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STATISTICAL REVIEW(S)



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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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Applicant: Galderma
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1 EXECUTIVE SUMMARY

The applicant, Galderma, is seeking approval of SOOLANTRA (ivermectin) 1% cream for the topical treatment of inflammatory lesions of rosacea in adults 18 years of age or older.

The applicant submitted data from two randomized, multicenter, placebo-controlled, parallel-group, pivotal Phase 3 trials (RD.06.SPR.18170 and RD.06.SPR.18171). The studies enrolled subjects aged 18 years and older with a diagnosis of papulopustular rosacea with 15 to 70 inflammatory lesions (papules and pustules) on the face, and an Investigator’s Global Assessment (IGA) score of 3 (moderate) or 4 (severe). Subjects applied study product once daily for 12 weeks. The protocol specified co-primary efficacy endpoints were the IGA success rate (proportion of subjects that achieve an IGA score of 0 or 1) at Week 12 and the absolute change in inflammatory lesion counts from baseline to Week 12. Percent change in inflammatory lesion counts from baseline to Week 12 was specified as the single secondary efficacy endpoint. The co-primary and secondary efficacy endpoints were all statistically significant ($p < 0.001$), see Table 1.

Table 1: Results for the Co-Primary and Secondary Efficacy Endpoints at Week 12 (ITT, LOCF)

Endpoints	Study 18170			Study 18171		
	SOOLANTRA (N=451)	Vehicle (N=232)	P-value	SOOLANTRA (N=459)	Vehicle (N=229)	P-value
Co-Primary: IGA Success ⁽¹⁾ : n (%)	173 (38.4%)	27 (11.6%)	<0.001 ⁽²⁾	184 (40.1%)	43 (18.8%)	<0.001 ⁽²⁾
Absolute Change in Inflammatory Lesion Counts: Mean (SD)	20.5 (16.0)	12.0 (13.5)	<0.001 ⁽³⁾	22.2 (14.9)	13.4 (14.5)	<0.001 ⁽³⁾
Secondary: Percent Change in Inflammatory Lesion Counts: Mean (SD)	64.9% (39.9)	41.6% (38.8)	<0.001 ⁽⁴⁾	65.7% (33.2)	43.4% (38.4)	<0.001 ⁽⁴⁾

Source: Reviewer’s Analysis

(1) Success is defined as achieving an IGA score of 0 (clear) or 1 (almost clear).

(2) P-value calculated from a CMH test stratified by analysis centers.

(3) P-value calculated based on an ANCOVA model with baseline lesion count, treatment, and analysis centers as factors.

(4) P-value was based a CMH test stratified by analysis centers using the RIDIT score and row mean difference.

ITT: Intent-to-treat, defined as all randomized subjects and to whom the study drug is dispensed.

LOCF: Last observation carried forward

SD: Standard Deviation

The protocol specified that ‘time to onset’ of efficacy will be determined using a conditional backward stepwise testing approach of the co-primary efficacy endpoints for the different weeks (Weeks 12, 8, 4, and 2). SOOLANTRA cream was statistically superior ($\alpha = 0.05$) to vehicle cream starting at Week 4, see Section 3.2.7 for more detail.

2 INTRODUCTION

2.1 Overview

The applicant, Galderma, is seeking approval of SOOLANTRA (ivermectin) 1% cream for the topical treatment of inflammatory lesions of rosacea in adults 18 years of age or older. The active ingredient, ivermectin, was approved in 1996 for the treatment of strongyloidiasis and onchocerciasis [STROMEKTOL[®] Tablets; NDA 050742] and in 2012 for the topical treatment of head lice infestations in patients 6 months of age and older [SKLICE[®] Lotion, 0.5%; NDA 202736].

2.1.1 Regulatory History

The sponsor submitted an Investigational New Drug (IND) application for the proposed product and indication in 2007 under IND 76064.

The Agency and the sponsor met for an End-of-Phase 2 (EOP2) meeting on March 18, 2008. For this meeting, the sponsor proposed to establish the safety and efficacy of their product in two, randomized, vehicle-controlled, Phase 3 trials. The sponsor proposed the co-primary endpoints of IGA success rate (defined as the percentage of subjects who achieve at least a 2-grade improvement from baseline) at Week 12 and percentage change in inflammatory lesion counts from baseline to Week 12. The Agency stated that success should be defined as those who are clear or almost clear on the IGA and recommended using absolute change in lesion counts as a co-primary endpoint instead of percent change.

On September 8, 2008, the sponsor submitted Phase 3 protocols for Special Protocol Assessment (SPA) and the SPA letter was sent to the sponsor on October 22, 2008. The letter contained agreements on study population, efficacy endpoints (i.e., endpoints recommended by the Agency during the EOP2 meeting), sample size, analysis population, analysis methodology, handling of missing data, and multiplicity adjustment to control the Type I error rate. The letter contained a couple of disagreements regarding safety monitoring. The sponsor and Agency had a teleconference on February 9, 2009 with the objective to clarify any issues regarding the SPA letter.

As part of their early clinical development program, the sponsor conducted a 52-week, open-label, uncontrolled, long-term safety study (Study 40051). Study 40051 elicited a safety signal of neutropenia and therefore was stopped. On December 20, 2010, the sponsor submitted a summary of the neutrophil counts from Study 40051 along with a Phase 2 protocol (Study 40106) to assess the hematological safety of the proposed product. On April 20, 2011, the Agency sent an advice letter stating that based on the safety signal detected in Study 40051 and the limitations of the studies that have been conducted to date, the proposed Phase 3 protocols (i.e., those reviewed under SPA) should be modified to include periodic laboratory monitoring. In addition, the Agency stated that the sponsor should modify their development plan to include adequate assessment of the effect of the proposed product on neutrophil count, and such study or studies should investigate long-term exposure with an adequate control.

On August 10, 2011, the sponsor and Agency met for a Pre-Phase 3 meeting. The sponsor proposed modifying their Phase 3 protocol to include a long-term safety phase (i.e., a 40-week safety period after a 12-week period to establish efficacy). For this 40-week safety phase, the sponsor proposed to have all subjects that were treated with ivermectin 1% cream during the 12-week efficacy phase to continue once daily ivermectin 1% cream and all the subjects that were treated with vehicle to switch to azelaic acid 15% gel twice daily. During the pre-Phase 3 meeting, the Agency recommended re-randomizing subjects to either ivermectin 1% cream or azelaic acid 15% gel rather than assigning all subjects randomized to ivermectin 1% cream to continue with ivermectin 1% cream and assigning all subjects to vehicle to begin treatment with azelaic acid. The Agency stated that this would help maintain blinding and minimize bias.

The sponsor submitted amended Phase 3 protocols (RD.06.SPR.18170 and RD.06.SPR.18171) on December 8, 2011 and an advice letter regarding the protocols were sent to the sponsor on April 16, 2012. In the advice letter, the Agency reiterated the comment from the Pre-Phase 3 meeting (8/10/2011) regarding re-randomizing subjects for the 40-week safety extension period.

On June 14, 2012, the sponsor submitted amended Statistical Analysis Plans (SAPs) for their identical Phase 3 trials (RD.06.SPR.18170 and RD.06.SPR.18171). On July 24, 2012, the sponsor submitted the amended Phase 3 protocols that go with the SAPs. In response to the Agency’s previous recommendations about re-randomizing subjects for the safety extension period, the sponsor proposed to “freeze” the Week 12 IGA and lesion count data points within 5 days of entry. The Agency did not send an advice letter for these submissions; instead, the Agency and the sponsor had a teleconference on November 26, 2012. During the meeting, the sponsor notified the Agency that the all subjects had already entered the safety extension period and re-randomization would not be possible.

On June 12, 2013, the Agency and the sponsor met for a Pre-NDA meeting. The Agency provided general comments on how the data should be submitted (data tabulation datasets, data definition files, annotated case report forms, and analysis datasets).

2.1.2 Clinical Studies Overview

The applicant submitted data from two Phase 3 trials (Studies 18170 and 18171). An overview of the trials is presented in Table 2.

Table 2: Clinical Study Overview

Study	Location	Study Population	Treatment Arms	Number of Subjects	Dates
18170	US (40 sites) & Canada (10 sites)	Male and female subjects with 15 to 70 inflammatory lesions (papules and pustules) on the face and an IGA \geq 3 (moderate)	SOOLANTRA	451	12/13/2011 – 7/18/2013
			Vehicle	232	
18171	US (40 sites) & Canada (10 sites)		SOOLANTRA	459	12/20/2011 – 8/1/2013
			Vehicle	229	

*Note that one subject (vehicle) in Study 18170 had 71 inflammatory lesions at baseline and one subject (vehicle) in Study 18171 had 14 inflammatory lesions at baseline.

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\NDA206255\0000\m5\datasets\18170\](\\cdsesub1\evsprod\NDA206255\0000\m5\datasets\18170)

[\\cdsesub1\evsprod\NDA206255\0000\m5\datasets\18171\](\\cdsesub1\evsprod\NDA206255\0000\m5\datasets\18171)

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

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

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The applicant conducted two identical Phase 3 studies. Both were randomized, multicenter, double-blind trials that consisted of the following periods:

- Vehicle-controlled Period (Part A; Weeks 0 to 12): subjects were randomized in a 2:1 ratio to either SOOLANTRA cream or vehicle cream. Subjects applied study product once daily (QD) at home for up to 12 weeks. Subjects were evaluated at baseline and Weeks 2, 4, 8, and 12.
- Long-term Safety Extension Period (Part B; Weeks 12 to 52): at Week 12 (after the Week 12 assessment), vehicle subjects were switched to azelaic acid 15% gel BID and SOOLANTRA subjects continue to use SOOLANTRA cream QD. The sponsor stated that this period of the trial was investigator-blinded. The investigator stopped treatment (SOOLANTRA or azelaic acid) if the subject had an IGA score of 0 (clear); however, subjects continued to attend the study visits as planned in the protocol. The protocol states that the decision to restart the treatment would be made by the investigator if the IGA score becomes ≥ 1 (almost clear). Subjects had scheduled visits at Weeks 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52.
- Safety Follow-up Period (4 weeks): subjects were followed for 4 weeks to enable the collection of safety data after the treatment was discontinued.

For enrollment, the protocol specified that subjects must be 18 years of age or older, have a diagnosis of papulopustular rosacea with 15 to 70 inflammatory lesions (papules and pustules) on the face, and an IGA score of 3 (moderate) or 4 (severe). The IGA scale is defined in Table 3.

The protocol specified the following co-primary efficacy endpoints:

1. IGA Success Rate, defined as the proportion of subjects with an IGA score of 0 (clear) or 1 (almost clear) at Week 12.
2. Absolute change in inflammatory lesion counts from baseline to Week 12.

The protocol specified a single secondary efficacy endpoint of percent change in inflammatory lesion counts from baseline to Week 12.

Table 3: Investigator’s Global Assessment (IGA) score

Grade	Score	Clinical Description
Clear	0	No inflammatory lesions present
Almost Clear	1	Very few small papules/pustules, very mild erythema present
Mild	2	Few small papules/pustules, mild erythema
Moderate	3	Several small or large papules/pustules, moderate erythema
Severe	4	Numerous small and/or large papules/pustules, severe erythema

3.2.2 Statistical Methodologies

The intent-to-treat (ITT) population was defined as all subjects randomized in the study and to whom the study drug is dispensed. The per-protocol (PP) population was defined as the ITT population, after exclusion of subjects deemed non-evaluable for efficacy due to major deviations from the protocol. The protocol categorized the major deviations into 4 categories:

- Entrance criteria deviations
- Non-compliance
- Concomitant therapies during the study, interfering with efficacy
- Administrative errors such as unblinding or medication dispensing errors

The protocol specified that the primary population for efficacy analyses will be the ITT population and that the efficacy analyses will be repeated based on the PP population to “confirm the results.”

The protocol specified a pooling strategy for centers that enrolled less than 15 subjects. These centers were pooled by ordering and combining the smallest with the largest. The process repeated until all pooled centers had at least 15 subjects. It should be noted that the pooling was done separately for the centers in the U.S. and Canada, which was not specified in the protocol. After pooling, the centers (pooled and non-pooled) were termed “analysis centers”.

For the analysis of the co-primary efficacy endpoint of IGA success at Week 12, the protocol-specified analysis method was the Cochran-Mantel-Haenszel (CMH) test stratified by analysis centers with a two-sided 0.05 significance level. The Breslow-Day test was performed to test for homogeneity of the odds ratio across analysis centers at the $\alpha = 0.10$ level. If the test was significant, the protocol specified a sensitivity analysis where the data will be analyzed excluding one analysis center at a time to identify the impact of each analysis center on the overall results.

For the analysis of the co-primary efficacy endpoint of absolute change in inflammatory lesion counts from baseline to Week 12, the protocol-specified analysis method was a two-way analysis of covariance (ANCOVA) model with the baseline inflammatory lesion counts as a covariate, and treatment and analysis center as factors.

The protocol specified that ‘time to onset’ of efficacy will be determined using a conditional backward stepwise testing approach for the different weeks (Weeks 12, 8, 4, and 2). If the co-

primary endpoints are statistically significant ($\alpha = 0.05$) at Week 12 (i.e., the primary time-point), then the co-primary endpoints will be tested at Week 8. If the co-primary endpoints are significant ($\alpha = 0.05$) at Week 8, then the co-primary endpoints will be tested at Week 4. Finally, if the co-primary endpoints at Week 4 are significant, then the co-primary endpoints at Week 2 will be tested.

For the analysis of the secondary efficacy endpoint of percent change in inflammatory lesion counts from baseline to Week 12, the protocol-specified analysis method was the Mann-Whitney test using the CMH procedure stratified by analysis centers with the RIDIT transformation and the row mean difference score.

The primary imputation method specified in the protocol is the last observation carried forward (LOCF) approach. The protocol also specified the following sensitivity analyses for the co-primary efficacy endpoints at Week 12:

- IGA Success Rate
 1. All missing data imputed as failures.
 2. All missing data imputed as successes.
 3. Multiple Imputation-MCMC Method: missing data was imputed using the Markov Chain Monte Carlo (MCMC) method, which creates multiple imputations by drawing simulations from a Bayesian predictive distribution with normal data. The applicant imputed the missing data 5 times.
- Absolute Change in Inflammatory Lesion Counts
 1. Missing Week 12 inflammatory lesion count imputed with the median lesion count of all IGA failures with respect to treatment group.
 2. Missing Week 12 inflammatory lesion count imputed with the median lesion count of all IGA successes with respect to treatment group.
 3. Multiple Imputation-MCMC Method: missing data was imputed using the Markov Chain Monte Carlo (MCMC) method, which creates multiple imputations by drawing simulations from a Bayesian predictive distribution with normal data. The applicant imputed the missing data 5 times.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Study 18170 enrolled and randomized a total of 683 subjects (451 to SOOLANTRA and 232 to vehicle) from 50 centers (40 in U.S. and 10 in Canada). Study 18171 enrolled and randomized a total of 688 subjects (459 to SOOLANTRA and 229 to vehicle) from 50 centers (40 in U.S. and 10 in Canada). In Study 18170, the proportion of subjects who discontinued during Part A (i.e., the vehicle-controlled period) was similar between the two treatment arms (8.2% for SOOLANTRA arm and 9.5% for vehicle arm). In Study 18171, a higher proportion of subjects in the vehicle arm (9.2%) discontinued during Part A compared to the SOOLANTRA arm (6.5%). The reasons for discontinuation are presented in Table 4.

Table 4: Disposition of Subjects (ITT)

	Study 18170		Study 18171	
	SOOLANTRA (N=451)	Vehicle (N=232)	SOOLANTRA (N=459)	Vehicle (N=229)
Discontinued in Part A	37 (8.2%)	22 (9.5%)	30 (6.5%)	21 (9.2%)
<i>Adverse Event</i>	7 (1.6%)	4 (1.7%)	6 (1.3%)	4 (1.7%)
<i>Lack of Efficacy</i>	0	1 (0.4%)	1 (0.2%)	0
<i>Subject's Request</i>	18 (4.0%)	7 (3.0%)	9 (2.0%)	8 (3.5%)
<i>Lost to Follow-Up</i>	7 (1.6%)	8 (3.4%)	8 (1.7%)	8 (3.5%)
<i>Protocol Violation</i>	2 (0.4%)	1 (0.4%)	4 (0.9%)	0
<i>Pregnancy</i>	2 (0.4%)	0	1 (0.2%)	0
<i>Other</i>	1 (0.2%)	1 (0.4%)	1 (0.2%)	1 (0.4%)

Source: Reviewer's Analysis

Baseline demographics were generally balanced across the treatment arms in both studies. In addition, the baseline demographics were similar between the two studies. The demographics for both studies are summarized in Table 5.

Table 5: Demographics (ITT)

	Study 18170		Study 18171	
	SOOLANTRA (N=451)	Vehicle (N=232)	SOOLANTRA (N=459)	Vehicle (N=229)
Age				
Mean (SD)	48.9 (12.1)	51.6 (11.9)	50.5 (12.3)	49.5 (12.2)
Median	49	52	50	50
Range	19 - 88	26 - 86	21 - 89	18 - 81
18-64	402 (89.1%)	200 (86.2%)	399 (86.9%)	200 (87.3%)
65+	49 (10.9%)	32 (13.8%)	60 (13.1%)	29 (12.7%)
Gender				
Male	137 (30.4%)	80 (34.5%)	145 (31.6%)	84 (36.7%)
Female	314 (69.6%)	152 (65.5%)	314 (68.4%)	145 (63.3%)
Race				
White	437 (96.9%)	220 (94.8%)	438 (95.4%)	218 (95.2%)
Black	6 (1.3%)	3 (1.3%)	6 (1.3%)	4 (1.7%)
Asian	3 (0.7%)	3 (1.3%)	10 (2.2%)	5 (2.2%)
Other	5 (1.1%)	6 (2.6%)	5 (1.1%)	2 (0.9%)
Ethnicity				
Hispanic or Latino	55 (12.2%)	23 (9.9%)	56 (12.2%)	31 (13.5%)
Not Hispanic or Latino	396 (87.8%)	209 (90.1%)	403 (87.8%)	198 (86.5%)
Skin Phototype				
I	39 (8.7%)	16 (6.9%)	48 (10.5%)	22 (9.6%)
II	185 (41.0%)	90 (38.8%)	211 (46.0%)	96 (41.9%)
III	167 (37.0%)	86 (37.1%)	139 (30.3%)	71 (31.0%)
IV	51 (11.3%)	26 (11.2%)	50 (10.9%)	31 (13.5%)
V	8 (1.8%)	11 (4.7%)	11 (2.4%)	7 (3.1%)
VI	1 (0.2%)	3 (1.3%)	0	2 (0.9%)
Country				
U.S.	367 (81.4%)	188 (81.0%)	361 (78.6%)	181 (79.0%)
Canada	84 (18.6%)	44 (19.0%)	98 (21.4%)	48 (21.0%)

Source: Reviewer's Analysis

SD: Standard Deviation

The baseline disease characteristics are presented in Table 6. In both studies, the baseline disease characteristics were generally balanced across the treatment arms. Approximately 18% of the subjects in Study 18170 had a baseline IGA score of 4, while approximately 24% of the subjects in Study 18171 had a baseline IGA score of 4. For enrollment, the protocol specified that subjects have 15 to 70 inflammatory lesion counts at baseline. One subject (randomized to vehicle) in Study 18170 had 71 inflammatory lesions at baseline and one subject (randomized to vehicle) in Study 18171 had 14 inflammatory lesions at baseline.

