ADENOCARCINOMA	9	4	0	3	0.950	0.972	1.000	0.952
		[49]	[52]	[44]	[36]	.	.	.	.
PANCREAS		(60)	(60)	(60)	(60)	.	.	.	.
	ADENOMA+CARCINOMA	2	3	0	2	0.559	0.548	1.000	0.585
		[47]	[52]	[44]	[36]	.	.	.	.
	ISLET_CELL_ADENOMA+CARCINOMA	2	2	0	2	0.475	0.729	1.000	0.585
		[47]	[52]	[44]	[36]	.	.	.	.
PITUITARY_GLAND		(60)	(60)	(60)	(60)	.	.	.	.
	ADENOMA+CARCINOMA	47	40	40	29	0.749	0.979	0.841	0.946
		[55]	[56]	[50]	[39]	.	.	.	.
SKIN_SUBCUTIS		(60)	(60)	(60)	(60)	.	.	.	.
	FIBROMA+FIBROSARCOMA	1	1	0	0	0.932	0.777	1.000	1.000
		[47]	[52]	[44]	[36]	.	.	.	.
THYROID_GLAND		(60)	(60)	(60)	(60)	.	.	.	.
	C_CELL_ADENOMA+CARCINOMA	10	4	6	3	0.857	0.985	0.883	0.970
		[49]	[52]	[45]	[36]	.	.	.	.
	FOLLICULAR_CELL_ADENOMA+CARCIN	4	4	2	1	0.902	0.698	0.883	0.947
		[47]	[52]	[44]	[36]	.	.	.	.
UTERUS_CERVIX		(60)	(60)	(60)	(60)	.	.	.	.
	ADENOMA+ADENOCARCINOMA	2	1	4	1	0.425	0.897	0.318	0.824
		[47]	[52]	[45]	[36]	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 3B1 (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Female Rats (Placebo Control)

Organ Name	Tumor Name	0 mg Cont N=60	5 mg Low N=60	20 mg Med N=60	40 mg High N=60	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
UTERUS_CERVIX	STROMAL_POLYP+SARCOMA	8	7	7	4	0.705	0.779	0.647	0.850
		[48]	[53]	[44]	[36]	.	.	.	.
adrenal glands		(60)	(60)	(60)	(60)	.	.	.	.
	CARCINOMA, CORTICAL	0	1	0	0	0.737	0.525	.	.
		[47]	[52]	[44]	[36]	.	.	.	.
	PHEOCHROMOCYTOMA	0	1	0	2	0.071	0.530	.	0.185
		[47]	[53]	[44]	[36]	.	.	.	.
brain		(60)	(60)	(60)	(60)	.	.	.	.
	ASTROCYTOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[47]	[52]	[44]	[36]	.	.	.	.
	CARCINOMA, PARS DISTALIS	1	1	1	2	0.196	0.777	0.742	0.400
		[47]	[52]	[45]	[36]	.	.	.	.
	MIXED GLIOMA	0	1	0	0	0.739	0.530	.	.
		[47]	[53]	[44]	[36]	.	.	.	.
cavity, abdomin		(60)	(60)	(60)	(60)	.	.	.	.
	ADENOCARCINOMA	0	0	0	1	0.201	.	.	0.434
		[47]	[52]	[44]	[36]	.	.	.	.
	ADENOCARCINOMA (PRIMARY SITE U	0	0	1	0	0.450	.	0.489	.
		[47]	[52]	[45]	[36]	.	.	.	.
	SCHWANNOMA	0	0	0	2	0.040	.	.	0.185
		[47]	[52]	[44]	[36]	.	.	.	.
cavity, oral		(60)	(60)	(60)	(60)	.	.	.	.
	CARCINOMA, SQUAMOUS CELL	0	0	1	0	0.447	.	0.484	.
		[47]	[52]	[44]	[36]	.	.	.	.
cavity, thoraci		(60)	(60)	(60)	(60)	.	.	.	.
	ADENOCARCINOMA	0	0	0	1	0.201	.	.	0.434
		[47]	[52]	[44]	[36]	.	.	.	.
	PHEOCHROMOCYTOMA	0	1	0	0	0.739	0.530	.	.
		[47]	[53]	[44]	[36]	.	.	.	.
esophagus		(60)	(60)	(60)	(60)	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	1	0	0	0.739	0.530	.	.
		[47]	[53]	[44]	[36]	.	.	.	.
heart		(60)	(60)	(60)	(60)	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	1	0	0	0.739	0.530	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 3B1 (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Female Rats (Placebo Control)

