CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022408Orig1s000

STATISTICAL REVIEW(S)

Biostatistics Team Leader Memorandum

NDA#:	22-408
Applicant:	ParaPRO
Drug Name:	(b) (4) (Spinosad (b) (4))
Indication:	Head lice (b) (4)
Documents Reviewed:	Sponsor's submission dated April, 13, 2010
Primary Statistical Reviewer:	Carin Kim, Ph.D.

I. Background:

The sponsor's clinical development program for this application involves two Phase 2 trials (Study 201-05 and Study 201-06) and two Phase 3 trials (SPN 301-07 and 302-07). The two Phase 3 trials were designed to establish the superiority of Spinosad over NIX. Each of the two Phase 3 trials met this objective, as has been discussed in the Statistical Review for this application, dated October 26, 2009, by Lisa Kammerman, Ph.D. From now on we will refer to the Phase 2 trials as Study 05 and Study 06 and the Phase 3 trials as Study 301 and Study 302.

One rather unusual regulatory issue regarding this application is that while this NDA was under review, the medical division approved Ulesfia (NDA 22-129) for the treatment of head lice. Ulesfia's active ingredient is benzyl alcohol at a concentration of 5%. In the current NDA the sponsor's product (Spinosad (b) (4)) contains benzyl alcohol (b) (4) found in the newly approved Ulesfia. Having benzyl alcohol approved as the active ingredient in Ulesfia raises the following two issues for Spinosad NDA: (i) whether Spinosad should now be viewed as a combination product and (ii) whether Spinosad would win over its vehicle (benzyl alcohol) if such an arm had been included in the Phase 3 trials. The Division of Dermatology and Dental Products held several internal meetings to clarify these questions and had a meeting with the sponsor on March 25, 2010 to discuss these issues. Whether Spinosad should be considered a combination product or not is beyond this reviewer's purview; however, regardless of the designation, the relevant question that remains is whether Spinosad would have won over its vehicle (benzyl alcohol) in order to establish the efficacy or the contribution of test drug. Ideally, this would be accomplished by conducting adequate and well-controlled clinical trials that would provide direct confirmation of the superiority of Spinosad over its benzyl

alcohol. As the completed Phase 3 trials were designed to establish superiority of Spinosad against NIX and none of them included a benzyl alcohol arm, it may be useful to estimate what be considered as a hypothetical upper bound for the response rate of benzyl alcohol as it would have been used in Phase 3 trials (treatment at Day 0 with retreatment at Day 7 for non-responding subjects) based on the results of the Phase 2 trials (Study 05 and Study 06). Then consider across-study comparison of this hypothetical upper bound with the lowest estimate of Spinosad response rate from the completed Phase3 trials (Study 301 and Study 302) for making judgment on the contribution of Spinosad over its vehicle. It should be noted that the goal of this exercise is not to derive reliable estimate of benzyl alcohol response rate or make formal statistical inference about the contribution of Spinosad over benzyl alcohol response rate, as this is difficult due to the differences in study design and consequently any estimate would be based on unverifiable assumptions. Instead, this comparison might be viewed as a sensitivity analysis intended to find out whether Spinosad retains a meaningful treatment effect over the estimated hypothetical upper bound for the response rate of benzyl alcohol.

The sponsor's two Phase 2 trials involved the comparison of Spinosad against benzyl alcohol. However, these two trials have different designs, which in turn differ from the design of the two Phase 3 trials. Consequently, there is no direct approach to the extrapolation of the efficacy results from these Phase 2 trials to the findings of the Phase 3 trials. In addition to the variation in design, it is also apparent that the efficacy results from the two Phase 2 trials were inconsistent, whether considering success rates at Day 7 or Day 14 after last treatment (the primary time point for the efficacy evaluation of Studies 301 and 302). Study 05 was a dose-ranging trial that only enrolled 9 subjects per treatment arm, while Study 06 was significantly larger, enrolling 43 and 36 subjects on the Spinosad and benzyl alcohol arms, respectively. The difference in the design of the two trials was discussed during a meeting with sponsor representatives on 3/25/2010 and in the sponsor's submission of 4/13/2010 that addressed the Agency's request to clarify potential reasons for the apparent inconsistency in observed response rates. Additionally, these differences are described in the Statistical Review of the sponsor's submission by the primary statistical reviewer, Carin Kim, Ph.D..

Noting that response rate at Day 14 after treatment with benzyl alcohol in Study 05 was much higher than that observed in Study 06 [8/9 (=88.9%) for two treatments including combing in Study 05 versus 11/43 (=25.58%) for one treatment application in Study 06], the discussion at sponsor's meeting of 3/25/2010 noted that "The Agency requested that the sponsor utilize study SPN-202-05 findings to obtain an estimate of the treatment effect for benzyl alcohol if it were to be used for 2 treatments as it was in the Phase 3 trials. Such an estimate may provide information to evaluate the contribution of spinosad over benzyl alcohol (vehicle)" .

Responding to the Agency's request, in a submission dated April 13, 2010, the sponsor noted that as Study 05 was very small and involved combing, it was not appropriate to use the results of this study to estimate the benzyl alcohol response rate. Instead the sponsor used efficacy results from Study 06 and made assumptions about the probability of success for those who needed to be re-treated and the probability of remaining success at Day 14 after being a success on Day 7, based on the results of the Spinosad treatment arms in the completed Phase 3 trials, as the design for Study 6 included only a single treatment application.

Dr. Kim in her review of the sponsor's submission of April 13, 2010 concluded that: "As for Study 201-05, this reviewer agrees with the Sponsor's conclusion (although the reviewer's arguments are different in reaching this conclusion) that Study 201-05 cannot be used to obtain an estimate of the treatment effect for benzyl alcohol if it were to be used for two treatments as it was in the Phase 3 trials." Furthermore, Dr. Kim concluded that: "This reviewer does not agree [with the sponsor] that the Study 202-06 can be used to obtain estimates of benzyl alcohol after two uses as were done in the Phase 3 trials". While Dr. Kim cited the justification for her conclusions, she did not provide an alternative approach for the utilization of the sponsor's available data to inform the regulatory decision-making process

However, this reviewer does believe that there is some utility in piecing together results from the two Phase 2 trials to derive what might be viewed as a potential "upper bound" estimate for benzyl alcohol response rate. If it appears, based on the results of this hypothetical, numerical exercise, that the Spinosad would have beat this 'upper bound' estimate of benzyl alcohol one

could conclude that the results from the trials, taken as a whole, appear to lend some support to the notion that Spinosad contributes to the efficacy beyond that of benzyl alcohol.

II. Analysis:

This reviewer's analytic methodology is based on pooling data from the two Phase 2 trials to get an "upper bound" estimate of the success rate for the benzyl alcohol. (Note: The fact that Study 05 involves combing is not of much concern in deriving the 'upper bound' estimate for the benzyl alcohol, as combing is expected to increase the efficacy.) Taking into account the difference in study sizes and the difference in the number of treatments in the two studies, the implications associated with pooling these two studies include the following:

1. The estimate of the response rate for the first application is mainly driven by the results of much larger Study 06;
2. The estimate of the response rate for the second application comes from the extrapolation of the results of Study 05 to Study 06, as Study 06 did not have a second treatment application. It should be noted here that the success rate for those who failed on the first treatment is relatively high (4/7) which is much higher than the response rate of the first treatment application observed in either Study (Thus one might conclude that this extrapolation is expected to inflate the benzyl alcohol response rate.); and
3. The probability that a subject remains a success at Day 14, given that this subject was success at Day 7, is calculated based on the results from the two studies.

The following results are calculated by pooling the response rates from the two studies at given time points (note that numbers in red refer to Study 05 and the numbers in black refer to Study 06):

(i) Pr (success at Day 7) = (1+21)/(9+43)= 0.423. (Note that in Study 05, the response rate at Day 7 after one treatment application is 2/9. However, the success of one of the two cases might be attributable to combing alone, as only one of the two subjects who were responders at Day 7 had been classified as a success prior to combing after the first treatment application. Therefore in this analysis, only one subject is counted as having a response at Day 7, with the response attributable to the vehicle treatment and not to combing.) Consequently, the probability of failure at Day 7 is 1 -0.423= 0.577.

(ii) Pr (success at Day 14| success at Day 7) = (1+11)/(1+21) = 0.5454.
(iii) Pr (success at Day 14 | failure at Day 7) = 4/7 =0.5714

Consequently, Pr (success at Day 14) = Pr (success at Day 14 | success at Day 7) x Pr (success at Day 7) + Pr (success at Day 14 | failure at Day 7) x Pr (failure at Day 7) = (0.5454)(0.423) + (0.5714)(0.577) = 0.5604.

To check the impact of the assumptions made in these calculations I consider these assumptions for driving the estimate of the Spinosad response rate from the Phase 2 trials and compare this estimate with those obtained from the Phase 3 trials. The results of these computations lead to: Pr (success 1 st treatment of Spinosad) = 0.8444. It can be seen that the efficacy results for Spinosad from the two Phase trials are very close to those of the Phase 3 trials (84.60% and 86.7% for Study 301 and Study 302, respectively). This provides some level of comfort that the assumptions used in driving the response rate of benzyl alcohol based on Study 05 and Study 06 might be reasonable. Figure 1 presents the results of these computations for ease of interpretation.

III. Conclusion:

An "upper bound" estimate of benzyl alcohol success rate is derived from the sponsor's completed two Phase 2 trials (Study 05 and Study 06). This estimate is higher than the sponsor's estimate of 0.39 (as shown from Figure 3-6 of the sponsor's submission) which is derived from Study 06 along using assumptions about success rates related to Spinosad from the completed Phase 3 trials. A limitation of the sponsor's computation is the assumption that the pattern of treatment success of benzyl alcohol is similar to that of the Spinosad. However, the efficacy results for benzyl alcohol show a different pattern than that observed for Spinosad. Even though this reviewer's estimate for the 'upper bound' for benzyl alcohol is higher than the sponsor's, the results appear to still offer some support for the sponsor's conclusions concerning the comparative effectiveness of Spinosad and its vehicle.

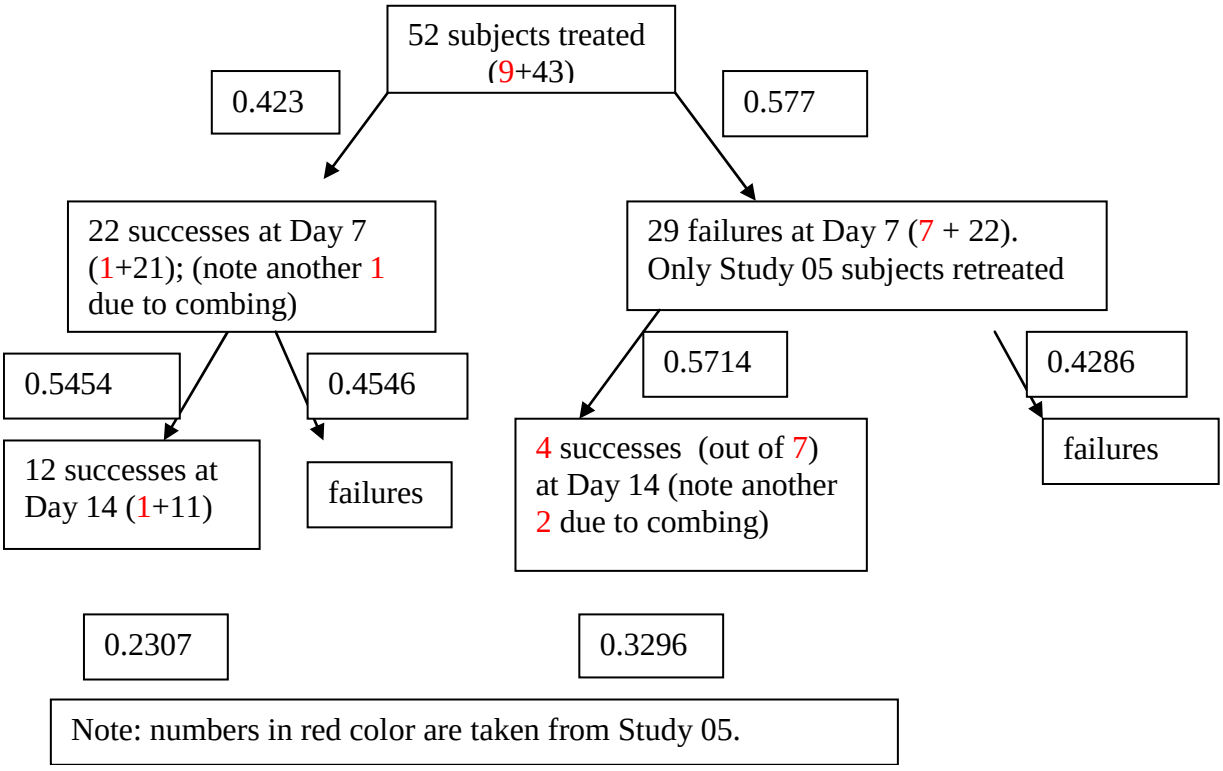
Please note that this exercise should be viewed as sensitivity analysis to find out whether we might still have a certain treatment effect for Spinosad beyond what could potentially be considered an upper limit for the efficacy of benzyl alcohol (given that the Phase 2 trials are not consistent in design and produced variable response rate estimates). Any conclusions from this hypothetical exploration depend on unverifiable assumptions and extrapolation of observed point estimates (i.e., the variability of these estimates is not used in this exercise), The goal here is not to get a reliable estimate for Benzyl alcohol to use for inferential decision-making or to establish the added efficacy of the Spinosad product – for this, we would need the usual adequate and well-controlled trials that are designed to provide direct comparisons of the Spinosad to its vehicle.

Mohamed Alosh, Ph.D.
Statistics Team Lead, DBIII

Stephen Wilson, DrPH
Division Director, DBIII

cc
Orig. NDA 22-408
DDDP/Walker
DDDP/Lindstrom
DDDP/Brown
DDDP/Williams
OBIO/Patrician
DBIII/Wilson
DBIII/Alosh
DBIII/Kim

Figure 1: Tree–diagram for estimating an 'upper bound' for benzyl alcohol response rates from Study 05 and Study 06



Note: numbers in red color are taken from Study 05.

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/s/

MOHAMED A ALOSH
01/07/2011

STEPHEN E WILSON
01/07/2011

NDA Statistical Report Review

NDA#:	22-408
Applicant:	ParaPRO
Drug Name:	(b) (4)
Indication:	Head lice
Documents Reviewed:	Appendix 2 (Statistical Report)
Medical Officer:	Patricia Brown, M.D., DDDP
Statistical Reviewer:	Carin Kim, Ph.D., DBIII

The sponsor's statistical analysis (Appendix 2) in this Complete Response submission is the same as that presented as the "statistical report" (SDN 15, dated April 19, 2010), and was the subject of statistical review dated May 19, 2010. Please refer to our previous statistical review for comments.