Table 6: Baseline Disease Characteristics (ITT)

	Study 18170		Study 18171	
	SOOLANTRA (N=451)	Vehicle (N=232)	SOOLANTRA (N=459)	Vehicle (N=229)
IGA				
3 (Moderate)	369 (81.8%)	191 (82.3%)	346 (74.4%)	176 (76.9%)
4 (Severe)	82 (18.2%)	41 (17.7%)	113 (24.6%)	53 (23.1%)
Inflammatory Lesion Counts				
Mean (SD)	31.0 (14.3)	30.5 (14.4)	33.3 (13.6)	32.2 (13.9)
Range	15 - 70	15 - 71	15 - 70	14 - 69

Source: Reviewer's Analysis
SD: Standard Deviation

3.2.4 Primary Efficacy Endpoints Results

SOOLANTRA cream was statistically superior ($p < 0.001$) to vehicle cream on both co-primary efficacy endpoints in both studies. The results from the ITT and PP analyses were similar. The ITT and PP results are presented in Tables 7 and 8, respectively.

Table 7: Results for the Co-Primary Efficacy Endpoints at Week 12 (ITT, LOCF)

Endpoint	Study 18170			Study 18171		
	SOOLANTRA (N=451)	Vehicle (N=232)	P-value	SOOLANTRA (N=459)	Vehicle (N=229)	P-value
IGA Success ⁽¹⁾ : n (%)	173 (38.4%)	27 (11.6%)	<0.001 ⁽²⁾	184 (40.1%)	43 (18.8%)	<0.001 ⁽²⁾
Absolute Change in Inflammatory Lesion Counts:						
Mean (SD)	20.5 (16.0)	12.0 (13.5)		22.2 (14.9)	13.4 (14.5)	
LS Mean	20.4	12.3	<0.001 ⁽³⁾	21.9	13.7	<0.001 ⁽³⁾

Source: Reviewer's Analysis

(1) Success is defined as achieving an IGA score of 0 (clear) or 1 (almost clear).

(2) P-value calculated from a CMH test stratified by analysis centers.

(3) P-value calculated based on an ANCOVA model with baseline lesion count, treatment, and analysis centers as factors.

SD: Standard Deviation

Table 8: Results for the Co-Primary Efficacy Endpoints at Week 12 (PP)

Endpoint	Study 18170			Study 18171		
	SOOLANTRA (N=402)	Vehicle (N=204)	P-value	SOOLANTRA (N=398)	Vehicle (N=198)	P-value
IGA Success ⁽¹⁾ : n (%)	163 (40.5%)	23 (11.3%)	<0.001 ⁽²⁾	163 (41.0%)	41 (20.7%)	<0.001 ⁽²⁾
Absolute Change in Inflammatory Lesion Counts:						
Mean (SD)	21.9 (15.2)	12.5 (12.3)		22.8 (14.3)	14.2 (14.5)	
LS Mean	21.8	12.9	<0.001 ⁽³⁾	22.4	14.3	<0.001 ⁽³⁾

Source: Reviewer's Analysis

(1) Success is defined as achieving an IGA score of 0 (clear) or 1 (almost clear).

(2) P-value calculated from a CMH test stratified by analysis centers.

(3) P-value calculated based on an ANCOVA model with baseline lesion count, treatment, and analysis centers as factors.

SD: Standard Deviation

3.2.5 Handling of Missing Data

Table 9 provides the number of subjects with missing data for the co-primary efficacy endpoints by week, treatment arm, and study. For the primary time-point (i.e., Week 12), the proportion of subjects with missing data in Study 18170 was similar between the two treatment arms (6.0% in SOOLANTRA arm and 7.4% in vehicle arm), while the proportion of subjects with missing data in Study 18171 was higher in the vehicle arm compared to the SOOLANTRA arm (4.4% in SOOLANTRA arm and 8.6% in vehicle arm).

Table 9: Missing Data for the Co-Primary Efficacy Endpoints by Week 12 (ITT)

	Study 18170		Study 18171	
	SOOLANTRA (N=451)	Vehicle (N=232)	SOOLANTRA (N=459)	Vehicle (N=229)
Week 2	9 (2.0%)	7 (3.0%)	16 (3.5%)	4 (1.7%)
Week 4	15 (3.3%)	6 (2.6%)	12 (2.6%)	13 (5.6%)
Week 8	28 (6.2%)	16 (6.9%)	21 (4.6%)	16 (6.9%)
Week 12	27 (6.0%)	17 (7.4%)	20 (4.4%)	20 (8.6%)

Source: Reviewer's Analysis

For the co-primary efficacy endpoint of IGA success at Week 12, the applicant conducted three sensitivity analyses for handling of missing data: (i) impute missing data as failures, (ii) impute missing data as successes, and (iii) multiple imputation (MI-MCMC). The results of these sensitivity analyses as well as the results with the primary imputation method (i.e., LOCF) are presented in Table 10. In both studies, the results were very similar across the different sensitivity analyses. This reviewer conducted an additional sensitivity where missing data was imputed under the worst case scenario (i.e., missing data imputed as failures in the SOOLANTRA arm and successes in the vehicle arm). In this extreme case, SOOLANTRA cream was still statistically superior ($p \leq 0.001$) to vehicle cream in both studies.

Table 10: Comparison of Different Approaches for Handling Missing Data for IGA Success⁽¹⁾ at Week 12 (ITT)

Imputation Method	Study 18170			Study 18171		
	SOOLANTRA (N=451)	Vehicle (N=232)	P-value ⁽²⁾	SOOLANTRA (N=459)	Vehicle (N=229)	P-value ⁽²⁾
LOCF (primary)	173 (38.4%)	27 (11.6%)	<0.001	184 (40.1%)	43 (18.8%)	<0.001
Failures	172 (38.1%)	26 (11.2%)	<0.001	183 (39.9%)	43 (18.8%)	<0.001
Successes	199 (44.1%)	43 (18.5%)	<0.001	203 (44.2%)	63 (27.5%)	<0.001
MI-MCMC ⁽³⁾	177 (39.2%)	30.4 (13.1%)	<0.001	188.8 (41.1%)	47.6 (20.8%)	<0.001
Worst Case ⁽⁴⁾	172 (38.1%)	43 (18.5%)	<0.001	183 (39.9%)	63 (27.5%)	0.001

Source: Reviewer's Analysis

(1) Success is defined as achieving an IGA score of 0 (clear) or 1 (almost clear).

(2) P-value calculated from a CMH test stratified by analysis centers.

(3) The rates displayed are the averages of the 5 imputed datasets.

(4) Worst Case: missing data imputed as failures for the SOOLANTRA arm and successes for the vehicle arm.

For the co-primary endpoint of absolute change in inflammatory lesion counts at Week 12, the applicant conducted three sensitivity analyses for handling of missing data: (i) impute missing data with the median lesion count of all IGA failures with respect to treatment group, (ii) impute missing data with the with the median lesion count of all IGA successes with respect to treatment group, and (iii) multiple imputation (MI-MCMC). The results of these sensitivity analyses as well as the results with the primary imputation method (i.e., LOCF) are presented in Table 11. In both studies, the results were very similar across the different sensitivity analyses.

Table 11: Comparison of Different Approaches for Handling Missing Data for Absolute Change in Inflammatory Lesion Counts at Week 12 (ITT)

Imputation Method	Study 18170			Study 18171		
	SOOLANTRA (N=451)	Vehicle (N=232)	P-value ⁽¹⁾	SOOLANTRA (N=459)	Vehicle (N=229)	P-value ⁽¹⁾
LOCF (primary)	20.5	12.0	<0.001	22.2	13.4	<0.001
From IGA Failures	21.3	12.6	<0.001	22.5	14.3	<0.001
From IGA Successes	21.6	13.1	<0.001	22.8	14.3	<0.001
MI-MCMC ⁽²⁾	20.8	12.5	<0.001	22.7	14.4	<0.001

Source: Reviewer's Analysis

(1) P-value calculated based on an ANCOVA model with baseline, treatment, and analysis centers as factors.

(2) The rates displayed are the averages of the 5 imputed datasets.

3.2.6 Secondary Efficacy Endpoints Results

The protocol specified a single secondary efficacy endpoint (i.e., percent change in inflammatory lesion counts from baseline to Week 12) and the results for both studies are presented in Table 12. SOOLANTRA cream was statistically superior ($p < 0.001$) to vehicle cream for this endpoint in both studies.

Table 12: Percent Change in Inflammatory Lesion Counts at Week 12 (ITT, LOCF)

	Study 18170			Study 18171		
	SOOLANTRA (N=451)	Vehicle (N=232)	P-value	SOOLANTRA (N=459)	Vehicle (N=229)	P-value
Mean (SD)	64.9% (39.9)	41.6% (38.8)	<0.001 ⁽¹⁾	65.7% (33.2)	43.4% (38.4)	<0.001 ⁽¹⁾

Source: Reviewer's Analysis

(1) P-value was based on the CMH test stratified by analysis centers using the RIDIT score and row mean difference.

SD: Standard Deviation

3.2.7 Efficacy over Time

The ‘time to onset’ of efficacy was determined using a conditional backward stepwise testing approach of the co-primary efficacy endpoints for the different weeks (Weeks 12, 8, 4, and 2). SOOLANTRA was statistically superior ($\alpha = 0.05$) to vehicle on the co-primary endpoints starting from Week 4, see Table 13 and Figures 1 and 2.

Table 13: Results for the Co-Primary Efficacy Endpoints over Time (ITT, LOCF)

	IGA Success ⁽¹⁾ : n (%)			Absolute Change in Inflammatory Lesion Counts: Mean (SD)		
	SOOLANTRA	Vehicle	P-value ⁽²⁾	SOOLANTRA	Vehicle	P-value ⁽³⁾
Study 18170	N=451	N=232		N=451	N=232	
Week 12	173 (38.4%)	27 (11.6%)	<0.001	20.5 (16.0)	12.0 (13.5)	<0.001
Week 8	104 (23.1%)	23 (9.9%)	<0.001	17.9 (14.8)	10.1 (14.0)	<0.001
Week 4	49 (10.9%)	13 (5.6%)	0.021	13.6 (14.9)	7.7 (12.3)	<0.001
Week 2	17 (3.8%)	5 (2.2%)	0.267	8.8 (13.4)	5.1 (11.1)	<0.001
Study 18171	N=459	N=229		N=459	N=229	
Week 12	184 (40.1%)	43 (18.8%)	<0.001	22.2 (14.9)	13.4 (14.5)	<0.001
Week 8	126 (27.5%)	28 (12.2%)	<0.001	19.8 (14.4)	11.2 (13.3)	<0.001
Week 4	54 (11.8%)	13 (5.7%)	0.014	14.3 (13.8)	7.8 (11.9)	<0.001
Week 2	16 (3.5%)	6 (2.6%)	0.551	9.1 (12.3)	6.3 (11.7)	0.006

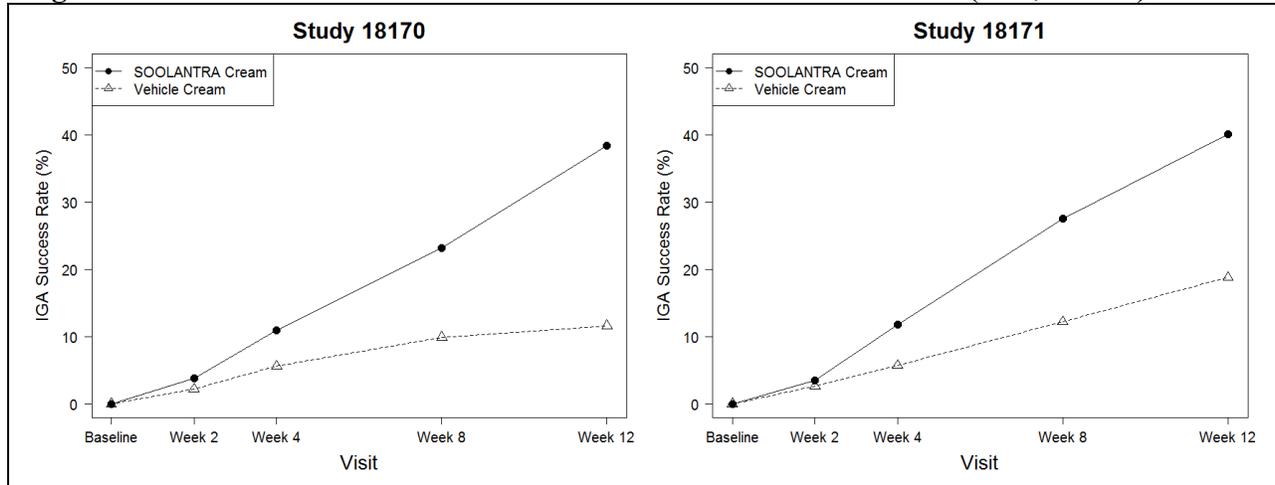
Source: Reviewer’s Analysis

(1) Success is defined as achieving an IGA score of 0 (Clear) or 1 (Almost Clear).

(2) P-value calculated from a CMH test stratified by analysis centers.

(3) P-value calculated based on an ANCOVA model with baseline lesion count, treatment, and analysis centers as factors.

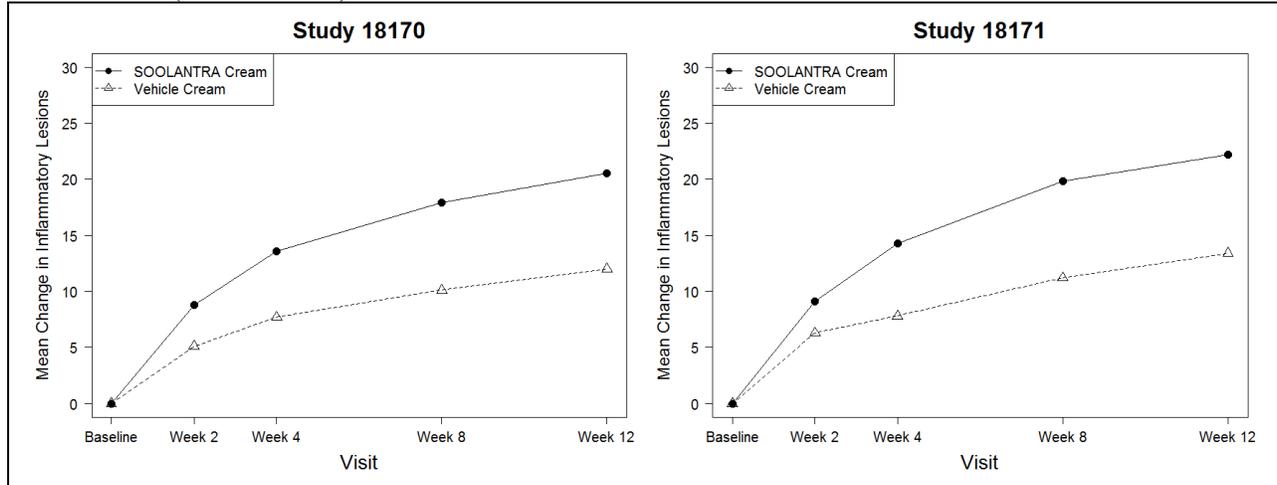
Figure 1: IGA Success⁽¹⁾ Rate over Time for Studies 18170 and 18171 (ITT, LOCF)



Source: Reviewer’s Analysis

(1) Success is defined as achieving an IGA score of 0 (clear) or 1 (almost clear).

Figure 2: Absolute Change in Inflammatory Lesion Counts over Time for Studies 18170 and 18171 (ITT, LOCF)



Source: Reviewer's Analysis

3.3 Evaluation of Safety

3.3.1 Extent of Exposure

The extent of exposure to study product during Part A (i.e., the vehicle-controlled period) is presented in Table 14. The planned duration of exposure for Part A in both studies was 12 weeks.

Table 14: Extent of Exposure during Part A (Weeks 0 to 12) in Studies 18170 and 18171 (Safety Population⁽¹⁾)

	Study 18170		Study 18171	
	SOOLANTRA (N=452)	Vehicle (N=231)	SOOLANTRA (N=458)	Vehicle (N=230)
Duration of Exposure (Days)				
Mean (SD)	81.1 (15.8)	80.8 (16.7)	82.2 (13.4)	80.4 (17.4)
Median	84	84	84	84
Range	1 - 106	1 - 131	1 - 126	1 - 120
Duration of Exposure Category				
1 to 14 Days	11 (2.4%)	5 (2.2%)	8 (1.7%)	6 (2.6%)
15 to 42 Days	13 (2.9%)	7 (3.0%)	5 (1.1%)	7 (3.0%)
43 to 70 Days	6 (1.3%)	7 (3.0%)	11 (2.4%)	6 (2.6%)
71 to 98 Days	417 (92.3%)	209 (90.5%)	430 (93.9%)	208 (90.4%)
≥ 99 Days	5 (1.1%)	3 (1.3%)	4 (0.9%)	3 (1.3%)
Average Daily Amount Used (grams)				
N	447	228	453	227
Mean (SD)	0.65 (0.66)	0.70 (0.36)	0.64 (0.33)	0.60 (0.30)
Median	0.56	0.64	0.57	0.58
Range	0.06 - 12.83 ⁽²⁾	0.08 - 1.89	0.10 - 2.03	0.08 - 1.65

Source: Reviewer's Analysis

(1) One subject (8294-005) in Study 18170 was planned to receive vehicle but received SOOLANTRA in error.

(2) The subject with a value of 12.83 had a duration of exposure of 1 day. The second largest value in this group was 1.77.