Organ Name	Tumor Name	0 mg Cont N=60	5 mg Low N=60	20 mg Med N=60	40 mg High N=60	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
heart	SARCOMA, HISTIOCYTIC	[47]	[53]	[44]	[36]	.	.	.	.
	SCHWANNOMA, ENDOCARDIAL	2	0	0	0	1.000	1.000	1.000	1.000
		[47]	[52]	[44]	[36]	.	.	.	.
lacrimal glands		(60)	(60)	(60)	(60)	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	1	0	0	0.739	0.530	.	.
		[47]	[53]	[44]	[36]	.	.	.	.
large intestine		(60)	(60)	(60)	(60)	.	.	.	.
	ADENOMA	0	0	1	0	0.447	.	0.484	.
		[47]	[52]	[44]	[36]	.	.	.	.
	FIBROSARCOMA	0	0	1	0	0.447	.	0.484	.
		[47]	[52]	[44]	[36]	.	.	.	.
larynx		(60)	(60)	(60)	(60)	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	1	0	0	0.739	0.530	.	.
		[47]	[53]	[44]	[36]	.	.	.	.
liver		(60)	(60)	(60)	(60)	.	.	.	.
	ADENOCARCINOMA	1	0	1	0	0.699	1.000	0.742	1.000
		[47]	[52]	[45]	[36]	.	.	.	.
	ADENOMA, HEPATOCELLULAR	0	3	0	0	0.857	0.141	.	.
		[47]	[52]	[44]	[36]	.	.	.	.
	LIPOMA	0	0	1	0	0.447	.	0.484	.
		[47]	[52]	[44]	[36]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	1	0	0	0.739	0.530	.	.
		[47]	[53]	[44]	[36]	.	.	.	.
lung		(60)	(60)	(60)	(60)	.	.	.	.
	ADENOCARCINOMA	1	0	1	1	0.322	1.000	0.742	0.682
		[47]	[52]	[45]	[36]	.	.	.	.
	CARCINOMA, CORTICAL	0	1	0	0	0.737	0.525	.	.
		[47]	[52]	[44]	[36]	.	.	.	.
	PHEOCHROMOCYTOMA	0	1	0	0	0.739	0.530	.	.
		[47]	[53]	[44]	[36]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	1	0	0	0.739	0.530	.	.
		[47]	[53]	[44]	[36]	.	.	.	.
lymph node, axi		(60)	(60)	(60)	(60)	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	1	0	0	0.739	0.530	.	.
		[47]	[53]	[44]	[36]	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 3B1 (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Female Rats (Placebo Control)

Organ Name	Tumor Name	0 mg Cont N=60	5 mg Low N=60	20 mg Med N=60	40 mg High N=60	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
lymph node, ili		(60)	(60)	(60)	(60)	.	.	.	.
	ADENOCARCINOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[47]	[52]	[44]	[36]	.	.	.	.
lymph node, man		(60)	(60)	(60)	(60)	.	.	.	.
	CARCINOMA, C-CELL	0	1	0	0	0.737	0.525	.	.
		[47]	[52]	[44]	[36]	.	.	.	.
	CARCINOMA, SQUAMOUS CELL	0	0	1	0	0.450	.	0.489	.
		[47]	[52]	[45]	[36]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	1	0	0	0.739	0.530	.	.
		[47]	[53]	[44]	[36]	.	.	.	.
lymph node, med		(60)	(60)	(60)	(60)	.	.	.	.
	PHEOCHROMOCYTOMA	0	1	0	0	0.739	0.530	.	.
		[47]	[53]	[44]	[36]	.	.	.	.
lymph node, mes		(60)	(60)	(60)	(60)	.	.	.	.
	HEMANGIOSARCOMA	0	0	1	1	0.139	.	0.484	0.434
		[47]	[52]	[44]	[36]	.	.	.	.
	LYMPHOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[47]	[52]	[44]	[36]	.	.	.	.
mammary gland		(60)	(60)	(60)	(60)	.	.	.	.
	ADENOCARCINOMA	9	3	0	3	0.934	0.990	1.000	0.952
		[49]	[52]	[44]	[36]	.	.	.	.
	ADENOMA	0	2	0	0	0.779	0.273	.	.
		[47]	[52]	[44]	[36]	.	.	.	.
	FIBROADENOMA	3	6	4	4	0.336	0.308	0.463	0.352
		[47]	[53]	[44]	[36]	.	.	.	.
multicentric ne		(60)	(60)	(60)	(60)	.	.	.	.
	LYMPHOMA	6	0	0	0	1.000	1.000	1.000	1.000
		[48]	[52]	[44]	[36]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	1	0	0	0.739	0.530	.	.
		[47]	[53]	[44]	[36]	.	.	.	.
ovaries		(60)	(60)	(60)	(60)	.	.	.	.
	GRANULOSA CELL TUMOR	0	0	2	0	0.422	.	0.231	.
		[47]	[52]	[44]	[36]	.	.	.	.
	SEX-CORD/STROMAL TUMOR	1	1	0	0	0.932	0.777	1.000	1.000
		[47]	[52]	[44]	[36]	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 3B1 (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Female Rats (Placebo Control)