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Mathematical Statistician, DBIII

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22408	ORIG-1	PARAPRO PHARMACEUTICALS LLC	SPINOSAD

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/s/

CARIN J KIM
08/25/2010

MOHAMED A ALOSH
08/25/2010

NDA Statistical Report Review

NDA#:	22-408
Applicant:	ParaPRO
Drug Name:	(b) (4)
Indication:	Head lice (b) (4)
Documents Reviewed:	Statistical Report following the CR
Medical Officer:	Patricia Brown, M.D., DDDP
Statistical Reviewer:	Carin Kim, Ph.D., DBIII

Background

The sponsor conducted three Phase 2 trials, two of which (Studies 201-05 and 202-06) compared the spinosad 1.0% to the benzyl alcohol arm. The third Phase 2 trial (Study 203-07) compared the spinosad 1.0% to NIX. Following these studies, the sponsor conducted two Phase 3 trials comparing the spinosad 1.0% to NIX.

While this NDA was under review, the medical division approved Ulesfia (NDA 22-129) for the treatment of head lice. Ulesfia's active ingredient is benzyl alcohol at a concentration of 5%. The sponsor's product (spinosad (b) (4)) contained benzyl alcohol (b) (4) . Because neither of the Phase 3 studies contained a benzyl alcohol treatment arm, the data from the Phase 3 studies cannot be used to discern the contribution of spinosad.

At the Type A post-action meeting on 3/25/2010, the Agency commented on the inconsistency in the response rates of the benzyl alcohol in the two Phase 2 trials. Following this meeting, the meeting discussion minutes below were sent to the sponsor on 4/9/2010:

2. The scientific data upon which your assertion that benzyl alcohol be considered an inactive ingredient is based. We would like your perspective on the vehicle response rates and the inconsistency in these rates in the following studies:
    a. a 22% and 89% treatment success rate for the vehicle in phase 2 study SPN-201-05 at days 7 and 14, respectively;
    b. a 49% and 26% treatment success rate for the vehicle in phase 2 study SPN-202-06 at days 7 and 14, respectively.

Meeting Discussion:
The sponsor noted that study SPN-202-05 had a different design than study SPN-202-06, including the number of treatments and combing which led to differences in efficacy results for benzyl alcohol. The Agency requested that the sponsor utilize study SPN-202-05 findings to obtain an estimate of the treatment effect for benzyl alcohol if it were to be used for 2 treatments as it was in the Phase 3 trials. Such an estimate may provide information to evaluate the contribution of spinosad over that of benzyl alcohol (vehicle).

In response, the sponsor submitted "statistical report" to address the Agency's request.

The Study 201-05 was small in size (9 subjects in spinosad arm, and 9 subjects in benzyl alcohol arm), and this study was different from Study 202-06 as summarized below:

- **Study 201-05**: subjects received treatment **twice** (Day 0 and Day 7), and the proportion of subjects with live lice and/or nits was tabulated pre- and post-treatment on Days 0, 7, and 14. This study also allowed **nit combing** on subjects after each treatment. (9 subjects in benzyl alcohol, and 9 subjects in spinosad 1.0% arm)
- **Study 202-06**: subjects received **one** treatment on Day 0, and the proportion of subjects with live lice and/or viable nits was tabulated on Days 7 and 14. Nit combing was **not** performed (43 subjects in the benzyl alcohol arm, and 39 subjects in the spinosad 1.0% arm).

The sponsor stated that Study 201-05 was biased 'in favor of the benzyl alcohol group' because while the success rate for the spinosad was maxed out to response rate of 100% at Day 0 after combing (i.e., "no opportunity for improvement" according to the sponsor), the benzyl alcohol group showed that they 'benefitted from a second treatment application".

The sponsor then stated that evaluation of subjects in Study 202-06 was similar to the evaluation of subjects who received only one treatment in the Phase 3 trials, because Study 202-06 was not confounded by the inclusion of combing. Based on this and also because Study 201-05 was small, which also provided the "bias in favor of benzyl alcohol", the sponsor used Study 202-06 instead "to predict the efficacy of a benzyl alcohol group in an idealized Phase 3 study".

Reviewer's Comment:
The sponsor stated that the spinosad group in Study 201-05 did not have any opportunity for improvement to show success, but the benzyl alcohol continued to show success after each treatment and each combing, and therefore, the study results are biased "in favor of benzyl alcohol". This reviewer disagrees with the sponsor's interpretation that the findings are 'biased in favor of benzyl alcohol' because while the benzyl alcohol without combing may be a non-durable effect, the "immediate" response rates were:

- *33% at Day 0 (among the 9 treated subjects, the success of 3 subjects can be attributed to benzyl alcohol treatment),*
- *57% at Day 7 (among the 7 subjects who were failures on Day 7, the success of 4 subjects can be attributed to benzyl alcohol treatment).*

In addition, the "immediate" response rates of combing were:

- *50% at Day 0 (among the 6 subjects who were failures at Day 0 after benzyl alcohol treatment, 3 subjects became success whose success can be attributed to combing)*
- *67% at Day 7 (among the 3 subjects who were failures at Day 7 after benzyl alcohol treatment, 2 subjects became success whose success can be attributed to combing).*

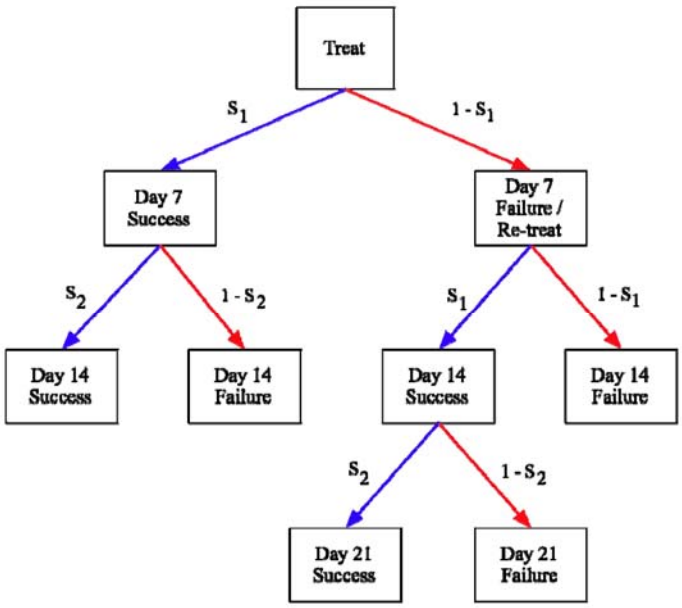
Due to the above findings, this reviewer does not find the study results to be biased in favor of benzyl alcohol, but rather would prefer the interpretation that the spinosad group does treat head lice (b) (4) faster than the benzyl alcohol group because at Day 0 before combing rate of 78% (among the 9 subjects, 7 subjects were success) was higher than that of the 'benzyl alcohol + combing' at Day 0 at 67% (among the 9 subjects, 6 subjects were success), and also that there are combing effect as well as some degree of benzyl alcohol

that may not be a durable effect (to Day 7 or to Day 14), but does have an immediate effect in killing head lice (b) (4)

Note that while the immediate response rates can be estimated, because both treatment and combing are involved at Days 0 and 7, the durable effect for benzyl alcohol at Days 7 and 14 cannot be estimated from this study. While the sponsor referenced the literature to note that the combing effect is about 38%, whether or not combing might have an additive or a multiplicative effect with benzyl alcohol cannot be determined from the studies that were conducted by the sponsor.

Based on the above justification, the sponsor proposed to model the potential benzyl alcohol effect based on estimated probabilities of success at each visit (Days 14 and 21). The following is a tree diagram that the sponsor used in modeling the benzyl alcohol effect.

Figure 3-3: Tree-diagram of Theoretical Results for the Phase 3 Studies



Note: S_1 and S_2 represent probabilities; successful pathways (i.e., lice-free) are depicted in blue, while failing pathways (i.e., live lice present) are depicted in red.

In the above tree diagram, S_1 denotes the proportion of subjects that would have been expected to present without live lice 7 days after the last treatment, S_2 denotes the proportion of subjects that would have been expected to still present without live 14 days after the last treatment.

In predicting the S_1 and S_2, the sponsor assumed that the probability of a subject being lice-free 7 days after the first treatment would be the same as the probability of a subject being lice-free 7 days after the second treatment (i.e., the probability for both the left and right branches is equal to S_1). Similarly, the sponsor assumed that the left and right branches of S_2 would be the same.

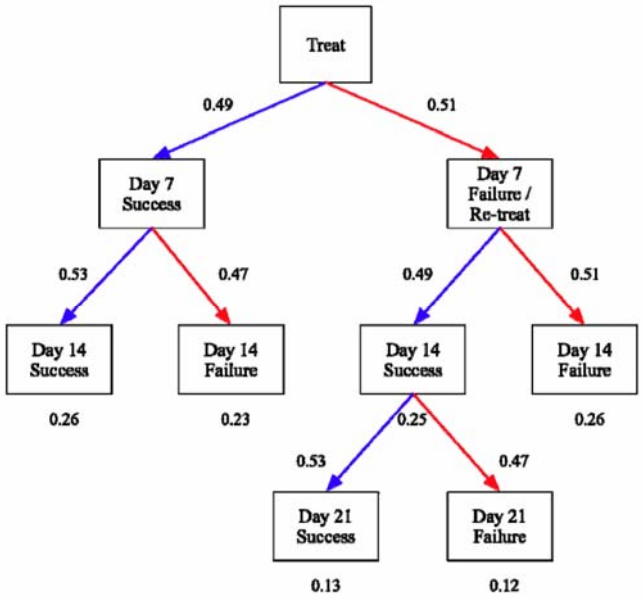
The sponsor assumed the same probabilities based on the results from conducting the Fisher's Exact test of the left and right S_1's of the spinosad product without nit combing

group in their Phase 3 trials. Specifically, the sponsor compared the left S_1 =0.77, and the right S_1 =0.64 using the Fisher's Exact test to conclude that the probabilities are not statistitically significantly different for the spinosad without combing group from their Phase 3 trials.

Using this assumption, the sponsor constructed a tree diagram for benzyl alcohol (diagram on the next page) to conclude the following:

- 49% of subjects would be lice-free at Day 7
- 26% would be lice-free at Day 14
- 51% would have live lice and Day 7, and if re-treated, and of those subjects, 49% would be live-free at Day 14, and 26% of the subjects would be lice-free at Day 21 (14 days after the last treatment).

Figure 3-6: **Tree-diagram of Theoretical Results for a Benzyl Alcohol-vehicle without Nit Combing Group Using the Phase 3 Study Design**



Note: Successful pathways (i.e., lice-free) are depicted in blue, while failing pathways (i.e., live lice present) are depicted in red.

Reviewer Comments:
The sponsor assumed the same success rates for the 'left' and the 'right branches'. They verified the validity of this assumption by conducting the Fisher's Exact test of comparing the S_1's for the left and the right branches of the spinosad product without combing from their Phase 3 trials. However, it should be noted that 1) the sponsor did not use the probabilities of success for the benzyl alcohol group, but used the spinosad group, 2) the Phase 3 trials that the sponsor used was not adequately powered to detect the difference in proportions using such test statistics. Therefore, the use of the sponsor's "theoretical" tree diagram may be limited in predicting the success rates of benzyl alcohol.

The sponsor further tried to estimate the 'pure benzyl alcohol effect' by subtracting the non-benzyl alcohol effect from the Ulesfia Phase 3 trials. The sponsor stated that the general

study designs were broadly similar to the spinosad Phase 3 trials, and noted the vehicle success rate was 15.4% for Ulesfia (please see table on the next page). Based on this, the sponsor attributed about 15% of the 26% of the benzyl alcohol effect at Day 14 to come from non-benzyl alcohol-containing excipients, and the rest of the 11% to come from benzyl alcohol alone. In addition, the sponsor noted that the benzyl alcohol tree diagram was an "aritificial use" (i.e, at the investigative sites) diagram, and that under "actual use" (i.e., at home), the sponsor expected that the benzyl alcohol alone might have less to contribute to the efficacy.

Table 4-1: Summary of Ulesfia Phase 3 Study Results (Primary ITT Subjects)

	Study 1		Study 2		Total	
	Ulesfia	**Vehicle**	**Ulesfia**	**Vehicle**	**Ulesfia**	**Vehicle**
N	63	62	64	61	127	123
Number Lice Free (%)	48 (76.2)	3 (4.8)	48 (75.0)	16 (26.2)	96 (75.6)	19 (15.4)

Source: Table 7 in reference 4
Note: Ulesfia contains benzyl alcohol, 5%, along with the vehicle. Vehicle contains the same inert ingredients as Ulesfia, but does not contain benzyl alcohol.

Reviewer's Comments:
By referencing the combined vehicle rate of 15% from the Ulesfia Phase 3 trials, the sponsor tried to compute the pure benzyl alcohol effect by subtracting this 15% from the 26% success rate of benzyl alcohol group at Day 14 from their Study 202-06. From this, the sponsor concluded that the benzyl alcohol by itself would have about 11% success. Furthermore, the sponsor stated that in "actual use" (i.e, at home) settings, this benzyl alcohol rate could be even lower, because Study 202-06 was done at an "artificial use" (i.e., at an investigational site) setting where the investigators applied treatments more rigorously that would have yielded higher success rates.

While this reviewer agrees that under "actual use", the success rates might be lower, it is unclear whether or not the benzyl alcohol would have an additive effect with the non-benzyl alcohol ingredients. Therefore, without knowing this factor, simple subtraction of the Ulesfia's combined effect of the non-benzyl alcohol (15%) from the sponsor's 26% success rate at Day 14, to conclude that the benzyl alcohol effect by itself would be as high as 11%, can not be justified.

Reviewer's Conclusion and Discussion:

The Agency requested that the sponsor "utilize Study 201-05 study findings to obtain an estimate of the treatment effect for benzyl alcohol if it were to be used for two treatments as it was in the Phase 3 trials. Such an estimate may provide information to evaluate the contribution of spinosad over that of benzyl alcohol (vehicle)." In response, the sponsor submitted a statistical report utilizing the Study 202-06 results instead of the Study 201-05 with the goal of predicting "the efficacy of a benzyl alcohol group in an idealized Phase 3 study".

As for Study 201-05, this reviewer agrees with the Sponsor's conclusion (although the reviewer's arguments are different in reaching this conclusion) that Study 201-05 cannot be used to obtain an estimate of the treatment effect for benzyl alcohol if it were to be used for two treatments as it was in the Phase 3 trials. The reviewer's reasons are listed below:

- While the immediate response rates can be estimated at Days 0 and 7, because both treatment and combing are involved, the "durable" effect for benzyl alcohol at Days 7 and 14 cannot be estimated from Study 201-05
- The trial was conducted under "artificial use" (i.e., at an investigational site), therefore, the success rate under "actual use" (i.e., at home) may be lower. However, the magnitude of reduction under "actual use" cannot be determined from this trial.
- The study was a single-center study with only 9 subjects in each arm, which makes it very difficult to conclude any meaningful statistical conclusion using this study alone.

As for the sponsor' approach in using Study 202-06, the sponsor obtained estimates of the benzyl alcohol treatment effect by using a tree diagram. In the tree diagram, the sponsor assumed that the success rates after the first treatment and the second treatment would be the same. The sponsor supported this assumption by conducting Fisher's Exact test on the "combined success rates" of the spinosad arm from the Phase 3 trials. It should be noted that 1) the sponsor did not use the probabilities of success for the benzyl alcohol group, but used the spinosad group, and 2) the Phase 3 trials that the sponsor used was not adequately powered to detect the difference in proportions using such test statistics. Therefore, the use of the sponsor's theoretical tree diagram may be limited in predicting the success rates of benzyl alcohol. This reviewer does not agree that the Study 202-06 can be used to obtain estimates of benzyl alcohol after two uses as were done in the Phase 3 trials.