SD: Standard Deviation

3.3.2 Adverse Events

Approximately 37-41% of SOOLANTRA and 37-39% of vehicle subjects experienced at least one adverse event. Approximately 1-2% of SOOLANTRA and 3% of vehicle subjects discontinued treatment due to adverse events. Table 15 presents an overview of adverse events reported during the vehicle-controlled period. The adverse events observed in at least 1% of subjects reported during the vehicle controlled period in Studies 18170 and 18171 are presented in Table 16.

Table 15: Overview of Adverse Events Reported during Part A (Weeks 0 to 12) in Studies 008 and 009 (Safety Population)

Subjects With:	Study 18170		Study 18171	
	SOOLANTRA (N=452)	Vehicle (N=231)	SOOLANTRA (N=458)	Vehicle (N=230)
Any AEs	183 (40.5%)	91 (39.4%)	167 (36.5%)	84 (36.5%)
Any Drug-related ⁽¹⁾ AEs	19 (4.2%)	18 (7.8%)	12 (2.6%)	15 (6.5%)
Any Severe AEs	5 (1.1%)	2 (0.9%)	12 (2.6%)	6 (2.6%)
Any Serious AEs	3 (0.7%)	1 (0.4%)	7 (1.5%)	4 (1.7%)
Any Serious Drug-related ⁽¹⁾ AEs	0	0	0	0
Subjects with Neutropenia	3 (0.7%)	0	0	2 (0.9%)
Subjects with Drug-related ⁽¹⁾ Neutropenia	1 (0.2%)	0	0	0
Any AEs Leading to Discontinuation	7 (1.5%)	6 (2.6%)	6 (1.3%)	6 (2.6%)
Any Drug-related ⁽¹⁾ AEs Leading to Discontinuation	6 (1.3%)	4 (1.7%)	1 (0.2%)	4 (1.7%)

Source: pg. 114 of Study Report for Study 18170 and pg. 115 of Study Report for Study 18171.

(1) Drug-related as assessed by the investigator.

Table 16: Adverse Events in >1% of Subjects in any Treatment Group during Part A (Weeks 0 to 12) by System Class and Preferred Term in Studies 18170 and 18171 (Safety Population)

System Organ Class / Preferred Term	Study 18170		Study 18171	
	SOOLANTRA (N=452)	Vehicle (N=231)	SOOLANTRA (N=458)	Vehicle (N=230)
Infections and infestations				
Nasopharyngitis	12 (2.7%)	6 (2.6%)	10 (2.2%)	6 (2.6%)
Upper respiratory tract infection	6 (1.3%)	2 (0.9%)	12 (2.6%)	8 (3.5%)
Sinusitis	5 (1.1%)	1 (0.4%)	9 (2.0%)	6 (2.6%)
Urinary tract infection	8 (1.8%)	1 (0.4%)	6 (1.3%)	2 (0.9%)
Ear infection	5 (1.1%)	1 (0.4%)	1 (0.2%)	3 (1.3%)
Bronchitis	4 (0.9%)	1 (0.4%)	1 (0.2%)	3 (1.3%)
Pharyngitis	0	0	2 (0.4%)	3 (1.3%)
Skin and subcutaneous tissue disorders				
Skin burning sensation	8 (1.8%)	6 (2.6%)	1 (0.2%)	4 (1.7%)
Skin irritation	5 (1.1%)	4 (1.7%)	3 (0.7%)	7 (3.0%)
Pruritus	3 (0.7%)	4 (1.7%)	4 (0.9%)	1 (0.4%)
Rosacea	3 (0.7%)	3 (1.3%)	1 (0.2%)	2 (0.9%)
Dermatitis contact	1 (0.2%)	0	4 (0.9%)	4 (1.7%)
Skin discomfort	0	0	0	3 (1.3%)
Musculoskeletal and connective tissue disorders				
Back pain	5 (1.1%)	1 (0.4%)	4 (0.9%)	0
Myalgia	2 (0.4%)	3 (1.3%)	0	1 (0.4%)
Arthralgia	4 (0.9%)	2 (0.9%)	2 (0.4%)	3 (1.3%)
Injury, poisoning and procedural complications				
Muscle strain	6 (1.3%)	1 (0.4%)	1 (0.2%)	0
Procedural pain	2 (0.4%)	2 (0.9%)	3 (0.7%)	3 (1.3%)
Gastrointestinal disorders				
Nausea	2 (0.4%)	3 (1.3%)	1 (0.2%)	1 (0.4%)
Diarrhoea	4 (0.9%)	0	3 (0.7%)	4 (1.7%)
Nervous system disorders				
Headache	13 (2.9%)	7 (3.0%)	9 (2.0%)	3 (1.3%)
Investigations				
C-reactive protein increased	3 (0.7%)	3 (1.3%)	3 (0.7%)	1 (0.4%)
Immune system disorders				
Seasonal allergy	7 (1.5%)	4 (1.7%)	5 (1.1%)	0
Vascular disorders				
Hypertension	3 (0.7%)	2 (0.9%)	2 (0.4%)	4 (1.7%)

Source: pg. 712-726 of Study Report for Study 18170 and pg. 695-710 of Study Report for Study 18171.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Baseline Disease Severity

The results for the co-primary efficacy endpoints by gender, race (white and non-white), age (18-64 and 65+) and baseline disease severity (IGA) subgroups for Studies 18170 and 18171 are presented in Tables 17 and 18, respectively. For IGA success at Week 12 in both studies, the treatment effect was greater in females versus males and the treatment effect was greater in

subjects aged 18-64 versus subjects aged 65+. It should be noted that there could be confounding. The male subgroup had a higher proportion of subjects aged 65+ than the female subgroup (20.3% vs. 7.9% in Study 18170 and 21.4% vs. 8.7% in Study 18171). For race, the treatment effect was similar between whites and non-whites. For baseline disease severity, the treatment effect was similar between the two subgroups.

Table 17: Results for the Co-Primary Efficacy Endpoints at Week 12 by Gender, Race, Age, and Baseline Disease Severity (IGA) for Studies 18170 (ITT, LOCF)

	IGA Success ⁽¹⁾ : n (%)		Absolute Change in Inflammatory Lesion Counts: Mean (SD)	
	SOOLANTRA (N=451)	Vehicle (N=232)	SOOLANTRA (N=451)	Vehicle (N=232)
Gender				
Male	40/137 (29.2%)	11/80 (13.8%)	23.2 (16.9)	12.0 (13.8)
Female	133/314 (42.4%)	16/152 (10.5%)	19.3 (15.4)	12.1 (13.4)
Race				
Non-White	5/14 (35.7%)	1/12 (8.3%)	17.4 (17.3)	13.2 (19.0)
White	168/437 (38.4%)	26/220 (11.8%)	20.6 (15.9)	12.0 (13.2)
Age				
18-64	157/402 (39.1%)	20/200 (10%)	20.4 (16.4)	11.8 (14.1)
65+	16/49 (32.7%)	7/32 (21.9%)	20.8 (12.3)	13.4 (9.8)
Baseline Disease Severity (IGA)				
3 - Moderate	149/369 (40.4%)	26/191 (13.6%)	17.9 (14.3)	11.9 (12.9)
4 - Severe	24/82 (29.3%)	1/41 (2.4%)	31.9 (17.8)	12.7 (16.5)

Source: Reviewer's Analysis

(1) Success is defined as achieving an IGA score of 0 (clear) or 1 (almost clear).

SD: Standard Deviation

Table 18: Results for the Co-Primary Efficacy Endpoints at Week 12 by Gender, Race, Age, and Baseline Disease Severity (IGA) for Studies 18171 (ITT, LOCF)

	IGA Success ⁽¹⁾ : n (%)		Absolute Change in Inflammatory Lesion Counts: Mean (SD)	
	SOOLANTRA (N=459)	Vehicle (N=229)	SOOLANTRA (N=459)	Vehicle (N=229)
Gender				
Male	89/145 (38.6%)	17/84 (20.2%)	23.3 (14.9)	14.3 (11.2)
Female	128/314 (40.8%)	26/145 (17.9%)	21.7 (14.9)	12.9 (16.1)
Race				
Non-White	9/21 (42.9%)	3/11 (27.3%)	25.0 (13.2)	17.0 (14.2)
White	175/438 (40.0%)	40/218 (18.3%)	22.1 (14.9)	13.2 (14.5)
Age				
18-64	152/399 (38.1%)	34/200 (17.0%)	21.9 (15.2)	13.4 (15.1)
65+	32/60 (53.3%)	9/29 (31.0%)	24.4 (12.7)	13.6 (9.0)
Baseline Disease Severity (IGA)				
3 - Moderate	150/346 (43.4%)	39/176 (22.2%)	20.5 (13.1)	13.8 (11.9)
4 - Severe	34/113 (30.1%)	4/53 (7.5%)	27.5 (18.4)	12.2 (20.9)

Source: Reviewer's Analysis

(1) Success is defined as achieving an IGA score of 0 (clear) or 1 (almost clear).

SD: Standard Deviation

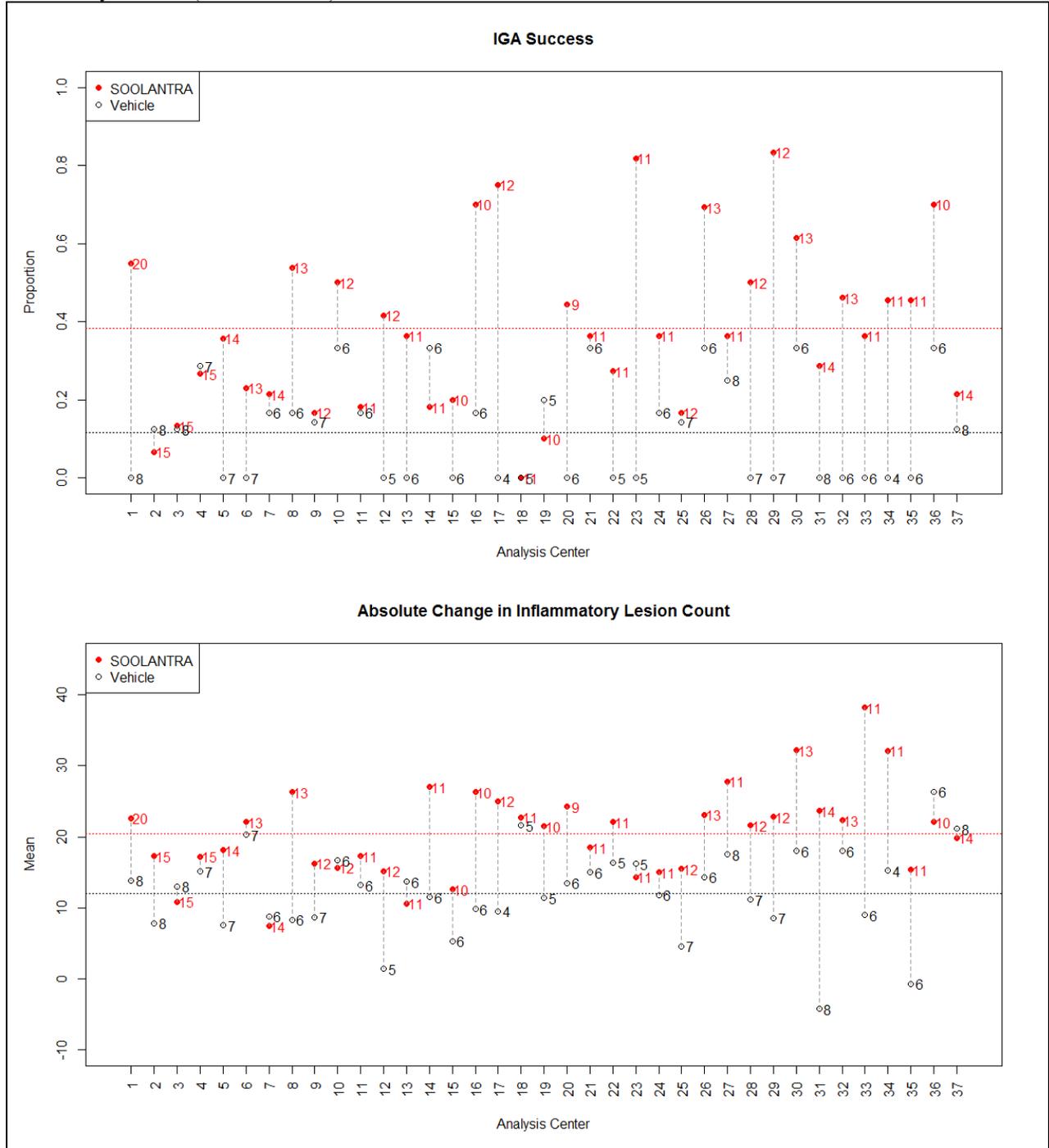
4.2 Center and Country

Studies 18170 and 18171 were both conducted at 50 centers (40 in U.S. and 10 in Canada). The protocol specified a pooling strategy for centers that enrolled less than 15 subjects. These centers were pooled by ordering and combining the smallest with the largest. The process repeated until all pooled centers had at least 15 subjects. It should be noted that the pooling was done separately for the centers in the U.S. and Canada, which was not specified in the protocol. For Study 18170, 20 of the 40 U.S. centers and 6 of the 10 Canadian centers enrolled less than 15 subjects. The pooling strategy yielded a total of 37 analysis centers (30 U.S. and 7 Canadian) for Study 18170. For Study 18171, 20 of the 40 U.S. centers and 5 of the 10 Canadian centers enrolled less than 15 subjects. The pooling strategy yielded a total of 35 analysis centers (28 U.S. and 7 Canadian) for Study 18171.

Figures 3 and 4 present the results for the co-primary efficacy endpoints at Week 12 by analysis centers for Studies 18170 and 18171, respectively. Per the protocol, the applicant conducted the Breslow-Day test for homogeneity of the odds ratio across analysis centers at $\alpha = 0.10$ level for the co-primary endpoint of IGA success rate at Week 12. The p-values from the Breslow-Day test were 0.078 for Study 18170 and 0.321 for Study 18171. Since the p-value for Breslow-Day test was 0.078 for Study 18170, the applicant systemically removed each analysis center and performed the Breslow-Day test to explore the possible source of the interaction effect. This procedure identified 5 analysis centers (1, 14, 17, 23, and 29) where the removal of any of the 5 analysis centers produced a non-significant ($\alpha = 0.10$) Breslow-Day test. Four of these analysis centers (1, 17, 23, and 29) had a large treatment effect for SOOLANTRA cream in comparison to vehicle cream. For analysis center 14, the vehicle cream had a higher IGA success rate than SOOLANTRA cream. To assess the influence of these centers on the overall treatment effect, the applicant conducted a sensitivity analyses where this endpoint was analyzed with the 5 analysis centers (96 subjects) were removed. While the treatment effect was slightly smaller with the removal of these centers, the results were still statistically significant ($p < 0.001$).

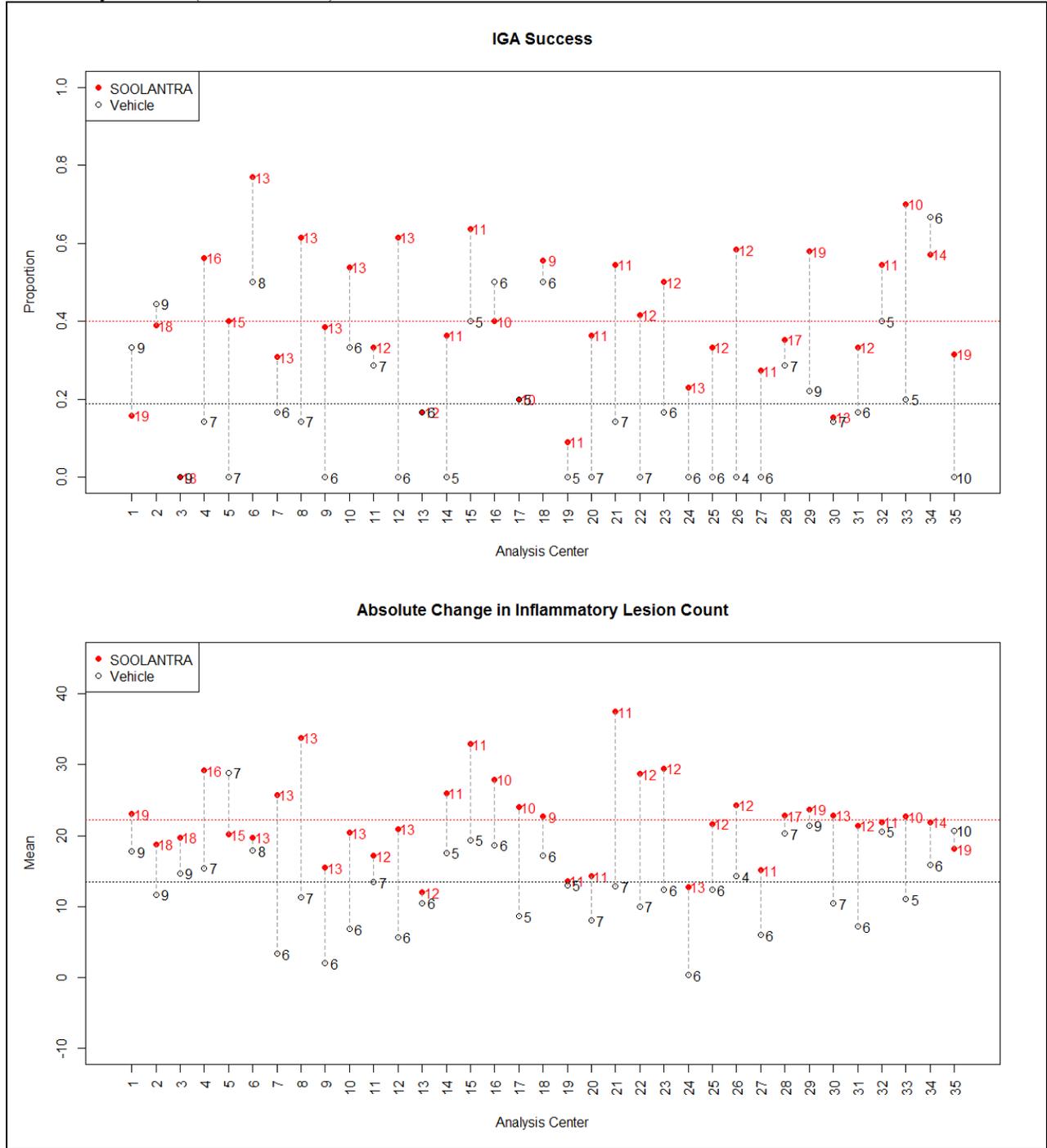
As the pooling process could mask center effects, this reviewer conducted a sensitivity analysis where each center (prior to pooling) was removed. For both studies and both co-primary endpoints, the removal of any one center did not affect the overall conclusions ($p < 0.001$).