Organ Name	Tumor Name	0 mg Cont N=60	5 mg Low N=60	20 mg Med N=60	40 mg High N=60	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
oviducts		(60)	(60)	(60)	(60)	.	.	.	.
	ADENOCARCINOMA	0	0	1	0	0.450	.	0.489	.
		[47]	[52]	[45]	[36]	.	.	.	.
pancreas		(60)	(60)	(60)	(60)	.	.	.	.
	ADENOCARCINOMA	0	0	1	0	0.450	.	0.489	.
		[47]	[52]	[45]	[36]	.	.	.	.
	ADENOMA, ACINAR CELL	0	1	0	0	0.737	0.525	.	.
		[47]	[52]	[44]	[36]	.	.	.	.
	ADENOMA, ISLET CELL	1	2	0	1	0.598	0.538	1.000	0.682
		[47]	[52]	[44]	[36]	.	.	.	.
	CARCINOMA, ISLET CELL	1	0	0	1	0.422	1.000	1.000	0.682
		[47]	[52]	[44]	[36]	.	.	.	.
	PHEOCHROMOCYTOMA	0	1	0	0	0.739	0.530	.	.
		[47]	[53]	[44]	[36]	.	.	.	.
pharynx		(60)	(60)	(60)	(60)	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	1	0	0	0.739	0.530	.	.
		[47]	[53]	[44]	[36]	.	.	.	.
pituitary gland		(60)	(60)	(60)	(60)	.	.	.	.
	ADENOMA, PARS DISTALIS	46	39	39	27	0.835	0.976	0.784	0.971
		[55]	[56]	[49]	[39]	.	.	.	.
	ADENOMA, PARS INTERMEDIA	0	1	1	0	0.564	0.530	0.484	.
		[47]	[53]	[44]	[36]	.	.	.	.
	CARCINOMA, PARS DISTALIS	1	1	1	2	0.196	0.777	0.742	0.400
		[47]	[52]	[45]	[36]	.	.	.	.
salivary gland,		(60)	(60)	(60)	(60)	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	1	0	0	0.739	0.530	.	.
		[47]	[53]	[44]	[36]	.	.	.	.
skeletal muscle		(60)	(60)	(60)	(60)	.	.	.	.
	ADENOCARCINOMA	0	0	0	1	0.201	.	.	0.434
		[47]	[52]	[44]	[36]	.	.	.	.
skin, subcutis		(60)	(60)	(60)	(60)	.	.	.	.
	FIBROMA	0	1	0	0	0.737	0.525	.	.
		[47]	[52]	[44]	[36]	.	.	.	.
	FIBROSARCOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[47]	[52]	[44]	[36]	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 3B1 (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Female Rats (Placebo Control)