Further, this reviewer does not agree with the sponsor's approach to determine the "pure benzyl alcohol effect" by referencing the non-benzyl alcohol effect from the Ulesfia Phase 3 trials. The sponsor concluded that the benzyl alcohol effect by itself would contribute to about 11% success after subtracting the non-benzyl alcohol effect of 15% (from Ulesfia trials). It is unclear whether the benzyl alcohol has an additive effect with the non-benzyl alcohol ingredients to allow it to be subtracted. Note also that the estimate of 15% for the vehicle effect in the Ulesfia trials came from averaging the results of one study with a vehicle response rate of 4% and one study with a vehicle response rate of 26%. This indicates that vehicle response rates can vary widely even for studies conducted under very similar conditions and therefore it is not possible to extrapolate that 15% would be a representative vehicle response rate for a benzyl alcohol-free vehicle. Therefore, the sponsor's approach to estimate the pure benzyl alcohol effect cannot be justified.

In conclusion, this reviewer agrees with the sponsor that the Study 201-05 has limited utility in obtaining the benzyl alcohol treatment effect if it were to be used for two treatments without combing. This reviewer's position is that such information can not be extrapolated from Study 202-06 either, as the study only involved one treatment at Day 0, therefore, the sponsor's tree diagram to predict the success rate of benzyl alcohol cannot be justified. Note that the goal of predicting the efficacy for the benzyl alcohol group differs from the goal of evaluating the contribution of spinosad over that of benzyl alcohol. Clearly, the sponsor did

not have a benzyl alcohol arm of two treatments without combing as a part of their clinical program, therefore, the sponsor's studies cannot be used to predict the efficacy for the benzyl alcohol if it were to be used for two treatments without combing.

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Orig. NDA 22-408
DDDP/Walker
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DDDP/Williams
OBIO/Patrician
DBIII/Wilson
DBIII/Alosh
DBIII/Kim

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22408	ORIG-1	PARAPRO PHARMACEUTICALS LLC	SPINOSAD

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/s/

CARIN J KIM
05/18/2010

MOHAMED A ALOSH
05/19/2010
Disagree with the primary reviewer's conclusion concerning the utility of the Phase 2 trials in evaluating success rates for the vehicle. Details are given in my memoradum.

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 22-408
Drug Name:	(b) (4) (spinosad)
Applicant:	Sponosor: The Dow Chemical Company
Documents Reviewed:	The sponsor's reports submitted on June 22, 2009, no electronic data submitted.
Review Priority:	Standard
Biometrics Division:	Division of Biometrics -6
Statistical Reviewer:	Min Min, Ph.D.
Concurring Reviewer:	Karl Lin, Ph.D.
Medical Division:	Division of Dermatology and Dental Products
Reviewing Pharmacologist:	Jianyong (Jerry) Wang, Ph.D.
Project Manager:	Williams, Dawn
Keywords:	Carcinogenicity, Dose response

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1. Background

In this submission the sponsor included reports of two systemic carcinogenicity studies, one in rats (104 weeks) and one in mice (18 months). These studies were intended to assess the carcinogenic potential of the test article, (b) (4) (XDE-105), which is for the treatment of lice, in rats and mice when administrated daily by diet. Results of this review have been discussed with the reviewing pharmacologist Dr. Wang.

2. Rat Study

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were four treated groups and one control group. Two hundred and fifty Fischer 344 rats of each sex were randomly allocated to treated and control groups. Four treated groups (50 animals/sex/group) received the test article, (b) (4) (XDE-105), daily via their diet for an intended period of 104 weeks. The time-weighted average dosages of (b) (4) ingested, based upon mean feed consumption and mean body weight data were 0, 2.4, 9.5, 24.1 and 49.1 mg/kg/day for males and 0, 3.0, 12.0, 30.3 and 62.8 mg/kg/day for females provided in the diets containing 0, 0.005, 0.02, 0.05 and 0.10% XDE-105, respectively. High-dose (0.10%) group males and females were terminated on test day 714 and 611, respectively, due to excessive mortality, an indication of exceeding a maximum-tolerated dose (MTD). In this review these dose groups would be referred to as the low, medium and high dose group, respectively. Treatment was administrated via their diets for about 104 weeks.

The study design is illustrated in the following table:

TABLE 1

XDE-105: TWO-YEAR CHRONIC TOXICITY, CHRONIC NEUROTOXICITY AND ONCOGENICITY STUDY IN FISCHER 344 RATS

STUDY DESIGN

Dose Levels (percent)	12-Month Sacrifice No. of Rats/Sex/Dose#	24-Month Sacrifice No. of Rats/Sex/Dose
0	15	50
0.005	15	50
0.02	15	50
0.05	15	50
0.1	15	50
TOTAL	150	500

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Study Parameters	No. of Rats/Sex/Dose Group@ 6 Months	12 Months	18 Months	24 Months
Hematology*	10	10	10	20
Clinical Chemistry*	10	10	10	20
Urinalysis*	10	10	10	20
Necropsy	--	10	--	50
Organ Weights	--	10	--	50
Histopathology **	--	10	--	50

@ Data will be collected only on surviving satellite group animals following 6 and 12 months dosing, while surviving animals will be used sequentially for data collection following 18 and 24 months dosing.

* Complete histopathology on high dose and control animals including those animals which die or are sacrificed in a moribund condition. Lungs, liver, kidneys, thyroid, gross lesions and all target tissues will be examined from the intermediate and low dose levels.

Values may actually be lower reflecting the number of surviving animals at scheduled evaluation dates.

Five animals per sex were pre-designated for neuropathologic evaluation and data are reported separately.

All animals were observed cageside at least twice daily for morbidity, moribundity, availability of feed and water, and clinical signs. Moribund animals that were not expected to survive until the next observation period, and any animals found dead, were necropsied. Animals found dead after routine working hours, during weekends or on holidays were refrigerated until the next scheduled workday and necropsied. Body weights were recorded for all animals prestudy, weekly for the first 13 weeks of the study, and at

approximately monthly intervals thereafter. Scheduled necropsies were supervised by a veterinary pathologist on all surviving rats/sex/dose from the final sacrifice group after approximately 12 and 24 months on study, respectively. To the greatest extent possible, a complete set of tissues was examined from all animals which died or were sacrificed moribund prior to the scheduled necropsies, with the exception of the male and female rats given 0.10% XDE-105. Multiple sections of many organs, as well as each organ for paired organs were examined.

Based on the results of histologic examination of the full set of tissues from the control and the high-dose group (0.10%)rats from the 12-month sacrifice and the control and the 0.05% dose group rats from the 24-month sacrifice, the following tissues were processed from the intermediate- and low dose levels: liver, kidneys, lungs, mesenteric lymph node (with adjacent tissue), thyroid with parathyroid glands, heart, skeletal muscle, tongue, stomach, mammary glands with skin, larynx, spleen, prostate and gross lesions. These tissues from intermediate- and low-dose levels were histologically examined because 1) they were required by governmental guidelines (liver, kidneys and lungs), 2) they were interpreted to be a target organ in a previous study (thyroid with parathyroid glands), 3) the incidence of the lesion between 0 and high-dose (12-months) or 0 and 0.05% groups (24-months) suggested a possible treatment-related effect (mesenteric lymph node with adjacent tissue, heart - females only, and larynx - females only), or 4) the tissues had gross lesions. The stomach, skeletal muscle, tongue, spleen, prostate, larynx (males), and heart (males) were not histologically examined from the 24-month sacrifice because the incidence and severity of lesions were similar between 0 and 0.05% group rats.

2.1. Sponsor's analyses

2.1.1. Survival analysis

Differences in mortality patterns were tested by the Gehan-Wilcoxon procedure (Breslow, 1970: $\alpha = 0.05$) for all animals scheduled for terminal sacrifice.

Sponsor's findings: Mortality data are summarized in Tables 1 and 2 and graphically represented in Figures 1 and 2. There were no statistically identified differences in overall moribundity/mortality pattern in male or female rats of the 0.005%,0.02% or 0.05%groups. Mortality rates at the end of the study were 28%, 38%, 34%, and 24%, for male rats and 30%, 14%, 12%, and 16% for female rats ingesting 0, 0.005, 0.02 or 0.05% XDE-105, respectively. The mortality rate for the 0.10% males was 80% through week 102 of the study and the mortality rates of 0.10% females was 60% through week 88 compared to 26% or 6% for the concurrent controls, respectively. These mortality rates exceeded the recommended 50% at 18 months or 75% at 24 months as specified in the guidelines (EPA-FIFRA, 1984; OECD, 1981; EEC, 1988; and MAFF, 1985). In addition, body weight gain deficits of these high-dose rats exceeded the 10-15% recommended for an MTD by the US EPA (Farber, 1987) and these animals appeared debilitated. Due to the excessive toxicity noted, the highdose males and females were terminated on test day 714 and 611, respectively.

Table 1: Mortality-Males

XDE-105: TWO-YEAR CHRONIC TOXICITY, CHRONIC NEUROTOXICITY AND ONCOGENICITY STUDY IN FISCHER 344 RATS

MORTALITY-MALES@

DOSE: %

TEST DAYS	0	0.005	0.02	0.05	0.10
001-028	0 0/50	0 0/50	0 0/50	0 0/50	0 0/50
029-056	0 0/50	0 0/50	0 0/50	0 0/50	0 0/50
057-084	0 0/50	0 0/50	0 0/50	0 0/50	0 0/50
085-112	0 0/50	0 0/50	0 0/50	0 0/50	0 0/50
113-140	0 0/50	0 0/50	0 0/50	0 0/50	0 0/50
141-168	0 0/50	0 0/50	0 0/50	0 0/50	0 0/50
169-196	0 0/50	0 0/50	0 0/50	0 0/50	0 0/50
197-224	0 0/50	0 0/50	0 0/50	0 0/50	0 0/50
225-252	0 0/50	0 0/50	0 0/50	0 0/50	0 0/50
253-280	0 0/50	0 0/50	0 0/50	0 0/50	0 0/50
281-308	0 0/50	0 0/50	0 0/50	0 0/50	2 1/50
309-336	0 0/50	0 0/50	0 0/50	0 0/50	2 1/50
337-364	0 0/50	0 0/50	0 0/50	0 0/50	2 1/50
365-392	0 0/50	0 0/50	0 0/50	0 0/50	2 1/50
393-420	0 0/50	0 0/50	2 1/50	0 0/50	2 1/50
421-448	2 1/50	0 0/50	2 1/50	0 0/50	2 1/50
449-476	2 1/50	0 0/50	2 1/50	2 1/50	2 1/50
477-504	2 1/50	0 0/50	2 1/50	2 1/50	4 2/50
505-532	4 2/50	0 0/50	2 1/50	2 1/50	4 2/50
533-560	4 2/50	4 2/50	4 2/50	4 2/50	6 3/50
561-588	6 3/50	6 3/50	4 2/50	6 3/50	6 3/50
589-616	10 5/50	8 4/50	6 3/50	12 6/50	14 7/50
617-644	10 5/50	10 5/50	8 4/50	12 6/50	26 13/50
645-672	12 6/50	16 8/50	14 7/50	14 7/50	54 27/50
673-700	22 11/50	24 12/50	20 10/50	22 11/50	70 35/50
701-728	26 13/50	36 18/50	34 17/50	24 12/50	80 40/50
729-734	28 14/50	38 19/50	34 17/50	24 12/50	*

@ DATA PRESENTED FIRST AS % MORTALITY AND FOLLOWED BY NUMBER DEAD OVER TOTAL NUMBER OF ANIMALS IN GROUP SCHEDULED FOR THE CHRONIC TOXICITY-ONCOGENICITY EVALUATION.
*0.10% DOSE MALES WERE SACRIFICED ON TEST DAY 714 DUE TO EXCESSIVE MORTALITY

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Table 2: Mortality-Females

XDE-105: TWO-YEAR CHRONIC TOXICITY, CHRONIC NEUROTOXICITY AND ONCOGENICITY STUDY IN FISCHER 344 RATS

MORTALITY-FEMALES@

DOSE: %

TEST-DAYS	0	0.005	0.02	0.05	0.10
001-028	0 0/50	0 0/50	0 0/50	0 0/50	0 0/50
029-056	0 0/50	0 0/50	0 0/50	0 0/50	0 0/50
057-084	0 0/50	0 0/50	0 0/50	0 0/50	0 0/50
085-112	0 0/50	0 0/50	0 0/50	0 0/50	0 0/50
113-140	0 0/50	0 0/50	0 0/50	0 0/50	0 0/50
141-168	0 0/50	0 0/50	0 0/50	0 0/50	0 0/50
169-196	0 0/50	0 0/50	0 0/50	0 0/50	0 0/50
197-224	0 0/50	0 0/50	0 0/50	0 0/50	0 0/50
225-252	0 0/50	0 0/50	0 0/50	0 0/50	0 0/50
253-280	0 0/50	0 0/50	0 0/50	0 0/50	0 0/50
281-308	0 0/50	0 0/50	0 0/50	0 0/50	0 0/50
309-336	0 0/50	0 0/50	0 0/50	0 0/50	0 0/50
337-364	0 0/50	0 0/50	0 0/50	0 0/50	0 0/50
365-392	0 0/50	0 0/50	0 0/50	0 0/50	0 0/50
393-420	0 0/50	0 0/50	0 0/50	0 0/50	0 0/50
421-448	0 0/50	0 0/50	0 0/50	0 0/50	0 0/50
449-476	0 0/50	0 0/50	0 0/50	0 0/50	2 1/50
477-504	0 0/50	2 1/50	0 0/50	0 0/50	10 5/50
505-532	2 1/50	2 1/50	0 0/50	0 0/50	18 9/50
533-560	2 1/50	2 1/50	2 1/50	0 0/50	34 17/50
561-588	4 2/50	4 2/50	4 2/50	0 0/50	52 26/50
589-616	6 3/50	6 3/50	4 2/50	0 0/50	60 30/50
617-644	8 4/50	6 3/50	4 2/50	4 2/50	*
645-672	8 4/50	6 3/50	6 3/50	8 4/50	*
673-700	18 9/50	6 3/50	8 4/50	12 6/50	*
701-728	28 14/50	12 6/50	10 5/50	16 8/50	*
729-736	30 15/50	14 7/50	12 6/50	16 8/50	*

@ DATA PRESENTED FIRST AS % MORTALITY AND FOLLOWED BY NUMBER DEAD OVER TOTAL NUMBER OF ANIMALS IN GROUP SCHEDULED FOR THE CHRONIC TOXICITY-ONCOGENICITY EVALUATION.
*0.10% DOSE GROUP FEMALES TERMINATED ON TEST DAY 611 DUE TO EXCESSIVE MORTALITY.