Figure 3: Results for the Co-Primary Efficacy Endpoints at Week 12 by Analysis Centers in Study 18170 (ITT, LOCF)



Source: Reviewer's Analysis

Figure 4: Results for the Co-Primary Efficacy Endpoints at Week 12 by Analysis Centers in Study 18171 (ITT, LOCF)



Source: Reviewer's Analysis

Table 19 presents the results of the co-primary efficacy endpoints at Week 12 by country (U.S. and Canada) for Studies 18170 and 18171. In general, the treatment effects were consistent between the countries in both studies.

Table 19: Results for the Co-Primary Efficacy Endpoints at Week 12 by Country (ITT, LOCF)

	Study 18170		Study 18171	
	SOOLANTRA (N=451)	Vehicle (N=232)	SOOLANTRA (N=459)	Vehicle (N=229)
IGA Success⁽¹⁾: n (%)				
U.S.	139/367 (37.9%)	24/188 (12.8%)	140/361 (38.8%)	32/181 (17.7%)
Canada	34/84 (40.5%)	3/44 (6.8%)	44/98 (44.9%)	11/48 (22.9%)
Absolute Change in Inflammatory Lesion Counts: Mean (SD)				
U.S.	19.5 (15.5)	12.1 (12.1)	22.4 (15.3)	12.7 (15.1)
Canada	24.5 (17.4)	11.6 (18.7)	21.7 (13.2)	16.0 (11.4)

Source: Reviewer's Analysis

(1) Success is defined as achieving an IGA score of 0 (clear) or 1 (almost clear).

SD: Standard Deviation

Three centers (8092, 8094, and 8060) in Study 18170 and two centers (8303 and 8069) in Study 18171 reported financial disclosures. This reviewer conducted a sensitivity analysis where the co-primary endpoints at Week 12 were analyzed with these centers removed. The results were very similar with these centers removed and were statistically significant (p-values<0.001).

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There were no major statistical issues affecting overall conclusions. For the handling of missing data, the results were similar between the primary imputation method of LOCF and the applicant's pre-specified sensitivity analyses. For the co-primary efficacy endpoint of IGA success rate at Week 12, this reviewer conducted an additional sensitivity analysis where missing data was imputed under the worst case scenario (i.e., missing data imputed as failures in the SOOLANTRA arm and successes in the vehicle arm). In this extreme case, SOOLANTRA cream was still statistically superior ($p \leq 0.001$) to vehicle cream in both studies.

Treatment effects were generally consistent across subgroups. The applicant's investigation of the treatment-by-center interaction focused on the effects after pooling (i.e., analysis centers). As the pooling process could mask center effects, this reviewer conducted a sensitivity analysis where each center (prior to pooling) was removed. For both studies and both co-primary efficacy endpoints, the removal of any one center did not affect the overall conclusions ($p < 0.001$).

5.2 Collective Evidence

SOOLANTRA cream 1% was superior to vehicle cream in the topical treatment of inflammatory lesions of rosacea in two studies. The studies enrolled subjects aged 18 years and older with a diagnosis of papulopustular rosacea with 15 to 70 inflammatory lesions (papules and pustules) on the face, and an IGA score of 3 (moderate) or 4 (severe). Subjects applied study product once daily for 12 weeks. The protocol specified co-primary efficacy endpoints were the IGA success rate (proportion of subjects that achieve an IGA score of 0 or 1) at Week 12 and the absolute change in inflammatory lesion counts from baseline to Week 12. Percent change in inflammatory lesion counts from baseline to Week 12 was specified as the single secondary efficacy endpoint. The co-primary and secondary efficacy endpoints were all statistically significant ($p < 0.001$), see Table 20.

Table 20: Results for the Co-Primary and Secondary Efficacy Endpoints at Week 12 (ITT, LOCF)

Endpoints	Study 18170			Study 18171		
	SOOLANTRA (N=451)	Vehicle (N=232)	P-value	SOOLANTRA (N=459)	Vehicle (N=229)	P-value
Co-Primary: IGA Success ⁽¹⁾ : n (%)	173 (38.4%)	27 (11.6%)	<0.001 ⁽²⁾	184 (40.1%)	43 (18.8%)	<0.001 ⁽²⁾
Absolute Change in Inflammatory Lesion Counts: Mean (SD)	20.5 (16.0)	12.0 (13.5)	<0.001 ⁽³⁾	22.2 (14.9)	13.4 (14.5)	<0.001 ⁽³⁾
Secondary: Percent Change in Inflammatory Lesion Counts: Mean (SD)	64.9% (39.9)	41.6% (38.8)	<0.001 ⁽⁴⁾	65.7% (33.2)	43.4% (38.4)	<0.001 ⁽⁴⁾

Source: Reviewer's Analysis

(1) Success is defined as achieving an IGA score of 0 (clear) or 1 (almost clear).

(2) P-value calculated from a CMH test stratified by analysis centers.

(3) P-value calculated based on an ANCOVA model with baseline lesion count, treatment, and analysis centers as factors.

(4) P-value was based a CMH test stratified by analysis centers using the RIDIT score and row mean difference.

SD: Standard Deviation

The protocol specified that 'time to onset' of efficacy will be determined using a conditional backward stepwise testing approach of the co-primary efficacy endpoints for the different weeks (Weeks 12, 8, 4, and 2). SOOLANTRA cream was statistically superior ($\alpha = 0.05$) to vehicle cream starting at Week 4, see Table 13 in Section 3.2.7.

5.3 Conclusions and Recommendations

Efficacy findings from the two pivotal trials (Studies 18170 and 18171) established that SOOLANTRA cream 1% applied once daily was superior to vehicle cream for the topical treatment of inflammatory lesions of rosacea in adults 18 years of age and older.

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Matthew Guerra, Ph.D.
Date: August 29, 2014

Statistical Team Leader: Mohamed Alosh, Ph.D.
Date: August 29, 2014

cc:

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DDDP/Lindstrom
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DDDP/Gould
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OBIO/Patrician
DBIII/Wilson
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/s/

MATTHEW W GUERRA
08/29/2014

MOHAMED A ALOSH
08/29/2014
Concur with the review



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

Addendum-1

To

NDA 206-255 Rat and Mouse Carcinogenicity Statistical Review

IND/NDA Number:	NDA 206-255
Drug Name:	CD5024
Indication(s):	Two Year Carcinogenicity Studies in Rat and Mouse
Applicant:	Sponsor: Galderma Research & Development 5 Cedar Brook Drive, Suite 1, Cranbury, NJ 0851 23606 Testing Facility: [REDACTED] (b) (4)
Documents Reviewed:	Electronic submission submitted on December 20, 2013 Electronic data submitted on December 12, 2013
Review Priority:	Standard
Biometrics Division:	Division of Biometrics - 6
Statistical Reviewer:	Mohammad Atiar Rahman, Ph.D.
Concurring Reviewer:	Karl Lin, Ph.D.
Medical Division:	Division of Dermatology and Dental Products
Reviewing Pharmacologist:	Jianyong Wang, Ph.D.
Project Manager:	Paul Phillips
Keywords:	Carcinogenicity, Dose response

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1. Introduction

A statistical review of a long term rat and mouse carcinogenicity study was completed and put in the DARRTS by this reviewer on 5/7/2014. In a later correspondence the reviewing pharmacologist suggested some additional analysis by combining the following organ and/or tumor types. This addendum contains the additional analysis.

2. Additional analysis requested by the reviewing pharmacologist

For male rats:

Combine hemangioma and hemangiosarcoma seen in all organs

Adrenal: Combine cortical adenoma and carcinoma; combine benign and malignant pheochromocytoma

Kidney: Combine lipoma and liposarcoma

Pancreas: Combine islet cell adenoma and carcinoma

Pituitary gland: combine adenoma and carcinoma

Skin: Combine fibroma and fibrosarcoma; combine lipoma and liposarcoma; combine sebaceous cell adenoma and carcinoma

Thymus: Combine benign and malignant thymoma

Thyroid gland: Combine C-cell adenoma and carcinoma; combine follicular cell adenoma and carcinoma

For female rats:

Combine hemangioma and hemangiosarcoma seen in all organs

Adrenal: Combine cortical adenoma and carcinoma

Mammary gland: Combine adenoma and adenocarcinoma

Ovary: Combine benign and malignant granulosa-theca cell tumors

Pancreas: combine islet cell adenoma and carcinoma

Pituitary gland: Combine adenoma and carcinoma

Skin: Combine lipoma and liposarcoma; Combine squamous cell papilloma and carcinoma

Thymus: Combine benign and malignant thymoma

Thyroid gland: Combine follicular cell adenoma and carcinoma

Tongue: Combine squamous cell papilloma and carcinoma

Uterus with cervix: Combine stromal polyp and stromal cell sarcoma

For male mice:

Combine hemangioma and hemangiosarcoma seen in all organs

Harderian gland: Combine adenoma and adenocarcinoma

Liver: Combine hepatocellular adenoma and carcinoma

Lung: Combine alveolar/bronchiolar adenoma and carcinoma

Skin: Combine squamous cell papilloma and carcinoma, in both treated area and untreated area

Thymus: Combine benign and malignant thymoma

Thyroid gland: Combine C-cell adenoma and carcinoma; Combine follicular cell adenoma and carcinoma

For female mice:

Combine hemangioma and hemangiosarcoma seen in all organs

Bone: Combine osteoma and osteosarcoma

Liver: Combine hepatocellular adenoma and carcinoma

Lung: Combine alveolar/bronchiolar adenoma and carcinoma

Ovary: Combine adenoma and adenocarcinoma; Combine cystadenoma and cystadenocarcinoma

Skin: Combine squamous cell papilloma, in both treated area and untreated area

Uterus: Combine adenoma and adenocarcinoma; Combine leiomyoma and leiomyosarcoma

3. Reviewer's analysis

The following tables contain this reviewer's analyses results:

Male Rats:

Table Addendum_1A: Tumor Rates and P-Values for Dose Response Relationships and Pairwise Comparisons Male Rats

Organ Name	Tumor Name	0 mg	1 mg	3 mg	9 mg	P_Value	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		Control N=72	Low N=72	Med N=72	High N=72	Dose Resp			
ADRENAL_GLAND	Cortical_Adenoma+Carcinoma	1	2	2	0	0.8182	0.5349	0.4939	1.0000
ADRENAL_MEDULLA	Pheochromocyt_Benign+Malignant	2	3	2	4	0.1563	0.5508	0.6844	0.2844
KIDNEY	Lipoma+Liposarcoma	2	1	0	1	0.6370	0.8915	1.0000	0.8473
PANCREAS	Islet_cell_Adenoma+Carcinoma	3	4	7	9	0.0121	0.5516	0.1549	0.0367
PTUITARY_GLAND	Adenoma+Carcinoma	22	12	15	22	0.0792	0.9929	0.9342	0.4408
SKIN_SUBCUTIS	Fibroma+Fibrosarcoma	5	2	1	1	0.9199	0.9536	0.9848	0.9783
	Lipoma+Liposarcoma	1	1	0	1	0.4857	0.7745	1.0000	0.7165
	Sebaceous_cell_Adenoma+Carcino	1	2	2	1	0.5342	0.5349	0.4939	0.7165
THYMUS	Thymoma_Benign+Malignant	2	9	3	4	0.5064	0.0387	0.4846	0.2774
THYROID_GLAD	Follicular_cell+Adenoma+Carcin	15	1	4	2	0.9951	1.0000	0.9988	0.9998
THYROID_GLAND	C-Cell_Adenoma+Carcinoma	7	1	3	5	0.3104	0.9978	0.9469	0.7459
WHOLE_BODY	Hemangioma+Hemangiosarcoma	7	2	5	7	0.1336	0.9879	0.8024	0.4890

Female Rats:

Table Addendum_1B: Tumor Rates and P-Values for Dose Response Relationships and Pairwise Comparisons Female Rats

Organ Name	Tumor Name	0 mg	1 mg	3 mg	9 mg	P_Value	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		Control N=72	Low N=72	Med N=72	High N=72	Dose Resp			
ADRENAL_GLAND	Cortical_Aden+Carci	2	0	2	1	0.5215	1.0000	0.6967	0.8652
OVARY	Granulosa-theca_cell_Benign+Ma	3	1	0	1	0.7821	0.9463	1.0000	0.9342
PANCREAS	Islet_cell_Adenoma+Carcinoma	2	3	0	6	0.0321	0.5232	1.0000	0.1252
PTUITARY_GLAND	Adenoma+Carcinoma	54	40	39	35	0.9819	0.9960	0.9988	0.9990
SKIN_SUBCUTIS	Lipoma+Liposarcoma	0	2	2	1	0.4129	0.2603	0.2562	0.4872
	Squamous_cell_Papilloma+Carcin	0	0	2	0	0.4812	.	0.2562	.
THYMUS	Thymoma_Benign+Malignant	3	8	6	5	0.4501	0.1130	0.2537	0.3211
THYROID_GLAND	Follicular_cell_Adenoma+Carcin	2	1	1	2	0.3768	0.8869	0.8841	0.6711
TONGE	Squamous_cell_Papilloma+Carcin	0	1	1	2	0.1109	0.5122	0.5082	0.2395
UTERUS_WITH_CER	Stromal_Polyp+Stromal_cell_sar	3	8	3	3	0.7668	0.1242	0.6757	0.6441
WHOLE_BODY	Hemangioma+Hemangiosarcoma	0	6	1	2	0.5591	0.0160*	0.5082	0.2395

Male Mice:

Table Addendum_2A: Tumor Rates and P-Values for Dose Response Relationships and Pairwise Comparisons Using Placebo Control Male Mice

Organ Name	Tumor Name	Placebo	1 mg	3 mg	10 mg	P_Value				
		Control N=60	Low N=60	Med N=60	High N=60	Dose Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H	
fff										
HARDERIAN_GLAND	Adenoma+Adenocarcinoma	5	2	4	2	0.7977	0.9333	0.7708	0.9377	
LIVER	Adenoma+Carcinoma	15	15	23	15	0.5328	0.5586	0.1284	0.5586	
LUNG	Aveolar_Bronchiolar_Adenoma+Ca	22	18	17	14	0.8833	0.8535	0.8627	0.9454	
SKIN_TREATED +UNTREATED	Squamous_cell_Papilloma+Carcin	1	1	1	0	0.8364	0.7468	0.7655	1.0000	
WHOLE_BODY	Hemangioma+Hemangiosarcoma	2	5	3	4	0.3836	0.2053	0.5119	0.3496	

Table Addendum_3A: Tumor Rates and P-Values for Dose Response Relationships and Pairwise Comparisons Using Water Control Male Mice

Organ Name	Tumor Name	Water	1 mg	3 mg	10 mg	P_Value				
		Control N=60	Low N=60	Med N=60	High N=60	Dose Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H	
fff										
HARDERIAN_GLAND	Adenoma+Adenocarcinoma	5	2	4	2	0.7722	0.9145	0.7221	0.9198	
LIVER	Adenoma+Carcinoma	10	15	23	15	0.2529	0.1400	0.0085*	0.1400	
LUNG	Aveolar_Bronchiolar_Adenoma+Ca	24	18	17	14	0.9104	0.8976	0.9043	0.9654	
SKIN_TREATED +UNTREATED	Squamous_cell_Papilloma+Carcin	0	1	1	0	0.6070	0.4634	0.4824	.	
WHOLE_BODY	Hemangioma+Hemangiosarcoma	3	5	3	4	0.4463	0.2903	0.6275	0.4600	

Table Addendum_4A: Tumor Rates and P-Values for Pairwise Comparisons of Placebo and Water Control Groups Male Mice

Organ Name	Tumor Name	Water	Placebo	P_Value
		Control N=60	Control N=60	
fff				
HARDERIAN_GLAND	Adenoma+Adenocarcinoma	5	5	0.5694
LIVER	Adenoma+Carcinoma	10	15	0.1563
LUNG	Aveolar_Bronchiolar_Adenoma+Ca	24	22	0.6616
SKIN_TREATED +UNTREATED	Squamous_cell_Papilloma+Carcin	0	1	0.4699
WHOLE_BODY	Hemangioma+Hemangiosarcoma	3	2	0.7889

Female Mice:

Table Addendum_3B: Tumor Rates and P-Values for Dose Response Relationships and Pairwise Comparisons Using Placebo Control Female Mice

Organ Name	Tumor Name	Placebo	1 mg	3 mg	10 mg	P_Value			
		Control N=60	Low N=60	Med N=60	High N=60	Dose Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
LIVER	Hepatocellular_Adenoma+Carcino	1	0	0	3	0.0548	1.0000	1.0000	0.3265
LUNG	Aveolar_Bronchiolar_Adenoma+Ca	13	13	12	13	0.6093	0.5355	0.7280	0.6693
OVARY	Cystadenoma+Cystadenocarcinoma	3	1	0	3	0.2868	0.9290	1.0000	0.6737
SKIN_TREATED+UNTREAT	Squamous_cell_Papilloma+Carcin	0	0	0	3	0.0168*	.	.	0.1296
UTERUS	Adenoma+Adenocarcinoma	1	1	1	1	0.5405	0.7334	0.7651	0.7651
	Leiomyoma+Leiomyosarcoma	2	4	1	2	0.6809	0.3017	0.8840	0.7012
WHOLE_BODY	Hemangioma+Hemangiosarcoma	5	2	2	3	0.6671	0.9285	0.9491	0.8825

Table Addendum_2B: Tumor Rates and P-Values for Dose Response Relationships and Pairwise Comparisons Using Water Control Female Mice

Organ Name	Tumor Name	Water	1 mg	3 mg	10 mg	P_Value			
		Control N=60	Low N=60	Med N=60	High N=60	Dose Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
LIVER	Hepatocellular_Adenoma+Carcino	0	0	0	3	0.0175*	.	.	0.1397
LUNG	Aveolar_Bronchiolar_Adenoma+Ca	12	13	12	13	0.6026	0.5297	0.7200	0.6615
OVARY	Cystadenoma+Cystadenocarcinoma	0	1	0	3	0.0397	0.4933	.	0.1397
SKIN_TREATED +UNTREATED	Squamous_cell_Papilloma+Carcin	0	0	0	3	0.0175*	.	.	0.1397
UTERUS	Adenoma+Adenocarcinoma	0	1	1	1	0.3250	0.4933	0.5250	0.5250
	Leiomyoma+Leiomyosarcoma	3	4	1	2	0.7902	0.5000	0.9533	0.8502
WHOLE_BODY	Hemangioma+Hemangiosarcoma	0	2	2	3	0.1254	0.2400	0.2725	0.1446