Organ Name	Tumor Name	0 mg Cont N=60	5 mg Low N=60	20 mg Med N=60	40 mg High N=60	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
skin, subcutis	SARCOMA, HISTIOCYTIC	0	1	0	0	0.739	0.530	.	.
		[47]	[53]	[44]	[36]	.	.	.	.
skin, treated		(60)	(60)	(60)	(60)	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	1	0	0	0.739	0.530	.	.
		[47]	[53]	[44]	[36]	.	.	.	.
skin, untreated		(60)	(60)	(60)	(60)	.	.	.	.
	ADENOMA, SEBACEOUS CELL	0	0	0	1	0.201	.	.	0.434
		[47]	[52]	[44]	[36]	.	.	.	.
	CARCINOMA, SQUAMOUS CELL	0	0	1	0	0.450	.	0.489	.
		[47]	[52]	[45]	[36]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	1	0	0	0.739	0.530	.	.
		[47]	[53]	[44]	[36]	.	.	.	.
small intestine		(60)	(60)	(60)	(60)	.	.	.	.
	LEIOMYOSARCOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[47]	[52]	[44]	[36]	.	.	.	.
	SCHWANNOMA	0	0	0	1	0.201	.	.	0.434
		[47]	[52]	[44]	[36]	.	.	.	.
spleen		(60)	(60)	(60)	(60)	.	.	.	.
	ADENOCARCINOMA	0	0	1	1	0.140	.	0.489	0.434
		[47]	[52]	[45]	[36]	.	.	.	.
stomach, nongla		(60)	(60)	(60)	(60)	.	.	.	.
	ADENOCARCINOMA	0	0	1	0	0.450	.	0.489	.
		[47]	[52]	[45]	[36]	.	.	.	.
thymus		(60)	(60)	(60)	(60)	.	.	.	.
	LYMPHOMA	6	0	0	0	1.000	1.000	1.000	1.000
		[48]	[52]	[44]	[36]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	1	0	0	0.739	0.530	.	.
		[47]	[53]	[44]	[36]	.	.	.	.
thyroid gland		(60)	(60)	(60)	(60)	.	.	.	.
	ADENOMA, C-CELL	10	3	6	3	0.826	0.995	0.883	0.970
		[49]	[52]	[45]	[36]	.	.	.	.
	ADENOMA, FOLLICULAR CELL	3	2	2	1	0.746	0.849	0.798	0.903
		[47]	[52]	[44]	[36]	.	.	.	.
	CARCINOMA, C-CELL	0	1	0	0	0.737	0.525	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 3B1 (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Female Rats (Placebo Control)

Organ Name	Tumor Name	0 mg Cont N=60	5 mg Low N=60	20 mg Med N=60	40 mg High N=60	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
thyroid gland	CARCINOMA, C-CELL	[47]	[52]	[44]	[36]	.	.	.	.
	CARCINOMA, FOLLICULAR CELL	1	2	0	0	0.923	0.538	1.000	1.000
		[47]	[52]	[44]	[36]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	1	0	0	0.739	0.530	.	.
		[47]	[53]	[44]	[36]	.	.	.	.
tongue		(60)	(60)	(60)	(60)	.	.	.	.
	CARCINOMA, SQUAMOUS CELL	0	0	1	0	0.450	.	0.489	.
		[47]	[52]	[45]	[36]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	1	0	0	0.739	0.530	.	.
		[47]	[53]	[44]	[36]	.	.	.	.
trachea		(60)	(60)	(60)	(60)	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	1	0	0	0.739	0.530	.	.
		[47]	[53]	[44]	[36]	.	.	.	.
urinary bladder		(60)	(60)	(60)	(60)	.	.	.	.
	ADENOCARCINOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[47]	[52]	[44]	[36]	.	.	.	.
uterus with cer		(60)	(60)	(60)	(60)	.	.	.	.
	ADENOCARCINOMA	2	1	3	1	0.480	0.897	0.479	0.824
		[47]	[52]	[45]	[36]	.	.	.	.
	ADENOMA	0	0	1	0	0.450	.	0.489	.
		[47]	[52]	[45]	[36]	.	.	.	.
	GRANULAR CELL TUMOR	2	1	0	1	0.703	0.897	1.000	0.824
		[47]	[52]	[44]	[36]	.	.	.	.
	POLYP, GLANDULAR	0	1	0	1	0.257	0.525	.	0.434
		[47]	[52]	[44]	[36]	.	.	.	.
	POLYP, STROMAL	8	6	7	3	0.789	0.856	0.647	0.929
		[48]	[53]	[44]	[36]	.	.	.	.
	SARCOMA, STROMAL	0	1	0	1	0.257	0.525	.	0.434
		[47]	[52]	[44]	[36]	.	.	.	.
	SCHWANNOMA	1	2	0	0	0.923	0.545	1.000	1.000
		[47]	[53]	[44]	[36]	.	.	.	.
zymbal`s gland		(60)	(60)	(60)	(60)	.	.	.	.
	CARCINOMA, SQUAMOUS CELL	0	0	1	0	0.450	.	0.489	.
		[47]	[52]	[45]	[36]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	1	0	0	0.739	0.530	.	.
		[47]	[53]	[44]	[36]	.	.	.	.