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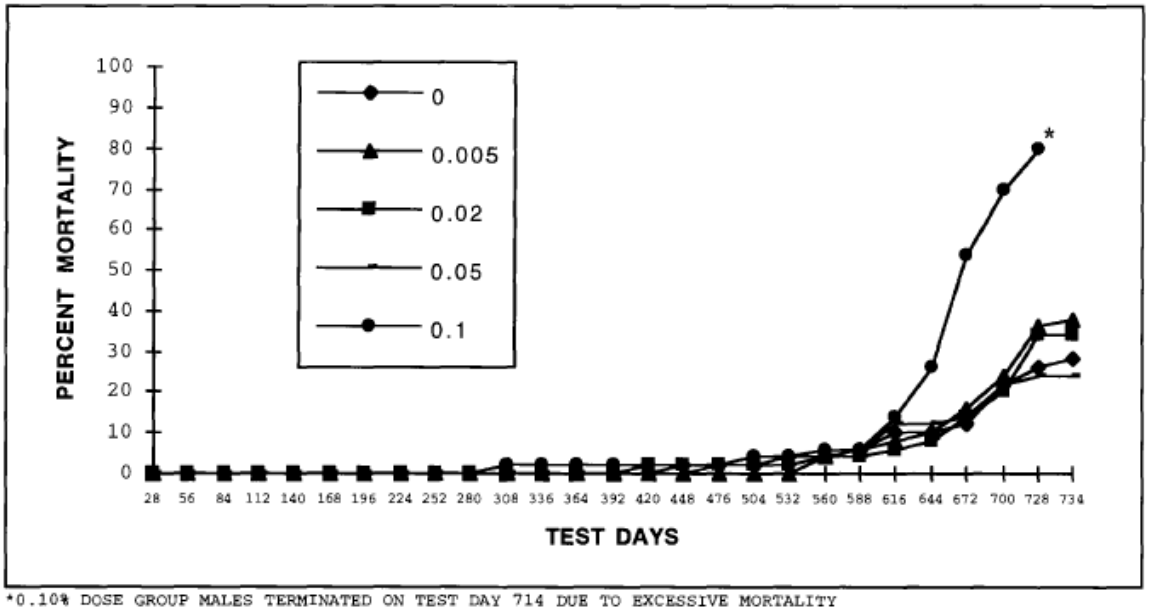
Figure 1: Kaplan-Meier plot of Survival in Male Rats

FIGURE 1

XDE-105: TWO-YEAR CHRONIC TOXICITY, CHRONIC NEUROTOXICITY AND ONCOGENICITY STUDY IN FISCHER 344 RATS

CUMULATIVE MORTALITY IN MALES



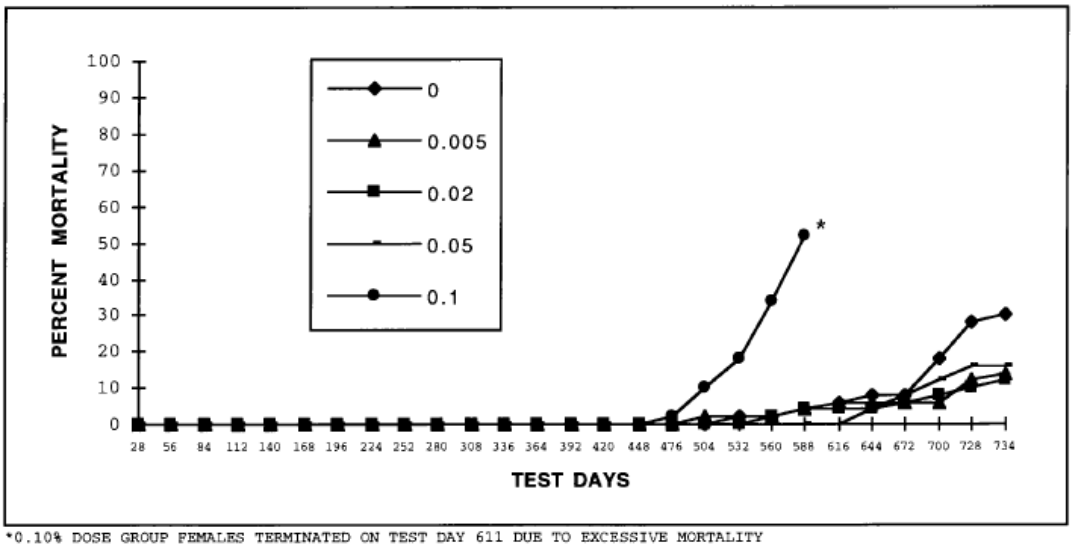
*0.10% DOSE GROUP MALES TERMINATED ON TEST DAY 714 DUE TO EXCESSIVE MORTALITY

Figure 2: Kaplan-Meier plot of Survival in Female Mice

FIGURE 2

XDE-105: TWO-YEAR CHRONIC TOXICITY, CHRONIC NEUROTOXICITY AND ONCOGENICITY STUDY IN FISCHER 344 RATS

CUMULATIVE MORTALITY IN FEMALES



*0.10% DOSE GROUP FEMALES TERMINATED ON TEST DAY 611 DUE TO EXCESSIVE MORTALITY

2.1.2. Tumor data analysis

Gross pathologic observations are tabulated and considered in the interpretation of final histopathologic data, but are not evaluated statistically. The cumulative incidence of appropriate histopathologic observations on all animals scheduled for the terminal sacrifice are used in statistical analysis.

For tissues where all animals in all dose groups are scheduled to be examined, the incidences of specific observations are first tested for deviation from linearity using ordinal spacings of the doses. If linearity is not rejected the data are then tested for a linear trend using the Cochran- Armitage Trend test. If the trend is statistically significant, or if significant deviation from linearity is found, incidences for each dose group are compared to that of the control group using a pairwise chi-square test with Yates continuity correction.

For tissues which are evaluated from all control and high dose rats, but only from selected rats in the intermediate dose groups, statistical analysis consists of the pairwise comparisons of control and high dose using the pairwise chi-square test with Yates continuity correction. The nominal alpha levels are as follows:

Chi-square test for lack of linearity (Armitage, 1971):	*alpha* = 0.01
Trend test (Armitage, 1971):	*alpha* = 0.02 two-sided
Pairwise Chi-square comparison test with Yate's continuity correction (Fle iss, 1981):	*alpha* = 0.05 one-sided

Sponsor's findings: Treatment-related effects occurred in the thyroid glands of male and female rats given 0.02 and 0.05% XDE-I05, in the mesenteric lymph nodes of male and female rats given 0.05% XDE-I05, and in the lungs of female rats given 0.05% XDE-I05. These effects consisted of vacuolation and inflammation of the thyroid glands, accumulation of reticuloendothelial cells in the mesenteric lymph node and inflammation of the lung. The severity of treatment-related alterations in the thyroid progressed with time. All other treatment-related histopathologic alterations did not progress or were resolved over time. There was no indication of an oncogenic effect in any tissue or organ at any dose level.

2.2. Reviewer's analyses

To verify sponsor's analyses and to perform the additional analysis suggested by the reviewing pharmacologist, this reviewer independently performed tumor data analyses. Data used in this reviewer's analyses were not provided by the sponsor electronically but came from sponsor's report.

2.2.1. Survival analysis

The survival analysis couldn't be conducted because the sponsor did not submit data electronically. However, from the sponsor's Kaplan-Meier plots presented in Figures 1 and 2, excluding the 0.10% group, the survivals of the 0, 0.005%, 0.02% and 0.05% groups were fairly similar. Since the data of the 0.1% group were not included in the tumor data analysis, the survival-unadjusted analysis results should be valid.

2.2.2. Tumor data analysis

The tumor data were analyzed for dose response relationships and pair-wise comparisons of vehicle control group with each of the treated groups for tumor types chosen by the reviewing pharmacologist Dr. Wang were performed using the Cochran-Armitage trend test described in Armitage (1955) and but using 0, 5, 20, 50 as the weights in the test on the data of tumor types that show possible significant trends and differences in tumor incidence by keying in the tumor incidence rates by hands from the sponsor hardcopy report. However, if there are significant trends and differences in survival among treatment groups, then survival-UNADJUSTED analysis will become invalid. In this situation, survival-ADJUSTED analysis has to be used, and the electronic tumor datasets are needed to perform the analysis. For the calculation of p-values the survival-unadjusted exact permutation method was used. The tumor rates and the p-values of the tested tumor types are listed in Tables 1 and 2 in the appendix for males and females, respectively.

It should be noted that the test for dose-response in tumor incidence is valid only for the tumor/tissue combinations in which all animals in all treatment groups were microscopically examined. For the tumor/tissue combinations in which not all the animals in the low and medium groups were microscopically examined, the results of control-high pairwise comparison should be used.

Multiple testing adjustment: Adjustment for the multiple dose response relationship testing was done using the criteria developed by Lin and Rahman (1998). The criteria recommend the use of a significance level α=0.025 for rare tumors and α=0.005 for common tumors for a submission with two species, and a significance level α=0.05 for rare tumors and α=0.01 for common tumors for a submission with only one species study in order to keep the false-positive rate at the nominal level of approximately 10%. A rare tumor is defined as one in which the spontaneous tumor rate is less than 1%. The adjustment for multiple pair-wise comparisons was done using the criteria developed by Haseman (1983) that recommends the use of a significance level α=0.05 for rare tumors and α=0.01 for common tumors, in order to keep the false-positive rate at the nominal level of approximately 10%.

The list of chosen tumor types suggested by the reviewing pharmacologist is the following:

Neoplastic findings with potential significant differences in male rats (50/sex/group).

Doses (%)	0	0.005	0.02	0.05	0.1
Mammary gland fibroadenoma (benign)	1	4	4	4	--
Pancreas adenoma (benign)	8	1	2	13	--
Skin keratoacanthoma (benign)	0	3	4	1	--
Thyroid gland adenoma (benign)	9	7	10	12	--
Thyroid gland carcinoma	0	2	1	1	--

Neoplastic findings with potential significant differences in female rats (50/sex/group).

Doses (%)	0	0.005	0.02	0.05	0.1
Thyroid gland adenoma (benign)	9	13	9	7	--
Thyroid gland carcinoma	2	1	1	3	--
Uterus adenocarcinoma	0	2	0	0	--
Uterus endometrial stromal polyp (benign)	18	18	25	23	--

Reviewer's findings: Following tumor types showed p-values less than or equal to 0.05 either tests for dose response relationship and/or pair-wise comparisons between vehicle control and each of individual treated groups.

Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pair-wise Comparisons (Control, low, medium and high dose groups)

	Tumor Name	Control N=50	0.005% Low N=50	0.02% Med N=50	0.05% High N=50	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Male	Pancreas adenoma (benign)	8	1	2	13	0.005	0.985	0.954	0.163

Based on the criteria of adjustment for multiple testing of trends proposed by Lin and Rahman, the incidence of none of any chosen tested tumor types in either sex was considered to have a statistically significant positive dose response relationship. Also based on the criteria by Haseman, the increased tumor incidences of none of any chosen tested tumor types were considered to be statistically significant when compared to the control group.

3. Mouse Study

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups and one control group. A total of 200 CD1 mice (50 animals/sex/group) were used in the study and allocated to 4 groups as follows. Three treated groups received the test article, (b) (4) (XDE-105), daily via their diet for an intended period of 18 months. The time weighted average dosages ingested, based upon mean feed consumption and mean body weight data were 0, 3.4, 11.4, and 50.9 mg/kg/ day for males, and 0,4.2, 13.8, and 67.0 mg/kg/ day for females provided in the diets containing a, 0.0025, 0.008, and 0.036% XDE-I05, respectively. High-dose (0.036%) group females were terminated on test day 455 due to markedly lower body weights, feed consumption, and excessive mortality, an indications of exceeding a maximum-tolerated dose (MTD).

All animals were observed cageside at least twice daily for morbidity, moribundity, mortality, availability of feed and water, and clinical signs. To the extent possible, these observations included an evaluation of the skin, fur, and mucous membranes, respiration, central nervous system functions, and behavior pattern. Moribund animals that were not expected to survive until the next observation period, and any animal found dead, were necropsied. Animals found dead after routine working hours, during weekends or on holidays were refrigerated until the next scheduled workday and necropsied. Body weights were recorded for all animals prestudy, weekly for the first thirteen weeks of the study, and at approximately monthly intervals thereafter. Body weight gains were subsequently calculated using these data.

In animals from the l8-month sacrifice, all tissues from control group males and females, middle-dose (0.008%) group females, and high-dose (0.036%) group males, were also processed by standard procedures for light microscopic evaulation (exception - joint). High-dose (0.036%) group females were terminated on test day 455 due to markedly lower body weight gains and excessive mortality indicative of exceeding the maximum-tollerated dose (MTD). Therefore, the tissues were saved but not evaluated since data from this group was of questionable value.

The study design is as the following table:

TABLE 1

XDE-105: 18-MONTH DIETARY ONCOGENICITY STUDY IN CD-1 MICE

STUDY DESIGN

Dose Levels (percent)	3-Month Sacrifice No. of Mice/Sex/Dose	12-Month Sacrifice No. of Mice/Sex/Dose	18-Month Sacrifice No. of Mice/Sex/Dose
0	9 or 10	10	50
0.0025	10	10	50
0.0080	10	10	50
0.0360	10	10	50
TOTAL	79	80	400

Study Parameters	No. of Mice/Sex/Dose Group@ 3 Months	12 Months	18 Months
Hematology*	9 or 10	10	20
Clinical Chemistry*	9 or 10	10	20
Necropsy	9 or 10	10	All
Organ Weights (brain, liver, kidneys, heart, testes, spleen)	9 or 10	10	All
Histopathology **	9 or 10	10	All

*Data will be collected only on surviving interim sacrifice animals of each dose group following 3- and 12-months of dosing, while surviving animals will be used sequentially for data collection following 18-months of dosing.
**Complete histopathology on high-dose and control animals including those animals which die or are sacrificed in a moribund condition. Liver, kidneys, lungs, gross lesions and all target tissues will be examined from low and intermediate dose groups of animals.
@ Number of mice may actually be lower reflecting the number of surviving animals at scheduled evaluation dates.

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3.1. Sponsor's analyses

3.1.1. Survival analysis

Survival data from the mouse study were analyzed by the sponsor using the same statistical methodologies that were used to analyze the survival data from the rat study but only for the control group and the treated groups. All statistical analysis was performed for males and females separately.

Sponsor's findings: The Kaplan-Meier product-limit survival curves from the sponsor's report are presented in Figure 3 and 4 for males and females, respectively. The cumulative mortality recorded throughout the study is summarized below table 3 and 4 for males and females, respsectively. There was no statistically identified effect on mortality in mice ingesting diets containing 0, 0.0025, 0.008 and 0.036 (males)% XDE-I05.