**Table Addendum_4B: Tumor Rates and P-Values for
Pairwise Comparisons of Placebo and Water Control Groups
Female Mice**

Organ Name	Tumor Name	Water Control N=60	Placebo Control N=60	P_Value WC vs. PC
ff				
LIVER	Hepatocellular_Adenoma+Carcino	0	1	0.5128
LUNG	Aveolar_Bronchiolar_Adenoma+Ca	12	13	0.5859
OVARY	Cystadenoma+Cystadenocarcinoma	0	3	0.1348
UTERUS	Adenoma+Adenocarcinoma	0	1	0.5128
	Leiomyoma+Leiomyosarcoma	3	2	0.8434
WHOLE_BODY	Hemangioma+Hemangiosarcoma	0	5	0.0333*

Summary Table:

**Tumor Types with significant Dose Response Relationship
and/or Pairwise Comparisons of Treated Groups with Control**

Rats study:

Sex	Organ Name	Tumor Name	Control	Low	Med	High	P_Value			
			N=72	N=72	N=72	N=72	Dose Resp	C vs L	C vs M	C vs H
Female	WHOLE_BODY	Hemangioma+Hemangiosarcoma	0	6	1	2	0.5591	0.0160*	0.5082	0.2395

Mouse Study:

Using Water Control

Sex	Organ Name	Tumor Name	Control	Low	Med	High	P_Value			
			N=60	N=60	N=60	N=60	Dose Resp	C vs L	C vs M	C vs H
Male	LIVER	Adenoma+Carcinoma	10	15	23	15	0.2529	0.1400	0.0085*	0.1400
Female	LIVER	Hepatocellular_Adenoma+Carcino	0	0	0	3	0.0175*	.	.	0.1397
	SKIN_TREATED	Squamous_cell_Papilloma	0	0	0	3	0.0175*	.	.	0.1397
	+UNTREATED	+Carcinoma								

Using Placebo Control

Sex	Organ Name	Tumor Name	Control	Low	Med	High	P_Value			
			N=60	N=60	N=60	N=60	Dose Resp	C vs L	C vs M	C vs H
Female	SKIN_TREATED+UNTREAT	Squamous_cell_Papilloma	0	0	0	3	0.0168*	.	.	0.1296
		+Carcinoma								

Mouse Pairwise Comparisons of Water and Placebo Control Groups

Sex	Organ Name	Tumor Name	Water	Placebo	P_Value
			Control N=60	Control N=60	
Female	WHOLE_BODY	Hemangioma+Hemangiosarcoma	0	5	0.0333*

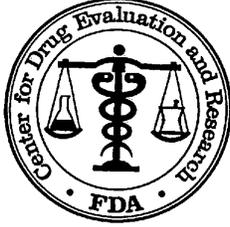
4. Conclusion

Based on the criteria of adjustment for multiple testing discussed in the rat data analysis section of the original review i.e. test dose response relationship at $\alpha=0.005$ for common tumors and $\alpha=0.025$ for rare tumors and pairwise comparisons of treated group with control at $\alpha=0.01$ for common tumors and $\alpha=0.05$ for rare tumors, all dose response relationship and/or pairwise comparison tests indicated by asterisk (*) in the summary table are considered to be statistically significant.

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/s/

MOHAMMAD A RAHMAN
07/01/2014



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 206-255
Drug Name:	CD5024
Indication(s):	Two Year Carcinogenicity Studies in Rat and Mouse
Applicant:	Sponsor: Galderma Research & Development 5 Cedar Brook Drive, Suite 1, Cranbury, NJ 0851 23606 Testing Facility: [REDACTED] (b) (4)
Documents Reviewed:	Electronic submission submitted on December 20, 2013 Electronic data submitted on December 12, 2013
Review Priority:	Standard
Biometrics Division:	Division of Biometrics - 6
Statistical Reviewer:	Mohammad Atiar Rahman, Ph.D.
Concurring Reviewer:	Karl Lin, Ph.D.
Medical Division:	Division of Dermatology and Dental Products
Reviewing Pharmacologist:	Jianyong Wang, Ph.D.
Project Manager:	Paul Phillips
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1. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were intended to assess the carcinogenic potential of CD5024 when administered daily via oral gavage to rats and via dermal application to mice for about two years. Results of this review have been discussed with the reviewing pharmacologist Dr. Wang.

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

2. Rat Study

Two separate experiments were conducted, one in male and one in female rats. In each of these two experiments there were three treated groups and one control group. Two hundred and eighty eight Crl: WI (Han) Wistar rats of each sex were assigned randomly to the treated and control groups in equal size of 72 rats per group. The dose levels for treated groups were 1, 3, or 9 mg/kg/day. In this review these dose groups would be referred to as the low, medium, and high dose groups, respectively. The rats in the control group were treated with vehicle (0.5 % (w/v) carboxymethylcellulose in water for injection).

During the administration period rats were observed twice daily to detect any clinical signs or reaction to treatment. A full clinical examination was performed once every 4 weeks until week 25 and once weekly thereafter. During the clinical observation the rats were palpated regularly. The detailed information concerning visible or palpable masses was recorded. The morbidity/mortality checks were performed at least twice daily.

All rats were weighed at the time of randomization, prior to dosing on day 0, once weekly for the first 16 weeks of treatment and once every 4 weeks thereafter. Due to the clinical signs observed, an additional body weight was recorded during weeks 1 and 2 for high dose females.

2.1. Sponsor's analyses

2.1.1. Survival analysis

The sponsor estimated the survival probability function of each treated group in each sex using the Kaplan-Meier product-limit method, and displayed the related survival plots graphically. The probabilities of dying before scheduled sacrifice were compared using the method elaborated by Peto et al. (1980) for fatal conditions, which is equivalent to the method of Cox (1972) in that it conditions on the numbers of survivors in each group at each time point of death. The sponsor also conducted a Kruskal-Wallis one-way analysis of variance by ranks based on week of death. The Peto and Kruskal-Wallis survival analyses included an analysis of dose response relationship.

Sponsor's findings: The sponsor's count showed 23 (32%), 13 (18%), 28 (39%) and 40 (56%) number (percentage) of deaths in male rats; and 25 (35%), 25 (35%), 25 (35%), and 24 (33%)

number (percentage) of deaths in female rats in control, low, medium, and high dose groups, respectively. The sponsor's analysis showed a statistically significant positive dose response relationship in mortality in male rats. The pairwise comparisons, in male rats, showed statistically significant increased mortality in the high dose group compared to the control. In female rats no such statistically significant difference in mortalities were found, overall or between treatment groups. Analysis in the combined sexes showed a statistically significant positive dose response relationship in mortality. The pairwise comparisons in the combined sex data showed statistically significant increased mortality in the high dose group compared to the control. The sponsor commented that the results in the combined sexes merely reflect the contribution of the results of male rats.

2.1.2. Tumor data analysis

The sponsor first classified the tumor types as incidental or fatal and analyzed them using the method illustrated by Peto et al. (1980). The tests were asymptotic in general; however exact tests were performed for tumors with low incidences. The time intervals used were 1-52, 53-72, 73-84, 85-92, 93-98, 99-104, and terminal sacrifice (105-108). The Fisher exact tests were used for pairwise comparisons of treated groups with the control. The analysis of tumor incidences were carried out for two sexes separately as well as both sexes combined.

Adjustment for multiple testing: The sponsor did not mention of any method in the report for the adjustment of multiple testing. The p-values were evaluated at 0.001, 0.01, 0.05 and 0.1 level of significance for two-tailed tests; or equivalently at 0.0005, 0.005, 0.025, and 0.05 level of significance for one-tailed tests for all tumors.

Sponsor's findings: The sponsor's analysis showed statistically significant positive dose response relationships in the incidences of adenoma in liver ($p < 0.01$), haemangioma ($p < 0.05$), combined incidences of haemangioma and haemangiosarcoma ($p < 0.05$), and haemangiomas ($p < 0.05$) in mesenteric lymph node, and islet cell adenoma in endocrine pancreas in male rats. Tests also showed statistically significant positive dose response relationships in the incidences of islet cell carcinoma in endocrine ($p < 0.05$) in female rats. When combining islet cell adenomas and carcinomas, this trend was significant in males and females separately ($p < 0.05$), and highly significant ($p < 0.001$) in males and females combined.

The sponsor's pairwise comparisons showed a higher incidence of islet cell tumours (mainly islet cell adenomas) in male rats at high dose group when compared with controls. In female rats, a higher incidence of islet cell tumours (mainly islet cell carcinomas) was also observed at high dose group. When combining males and females, the higher incidence of islet cell tumours in the high dose group became clearly significant.

Sponsor's analysis further showed that there was a higher incidence of malignant lymphomas (pleomorphic type) in male rats given the medium dose group when compared with controls and background data. The incidence of malignant lymphomas in other groups was consistent with background data. Since there was no significant trend, the sponsor considered this effect of the test item unlikely.

The sponsor noted that since the Wistar strain is especially prone to mesenteric lymph node tumours and related changes, the toxicological relevance of these findings is equivocal. Additionally, since there were no statistically significant differences between treated groups and controls, and the incidence of mesenteric lymph node tumours was within background data, the sponsor considered an effect of the test item as unlikely.

2.2. Reviewer's analyses

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

2.2.1. Survival analysis

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

Reviewer's findings: This reviewer's analysis showed 23 (32%), 13 (18%), 28 (39%) and 40 (56%) number (percentage) of deaths in male rat; and 25 (35%), 25 (35%), 25 (35%), and 24 (33%) number (percentage) of deaths in female rat in control, low, medium, and high dose groups, respectively. The tests showed statistically significant positive dose response relationship in mortality across control and treated groups in male rats. The pairwise comparisons showed statistically significant increased mortality in the male rat high dose group.

2.2.2. Tumor data analysis

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

$s_h = \left(\frac{w_h}{w_{\max}} \right)^k < 1$. The adjusted group size is defined as $\sum s_h$. As an interpretation, an animal with

score $s_h = 1$ can be considered as a whole animal while an animal with score $s_h < 1$ can be considered

as a partial animal. The adjusted group size $\sum s_h$ is equal to N (the original group size) if all animals live up to the end of the study or if each animal that dies before the terminal sacrifice develops at least one tumor, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data. For the calculation of p-values the exact permutation method was used. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A and 3B in the appendix for male and female rats, respectively.

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

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

Reviewer’s findings: Following tumor types showed p-values less than or equal to 0.05 either for dose response relationship and/or pairwise comparisons of treated groups and control.

Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship and/or Pairwise Comparisons of Treated Groups and Control in Rats

Sex	Organ Name	Tumor Name	Control	Low	Med	High	P-Value			
			N=72	N=72	N=72	N=72	Dose Resp	C vs. L	C vs. M	C vs. H

Male	ADRENAL MEDULLA	Malignant pheochromocytoma,	0	0	0	2	0.0493	.	.	0.2188
	LIVER	Hepatocellular adenoma,	0	1	2	9	<0.001*	0.5231	0.2439	<0.001*
	MESENT. LYMPH N	Hemangioma,	4	1	2	6	0.0423	0.9774	0.8926	0.2872
	PANCREAS, ENDOC	Islet cell adenoma,	2	3	4	7	0.0163	0.5439	0.3321	0.0531
	PITUITARY GLAND	Adenoma of pars distalis,	20	10	13	21	0.0498	0.9944	0.9418	0.3747
	SYSTEMIC NEOPLA	Malignant lymphoma,	0	2	6	2	0.2380	0.2755	0.0145*	0.2188
Female	PANCREAS, ENDOC	Islet cell carcinoma,	2	1	0	5	0.0246	0.8869	1.0000	0.2056

*Statistically significant

Based on the criteria of adjustment for multiple testing discussed above, the incidence of hepatocellular adenoma in male rats was considered to have statistically significant dose response relationship. Also in male rats, the pairwise comparison showed statistically significant increased incidences of hepatocellular adenoma in the high dose group compared to the control, and malignant lymphoma in systemic neoplasms in the medium dose group compared to the control.

3. Mouse Study

Two separate experiments were conducted, one in male and one in female mice. In each of these two experiments there were three treated groups, one water control group, and one placebo control group. Three hundred Swiss Crl:CD1 (ICR) mice of each sex were assigned randomly to the treated and control groups in equal size of 60 mice per group. The dose levels for treated groups were 0.1%, 0.3%, and 1.0% concentration. In this review these dose groups would be referred to as the low, medium, and high dose groups, respectively. The mice in placebo treatment group were treated with placebo (CD5024 placebo cream), while the mice in the water control group received water for injection.

The study was originally scheduled for 104 weeks. However, due to the excessive mortality observed in all groups and following FDA recommendations, the treatment was stopped during week 92 for low dose males, week 95 for placebo control males, week 100 for water control, medium and high dose males and low dose females, week 101 for water control females. Also following the FDA comments and recommendations the surviving mice were killed during week 100 for male high dose group, week 101 for other male groups and during week 105/106 for all female groups.

Like the rats, during the administration period all mice were observed daily for general conditions. A full clinical examination was performed once every 4 weeks until week 25, then once weekly thereafter. During the clinical observation the mice were palpated regularly. The detailed information concerning visible or palpable masses was recorded. Morbidity/mortality checks were performed at least twice daily.

All mice were weighed at the time of randomization, prior to dosing on day 0, once weekly for the first 16 weeks of treatment and once every 4 weeks thereafter, at the end of the treatment period (except for males water control group), and termination.

3.1. Sponsor's analyses

The sponsor carried out the analysis of survival and tumor data by comparing the two control groups, comparing the treated groups with the combined controls, and comparing the treated groups with the placebo controls.

3.1.1. Survival analysis

The sponsor used similar methodologies to analyze the mouse survival data as they used to analyze the rat survival data.

Sponsor's findings: The sponsor's count showed 38%, 28%, 25%, 33%, and 33% mortality in male mice ; and 33%, 33%, 28%, 33%, and 43% mortality in female mice in water control, placebo control, low, medium, and high dose groups, respectively. Sponsor's analysis did not show any statistically significant dose response relationship or pairwise difference in mortality in any of the treated groups compared to either placebo or water control group in either sex. The placebo and water control groups also did not show any difference in mortality.

3.1.2. Tumor data analysis

The sponsor used similar methodologies to analyze the mouse tumor data as they used to analyze the rat tumor data. For incidental tumours, the sponsor used the following time intervals in weeks: 1-52, 53-72, 73-80, 81-84, 85-88, 89-92, 93-96 and 97 onwards. For males, the final time interval was weeks 100-101, and for females that was weeks 105-106.

Adjustment for multiple testing: The sponsor did not mention of any method in the report for the adjustment of multiple testing. Similar to rat tumor data analysis, the p-values were evaluated at 0.001, 0.01, 0.05 and 0.1 level of significance for two-tailed tests; or equivalently at 0.0005, 0.005, 0.025, and 0.05 level of significance for one-tailed tests for all tumors.

Sponsor's findings: The sponsor's analyses did not show statistically significant positive dose response relationship in any of the individual observed tumor types, however showed a statistically significant positive dose response relationship in the combined incidences of adenocarcinoma, adenoma, adenomyosis and cystic endometrial hyperplasia ($p < 0.05$) when treated groups were compared with combined control groups in uterus. However, when this comparison was done with the placebo control group only (omitting the water control group), no significant trend was seen. Because of the second result, the sponsor considered the relevance of this finding as doubtful.

3.2. Reviewer's analyses

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

For the analysis of both the survival data and the tumor data this reviewer used similar methodologies as he used for the analyses of the rat survival and tumor data.

For appropriate interpretation of the data from studies with a negative and a placebo control group, the FDA guidance for tumor data analysis suggests analyzing the data from treated groups along with the data from placebo control group. Following this suggestion, this reviewer conducted his primary analysis using the data from placebo control, low, medium, and high dose groups. However, this reviewer also performed some additional analyses including the water control groups. Results from all these analyses have been reported in this review.

3.2.1. Survival analysis

The Kaplan-Meier curves for survival rates of all treatment groups are given in Figures 2A and 2B in the appendix for male and female mice, respectively. The intercurrent mortality data of all treatment groups are given in Tables 4A and 4B in the appendix for male and female mice, respectively. Results of the tests for dose response relationship and homogeneity of survivals for placebo control, low, medium, and high dose groups are given in Tables 5A and 5B in the appendix for male and female mice, respectively.

Reviewer’s findings: This reviewer’s analysis showed 23 (38%), 17 (28%), 15 (25%), 20 (33%) and 20 (33%) number (percent) of survivor in male mice, and 20 (33%), 20 (33%), 17 (28%), 20 (33%), and 26 (43%) number (percent) of survivor in female mice in water control, placebo control, low, medium, and high dose groups, respectively. The tests did not show statistically significant dose response relationship in mortality across the treatment groups in either sex. The pairwise comparison also did not show statistically significant difference in mortality among treatment groups in either sex.

3.2.2. Tumor data analysis

The tumor rates and the p-values of the tested tumor types using the placebo control and treated groups are given in Tables 6A and Table 6B in the appendix, for male and female mice respectively. The tumor rates and the p-values of the tested tumor types using the water control and treated groups are given in Tables 7A and Table 7B in the appendix, for male and female mice respectively. The pairwise comparisons of water and placebo control groups are given in Tables 8A and Table 8B in the appendix, for male and female mice respectively.

Reviewer’s findings: Following tumor type showed p-values less than or equal to 0.05 either for dose response relationship and/or pairwise comparisons of treated groups with control.

Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship and/or Pairwise Comparisons of Treated Groups with Control in Mice

Sex	Organ Name	Tumor Name	Control	Low	Med	High	P_Value			
			N=60	N=60	N=60	N=60	Dose Resp	C vs L	C vs M	C vs H
Male										
(Using placebo control group)										
	KIDNEYS	Adenoma, solid	0	0	0	3	0.0150*	.	.	0.1201
(Using water control group)										
	KIDNEYS	Adenoma, solid	1	0	0	3	0.0452	1.0000	1.0000	0.2636
	LIVER	Hepatocellular adenoma,	9	14	18	10	0.5575	0.1218	0.0324	0.3846
		Hepatocellular carcinoma,	2	4	7	8	0.0363	0.2819	0.0783	0.0375
(using placebo control group)										
	LIVER	Hepatocellular adenoma,	0	0	0	3	0.0168*	.	.	0.1296
(Using water control group)										
	LIVER	Hepatocellular adenoma,	0	0	0	3	0.0175*	.	.	0.1397

*Statistically significant

Based on the criteria of adjustment for multiple testing discussed in the rat data analysis section, the incidences of kidneys solid adenoma in male mice, and hepatocellular adenoma in female mice were considered to have statistically significant dose response relationship. In female mice, similar statistically significant dose response relationship was also found in the incidence of hepatocellular adenoma using the water control group. The pairwise comparisons did not show statistically significant increased incidence in any other observed tumor types in any treated group compared to their respective placebo control in either sex.