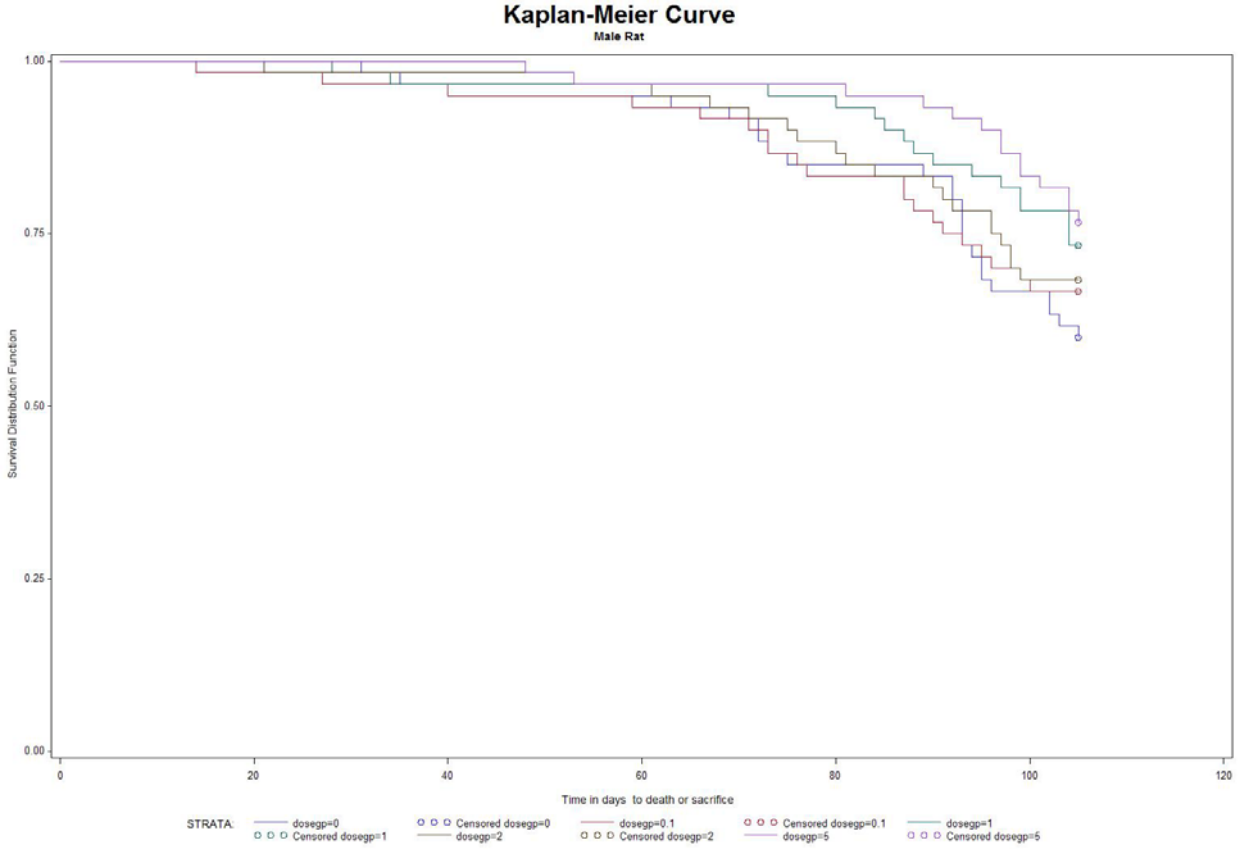
Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Figure 1A: Kaplan-Meier Survival Functions for Male Rats