Table 3: Cumulative mortality in Male Mice

XDE-105: 18-MONTH DIETARY ONCOGENICITY STUDY IN CD-1 MICE

CUMULATIVE MORTALITY-MALES@

TEST DAYS	DOSE: % 0	.0025	.008	.036
001-028	0 0/50	0 0/48	0 0/49	0 0/48
029-056	0 0/50	0 0/48	0 0/49	0 0/48
057-084	0 0/50	0 0/48	0 0/49	0 0/48
085-112	0 0/50	0 0/48	0 0/49	0 0/48
113-140	0 0/50	0 0/48	0 0/49	0 0/48
141-168	0 0/50	2 1/48	2 1/49	0 0/48
169-196	0 0/50	2 1/48	2 1/49	2 1/48
197-224	2 1/50	2 1/48	4 2/49	2 1/48
225-252	2 1/50	2 1/48	4 2/49	2 1/48
253-280	2 1/50	2 1/48	4 2/49	2 1/48
281-308	2 1/50	2 1/48	6 3/49	4 2/48
309-336	4 2/50	2 1/48	6 3/49	4 2/48
337-364	6 3/50	2 1/48	10 5/49	4 2/48
365-392	6 3/50	8 4/48	10 5/49	4 2/48
393-420	6 3/50	17 8/48	14 7/49	8 4/48
421-448	6 3/50	21 10/48	16 8/49	13 6/48
449-476	8 4/50	25 12/48	18 9/49	19 9/48
477-504	10 5/50	27 13/48	20 10/49	29 14/48
505-532	18 9/50	31 15/48	20 10/49	40 19/48
533-560	24 12/50	35 17/48	29 14/49	44 21/48

@ DATA PRESENTED FIRST AS % MORTALITY AND FOLLOWED BY NUMBER DEAD OVER TOTAL NUMBER OF ANIMALS IN GROUP SCHEDULED FOR THE CHRONIC TOXICITY-ONCOGENICITY EVALUATION. ANIMALS WITH FINAL STATUS OF ACCIDENTAL DEATH WERE NOT INCLUDED IN ANALYSIS.

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Table 4: Cumulative mortality in Female Mice

XDE-105: 18-MONTH DIETARY ONCOGENICITY STUDY IN CD-1 MICE

CUMULATIVE MORTALITY-FEMALES@

TEST-DAYS	DOSE: % 0	.0025	.008	0.036%
001-028	2 1/50	2 1/50	0 0/48	0 0/50
029-056	2 1/50	2 1/50	0 0/48	0 0/50
057-084	2 1/50	2 1/50	0 0/48	0 0/50
085-112	2 1/50	2 1/50	0 0/48	0 0/50
113-140	2 1/50	2 1/50	0 0/48	0 0/50
141-168	2 1/50	2 1/50	0 0/48	0 0/50
169-196	2 1/50	2 1/50	0 0/48	4 2/50
197-224	2 1/50	2 1/50	0 0/48	4 2/50
225-252	2 1/50	2 1/50	0 0/48	6 3/50
253-280	2 1/50	2 1/50	2 1/48	16 8/50
281-308	2 1/50	4 2/50	2 1/48	22 11/50
309-336	4 2/50	4 2/50	2 1/48	30 15/50
337-364	6 3/50	4 2/50	2 1/48	36 18/50
365-392	8 4/50	6 3/50	2 1/48	44 22/50
393-420	10 5/50	8 4/50	2 1/48	48 24/50
421-448	10 5/50	14 7/50	2 1/48	60 30/50
449-476	12 6/50	14 7/50	6 3/48	60 30/50*
477-504	14 7/50	22 11/50	10 5/48	
505-532	18 9/50	24 12/50	13 6/48	
533-552	18 9/50	26 13/50	13 6/48	

@ DATA PRESENTED FIRST AS % MORTALITY AND FOLLOWED BY NUMBER DEAD OVER TOTAL NUMBER OF ANIMALS IN GROUP SCHEDULED FOR THE CHRONIC TOXICITY-ONCOGENICITY EVALUATION. ANIMALS WITH FINAL STATUS OF ACCIDENTAL DEATH WERE NOT INCLUDED IN ANALYSIS.
* 0.036% DOSE GROUP WAS TERMINATED ON TEST DAY 455 DUE TO EXCESSIVE BODY WEIGHT GAIN DEFICIT AND EXCESSIVE MORTALITY.

Figure 3: Kaplan-Meier plot of Survival in Male Mice

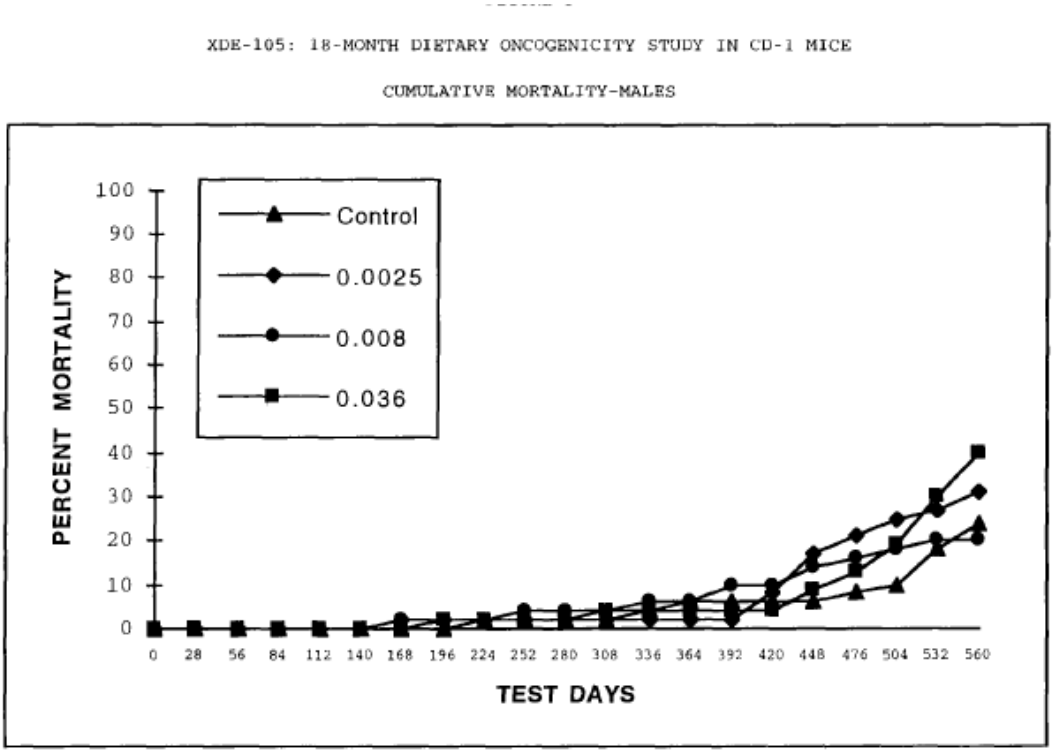

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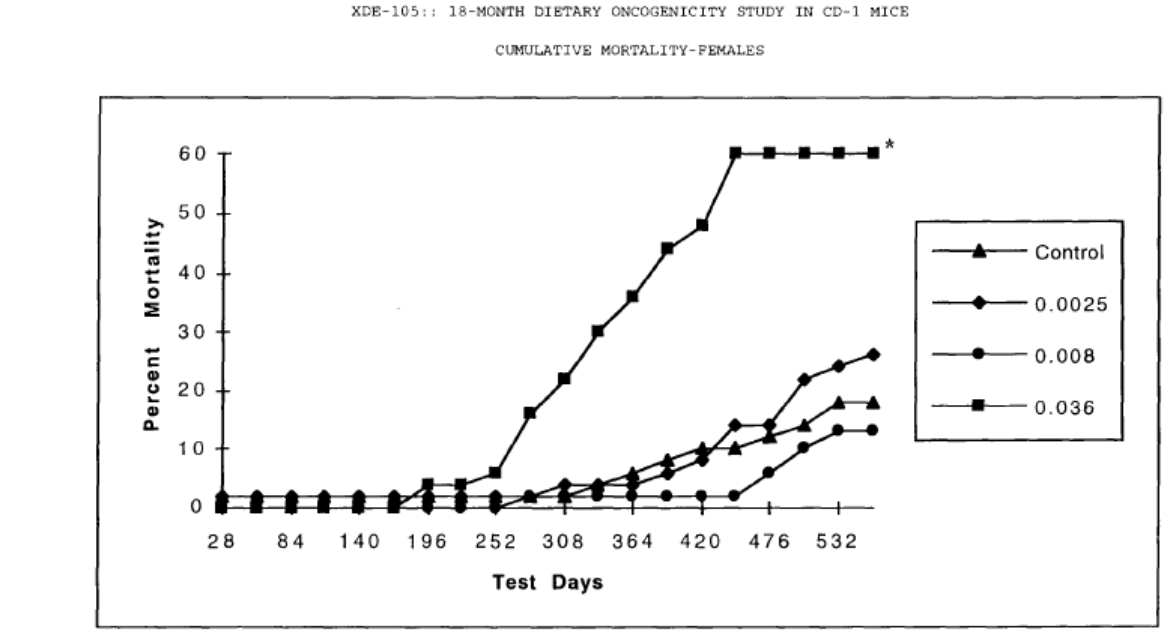
Figure 4: Kaplan-Meier plot of Survival in Female Mice



* 0.036% DOSE GROUP WAS TERMINATED ON TEST DAY 455 DUE TO EXCESSIVE BODY WEIGHT GAIN DEFICIT AND EXCESSIVE MORTALITY.

3.1.2. Tumor data analysis

Tumor data from the mouse study were also analyzed by the sponsor using the same statistical methodologies that were used to analyze the tumor data from the rat study against control.

Sponsor's findings: The incidence of tumors in mice administered XDE-I05 for up to 18 months was not statistically increased relative to controls.

3.2. Reviewer's analyses

This reviewer independently performed tumor data analyses from the mouse study. For the mouse data analyses this reviewer used similar methodologies that she used to analyze the data from the rat study. As in rat studies, data were not provided by the sponsor electronically.

3.2.1. Survival analysis

No analysis was conducted because of no electronic data submitted from sponsor. However, from the sponsor's Kaplan-Meier plots of survival of functions, the survivals of male mice were fairly similar, and therefore, the results of the survival-unadjusted analysis of the tumor data should be valid. But it is different in female mice, the high dose group had much higher mortality than the other three treatment groups. However, the tumor data of the 0.036% dose group were excluded in the tumor data analysis. Therefore, the results of survival-unadjusted tumor data analysis for female mice should be valid too.

3.2.2. Tumor data analysis

The tumor rates and the p-values of the tumor types tested for dose response relationship and pair-wise comparisons of vehicle control and treated groups are given in Table 3 and 4 in the appendix for males and females, respectively.

It should be noted that the test for dose-response in tumor incidence is valid only for the tumor/tissue combinations in which all animals in all treatment groups were microscopically examined. For the tumor/tissue combinations in which not all the animals in the low and medium groups were microscopically examined, the results of control-high pairwise comparison should be used.

The list of chosen tumor types suggested by the reviewing pharmacologist is the following:

XDE-105: 18-month dietary carcinogenicity study in CD-1 mice.
Doses: 0, 0.0025, 0.008, and 0.036% XDE-I05. High-dose (0.036%) group females were terminated on Day 455.

Neoplastic findings with potential significant differences in male mice (50/sex/group).

Doses (%)	0	0.0025	0.008	0.036
Lung adenoma (benign)	12	6	17	13
Lymphosarcoma and/or Leukemia (combined)	0	3	2	0

Neoplastic findings with potential significant differences in female mice (50/sex/group).

Doses (%)	0	0.0025	0.008	0.036
Liver adenoma (benign)	0	1	3	--
Lung adenoma (benign)	10	13	5	--
Hemangioma and/or hemangiosarcoma (combined, any site)	4	6	9	--

Reviewer's findings:

Based on the criteria of adjustment for multiple testing of trends proposed by Lin and Rahman, the incidence of none of any chosen tested tumor types in either sex was considered to have a statistically significant positive dose response relationship. Also based on the criteria by Haseman, the increased tumor incidences of none of any chosen tested tumor types were considered to be statistically significant when compared to the control group.

4. Summary

In this submission the sponsor included reports of two systemic carcinogenicity studies, one in rats (104 weeks) and one in mice (18 months). These studies were intended to assess the carcinogenic potential of the test article, (b) (4) (XDE-105), which is for the treatment of lice, in rats and mice when administrated daily by diet.

Rat Study: Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were four treated groups and one control group. Two hundred and fifty Fischer 344 rats of each sex were randomly allocated to treated and control groups. Four treated groups (50 animals/sex/group) received the test article (b) (4) (XDE-105), daily via their diet for an intended period of 104 weeks. The time-weighted average dosages ingested, based upon mean feed consumption and mean body weight data were 2.4, 9.5, 24.1 and 49.1 mg/kg/day for males and 0, 3.0, 12.0, 30.3 and 62.8 mg/kg/day for females provided diets containing 0.005, 0.02, 0.05 and 0.10% XDE-105, respectively. High-dose (0.10%) group males and females were terminated on test day 714 and 611, respectively, due to excessive mortality indicative of exceeding a maximum-tolerated dose (MTD). In this review these dose groups would be referred to as the low, medium and high dose group, respectively. Treatment was administrated via their diets for about 104 weeks.

The survival analysis couldn't be conducted because the sponsor did not submit data electronically. However, from the sponsor's Kaplan-Meier plots presented in Figures 1 and 2, excluding the 0.10% group, the survivals of the 0, 0.005%, 0.02% and 0.05% groups were fairly similar. Since the data of the 0.1% group were not included in the tumor data analysis, the survival-unadjusted analysis results should be valid.

The tests showed no statistically significant positive dose response relationship in incidence in any of the tested tumor types. Pair-wise comparisons showed no statistically significantly increased incidence of any tumor type in the treated groups compared to the vehicle control group.

It should be noted that the test for dose-response in tumor incidence is valid only for the tumor/tissue combinations in which all animals in all treatment groups were microscopically examined. For the tumor/tissue combinations in which not all the animals in the low and medium groups were microscopically examined, the results of control-high pairwise comparison should be used.

Mouse Study: Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups and one control groups. A total of 200 CD1 mice (50 animals/sex/group) were used in the study and allocated to 4 groups as follows. Three treated groups received the test article, (b) (4) (XDE-105), daily via their diet for an intended period of 18 months. The time weighted average dosages ingested, based upon mean feed consumption and mean body weight data were a, 3.4, 11.4, and 50.9 mg/kg/ day for males, and 0,4.2, 13.8, and 67.0 mg/kg/ day for females provided diets containing a, 0.0025, 0.008, and 0.036% XDE-I05, respectively. High-dose (0.036%) group females were terminated on test day 455 due to markedly lower body weights, feed consumption, and excessive mortality indicative of exceeding a maximum-tolerated dose (MTD).

The survival analysis couldn't be conducted because the sponsor did not submit data electronically. However, from the sponsor's Kaplan-Meier plots presented in Figures 1 and 2, excluding the 0.10% group, the survivals of the 0, 0.005%, 0.02% and 0.05% groups were fairly similar. Since the data of the 0.1% group were not included in the tumor data analysis, the survival-unadjusted analysis results should be valid.

The tests showed no statistically significant positive dose response relationship in incidence in any of the tested tumor types. Pair-wise comparisons showed no statistically significantly increased incidence of any tumor type in the treated groups compared to the vehicle control group.

It should be noted that the test for dose-response in tumor incidence is valid only for the tumor/tissue combinations in which all animals in all treatment groups were microscopically examined. For the tumor/tissue combinations in which not all the animals in the low and medium groups were microscopically examined, the results of control-high pairwise comparison should be used.