Reviewer’s comment: *The sponsor’s analysis showed a statistically significant positive dose response relationship in the combined incidences of adenocarcinoma, adenoma, adenomyosis and cystic endometrial hyperplasia (p < 0.05) when treated groups were compared with combined control groups in uterus. The submitted data did not have observations for adenomyosis and cystic endometrial hyperplasia. The analysis of combined incidences of adenocarcinoma and adenoma using the combined placebo was as follows:*

Analysis of Combined Incidences of Uterus Adenocarcinoma and Adenoma Using Combined Placebo

Sex	Organ Name	Tumor Name	Control	Low	Med	High	P_Value			
			N=60	N=60	N=60	N=60	Dose Resp	C vs L	C vs M	C vs H
Female	UTERUS	Adenoma+Adenocarcinoma	1	1	1	1	0.3686	0.5419	0.5794	0.5794

The analysis showed neither statistically significant dose response relationship nor pairwise comparison of any of the treated groups with the combined control.

4. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were intended to assess the carcinogenic potential of CD5024 when administered daily via oral gavage to rats and via dermal application to mice for about two years.

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

Rat Study: Two separate experiments were conducted, one in male and one in female rats. In each of these two experiments there were three treated groups and one control group. Two hundred and eighty eight CrI: WI (Han) Wistar rats of each sex were assigned randomly to the treated and control groups in equal size of 72 rats per group. The dose levels for treated groups were 1, 3, or 9 mg/kg/day. The rats in the control group were treated with vehicle (0.5 % (w/v) carboxymethylcellulose in water for injection).

During the administration period rats were observed twice daily to detect any clinical signs or reaction to treatment. A full clinical examination was performed once every 4 weeks until week 25, and once weekly thereafter. During the clinical observation the details of visible or palpable masses was recorded. The morbidity/mortality checks were performed at least twice daily. The body weights were taken prior to dosing on day 0, once weekly for the first 16 weeks of treatment and once every 4 weeks thereafter.

The tests showed statistically significant positive dose response relationship in mortality across control and treated groups in male rats. The pairwise comparisons showed statistically significant increased mortality in the male rat high dose group. The tests showed statistically significant dose response relationship in the incidence of hepatocellular adenoma in male rats. Also in male rats, the pairwise comparison showed statistically significant increased incidences of hepatocellular adenoma, and malignant lymphoma in systemic neoplasms in the high dose group compared to the control.

Mouse Study: Two separate experiments were conducted, one in male and one in female mice. In each of these two experiments there were three treated groups, one water control group, and one placebo control group. Three hundred Swiss Crl:CD1 (ICR) mice of each sex were assigned randomly to the treated and control groups in equal size of 60 mice per group. The dose levels for treated groups were 0.1%, 0.3%, and 1.0% concentration. The mice in placebo treatment group were treated with placebo (CD5024 placebo cream), while the mice in the water control group received water for injection.

The study was originally scheduled for 104 weeks. However, due to the excessive mortality observed in all groups and following FDA recommendations, the treatment was stopped during week 92 for low dose males, week 95 for placebo control males, week 100 for water control, medium and high dose males and low dose females, week 101 for water control females. Also following the FDA comments and recommendations the surviving mice were killed during week 100 for high dose males, week 101 for other male groups and during week 105/106 for all female groups.

During the administration period all mice were observed daily for general conditions. A full clinical examination was performed once every 4 weeks until week 25, and once weekly thereafter. During the clinical observation the mice were palpated regularly. The detailed information concerning visible or palpable masses was recorded. The morbidity/mortality checks were performed at least twice daily. All mice were weighed at the time of randomization, prior to dosing on day 0, once weekly for the first 16 weeks of treatment and once every 4 weeks thereafter, at the end of the treatment period (except for male water control group), and termination.

The tests did not show statistically significant dose response relationship in mortality across the treatment groups in either sex. The pairwise comparison also did not show statistically significant difference in mortality among treatment groups in either sex. The tests showed statistically significant dose response relationship in the incidences of kidneys solid adenoma in male mice, and hepatocellular adenoma in female mice. In female mice, statistically significant dose response relationship was also found in the incidence of hepatocellular adenoma using the water control group. The pairwise comparisons did not show statistically significant increased incidence in any other observed tumor types in any treated group compared to their respective placebo control in either sex.

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5. Appendix

**Table 1A: Intercurrent Mortality Rate
Male Rats**

Week	0 mg kg day		1 mg kg day		3 mg kg day		9 mg kg day	
	No. of Death	%Cum. %						
0 - 52	4	5.56	.	.	4	5.56	1	1.39
53 - 78	3	9.72	1	1.39	5	12.50	11	16.67
79 - 91	4	15.28	5	8.33	4	18.06	14	36.11
92 - 104	12	31.94	7	18.06	15	38.89	14	55.56
Ter. Sac.	49	68.06	59	81.94	44	61.11	32	44.44

Total	N=72		N=72		N=72		N=72	

*Cum. %: Cumulative percentage, except for Ter. Sac.

**Table 1B: Intercurrent Mortality Rate
Female Rats**

Week	0 mg kg day		1 mg kg day		3 mg kg day		9 mg kg day	
	No. of Death	%Cum. %						
0 - 52	1	1.39	1	1.39	.	.	7	9.72
53 - 78	8	12.50	4	6.94	8	11.11	6	18.06
79 - 91	9	25.00	9	19.44	6	19.44	4	23.61
92 - 104	7	34.72	11	34.72	11	34.72	7	33.33
Ter. Sac.	47	65.28	47	65.28	47	65.28	48	66.67

Total	N=72		N=72		N=72		N=72	

*Cum. %: Cumulative percentage, except for Ter. Sac.

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

Test	Statistic	P_Value

Dose-Response	Likelihood Ratio	<0.0001
Homogeneity	Log-Rank	<0.0001

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

Test	Statistic	P_Value

Dose-Response	Likelihood Ratio	0.9954
Homogeneity	Log-Rank	0.9998

**Table 3A: Tumor Rates and P-Values for Dose Response Relationships and Pairwise Comparisons
Male Rats**

Organ Name	Tumor Name	0 mg	1 mg	3 mg	9 mg	P_Value	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		Control N=72	Low N=72	Med N=72	High N=72	Dose Resp			
fff									
ADRENAL GLANDS	Cortical adenoma,	1	2	1	0	0.8532	0.5349	0.7480	1.0000
	Cortical carcinoma,	0	0	1	0	0.4694	.	0.4959	.
ADRENAL MEDULLA	Benign pheochromocytoma,	2	3	2	2	0.5061	0.5508	0.6844	0.6442
	Malignant pheochromocytoma,	0	0	0	2	0.0493	.	.	0.2188
BONE	Osteosarcoma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000
BRAIN	Granular cell tumor,	2	3	0	0	0.9814	0.5508	1.0000	1.0000
	Malignant Astrocytoma,	1	0	1	1	0.3408	1.0000	0.7480	0.7165
	Oligodendroglioma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000
COLON	Adenocarcinoma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000
EPIDIDYIMIDES	Malignant Schwannoma,	0	0	1	0	0.4694	.	0.4959	.
HEART	Myxoma,	2	0	0	0	1.0000	1.0000	1.0000	1.0000
JEJUNUM	Adenocarcinoma,	0	0	0	1	0.2204	.	.	0.4655
KIDNEYS	Lipoma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	Liposarcoma,	1	1	0	1	0.4857	0.7745	1.0000	0.7165
LIVER	Hepatocellular adenoma,	0	1	2	9	<0.001*	0.5231	0.2439	<0.001*
LUNG	Bronchiolo-alveolar adenoma,	1	0	0	1	0.3929	1.0000	1.0000	0.7165
MAMMARY GLAND	Fibroadenoma,	2	0	1	0	0.8729	1.0000	0.8750	1.0000
MESENT. LYMPH N	Hemangioma,	4	1	2	6	0.0423	0.9774	0.8926	0.2872
	Hemangiosarcoma,	0	1	3	1	0.3195	0.5231	0.1189	0.4655
NASAL CAVITIES	Malignant Schwannoma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000
NASAL MUCOSA	Anaplastic Carcinoma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000
ORAL CAVITY	Squamous cell carcinoma,	1	1	1	0	0.8020	0.7706	0.7439	1.0000
PANCREAS, ENDOC	Islet cell adenoma,	2	3	4	7	0.0163	0.5439	0.3321	0.0531
	Islet cell carcinoma,	1	1	3	2	0.2264	0.7745	0.3033	0.4479
PANCREAS, EXOCR	Acinar cell adenocarcinoma,	0	1	0	0	0.7469	0.5231	.	.
PARATHYROID GLA	Adenoma,	3	1	1	0	0.9633	0.9509	0.9386	1.0000
PAROTID GLAND,	Adenoma,	0	1	0	0	0.7469	0.5231	.	.
	Schwannoma,	0	0	1	0	0.4694	.	0.4959	.
PAROTID GLAND,	Schwannoma,	0	1	0	0	0.7469	0.5231	.	.

**Table 3A: Tumor Rates and P-Values for Dose Response Relationships and Pairwise Comparisons
Male Rats**

Organ Name	Tumor Name	0 mg	1 mg	3 mg	9 mg	P_Value				
		Control N=72	Low N=72	Med N=72	High N=72	Dose Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H	
fff										
PITUITARY GLAND	Adenoma of pars distalis,	20	10	13	21	0.0498	0.9944	0.9418	0.3747	
	Adenoma of pars intermedia,	3	2	0	1	0.8138	0.8449	1.0000	0.9221	
	Carcinoma of pars distalis,	0	0	2	0	0.4542	.	0.2439	.	
	Malignant Schwannoma,	0	0	0	1	0.2204	.	.	0.4655	
PROSTATE GLAND	Adenoma,	4	0	0	4	0.1143	1.0000	1.0000	0.5618	
	Adjacent tissue ganglioneuroma	0	0	1	0	0.4694	.	0.4959	.	
RECTUM	Squamous cell carcinoma,	0	0	0	1	0.2204	.	.	0.4655	
SEMINAL VESICLE	Adenoma,	0	0	0	1	0.2204	.	.	0.4655	
SKIN/SUBCUTIS	Basal cell carcinoma,	0	1	0	0	0.7469	0.5231	.	.	
	Benign Schwannoma,	0	1	0	0	0.7469	0.5231	.	.	
	Fibrolipoma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000	
	Fibroma,	5	2	0	1	0.9306	0.9536	1.0000	0.9783	
	Fibrosarcoma,	0	0	1	0	0.4694	.	0.4959	.	
	Hemangioma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000	
	Hemangiosarcoma,	2	0	0	0	1.0000	1.0000	1.0000	1.0000	
	Keratoacanthoma,	4	7	4	2	0.8624	0.3203	0.6231	0.8621	
	Lipoma,	1	1	0	0	0.9367	0.7745	1.0000	1.0000	
	Liposarcoma,	0	0	0	1	0.2204	.	.	0.4655	
	Malignant Schwannoma,	0	1	0	0	0.7469	0.5231	.	.	
	Myxosarcoma,	1	1	0	0	0.9367	0.7745	1.0000	1.0000	
	Osteosarcoma,	0	0	0	1	0.2204	.	.	0.4655	
	Sarcoma (not otherwise	0	1	0	1	0.2809	0.5231	.	0.4655	
	Sebaceous cell adenoma,	1	2	2	0	0.8182	0.5349	0.4939	1.0000	
Sebaceous cell carcinoma,	0	0	0	1	0.2204	.	.	0.4655		
Squamous cell carcinoma,	0	1	0	0	0.7480	0.5267	.	.		
Squamous cell papilloma,	0	2	0	1	0.3916	0.2717	.	0.4655		
Trichoepithelioma,	3	0	0	2	0.3418	1.0000	1.0000	0.7661		
Trichofolliculoma,	0	1	0	0	0.7469	0.5231	.	.		
SPINAL CORD, CE	Malignant astrocytoma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000	
SPLEEN	Sarcoma (not otherwise	0	0	1	0	0.4694	.	0.4959	.	
SUBLING.GLAND,	Anaplastic carcinoma,	0	0	0	1	0.2236	.	.	0.4701	
SYSTEMIC NEOPLA	Histiocytic sarcoma,	0	1	0	0	0.7469	0.5231	.	.	
	Malignant lymphoma,	0	2	6	2	0.2380	0.2755	0.0145*	0.2188	
TESTES	Benign Leydig cell tumor,	1	1	0	2	0.1933	0.7745	1.0000	0.4479	
THYMUS	Benign thymoma,	1	6	1	4	0.2302	0.0732	0.7439	0.1427	
	Malignant thymoma,	1	3	2	0	0.8689	0.3452	0.4939	1.0000	
THYROID GLAND	C-cell adenoma,	7	1	2	5	0.3044	0.9978	0.9817	0.7459	
	C-cell carcinoma,	1	0	1	0	0.7195	1.0000	0.7480	1.0000	
	Follicular cell adenoma,	13	1	2	2	0.9906	1.0000	0.9997	0.9994	

**Table 3A: Tumor Rates and P-Values for Dose Response Relationships and Pairwise Comparisons
Male Rats**

Organ Name	Tumor Name	0 mg	1 mg	3 mg	9 mg	P_Value	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		Control N=72	Low N=72	Med N=72	High N=72	Dose Resp			
THYROID GLAND	Follicular cell carcinoma,	2	1	2	0	0.8585	0.8943	0.6844	1.0000
TONGUE	Granular cell tumor,	1	0	0	0	1.0000	1.0000	1.0000	1.0000
TOOTH/TEETH	Ameloblastoma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000
ZYMBAL'S GLANDS	Carcinoma of the auditory	2	1	2	0	0.8563	0.8915	0.6783	1.0000

**Table 3B: Tumor Rates and P-Values for Dose Response Relationships and Pairwise Comparisons
Female Rats**

Organ Name	Tumor Name	0 mg	1 mg	3 mg	9 mg	P_Value				
		Control N=72	Low N=72	Med N=72	High N=72	Dose Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H	
fff										
ADRENAL GLANDS	Cortical adenoma,	2	0	2	0	0.8155	1.0000	0.6967	1.0000	
	Cortical carcinoma,	0	0	0	1	0.2355	.	.	0.4872	
ADRENAL MEDULLA	Benign pheochromocytoma,	2	0	2	2	0.2760	1.0000	0.6967	0.6647	
BRAIN	Granular cell tumor,	1	2	2	0	0.8411	0.5184	0.5124	1.0000	
	Malignant Astrocytoma,	0	1	0	0	0.7521	0.5122	.	.	
	Oligodendroglioma,	1	1	0	0	0.9393	0.7641	1.0000	1.0000	
CERVIX	Endometrial adenocarcinoma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000	
	Endometrial stromal polyp,	1	0	0	1	0.4163	1.0000	1.0000	0.7392	
JEJUNUM	Leiomyoma,	0	0	1	0	0.4917	.	0.5082	.	
KIDNEYS	Liposarcoma,	2	1	0	0	0.9853	0.8869	1.0000	1.0000	
	Tubular cell adenoma,	1	0	0	1	0.4163	1.0000	1.0000	0.7392	
LIVER	Cholangiocellular carcinoma,	0	0	1	0	0.4917	.	0.5082	.	
	Hepatocellular adenoma,	1	0	0	1	0.4163	1.0000	1.0000	0.7392	
LUNG	Bronchiolo-alveolar adenoma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000	
MAMMARY GLAND	Adenocarcinoma,	2	3	6	5	0.1371	0.5232	0.1528	0.2056	
	Adenolipoma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000	
	Adenoma,	0	0	0	1	0.2355	.	.	0.4872	
	Fibroadenoma,	33	26	28	11	0.9999	0.9312	0.8542	1.0000	
MESENT. LYMPH N	Hemangioma,	0	4	1	2	0.3852	0.0656	0.5082	0.2395	
OVARIES	Benign granulosa-theca cell	1	0	0	1	0.4163	1.0000	1.0000	0.7392	
	Malignant granulosa-theca cell	2	1	0	0	0.9853	0.8869	1.0000	1.0000	
PANCREAS, ENDOC	Islet cell adenoma,	0	2	0	1	0.4194	0.2603	.	0.4872	
	Islet cell carcinoma,	2	1	0	5	0.0246	0.8869	1.0000	0.2056	
PARATHYROID GLA	Adenoma,	0	0	0	1	0.2355	.	.	0.4872	
PAROTID GLAND,	Adenoma,	1	1	0	0	0.9393	0.7641	1.0000	1.0000	
PAROTID GLAND,	Schwannoma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000	
PITUITARY GLAND	Adenoma of pars distalis,	50	36	38	35	0.9046	0.9946	0.9920	0.9898	
	Adenoma of pars intermedia,	2	1	0	0	0.9853	0.8869	1.0000	1.0000	
	Carcinoma of pars distalis,	2	4	1	0	0.9709	0.3553	0.8811	1.0000	
SKIN/SUBCUTIS	Fibroma,	0	0	0	2	0.0562	.	.	0.2395	
	Hemangiosarcoma,	0	2	0	0	0.8097	0.2603	.	.	
	Lipoma,	0	2	1	1	0.3966	0.2603	0.5082	0.4872	
	Liposarcoma,	0	0	1	0	0.4917	.	0.5082	.	
	Sarcoma (not otherwise	0	0	0	1	0.2387	.	.	0.4915	

**Table 3B: Tumor Rates and P-Values for Dose Response Relationships and Pairwise Comparisons
Female Rats**

Organ Name	Tumor Name	0 mg	1 mg	3 mg	9 mg	P_Value	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		Control N=72	Low N=72	Med N=72	High N=72	Dose Resp			
fff									
SKIN/SUBCUTIS	Squamous cell carcinoma,	0	0	1	0	0.4917	.	0.5082	.
	Squamous cell papilloma,	0	0	1	0	0.4917	.	0.5082	.
	Trichoepithelioma,	0	0	0	1	0.2355	.	.	0.4872
SYSTEMIC NEOPLA	Histiocytic sarcoma,	0	0	1	0	0.4917	.	0.5082	.
	Malignant lymphoma,	0	0	1	1	0.1785	.	0.5082	0.4915
THYMUS	Benign thymoma,	3	6	6	5	0.3392	0.2620	0.2537	0.3211
	Malignant Schwannoma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	Malignant thymoma,	0	2	0	0	0.8097	0.2603	.	.
THYROID GLAND	C-cell adenoma,	6	1	0	3	0.6276	0.9946	1.0000	0.9059
	Follicular cell adenoma,	2	1	1	1	0.6574	0.8869	0.8841	0.8685
	Follicular cell carcinoma,	0	0	0	1	0.2355	.	.	0.4872
TONGUE	Squamous cell carcinoma,	0	1	1	1	0.2849	0.5122	0.5082	0.4915
	Squamous cell papilloma,	0	0	0	1	0.2355	.	.	0.4872
UTERUS	Endometrial stromal polyp,	3	7	3	1	0.9486	0.1822	0.6757	0.9342
	Stromal cell sarcoma,	0	1	0	2	0.1000	0.5161	.	0.2395
VAGINA	Endometrial stromal polyp,	2	0	0	1	0.5765	1.0000	1.0000	0.8718
ZYMBAL'S GLANDS	Carcinoma of the auditory	3	1	1	0	0.9684	0.9444	0.9425	1.0000

Table 4A: Intercurrent Mortality Rate in Male Mice

Week	Water Control		Placebo Control		0.1%		0.3%		1.0%	
	No. of Death	%Cum. %	No. of Death	%Cum. %	No. of Death	%Cum. %	No. of Death	%Cum. %	No. of Death	%Cum. %
0 - 52	4	6.67	4	6.67	4	6.67	2	3.33	6	10.00
53 - 78	6	16.67	11	25.00	16	33.33	15	28.33	13	31.67
79 - 91	18	46.67	23	63.33	19	65.00	15	53.33	17	60.00
92 - 100	9	61.67	5	71.67	6	75.00	8	66.67	4	66.67
*Ter. Sac.	23	38.33	17	28.33	15	25.00	20	33.33	20	33.33
Total	N=60		N=60		N=60		N=60		N=60	

Cum. %: Cumulative percentage, except for Ter. Sac.