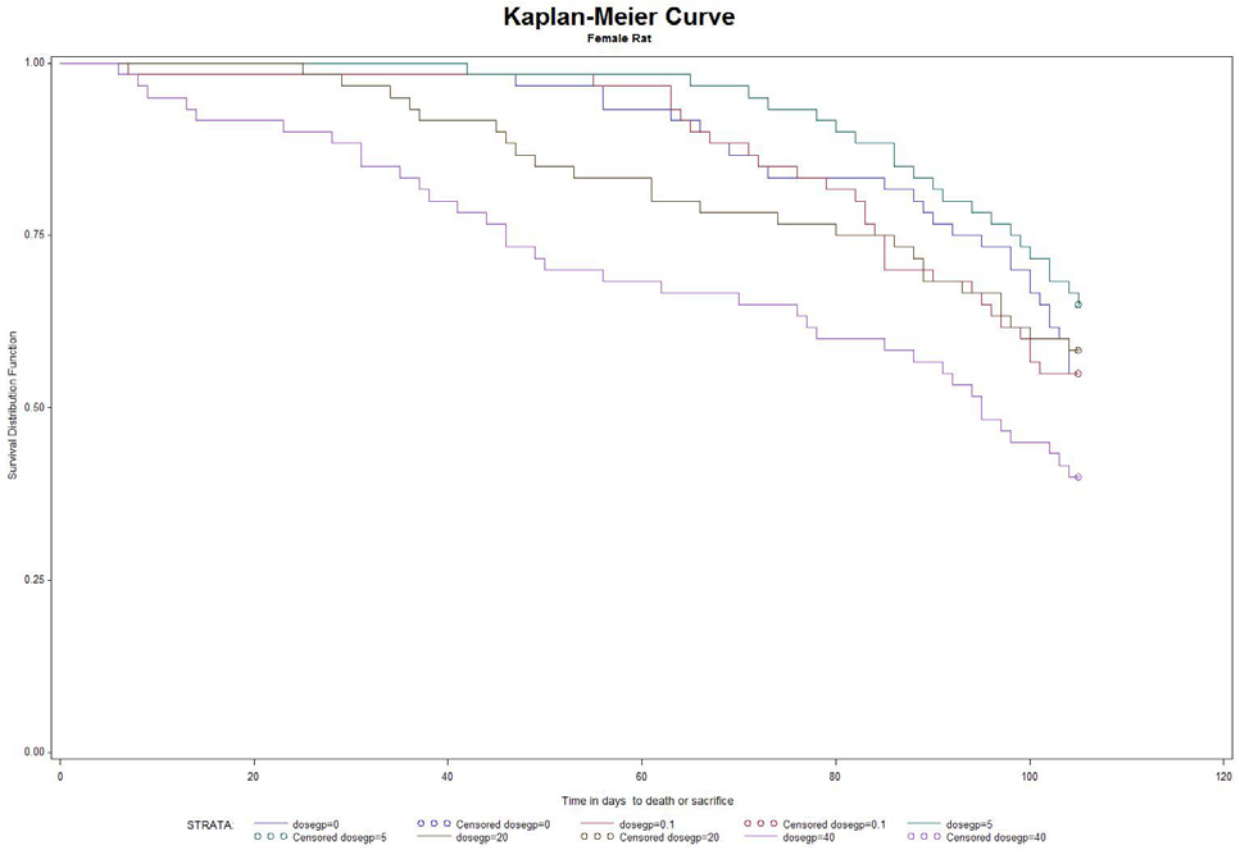
Male Rats (five groups)



X-Axis: Weeks, Y-Axis: Survival rates

Figure 1B: Kaplan-Meier Survival Functions for Female Rats

Female Rats (five groups)



X-Axis: Weeks, Y-Axis: Survival rates

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/s/

MIN MIN
03/27/2013

KARL K LIN
03/27/2013
Concur with review

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 204708 **Applicant:** Galderma Research and Development, Inc., Cranbury, NJ **Stamp Date:** 10/25/2012

Drug Name: Mirvaso (brimonidine tartrate) Gel, 0.5% **NDA/BLA Type:** 505(b)(2)

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? __YES_____

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

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

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Matthew Guerra, Ph.D.	12/11/2012
Reviewing Statistician	Date
Mohamed Alosh, Ph.D.	12/11/2012
Supervisor/Team Leader	Date

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/s/

MATTHEW W GUERRA
12/11/2012

MOHAMED A ALOSH
12/12/2012