Min Min, Ph.D.
Mathematical Statistician

Concur: Karl Lin, Ph.D.
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Archival NDA 22-408
Dr. Jianyong Wang
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Dr. Min

5. Appendix

Table 1: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Rats (control, low, medium and high dose groups)

Tumor Name	Control N=50	0.005% Low N=50	0.02% Med N=50	0.05% High N=50	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Mammary gland fibroadenoma (benign)	1	4	4	4	0.214	0.181	0.181	0.181
Pancreas adenoma (benign)	8	1	2	13	0.005	0.985	0.954	0.163
Skin keratoacanthoma (benign)	0	3	4	1	0.506	0.121	0.059	0.500
Thyroid gland adenoma (benign)	9	7	10	12	0.135	0.607	0.500	0.312
Thyroid gland carcinoma	0	2	1	1	0.421	0.248	0.500	0.500

Table 2: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Female Rats (control, low, medium and high dose groups)

Tumor Name	Control N=50	0.005% Low N=50	0.02% Med N=50	0.05% High N=50	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Thyroid gland adenoma (benign)	9	13	9	7	0.855	0.235	0.602	0.607
Thyroid gland carcinoma	2	1	1	3	0.212	0.500	0.500	0.500
Uterus adenocarcinoma	0	2	0	0	0.751	0.248	.	.
Uterus endometrial stromal polyp	18	18	25	23	0.117	0.582	0.113	0.208

Table 3: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Mice (control, low, medium and high dose groups)

Tumor Name	Control N=50	0.0025% Low N=50	0.008% Med N=50	0.036% High N=50	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Lung adenoma	12	6	17	13	0.242	0.904	0.189	0.500
Lymphosarcoma and/or stromal polyp	0	3	2	0	0.815	0.121	0.248	.

Table 4: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Female Mice (control, low and medium dose groups)

Tumor Name	Control N=50	0.0025% Low N=50	0.008% Med N=50	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M
Liver adenoma (benign)	0	1	3	0.079	0.370	0.117
Lung adenoma (benign)	10	13	5	0.060	0.500	0.121
Hemangioma and/or hemangiosarcoma (combined, any site)	4	6	9	0.947	0.318	0.869

6. References:

1. Armitage, P. (1955). "Tests for linear trends in proportions and frequencies." *Biometrics*, 11, 375-386.

2. Cox D. R. (1972) "Regression models and life tables", *Journal of the Royal Statistical Society*, B, 34, 187-220.

3. Gehan (1965) "A generalized Wilcoxon test for comparing arbitrarily singly censored samples", *Biometrika*, 52, 203-223.

4. Haseman, J (1983), "A re-examination of false-positive rates for carcinogenesis studies", *Fundamental and Applied Toxicology*, 3: 334-339.

5. Lin, K.K. and Rahman, M.A. (1998), "Overall false positive rates in tests for linear trend in tumor incidence in animal carcinogenicity studies of new drugs", *Journal of Biopharmaceutical Statistics,* 8(1), 1-15.

6. Rahman, M.A. and Lin, K.K. (2008), "A comparison of False Positive Rates of Peto and Poly-3 Methods for Long-Term Carcinogenicity Data Analysis Using Multiple Comparison Adjustment Method Suggested by Lin and Rahman", *Journal of Biopharmaceutical Statistics,* 18:5, 849-858.

7. Peto, R., M.C. Pike, N.E. Day, R.G. Gray, P.N. Lee, S. Parish, J. Peto, Richards, and J.Wahrendorf (1980), "Guidelines for sample sensitive significance test for carcinogenic effects in long-term animal experiments", Long term and short term screening assays for carcinogens: A critical appraisal, International agency for research against cancer monographs, *Annex to supplement, World Health Organization, Geneva,* 311-426.

8. Tarone RE (1975), "Test for trend in life table analysis", *Biometrika*, 62: 679-82.

9. U.S. Department of Health and Human Services, "Guidance for Industry: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals", Center for Drug E valuation and Research, Food and Drug Administration, Sliver Spring, Maryland, 2001.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22408	ORIG-1	PARAPRO PHARMACEUTICALS LLC	SPINOSAD

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

/s/

MIN MIN
12/03/2009

KARL K LIN
12/03/2009
Concur with 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

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	NDA 22-408
Drug Name:	(b) (4) (spinosad (b) (4))
Indication(s):	Treatment of head lice (pediculosis capitis) infestations including lice (b) (4) in patients (b) (4)
Applicant:	ParaPRO Pharmaceuticals, LLC
Date(s):	Letter date: 1/22/09 PDUFA goal date: 11/20/09
Review Priority:	Standard
Biometrics Division:	DB3
Statistical Reviewer:	Lisa A. Kammerman, Ph.D. Carin Kim, Ph.D.
Concurring Reviewers:	Mohamed Alosh, Ph.D.
Medical Division:	Division of Dermatology and Dental Products
Clinical Team:	Patricia Brown, MD
Project Manager:	LCDR Dawn Williams, RN, BSN, USPHS

Keywords: Clinical studies, NDA review, head lice

Table of Contents

FIGURES

TABLES

1. EXECUTIVE SUMMARY

1.1. Conclusions and Recommendations

The data submitted with this application appear to support the efficacy of [redacted] (spinosad [redacted])[1] for the treatment of head lice in patients [redacted]. Two Phase 3 studies and one of the three Phase 2 studies provide the primary evidence.

This conclusion, however, is tempered by statements in the clinical study reports for the Phase 3 studies that indicate a single household may been enrolled more than once or as more than one household. Although the study reports state all efficacy results were examined for the impact of the same household being entered more than once, the submission does not present the results from this examination. Neither does the submission document the number of households that were enrolled more than once.

Responses from households that are enrolled more than once or from households that are enrolled as more than one household are correlated and, therefore, cannot be assumed to be independent. Independence of observations is a key assumption of the analyses of the primary endpoint. The applicant needs to provide further information on the households that were enrolled more than once or as more than one household. Further, the applicant needs to provide analyses that include each household only once.

Until the issue of households being enrolled more than once or as separate households is resolved, the results from the Phase 3 studies should be viewed with caution.

The two Phase 3 studies shared a common protocol. Subjects were randomized to NatrOVA with nit combing, NatrOVA without nit combing or NIX with nit combing in a 1:4:4 ratio. The primary endpoint was the proportion of subjects who were lice free 14 days after their last treatment. Using a simple difference between proportions of subjects who were lice free, with 95% confidence the true treatment effect for NatrOVA without nit combing relative to NIX could range from 27% to 52% based on the results from the first study and could range from 31% to 57% based on the results from the second study.

When interpreting the results of the Phase 3 studies, it is important to keep in mind that although the studies were investigator-blinded and were intended to be double-blinded, subjects could have inadvertently revealed their treatment assignment to the investigators. For example, two of the treatment arms required nit combing. Subjects who did not receive combs may have known they were randomized to NatrOVA without combing. Further, the name of the treatment product was printed on study product packaging. Although subjects were instructed not to reveal this information, there is no guarantee that there was 100% compliance. Recognizing this issue, the

[1] For this review, I use [redacted](spinosad [redacted]) to refer to the drug product. However, the trade name of the to-be-marketed formulation is under review and will likely be changed. In addition, chemistry reviewers have determined the product is more accurately represented as Tradename (spinosad) Suspension, 0.9%.

applicant used a variety of analyses to explore the impact of the inadvertent unblinding on the efficacy conclusions. Their analyses suggest that the conclusion of efficacy is not compromised.

While this NDA was under review, the medical division approved Ulesfia (NDA 22-129) for the treatment of head lice. Ulesfia's active ingredient is benzyl alcohol at a concentration of 5%. Benzyl alcohol is also a component of (b) (4) formulation (b) (4)

Given that benzyl alcohol is effective in the treatment of head lice, an important review issue is assessing the contribution of spinosad to the efficacy of (b) (4) for the treatment of head lice. Because neither of the Phase 3 studies contained a benzyl alcohol treatment arm, the data from the Phase 3 studies cannot be used to discern the contribution of spinosad.

The Phase 2 studies, however, contained a benzyl alcohol treatment arm. One of these three Phase 2 studies had a sample size that was large enough to permit a statistical analysis. The results of this study (SPN 202-06) showed the differences between Spinosad 1% and vehicle, which includes benzyl alcohol, in the Day 14 response rates was statistically significant ($p<0.001$). Using a simple difference between proportions of subjects who were lice free at Day 14, with 95% confidence the true treatment effect for Spinosad 1% relative to vehicle could range from 27% to 52%.

1.2. Brief Overview of Clinical Studies

The submission contains data from two identical Phase 3 studies (SPN 301-07 and SPN 302-07), both conducted in the United States, and three Phase 2 studies; see Table 1.

The Phase 3 studies were active-controlled and evaluator/investigator-blinded. Their goal was to show superiority of NatrOVA to NIX in subjects infested with *P. capitis*. Eligible subjects were 6 months of age or older and presented with active cases of head lice.

Households were randomized (4:4:1) to NatrOVA without nit combing, NIX, or NatrOVA with nit combing. Subjects were evaluated for efficacy on Day 7 and again on Day 14. The youngest subject in a household was identified as the primary subject for purposes of the primary efficacy analysis. Treatment was to be applied at the time of randomization and, if needed, at Day 7. Subjects who required a second application at Day 7 and who were lice-free on Day 14 were evaluated on Day 21.

The primary efficacy endpoint in the Phase 3 studies was the proportion of primary subjects in the randomized households who were lice free 14 days after the last treatment.

Because benzyl alcohol, which is a component of (b) (4) formulation, is now an approved product for the treatment of lice, determining whether spinosad contributes to the efficacy of (b) (4) is an important review issue. When the (b) (4) NDA was submitted in January

2009, no products containing benzyl alcohol alone had been approved for the treatment of head lice. While the NDA was under review, however, the medical division approved Ulesfia (NDA 22-129) for the treatment of head lice. Ulesfia's active ingredient is benzyl alcohol 5%.

Although (b) (4) Phase 3 studies do not have a treatment arm that contains only benzyl alcohol, comparator arms containing only benzyl alcohol are found in the three Phase 2 studies. Two of the three Phase 2 studies enrolled too few subjects to allow for meaningful statistical comparisons: SPN 201-05 (n=36) and SPN 202-06 (n=26). The third Phase 2 study, SPN 202-06 (n=122), contains data from 40 subjects randomized to NatrOVA (0.5%), 39 subjects randomized to NatrOVA (1.0%) and 43 subjects randomized to vehicle. These numbers were sufficient for statistical comparisons.

Table 1. Overview of Efficacy and Safety Studies

Study	Type	Treatments	Number of Primary Subjects	Study Dates
SPN 201-05	Phase 2A Dose Ranging	NatrOVA (0.5%) NatrOVA (1.0%) NatrOVA (2.0%) Vehicle	8 9 20 9	09/2005 to 11/2005
SPN 202-06	Phase 2 Dose Ranging	NatrOVA (0.5%) NatrOVA (1.0%) Vehicle	40 39 43	03/2006 to 07/2006
SPN 203-07	Phase 2B Pilot	NatrOVA (1.0%) Vehicle	11 13	03/2007 to 07/2007
SPN 301-07	Phase 3 Superiority	NatrOVA (with combing) NatrOVA (without combing) NIX	23 91 89	09/2007 to 04/2008
SPN 302-07	Phase 3 Superiority	NatrOVA (with combing) NatrOVA (without combing) NIX	21 83 84	09/2007 to 04/2008

1.3. Statistical Issues and Findings

The primary statistical issues are the lack of blinding on the part of study participants who were enrolled in the Phase 3 studies and the potential for them to reveal treatment-related information to study site personnel, the contribution of spinosad to the efficacy of (b) (4) and households being enrolled multiple times.

Subjects may have been aware of their treatment assignments. For example, because subjects who were randomized to the active comparator, NIX, were given nit combs and instructed to use them, subjects who did not receive a nit comb with their randomized treatment may have been

aware they were receiving NatrOVA.

Moreover, the name of the treatment product was printed on the "Instruction for Use" provided with the study product packaging. Although the contract research organization notified study sites to instruct subjects they should not speak of their study treatment with anyone other than the "Master Product Distributor", who was the only person at each site who was unblinded to study treatment, there is no guarantee that study subjects did not reveal their treatment assignment.

Recognizing this issue, the applicant used a variety of analyses to explore the impact of the inadvertent unblinding on the efficacy conclusions. Their analyses suggest that the conclusion of efficacy is not compromised.

While the results from the Phase 3 studies demonstrate efficacy of (b) (4) relative to NIX, the Phase 3 studies do not allow for a comparison between the (b) (4) formulation, which contains spinosad (b) (4) and benzyl alcohol (b) (4), and benzyl alcohol alone. The Phase 2 studies contained a benzyl alcohol comparator arm. One of the studies was sufficiently large to allow for statistical comparisons. The results of this study showed that (b) (4) was superior to benzyl alcohol.

The clinical study reports for the Phase 3 studies that indicate a single household may been enrolled more than once or as more than one household. Although the study reports state all efficacy results were examined for the impact of the same household being entered more than once, the submission does not present the results from this examination. Neither does the submission document the number of households that were enrolled more than once.

Responses from households that are enrolled more than once or from households that are enrolled as more than one household are correlated and, therefore, cannot be assumed to be independent. Independence of observations is a key assumption of the analyses of the primary endpoint. The applicant needs to provide further information on the households that were enrolled more than once or as more than one household. Further, the applicant needs to provide analyses that include each household only once.

2. INTRODUCTION

2.1. Overview

The applicant is seeking approval (b) (4) for the treatment of head lice infestations in patients (b) (4). To support this claim, the applicant submitted two Phase 3 studies that evaluated (b) (4) against an active control, NIX with nit combing.

Because (b) (4) contains benzyl alcohol, which has been established as efficacious in the treatment of head lice, I also reviewed the results of a Phase 2 study that included a benzyl alcohol arm and a spinosad 1% treatment arm.

2.2. Data Sources

- Electronic submission: \\Cdsesub1\evsprod\NDA022408\0000
- Datasets
  - SPN-301-07: \\Cdsesub1\evsprod\NDA022408\0000\m5\datasets\spn-301-07
  - SPN-302-07: \\Cdsesub1\evsprod\NDA022408\0000\m5\datasets\spn-302-07
  - SPN-202-06: \\Cdsesub1\evsprod\NDA022408\0000\m5\datasets\spn-202-06\listings

3. STATISTICAL EVALUATION

3.1. Evaluation of Efficacy

Because the studies are identically designed, my reviews of the Phase 3 studies are combined into a single section; see Section 3.1.1. I also review one of the Phase 2 studies, SPN 202-06, in order to assess the contribution of spinosad 1% to the efficacy of (b) (4) formulation, which contains (b) (4) benzyl alcohol; see Section 3.1.2.

3.1.1. Phase 3 studies: SPN 301-07 and SPN 302-07

3.1.1.1. Study Design

Studies SPN 301-07 and SPN 302-07 shared a common protocol and are entitled, "A comparative safety and efficacy study between NatrOVA® Crème Rinse in subjects ≥ 6 months of age with *Pediculosis capitis*." The studies were active-controlled and evaluator/investigator-blinded. The primary objective of the studies was to compare the proportion of subjects who were lice free among those randomized to NatrOVA without nit combing to the proportion of subjects who were lice free among those randomized to NIX with nit combing.

The clinical study reports indicate a third treatment arm, NatrOVA with nit combing, was included to help preserve the blind and to provide a general comparison. However, only the NIX bottle and NatrOVA bottle with nit combing contained a comb. To maintain blinding, subjects were instructed not to discuss any aspects of the treatment process with the evaluators or investigators.