* Animals of male high dose group were sacrificed on Week 100 and those from other groups were sacrificed on Week 101.

Table 4B: Intercurrent Mortality Rate Female Mice

Week	Water Control		Placebo Control		0.1%		0.3%		1.0%	
	No. of Death	%Cum. %	No. of Death	%Cum. %	No. of Death	%Cum. %	No. of Death	%Cum. %	No. of Death	%Cum. %
0 - 52	4	6.67	5	8.33	6	10.00	3	5.00	2	3.33
53 - 78	13	28.33	10	25.00	12	30.00	7	16.67	12	23.33
79 - 91	14	51.67	13	46.67	13	51.67	16	43.33	12	43.33
92 - 104	9	66.67	12	66.67	12	71.67	14	66.67	8	56.67
Ter. Sac.	20	33.33	20	33.33	17	28.33	20	33.33	26	43.33
Total	N=60		N=60		N=60		N=60		N=60	

Cum. %: Cumulative percentage, except for Ter. Sac.

Table 5A: Intercurrent Mortality Comparison Male Mice Using Placebo Control and Treated Groups

Test	Statistic	P_Value
Dose-Response	Likelihood Ratio	0.5018
Homogeneity	Log-Rank	0.6877

Table 5B: Intercurrent Mortality Comparison Female Mice Using Placebo Control and Treated Groups

Test	Statistic	P_Value
Dose-Response	Likelihood Ratio	0.1262
Homogeneity	Log-Rank	0.3580

**Table 6A: Tumor Rates and P-Values for Dose Response Relationships and Pairwise Comparisons
Male Mice Using Placebo Control Group**

Organ Name	Tumor Name	Placebo	0.1%	0.3%	1.0%	P_Value			
		Control N=60	Low N=60	Med N=60	High N=60	Dose Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
ADIPOSE TISSUE	Ossifying sarcoma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000
ADRENAL CORTICE	Subcapsular adenoma,	2	1	3	3	0.2416	0.8700	0.5122	0.5000
BRAIN	Meningeal sarcoma,	0	0	0	1	0.2516	.	.	0.5000
CECUM	Adenocarcinoma,	0	1	0	0	0.7500	0.4935	.	.
COLON	Adenocarcinoma,	0	1	0	0	0.7484	0.4868	.	.
EPIDIDYMIDES	Benign Schwannoma,	1	0	1	0	0.7643	1.0000	0.7655	1.0000
	Hemangioma,	0	1	0	0	0.7500	0.4935	.	.
FEMUR	Osteoma,	0	0	1	0	0.5128	.	0.5125	.
HARDERIAN GLAND	Adenocarcinoma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	Adenoma,	4	2	4	2	0.7263	0.8877	0.6712	0.8939
HEART	Hemangioma,	0	0	0	1	0.2516	.	.	0.5000
KIDNEYS	Adenoma, solid	0	0	0	3	0.0150*	.	.	0.1201
LARYNX	Squamous cell papilloma,	0	0	1	0	0.5128	.	0.5125	.
LIVER	Hemangioma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	Hemangiosarcoma,	1	2	2	1	0.6009	0.4805	0.5094	0.7468
	Hepatocellular adenoma,	12	14	18	10	0.7333	0.3531	0.1478	0.6853
	Hepatocellular carcinoma,	5	4	7	8	0.1433	0.7334	0.4301	0.2898
LUNG	Alveolar/bronchiolar adenoma,	15	14	13	10	0.8893	0.7038	0.7787	0.9243
	Alveolar/bronchiolar carcinoma	9	4	10	4	0.8359	0.9545	0.4527	0.9497
LYMPH NODES	Hemangioma,	0	1	0	0	0.7484	0.4868	.	.
	Hemangiosarcoma,	0	0	1	0	0.5128	.	0.5125	.
PANCREAS	Acinar cell adenocarcinoma,	0	0	0	1	0.2516	.	.	0.5000
PITUITARY GLAND	Adenoma of pars distalis,	1	0	0	0	1.0000	1.0000	1.0000	1.0000
PROSTATE GLAND	Adenoma,	0	0	0	1	0.2516	.	.	0.5000
SEMINAL VESICLE	Adenoma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	Leiomyoma,	0	1	0	0	0.7500	0.4935	.	.
SKIN, TREAT.ARE	Squamous cell carcinoma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	Squamous cell papilloma,	0	0	1	0	0.5128	.	0.5125	.
SKIN/SUBCUTIS	Hemangiosarcoma,	0	0	0	1	0.2516	.	.	0.5000
	Squamous cell papilloma,	0	1	0	0	0.7500	0.4935	.	.

**Table 6A: Tumor Rates and P-Values for Dose Response Relationships and Pairwise Comparisons
Male Mice Using Placebo Control Group**

Organ Name	Tumor Name	Placebo	0.1%	0.3%	1.0%	P_Value				
		Control N=60	Low N=60	Med N=60	High N=60	Dose Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H	
fff										
SPLEEN	Hemangiosarcoma,	0	1	0	1	0.3129	0.4935	.	0.5000	
STOMACH	Adenoma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000	
SYSTEMIC NEOPLA	Histiocytic sarcoma,	0	1	1	2	0.1245	0.4935	0.5125	0.2532	
	Malignant lymphoma,	1	2	4	2	0.4291	0.4901	0.2036	0.5096	
	Malignant mast cell tumor,	0	0	0	1	0.2516	.	.	0.5000	
	Plasma cell tumor,	0	1	0	0	0.7500	0.4935	.	.	
TAIL	Malignant Schwannoma,	0	0	0	1	0.2516	.	.	0.5000	
TESTES	Benign Leydig cell tumor,	1	0	0	1	0.4411	1.0000	1.0000	0.7532	
THYROID GLAND	Follicular cell adenoma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000	
URINARY BLADDER	Mesenchymal proliferative	1	1	0	0	0.9387	0.7468	1.0000	1.0000	

**Table 6B: Tumor Rates and P-Values for Dose Response Relationships and Pairwise Comparisons
Female Mice Using Placebo Control Group**

Organ Name	Tumor Name	Placebo	0.1%	0.3%	1.0%	P_Value			
		Control N=60	Low N=60	Med N=60	High N=60	Dose Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
ADRENAL CORTICES	Subcapsular adenoma,	0	0	0	1	0.2609	.	.	0.5122
BONE, RIB	Osteoma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000
CERVIX	Leiomyoma,	0	0	0	1	0.2654	.	.	0.5181
	Stromal polyp,	0	0	0	1	0.2609	.	.	0.5122
CLITORAL GLANDS	Adenoma in adjacent skin,	0	1	0	0	0.7516	0.4805	.	.
ETHMOIDAL MUCOSA	Osteoma,	0	1	0	1	0.3245	0.4805	.	0.5122
FEMUR	Osteoma,	1	0	1	0	0.7726	1.0000	0.7648	1.0000
	Osteosarcoma,	0	0	0	1	0.2609	.	.	0.5122
HARDERIAN GLANDS	Adenoma,	1	0	1	1	0.4254	1.0000	0.7651	0.7708
LIVER	Hemangioma,	1	0	0	1	0.4549	1.0000	1.0000	0.7651
	Hemangiosarcoma,	0	2	2	1	0.4682	0.2276	0.2593	0.5122
	Hepatocellular adenoma,	0	0	0	3	0.0168*	.	.	0.1296
	Hepatocellular carcinoma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000
LUNG	Alveolar/bronchiolar adenoma,	8	10	6	6	0.8299	0.3299	0.8216	0.8092
	Alveolar/bronchiolar carcinoma	6	4	7	7	0.3757	0.7994	0.5377	0.5732
	Malignant Schwannoma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000
MAMMARY GLAND	Adenoacanthoma,	1	0	0	2	0.1669	1.0000	1.0000	0.5185
	Adenocarcinoma,	1	3	4	3	0.3542	0.2785	0.2111	0.3358
OVARIES	Adenocarcinoma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	Benign granulosa cell tumor,	0	1	0	2	0.1203	0.4805	.	0.2654
	Benign luteoma,	3	1	5	2	0.6305	0.9325	0.3842	0.8420
	Benign thecoma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	Cystadenocarcinoma,	0	0	0	1	0.2609	.	.	0.5122
	Cystadenoma,	3	1	0	2	0.5179	0.9290	1.0000	0.8277
	Hemangioma,	0	0	0	1	0.2609	.	.	0.5122
	Hemangiosarcoma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	Leiomyoma,	0	0	1	0	0.5217	.	0.5122	.
Tubulostromal adenoma,	0	0	1	0	0.5217	.	0.5122	.	
PARATHYROID GLANDS	Adenoma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000
PITUITARY GLAND	Adenoma of pars distalis,	2	3	4	5	0.1637	0.4625	0.3732	0.2368
SKIN, TREAT.AREA	Squamous cell papilloma,	0	0	0	2	0.0668	.	.	0.2593
SKIN/SUBCUTIS	Hemangioma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	Malignant Schwannoma,	0	1	0	0	0.7516	0.4805	.	.
	Osteosarcoma,	0	0	1	0	0.5247	.	0.5181	.
	Sarcoma (not otherwise	0	0	2	1	0.2199	.	0.2593	0.5122
	Squamous cell papilloma,	0	0	0	1	0.2609	.	.	0.5122

**Table 6B: Tumor Rates and P-Values for Dose Response Relationships and Pairwise Comparisons
Female Mice Using Placebo Control Group**

Organ Name	Tumor Name	Placebo	0.1%	0.3%	1.0%	P_Value				
		Control N=60	Low N=60	Med N=60	High N=60	Dose Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H	
fff										
SPINAL CORD, LUMBAR	Malignant Schwannoma,	0	1	0	0	0.7516	0.4805	.	.	
SPINAL CORD, THORAC.	Osteoma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000	
SPLEEN	Hemangiosarcoma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000	
STOMACH	Adenoma,	0	0	0	1	0.2609	.	.	0.5122	
	Squamous cell papilloma,	1	0	0	1	0.4549	1.0000	1.0000	0.7651	
SYSTEMIC NEOPLASMS	Histiocytic sarcoma,	3	3	4	2	0.7383	0.6253	0.5270	0.8347	
	Malignant lymphoma,	14	9	4	7	0.9299	0.8979	0.9986	0.9781	
	Malignant mast cell tumor,	0	0	1	0	0.5217	.	0.5122	.	
	Myeloid leukemia,	0	0	0	1	0.2609	.	.	0.5122	
TAIL	Benign Schwannoma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000	
THYMUS	Malignant thymoma,	0	0	1	0	0.5217	.	0.5122	.	
UTERUS	Adenocarcinoma,	1	1	0	1	0.5509	0.7334	1.0000	0.7651	
	Adenoma,	0	0	1	0	0.5217	.	0.5122	.	
	Adenomatous polyp,	6	1	2	5	0.3321	0.9922	0.9759	0.7684	
	Granular cell tumor,	1	0	0	1	0.4525	1.0000	1.0000	0.7590	
	Hemangioma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000	
	Hemangiosarcoma,	0	0	0	1	0.2654	.	.	0.5181	
	Leiomyoma,	2	3	1	0	0.9676	0.4507	0.8840	1.0000	
	Leiomyosarcoma,	0	1	0	2	0.1165	0.4805	.	0.2593	
	Sarcoma (not otherwise stromal cell sarcoma),	2 0	0 0	0 0	1 1	0.5962 0.2609	1.0000 .	1.0000 .	0.8840 0.5122	
VAGINA	Leiomyosarcoma,	0	0	1	0	0.5247	.	0.5181	.	

**Table 7A: Tumor Rates and P-Values for Dose Response Relationships and Pairwise Comparisons
Male Mice Using Water Control Group**

Organ Name	Tumor Name	Water	0.1%	0.3%	1.0%	P_Value	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		Control N=60	Low N=60	Med N=60	High N=60	Dose Resp			
fff									
ADRENAL CORTICE	Adenoma (non subcapsular type)	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	Subcapsular adenoma,	5	1	3	3	0.5243	0.9767	0.8258	0.8160
BRAIN	Meningeal sarcoma,	0	0	0	1	0.2438	.	.	0.4699
CECUM	Adenocarcinoma,	0	1	0	0	0.7267	0.4634	.	.
COLON	Adenocarcinoma,	0	1	0	0	0.7250	0.4568	.	.
EPIDIDYIMIDES	Benign Schwannoma,	0	0	1	0	0.4969	.	0.4824	.
	Hemangioma,	0	1	0	0	0.7267	0.4634	.	.
FEMUR	Osteoma,	0	0	1	0	0.4969	.	0.4824	.
HARDERIAN GLAND	Adenoma,	5	2	4	2	0.7722	0.9145	0.7221	0.9198
HEART	Hemangioma,	0	0	0	1	0.2438	.	.	0.4699
KIDNEYS	Adenoma, solid	1	0	0	3	0.0452	1.0000	1.0000	0.2636
LARYNX	Squamous cell papilloma,	0	0	1	0	0.4969	.	0.4824	.
LIVER	Hemangiosarcoma,	2	2	2	1	0.7104	0.6346	0.6648	0.8559
	Hepatocellular adenoma,	9	14	18	10	0.5575	0.1218	0.0324	0.3846
	Hepatocellular carcinoma,	2	4	7	8	0.0363	0.2819	0.0783	0.0375
LUNG	Alveolar/bronchiolar adenoma,	16	14	13	10	0.8810	0.6718	0.7526	0.9137
	Alveolar/bronchiolar carcinoma	10	4	10	4	0.8620	0.9669	0.5062	0.9631
LYMPH NODES	Hemangioma,	0	1	0	0	0.7250	0.4568	.	.
	Hemangiosarcoma,	0	0	1	0	0.4969	.	0.4824	.
MESENT. LYMPH N	Hemangioma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000
PANCREAS	Acinar cell adenocarcinoma,	0	0	0	1	0.2438	.	.	0.4699
PROSTATE GLAND	Adenoma,	0	0	0	1	0.2438	.	.	0.4699
SEMINAL VESICLE	Adenoma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	Leiomyoma,	0	1	0	0	0.7267	0.4634	.	.
SKIN, TREAT.ARE	Squamous cell papilloma,	0	0	1	0	0.4969	.	0.4824	.
SKIN/SUBCUTIS	Hemangiosarcoma,	0	0	0	1	0.2438	.	.	0.4699
	Squamous cell papilloma,	0	1	0	0	0.7267	0.4634	.	.
SPLEEN	Hemangiosarcoma,	0	1	0	1	0.2937	0.4634	.	0.4699
SYSTEMIC NEOPLA	Histiocytic sarcoma,	0	1	1	2	0.1115	0.4634	0.4824	0.2238
	Malignant lymphoma,	7	2	4	2	0.8940	0.9724	0.8792	0.9769

**Table 7A: Tumor Rates and P-Values for Dose Response Relationships and Pairwise Comparisons
Male Mice Using Water Control Group**

Organ Name	Tumor Name	Water	0.1%	0.3%	1.0%	P_Value			
		Control N=60	Low N=60	Med N=60	High N=60	Dose Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
fff									
SYSTEMIC NEOPLA	Malignant mast cell tumor,	0	0	0	1	0.2438	.	.	0.4699
	Plasma cell tumor,	0	1	0	0	0.7267	0.4634	.	.
TAIL	Malignant Schwannoma,	0	0	0	1	0.2438	.	.	0.4699
TESTES	Benign Leydig cell tumor,	1	0	0	1	0.4292	1.0000	1.0000	0.7220
THYMUS	Malignant thymoma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000
THYROID GLAND	Follicular cell adenoma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000
URINARY BLADDER	Mesenchymal proliferative	1	1	0	0	0.9266	0.7151	1.0000	1.0000

**Table 7B: Tumor Rates and P-Values for Dose Response Relationships and Pairwise Comparisons
Female Mice Using Water Control Group**