Healthy subjects within a household who were six months of age or older and who presented with at least three live lice at screening were eligible for the studies. Subjects were not to use any other form of lice treatment during the course of the study, or to cut or chemically treat their hair. Potential subjects receiving certain concomitant treatments or treatment for lice were

excluded from the study.

A "household" was a group of related or unrelated individuals who lived in the same dwelling and shared a common living space. The "primary" subject in each household was considered the youngest person within that household who had at least three live lice present at the screening visit. A single individual was considered to represent a "household" if this single individual met the criteria for the "primary" subject.

Randomization was stratified by study site. Eligible households were randomized to NatrOVA without nit combing, NatrOVA with nit combing, or NIX. The test article was to be given to subjects at the time of randomization (Day 0) and treatment was to be applied at home within 24 hours.

All subjects who were treated on Day 0 were to return to the study site on Day 1 for evaluation of ocular and scalp irritation and for side effects. Subjects were to return again for evaluation on Day 7. Subjects with live lice at Day 7 received a second box of test article. Subjects who were lice free at Day 7 were to return on Day 14 for evaluation. Subjects with live lice and who received a second box of test article were to return on Day 14 and Day 21.

The protocol indicated that at least two study sites were to be chosen to collect blood specimens from pediatric subjects for safety evaluations. However, the process for selecting these subjects was not discussed.

The primary study endpoint was the proportion of primary subjects in the enrolled households who are lice free 14 days after the last treatment.

The study was powered to compare the NatrOVA without combing and NIX treatment arms. With 76 primary subjects randomized to NatrOVA without nit combing and 76 primary subjects randomized to NIX, the study had 80% power to detect a treatment difference of 21% between the two treatment arms[2]. This assumes a Type I error rate of 0.05 (two-sided) and a success rate of 86% in the NatrOVA without nit combing treatment arm. In addition, the sample size calculations indicate an additional 19 subjects were to be randomized to NatrOVA with combing in order to achieve a randomization ratio of 4:4:1.

Although the sample size calculations were based on a continuity corrected chi-square test, the protocol specified a logistic regression analysis to assess the treatment effect. The protocol indicates the logistic regression model would include terms for study site and for treatment by site interaction. In the event some study sites enrolled fewer than eight subjects in the NatrOVA (without nit combing) and NIX treatment arms and fewer than two subjects in the NatrOVA (with nit combing) treatment arm, the protocol defined a process for combining data from smaller study sites with data from larger sites.

[2] The protocol for Study SPN-301-07 contains what is apparently a typographical error. Section 12.2 of the study protocol states: "the study would be expected to find that difference to be significant 80% of the time (i.e., 90% power)." However, the protocol for Study SPN-302-07 and the clinical study reports all indicate 80% power.

The applicant calculated the observed success rates by dividing the number of successes by the number of subjects. Additionally, the applicant used the logistic regression models to estimate the treatment success rates and their corresponding confidence intervals for the NatrOVA without nit combing and NIX treatment groups. To obtain these estimates, the parameters obtained from the logistic regression models were transformed into the treatment success rates (*p*) and their confidence intervals [*LCI(p), UCI(p)*]:

$$p = \frac{e^{\textit{point estimate}}}{1+e^{\textit{point estimate}}};\quad LCI(p) = \frac{e^{\textit{LCI}\text{ point estimate}}}{1+e^{\textit{LCI}\text{ point estimate}}};\ UCI(p) = \frac{e^{\textit{UCI}\text{ point estimate}}}{1+e^{\textit{UCI}\text{ point estimate}}}$$

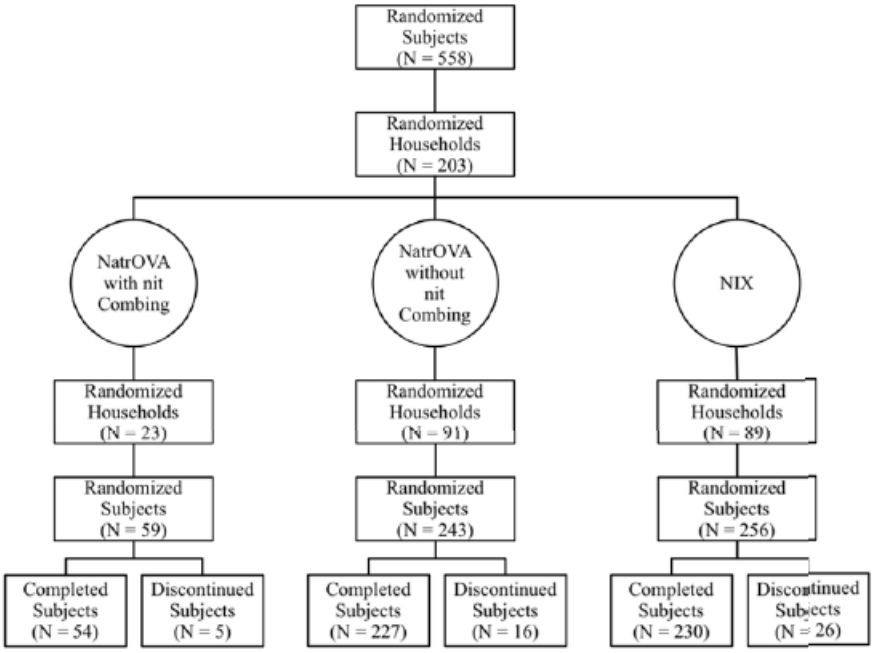
Table 4 and Table 5 of this review contain these within-treatment estimates. Differences between the treatment groups were not provided.

Missing final evaluation data were imputed using last observation carried forward (LOCF). Three sensitivity analysis methods were used to confirm the findings of the analyses that used LOCF.

3.1.1.2. Description of Subjects

The two Phase 3 studies enrolled approximately the same numbers of households and subjects. In Study SPN-301-07, 203 households (558 subjects) were randomized; in Study SPN-302-07, 188 households (480 subjects) were randomized. Similar proportions of subjects completed the studies (SPN-301-07: 91.6%; SPN-302-07: 91.3%). Each study was conducted in six non-overlapping clinical sites in the US. Figure 1 (SPN-301-07) and Figure 2 (SPN-302-07) show the disposition of subjects in the two Phase 3 studies.

Figure 1. Disposition of Subjects: SPN-301-07

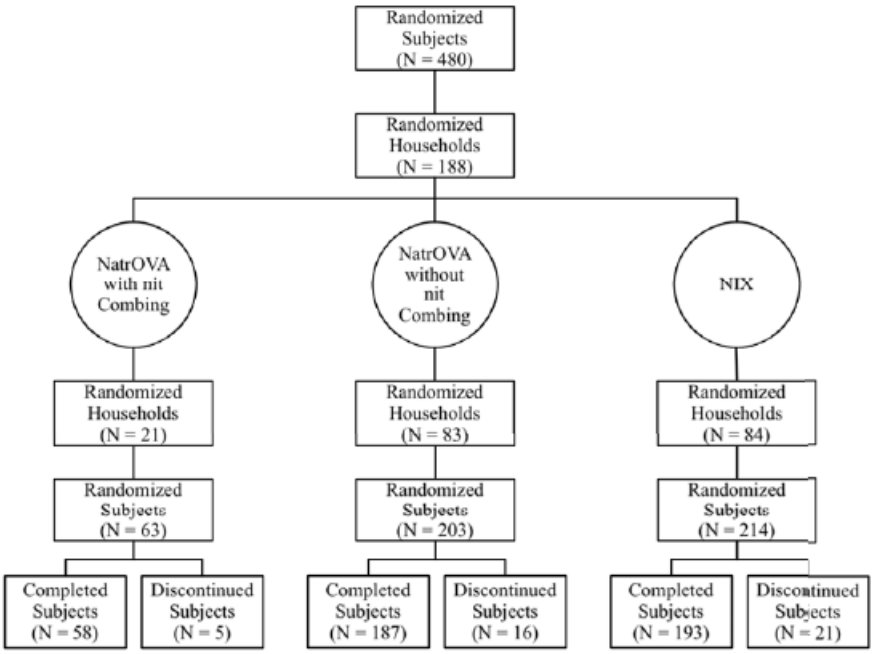


(Note: A primary subject was identified within each household as the youngest member with three live lice at Day 0. Thus, the number of primary subjects was equal to the number of households. The total number of subjects included all randomized household members [i.e., primary and non-primary subjects combined].)

SOURCE: Clinical Study Report for study SPN-301-07, Figure 10.1-1

Source: Clinical Study Report for Study SPN-301-07, Figure 10.1-1

Figure 2. Disposition of Subjects: SPN-302-07



(Note: A primary subject was identified within each household as the youngest member with three live lice at Day 0. Thus, the number of primary subjects was equal to the number of households. The total number of subjects included all randomized household members [i.e., primary and non-primary subjects combined].)

SOURCE: Clinical Study Report for study SPN-302-07, Figure 10.1-1

Source: Clinical Study Report for Study SPN-302-07, Figure 10.1-1

The demographics for the two studies were also comparable. Among the primary subjects who were randomized, the average age was 10 years in SPN-301-07 and 9 years in SPN-301-07. Close to 90% of the subjects were female, 62% were Caucasian and 32% were Hispanic. See Table 2 and Table 3 for detailed summaries of the demographics for the two studies.

Table 2. SPN-301-07: Summary of demographic characteristics

	NatrOVA® Crème Rinse		Nix® Crème Rinse	Total
	With Nit Combing (N=23)	Without Nit Combing (N=91)	(N=89)	(N=203)
Age (years)				
N	23	91	89	203
Mean	11	9.1	10	9.9
STD	11.6	10.1	12.8	11.5
Median	9.0	6.0	7.0	7.0
Min. to Max.	1 to 52	0 to 63	0 to 84	0 to 84
≤ 4 years	6 (26.1%)	26 (28.6%)	27 (30.3%)	59 (29.1%)
5 to 9 years	7 (30.4%)	42 (46.2%)	32 (36.0%)	81 (39.9%)
10 to 14 years	6 (26.1%)	13 (14.3%)	16 (18.0%)	35 (17.2%)
≥ 15 years	4 (17.4%)	10 (11.0%)	14 (15.7%)	28 (13.8%)
Gender				
N	23	91	89	203
Male	4 (17.4%)	13 (14.3%)	12 (13.5%)	29 (14.3%)
Female	19 (82.6%)	78 (85.7%)	77 (86.5%)	174 (85.7%)
Predominant race				
N	23	91	89	203
Caucasian	12 (52.2%)	55 (60.4%)	58 (65.2%)	125 (61.6%)
Black	0 (0.0%)	0 (0.0%)	1 (1.1%)	1 (0.5%)
Asian	1 (4.3%)	1 (1.1%)	2 (2.2%)	4 (2.0%)
Native American	1 (4.3%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Hispanic	8 (34.8%)	32 (35.2%)	26 (29.2%)	66 (32.5%)
Other[b]	1 (4.3%)	3 (3.3%)	2 (2.2%)	6 (3.0%)

Source: Clinical Study Report for Study SPN-301-07, Table 14.1.1.1

Table 3. SPN-302-07: Summary of demographic characteristics

	NatrOVA® Crème Rinse		Nix® Crème Rinse	Total
	With Nit Combing (N=21)	Without Nit Combing (N=83)	(N=84)	(N=188)
Age (years)				
N	21	83	84	188
Mean	6.7	8.6	8.9	8.5
STD	4.47	9.29	10.5	9.43
Median	6.0	7.0	7.0	7.0
Min. to Max.	1 to 22	1 to 64	1 to 68	1 to 68
≤ 4 years	7 (33.3%)	23 (27.7%)	28 (33.3%)	58 (30.9%)
5 to 9 years	11 (52.4%)	40 (48.2%)	34 (40.5%)	85 (45.2%)
10 to 14 years	2 (9.5%)	12 (14.5%)	13 (15.5%)	27 (14.4%)
≥ 15 years	1 (4.8%)	8 (9.6%)	9 (10.7%)	18 (9.6%)
Gender				
N	21	83	84	188
Male	3 (14.3%)	12 (14.5%)	6 (7.1%)	21 (11.2%)
Female	18 (85.7%)	71 (85.5%)	78 (92.9%)	167 (88.8%)
Predominant race				
N	21	83	84	188
Caucasian	13 (61.9%)	53 (63.9%)	52 (61.9%)	118 (62.8%)
Black	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asian	0 (0.0%)	1 (1.2%)	0 (0.0%)	1 (0.5%)
Native American	0 (0.0%)	1 (1.2%)	0 (0.0%)	1 (0.5%)
Hispanic	8 (38.1%)	25 (30.1%)	28 (33.3%)	61 (32.4%)
Other[b]	0 (0.0%)	3 (3.6%)	4 (4.8%)	7 (3.7%)

Source: Clinical Study Report for Study SPN-302-07, Table 14.1.1.1

3.1.1.3. Results

Efficacy

The results from the two Phase 3 studies were comparable. Approximately 85% of those randomized to NatrOVA were lice-free two weeks following their last treatment compared to about 45% of those randomized to NIX. These treatment differences were statistically significant (p<.001). The tables below summarize the results for the studies; see Table 4 and 5.

Because the independent terms included in a logistic model are assumed to have a multiplicative effect on the dependent variable, an assumption that may not be valid, I reanalyzed the data using a Cochran-Mantel-Haenszel analysis, stratified by study site. The results showed the difference between NatrOVA without nit combing and NIX was statistically significant (p<0.001) for each study.

The submission did not provide estimates of the treatment effects and their corresponding 95% confidence intervals. Using a difference in proportions, I calculated the following:

Study SPN-301-07
Treatment effect: 40%
95% confidence interval: [27%, 52%]

Study SPN-302-07
Treatment effect: 44%
95% confidence interval: [32%, 56%]

With 95% confidence, the true treatment effect can range from 27% to 52% based on the data from SPN-301-07, and from 32% to 56% based on the data from SPN-302-07.

Further analyses suggested that the efficacy results appeared consistent across study sites.

Table 4. Efficacy results for Study SPN-301-07

	NatrOVA		
	With Nit Combing (N=23)	Without Nit Combing (N=91)	NIX (N=89)
Treatment success/failure[a]			
N	23	91	89
Failure (live lice present)	4 (17.4%)	14 (15.4%)	49 (55.1%)
Success (no live lice present)	19 (82.6%)	77 (84.6%)	40 (44.9%)
Estimated success rate[b]		89.4%	44.8%
95% CI for estimated success rate[b]		(80.8%, 94.4%)	(32.7%, 57.5%)
P-value vs. Nix® Crème Rinse[b]		<.001	

[a] 14 days after last treatment is Day 14 for subjects who were treated once and Day 21 for subjects who were treated twice.
[b] Logistic regression with factors for analysis site and treatment group; CIs are presented as lower and upper bounds.

Source: ISE, Table 6.2.1.4.1-1

Table 5. Efficacy results for Study SPN-302-07

	NatrOVA		
	With Nit Combing (N=21)	Without Nit Combing (N=83)	NIX (N=84)
Treatment success/failure[a]			
N	21	83	84
Failure (live lice present)	4 (19.0%)	11 (13.3%)	48 (57.1%)
Success (no live lice present)	17 (81.0%)	72 (86.7%)	36 (42.9%)
Estimated success rate[b]		89.1%	45.1%
95% CI for estimated success rate[b]		(80.4%, 94.2%)	(33.8%, 56.8%)
P-value vs. Nix® Crème Rinse[b]		<.001	

[a] 14 days after last treatment is Day 14 for subjects who were treated once and Day 21 for subjects who were treated twice.
[b] Logistic regression with factors for analysis site and treatment group; CIs are presented as lower and upper bounds.