Organ Name	Tumor Name	Water	0.1%	0.3%	1.0%	P_Value	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		Control N=60	Low N=60	Med N=60	High N=60	Dose Resp			
fff									
ADRENAL CORTICE	Subcapsular adenoma,	1	0	0	1	0.4598	1.0000	1.0000	0.7775
CERVIX	Leiomyoma,	0	0	0	1	0.2688	.	.	0.5309
	Stromal polyp,	0	0	0	1	0.2642	.	.	0.5250
CLITORAL GLANDS	Adenoma in adjacent skin,	0	1	0	0	0.7610	0.4933	.	.
ETHMOIDAL MUCOS	Osteoma,	0	1	0	1	0.3327	0.4933	.	0.5250
FEMUR	Osteoma,	0	0	1	0	0.5312	.	0.5309	.
	Osteosarcoma,	0	0	0	1	0.2642	.	.	0.5250
HARDERIAN GLAND	Adenoma,	2	0	1	1	0.6203	1.0000	0.8973	0.9011
LIVER	Hemangioma,	0	0	0	1	0.2642	.	.	0.5250
	Hemangiosarcoma,	0	2	2	1	0.4791	0.2400	0.2725	0.5250
	Hepatocellular adenoma,	0	0	0	3	0.0175*	.	.	0.1397
LUNG	Alveolar/bronchiolar adenoma,	8	10	6	6	0.8545	0.3948	0.8587	0.8480
	Alveolar/bronchiolar carcinoma	4	4	7	7	0.2553	0.6293	0.3363	0.3669
MAMMARY GLAND	Adenoacanthoma,	0	0	0	2	0.0685	.	.	0.2725
	Adenocarcinoma,	1	3	4	3	0.3683	0.2973	0.2289	0.3560
OVARIES	Benign granulosa cell tumor,	2	1	0	2	0.4038	0.8751	1.0000	0.7376
	Benign luteoma,	2	1	5	2	0.5371	0.8751	0.2595	0.7376
	Cystadenocarcinoma,	0	0	0	1	0.2642	.	.	0.5250
	Cystadenoma,	0	1	0	2	0.1209	0.4933	.	0.2725
	Hemangioma,	1	0	0	1	0.4598	1.0000	1.0000	0.7775
	Leiomyoma,	0	0	1	0	0.5283	.	0.5250	.
Tubulostromal adenoma,	0	0	1	0	0.5283	.	0.5250	.	
PARATHYROID GLA	Adenoma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000
PITUITARY GLAND	Adenoma of pars distalis,	3	3	4	5	0.2522	0.6499	0.5699	0.4142
SKIN, TREAT.ARE	Squamous cell papilloma,	0	0	0	2	0.0685	.	.	0.2725
SKIN/SUBCUTIS	Malignant Schwannoma,	0	1	0	0	0.7610	0.4933	.	.
	Osteosarcoma,	0	0	1	0	0.5312	.	0.5309	.
	Sarcoma (not otherwise	2	0	2	1	0.5866	1.0000	0.7199	0.8929
	Squamous cell papilloma,	0	0	0	1	0.2642	.	.	0.5250
SPINAL CORD, LU	Malignant Schwannoma,	0	1	0	0	0.7610	0.4933	.	.
STOMACH	Adenoma,	1	0	0	1	0.4598	1.0000	1.0000	0.7775
	Osteosarcoma,	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	Squamous cell papilloma,	0	0	0	1	0.2642	.	.	0.5250
SYSTEMIC NEOPLA	Histiocytic sarcoma,	3	3	4	2	0.7519	0.6501	0.5553	0.8493

**Table 7B: Tumor Rates and P-Values for Dose Response Relationships and Pairwise Comparisons
Female Mice Using Water Control Group**

Organ Name	Tumor Name	Water	0.1%	0.3%	1.0%	P_Value	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		Control N=60	Low N=60	Med N=60	High N=60	Dose Resp			
fff									
SYSTEMIC NEOPLA	Malignant lymphoma,	13	9	4	7	0.9105	0.8669	0.9976	0.9680
	Malignant mast cell tumor,	1	0	1	0	0.7791	1.0000	0.7775	1.0000
	Myeloid leukemia,	0	0	0	1	0.2642	.	.	0.5250
THYMUS	Malignant thymoma,	0	0	1	0	0.5283	.	0.5250	.
UTERUS	Adenocarcinoma,	0	1	0	1	0.3327	0.4933	.	0.5250
	Adenoma,	0	0	1	0	0.5283	.	0.5250	.
	Adenomatous polyp,	4	1	2	5	0.1698	0.9688	0.9154	0.5479
	Granular cell tumor,	0	0	0	1	0.2642	.	.	0.5250
	Hemangiosarcoma,	0	0	0	1	0.2688	.	.	0.5309
	Leiomyoma,	2	3	1	0	0.9720	0.4872	0.8973	1.0000
	Leiomyosarcoma,	1	1	0	2	0.2611	0.7467	1.0000	0.5380
	Sarcoma (not otherwise Stromal cell sarcoma,	0 0	0 0	0 0	1 1	0.2642 0.2642	.	.	0.5250 0.5250
VAGINA	Leiomyosarcoma,	0	0	1	0	0.5312	.	0.5309	.

Table 8A: Tumor Rates and P-Values for Pairwise Comparisons of Water and Placebo Controls Male Mice

Organ Name	Tumor Name	Water Control	Placebo Control	P_Value WC vs. PC
ADIPOSE TISSUE	Ossifying sarcoma,	0	1	0.4699
ADRENAL CORTICE	Adenoma (non subcapsular type)	1	0	1.0000
	Subcapsular adenoma,	5	2	0.9198
EPIDIDYMIDES	Benign Schwannoma,	0	1	0.4699
HARDERIAN GLAND	Adenocarcinoma,	0	1	0.4762
	Adenoma,	5	4	0.6955
KIDNEYS	Adenoma, solid	1	0	1.0000
LIVER	Hemangioma,	0	1	0.4699
	Hemangiosarcoma,	2	1	0.8610
	Hepatocellular adenoma,	9	12	0.2886
	Hepatocellular carcinoma,	2	5	0.1883
LUNG	Alveolar/bronchiolar adenoma,	16	15	0.5520
	Alveolar/bronchiolar carcinoma	10	9	0.6570
MESENT. LYMPH N	Hemangioma,	1	0	1.0000
PITUITARY GLAND	Adenoma of pars distalis,	0	1	0.4699
SEMINAL VESICLE	Adenoma,	1	1	0.7220
SKIN, TREAT.ARE	Squamous cell carcinoma,	0	1	0.4699
STOMACH	Adenoma,	0	1	0.4699
SYSTEMIC NEOPLA	Malignant lymphoma,	7	1	0.9951
TESTES	Benign Leydig cell tumor,	1	1	0.7220
THYMUS	Malignant thymoma,	1	0	1.0000
THYROID GLAND	Follicular cell adenoma,	1	1	0.7286
URINARY BLADDER	Mesenchymal proliferative	1	1	0.7220

Table 8B: Tumor Rates and P-Values for Pairwise Comparisons of Water and Placebo Controls Female Mice

Organ Name	Tumor Name	Water Control	Placebo Control	P_Value WC vs. PC
ADRENAL CORTICE	Subcapsular adenoma,	1	0	1.0000
BONE, RIB	Osteoma,	0	1	0.5190
FEMUR	Osteoma,	0	1	0.5190
HARDERIAN GLAND	Adenoma,	2	1	0.8891
LIVER	Hemangioma,	0	1	0.5128
	Hepatocellular carcinoma,	0	1	0.5128
LUNG	Alveolar/bronchiolar adenoma,	8	8	0.6700
	Alveolar/bronchiolar carcinoma	4	6	0.4187
	Malignant Schwannoma,	0	1	0.5128
MAMMARY GLAND	Adenoacanthoma,	0	1	0.5128
	Adenocarcinoma,	1	1	0.7659
OVARIES	Adenocarcinoma,	0	1	0.5128
	Benign granulosa cell tumor,	2	0	1.0000
	Benign luteoma,	2	3	0.5247
	Benign thecoma,	0	1	0.5128
	Cystadenoma,	0	3	0.1348
	Hemangioma,	1	0	1.0000
	Hemangiosarcoma,	0	1	0.5190
PARATHYROID GLA	Adenoma,	1	1	0.7659
PITUITARY GLAND	Adenoma of pars distalis,	3	2	0.8364
SKIN/SUBCUTIS	Hemangioma,	0	1	0.5128
	Sarcoma (not otherwise	2	0	1.0000
SPINAL CORD, TH	Osteoma,	0	1	0.5128
SPLEEN	Hemangiosarcoma,	0	1	0.5128
STOMACH	Adenoma,	1	0	1.0000
	Osteosarcoma,	1	0	1.0000

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

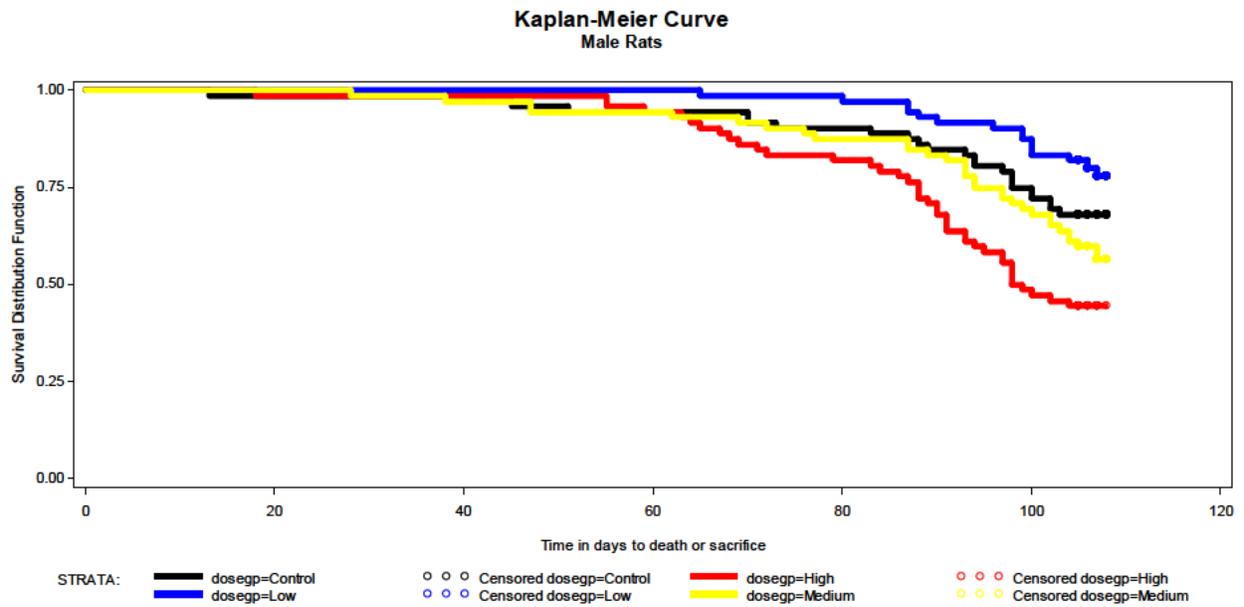


Figure 1B: Kaplan-Meier Survival Functions for Female Rats

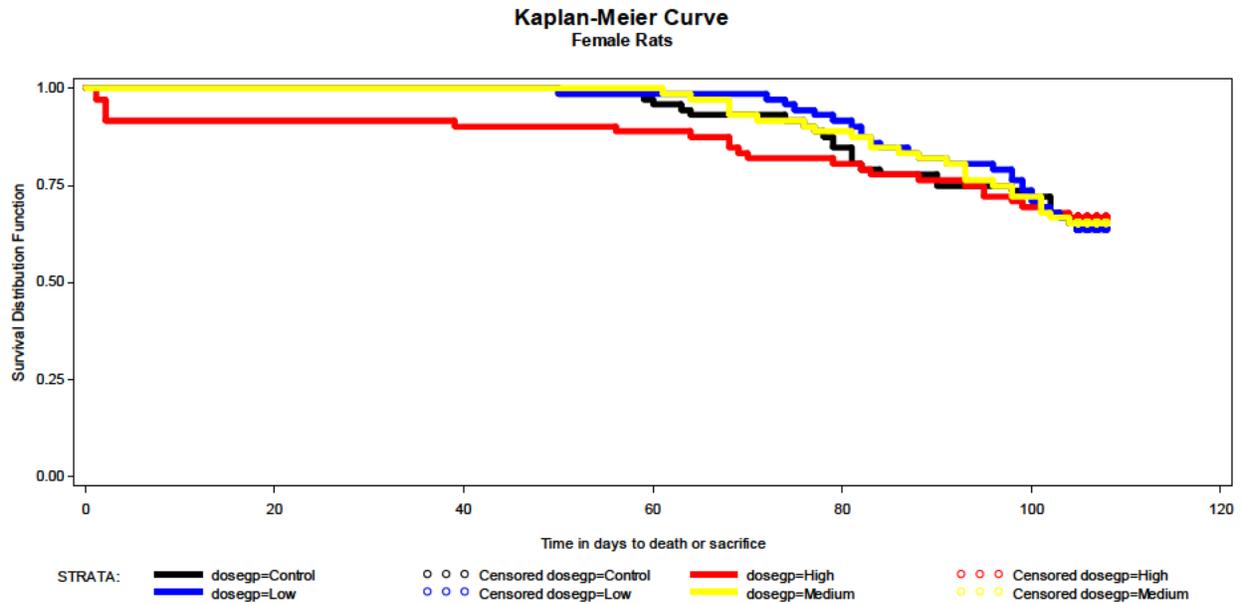


Figure 2A: Kaplan-Meier Survival Functions for Male Mice

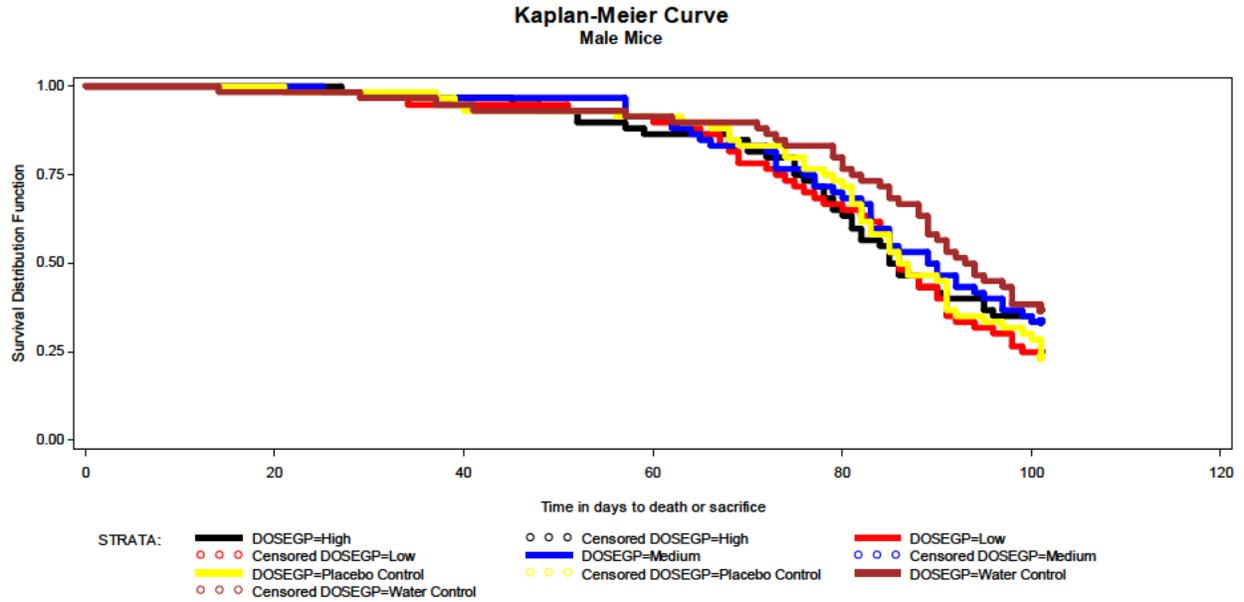
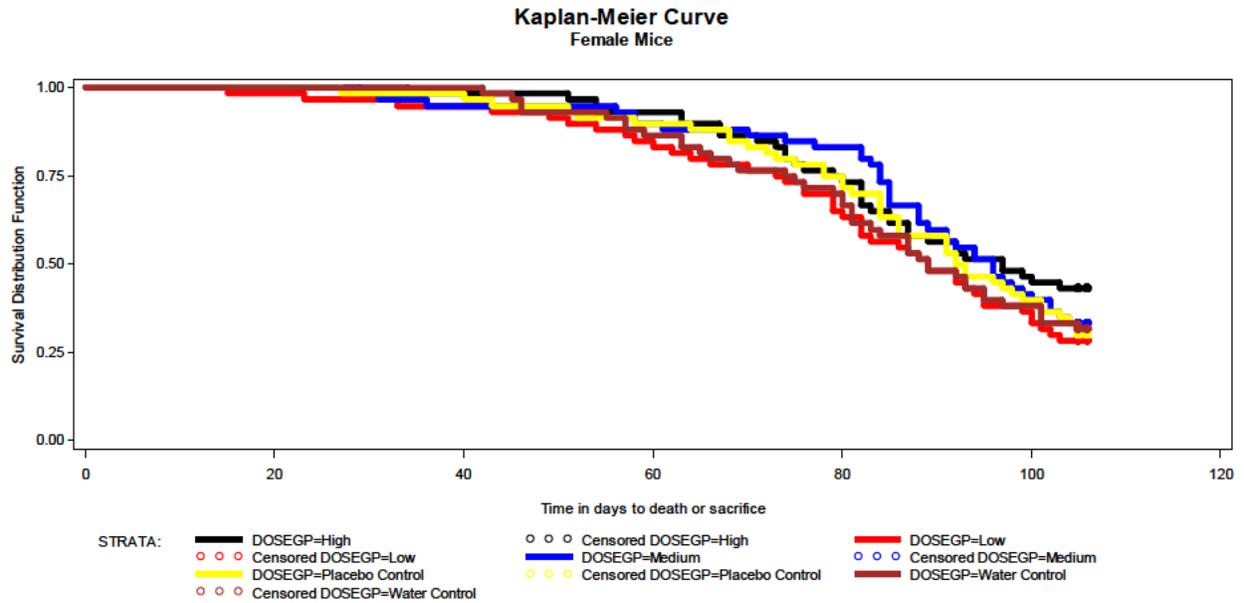


Figure 2B: Kaplan-Meier Survival Functions for Female Mice



6. References

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/s/

MOHAMMAD A RAHMAN
05/07/2014

KARL K LIN
05/07/2014
Concur with review

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 206255

Applicant: Galderma Research and Development, LLC

Stamp Date: 12/20/2013

Drug Name: Ivermectin Cream, **NDA/BLA Type:** 505(b)(2)
1%

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

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

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.	February 6, 2014
Reviewing Statistician	Date
Mohamed Aloh, Ph.D.	February 6, 2014
Supervisor/Team Leader	Date

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/s/

MATTHEW W GUERRA
02/06/2014

MOHAMED A ALOSH
02/06/2014