Source: ISE, Table 6.2.1.4.2-1

The following descriptive information summarizes the percentages of subjects who received only a single application of study treatment, and the percentages of subjects who were treatment successes after receiving their first application of study treatment. Note that the denominators are the number of subjects randomized to their respective treatment group.

The percentages of primary subjects who received only a single application of study treatment were:

NatrOVA without combing: 72% (66/91) (SPN-301-07), 83% (69/83) (SPN-302-07)
NIX with combing: 37% (33/89) (SPN-301-07), 39% (33/84) (SPN-302-07)

The treatment success rates among all primary subjects after they received their first application of study treatment:

NatrOVA without combing: 68% (62/91) (SPN-301-07), 76% (63/83) (SPN-302-07)
NIX with combing: 25% (22/89) (SPN-301-07), 26% (22/84) (SPN-302-07)

Effects of treatment blinding

The applicant investigated whether the lack of double blinding and the potential for the investigators to become unblinded affected the efficacy results. They did four evaluations to investigate whether subject knowledge of the assigned treatments influenced their use to the extent that treatment success rates were affected. The four evaluations included:

- Inter-study comparisons of the efficacy results reported in the NatrOVA without nit combing group
- Similar comparisons of the efficacy results reported in the NIX treatment group
- An evaluation of the differences reported between the NatrOVA without nit combing and NIX treatment groups
- An investigation into the possible misuse of nit combs

The applicant concluded that subject knowledge did not substantially affect study outcomes. This is supported by subject compliance reports, and the similarity of the outcomes in the NatrOVA without combing group to those in SPN-202-06, and similarity of the outcomes to those reported in the literature.

Multiple enrollments of the same household

The study reports indicate a single physical household may have been enrolled as more than one household or multiple times; see Section 9.7.1.3 in the CSRs. If a household was re-enrolled because of re-infestation, data from both infestations were included in the analysis.

In other cases, an actual household may have been divided into two household units if the actual household contained more than six members or if the actual household contained different member groups (e.g., visiting stepchildren, visiting grandchildren, visiting children of shared custody, new foster children). In these cases, data from both household units were included in the efficacy analyses.

Although the study reports indicate that results were examined for the impact of the same household being entered more than once or a more than one "household", the study reports do not discuss the degree of multiple enrollments, the methodology used to assess the impact on the overall results.

The subject outcomes arising from related household units are correlated and, therefore, cannot be assumed to be independent. Because independence of observations is an important assumption for the analyses of the primary endpoints among the primary subjects, each household should be represented only once in the primary analysis. The applicant needs to provide analyses that exclude multiple enrollments in order for us to assess the efficacy of NatrOVA.

3.1.2. Phase 2 study: SPN-202-06

This Phase 2 study permitted a comparison between the NatrOVA formulation and benzyl alcohol. When reading this section, keep in mind that each of the three strengths of spinosad contains benzyl alcohol at a concentration of (b) (4). Spinosad 0.0% represents the vehicle, which contains benzyl alcohol but no spinosad.

3.1.2.1. Study Design

Study SPN-202-06, "Efficacy and safety of different strengths of Spinosad Topical Crème Rinse (0.0%, 0.5% or 1.0%) in subjects ≥ 2 years of age with *Pediculosis capitis* – a dose ranging study," was a multi-center, randomized, investigator-blind study. The study objective was to determine the safety and efficacy of different strengths of a single, 10-minute no comb treatment of spinosad as compared to a vehicle control in subjects who had been infested with at least a mild case of *Pediculosis capitis*.

Healthy subjects who had at least three live lice and the presence of nits, and who were two years of age or older were eligible for the study. Subjects were not to use any other lice treatment

during the study nor were they to use a comb or to cut or chemically treat their hair.

Subjects were randomized to one of three treatment arms:

- Spinosad Crème Rinse, 1.0%
- Spinosad Crème Rinse, 0.5%
- Spinosad Placebo Crème Rinse, 0.0%

A study technician applied a single 10 minute application at the time of randomization. Approximately one hour after treatment, a subject's head and scalp were evaluated for adverse events. Subjects were to return for an evaluation on Day 7. If live lice were observed at Day 7, the subject was considered a treatment failure, was provided NIX for home treatment and was discontinued from the study.

Subjects who had no live lice at Day 7 but appeared to have potentially viable nits had 5-10 hairs with potentially viable nits clipped and incubated to determine viability. If any of the nits hatched within 10 days, the subjects were considered treatment failures, provided NIX for home use and were discontinued from the study.

Subjects who were lice and viable nit free at Day 7 returned for a Day 14 evaluation. If they were lice free and were determined to be free of viable nits (by inspection or incubation), they were considered a treatment success.

The primary study endpoint was the proportion of subjects free of live lice (no live lice or viable nits) on Day 7 and Day 14 after the applied treatment.

Although the study protocol indicates 120 subjects were to be enrolled, neither the protocol nor the study report provides a rationale for this sample size. The protocol specified a chi-square test as the primary analysis for comparing treatment success rates.

The applicant's intent-to-treat (ITT) population was the primary population for analysis of adverse events. This safety population included subjects who received treatment and who returned for at least one post application visit.

The applicant's per protocol (PP) population was used as the primary population for the analyses of efficacy. This population included all subjects who complied with the protocol and had outcome data for all required visits. It also included subjects who discontinued because of a treatment-related adverse event and subjects who terminated early due to treatment failure.

Note that the applicant's ITT and PP populations differed by a single subject (Subject 526), which is discussed in the following section.

3.1.2.2. Description of subjects

Study SPN-202-06 enrolled 122 subjects from five study sites. Table 6 and Table 7 show

summary statistics for age, gender and race both overall and by treatment group. Although the proportion of female subjects was similar to those for the Phase 3 studies, the typical subject was somewhat older and was more likely to be Caucasian.

Table 6. Study SPN-202-06: Summary statistics for age, gender, race

Summary Table of Subject Age, Gender, Race (All Treated Subjects)		
Age:	Mean	12.3
	Std. Dev.	11.3
	Median	9.0
	Minimum	2.0
	Maximum	60.0
Gender:	Female: 106 (86.9%)	Male: 16 (13.1%)
Race:	Caucasian: 95 (77.9%)	Hispanic: 19 (15.6%)
	Black: 0 (0%)	Native American: 0 (0%)
	Asian: 0 (0%)	Other: 8 (6.6%)

Source: Table 11.2-1, Clinical Study Report for SPN-202-06.

Table 7. Study SPN-202-06: Summary statistics for age, gender, race by treatment group

Summary Table of Age, Gender, Race Treatment Group)				
AGE	**A (n=39) Spinosad Crème Rinse (1.0%)**	**B (n=43) Spinosad Crème Rinse (0.0%)**	**C (n=40) Spinosad Crème Rinse (0.5%)**	**ANOVA p-value**
Mean	12.4	10.7	14.1	
Std. Dev.	11.2	10.3	12.3	
Median	8.0	7.0	9.0	0.3926[1]
Minimum	2.0	2.0	4.0	
Maximum	56.0	60.0	47.0	
GENDER	**A**	**B**	**C**	**Chi-squared p-value**
Female	35 (89.7%)	35 (81.4%)	36 (90.0%)	
Male	4 (10.3%)	8 (18.6%)	4 (10.0%)	0.4153[1]
Total (n=122)	39	43	40	
RACE	**A**	**B**	**C**	**Chi-squared p-value**
Caucasian	30 (76.9%)	33 (76.7%)	32 (80.0%)	
Black	0 (0%)	0 (0%)	0 (0%)	
Asian	0 (0%)	0 (0%)	0 (0%)	>0.5000[1]
Hispanic	6 (15.4%)	8 (18.6%)	5 (12.5%)	
Other	3 (7.7%)	2 (4.7%)	3 (7.5%)	

Source: Table 11.2-2, Clinical Study Report for SPN-202-06.

The applicant excluded two subjects from the ITT population (Table 8), leaving 120 subjects who were evaluable for safety. In addition to these two subjects, the per protocol population excluded an additional subject from the 1.0% Spinosad treatment arm, see Table 9, resulting in 119 subjects who were evaluated for efficacy: 43 randomized to 0.0% Spinosad, 40 randomized to 0.5% Spinosad and 36 randomized to 1.0% Spinosad.

Table 8. Subjects excluded from the applicant's ITT population and safety analysis

Subject No.	Reason for Exclusion from ITT Population
538	Protocol Violation (missed the number of required visits) Subject lost to follow-up after numerous contact attempts. Adverse event status could not be determined. (Included in the Irritation Analysis only - n=121)
327	Product application error – subject had no adverse events

Source: Table 11.1-2, Clinical Study Report for SPN-202-06.

Table 9. Subjects excluded from the applicant's per protocol population and efficacy analysis

Subject No.	Treatment	Reason for Exclusion from PP Population
526	A	Protocol Violation (missed the number of required visits)
538	A	Protocol Violation (missed the number of required visits)
327	A	Product application error

Source: Table 11.1-1, Clinical Study Report for SPN-202-06.

3.1.2.3. Results

Although the primary endpoint for the Phase 2 study was the proportion of subjects who were lice-free at Day 7 and again at Day 14 after their last treatment, we report here the results for Day 14 only, which was the primary endpoint for the Phase 3 studies. The results of the applicant's analyses of efficacy at Day 14 show that both concentrations of Spinosad were superior to placebo ($p<.0001$); see Table 10.

Table 10. SPN-202-06: Efficacy results at Day 14 following last treatment

Assessment of Success/Failure Rates - Comparing A vs. B			
	A (n=36) Spinosad Crème Rinse (1.0%)	B (n=43) Spinosad Crème Rinse (0.0%)	Chi-squared p-value
Success	31 (86.11%)	11 (25.58%)	<0.0001[1]
Failure	5 (13.89%)	32 (74.42%)	
Assessment of Success/Failure Rates - Comparing C vs. B			
	C (n=40) Spinosad Crème Rinse (0.5%)	B (n=43) Spinosad Crème Rinse (0.0%)	Chi-square p-value
Success	33 (82.50%)	11 (25.58%)	<0.0001[1]
Failure	7 (17.50%)	32 (74.42%)	

Source: Table 11.4.1.1-2, Clinical Study Report for SPN-202-06.

We redid the efficacy analyses by including the three subjects that the applicant had excluded from their analyses. The FDA's ITT analyses show the proportion of successes was higher among subjects randomized to Spinosad 1.0% than those randomized to vehicle at Day 14 ($p<0.001$)[3]; see Table 11. At Day 14, 82% of the Spinosad 1.0% subjects reached success status while 28% of the vehicle arm subjects were successes.

[3] Because the applicant did not provide data by study sites, the CMH analysis was not stratified by center.

The difference in success rates (%) between the Spinosad 1.0% arm and the vehicle arm was 54% with a 95% CI of (36.1%, 72.2%). Thus, with 95% confidence, the true treatment effect ranges from 36% to 73%.

Table 11. Number (%) of successes at Day 14 (FDA's ITT) following last treatment, comparing the Spinosad 1.0% arm to the vehicle arm in Study SPN 202-06.

	Spinosad 1.0% N=39	Vehicle N=43	p-value*
Number (%) of successes**	32 (82.05%) (66.47%, 92.46%)**	12 (27.91%) (15.33%, 43.67%)**	<0.0001

* p-value was calculated using the Chi-square test.
** exact 95% confidence intervals
Source: Statistical reviewer's analysis

3.2. Evaluation of Safety

See Medical Officer's review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Because the Phase 3 studies comprised approximately 90% female subjects, the small number of male subjects did not allow for a meaningful analysis of subgroups defined by gender. The treatment effects were statistically significant among Caucasians and among Hispanics. Other ethnic subgroups did not have sufficient sample sizes to allow for statistical comparisons.

5. SUMMARY AND CONCLUSIONS

5.1. Statistical Issues and Collective Evidence

A major issue is the statement in the submission that households may been enrolled more than once or as more than one household. Information from households that are enrolled more than once is correlated, which violates the assumption of independence needed for the analyses of the primary endpoint. The NDA did not identify the number of households and primary subjects who were affected, nor did the NDA provide analyses that excluded these households. The applicant needs to provide this information.

According to the protocol, the studies were active-controlled and evaluator/investigator-blinded and were intended to be double-blind. However, subjects were not blinded to treatment. In a "Note to File" dated 10/24/2007, the applicant documented that the study product name was printed on the 'Instruction for Use' provided within the study product packaging. The contract research organization notified the study sites to instruct subjects that they should "never speak of

study treatment with anyone other than the Master Product Distributor," the only person at each study site who was unblinded to treatment assignment.

In addition, only subjects randomized to NIX and NatrOVA with nit combing received nit combs. Subjects randomized to NatrOVA without nit combing did not receive a comb. To maintain blinding of the evaluators and investigators, subjects were instructed not to discuss any aspects of the treatment process with the evaluators or investigators.

The applicant investigated whether the lack of double blinding and the potential for the investigators to become unblinded affected the efficacy results. The applicant concluded that subject knowledge did not substantially affect study outcomes in the Phase 3 studies. This conclusion is supported by subject compliance reports, and the similarity of the outcomes in the NatrOVA without combing group to those in a Phase 2 study (SPN-202-06), and similarity of the outcomes to those reported in the literature.

Although we can never be certain that evaluators and subjects were not influenced by their knowledge of treatment assignment, the applicant's exploratory analyses coupled with the size of the treatment effect would suggest that the effect was likely minimal.

A second issue is whether spinosad or benzyl alcohol or both account for the (b) (4) treatment effect seen in the Phase 3 studies. If (b) (4) were viewed as a combination product composed of spinosad (b) (4) and benzyl alcohol (b) (4), then (b) (4) would need to be shown superior to each of its components. The NDA did not have a study that contained all three treatment arms. We did, however, evaluate the results of one study (SPN 202-06), which had a treatment arm containing only benzyl alcohol. The results from this study showed spinosad 1% was superior to benzyl alcohol (b) (4) in the treatment of head lice.

5.2. Conclusions and Recommendations

The evidence submitted in this NDA appears to support the efficacy of (b) (4) in the treatment of head lice. This conclusion is based primarily on two Phase 3 studies, whose primary endpoint was the proportion of subjects who were lice-free fourteen days following their last treatment. We can be 95% confident that the true response rate for (b) (4) without combing is 27% to 52% better than the response rate for NIX based on the results from the first study, and by 31% to 57% better than the response rate for NIX based on the results from the second study.

However, until the issue of households being enrolled more than once or as separate households is resolved, these results should be viewed with caution.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22408	ORIG-1	PARAPRO PHARMACEUTICALS LLC	SPINOSAD

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

/s/

LISA A KAMMERMAN
10/26/2009

MOHAMED A ALOSH
10/26/2009

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 22-408 **Applicant: ParaPRO** **Stamp Date: 1/23/2009**

Drug Name: (b) (4) **NDA/BLA Type:**

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? _____

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

Reviewing Statistician	Date
Supervisor/Team Leader	Date

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/s/

Carin Kim
3/19/2009 09:53:10 AM
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Mohamed Alosh
3/19/2009 11:24:59 AM
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