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.

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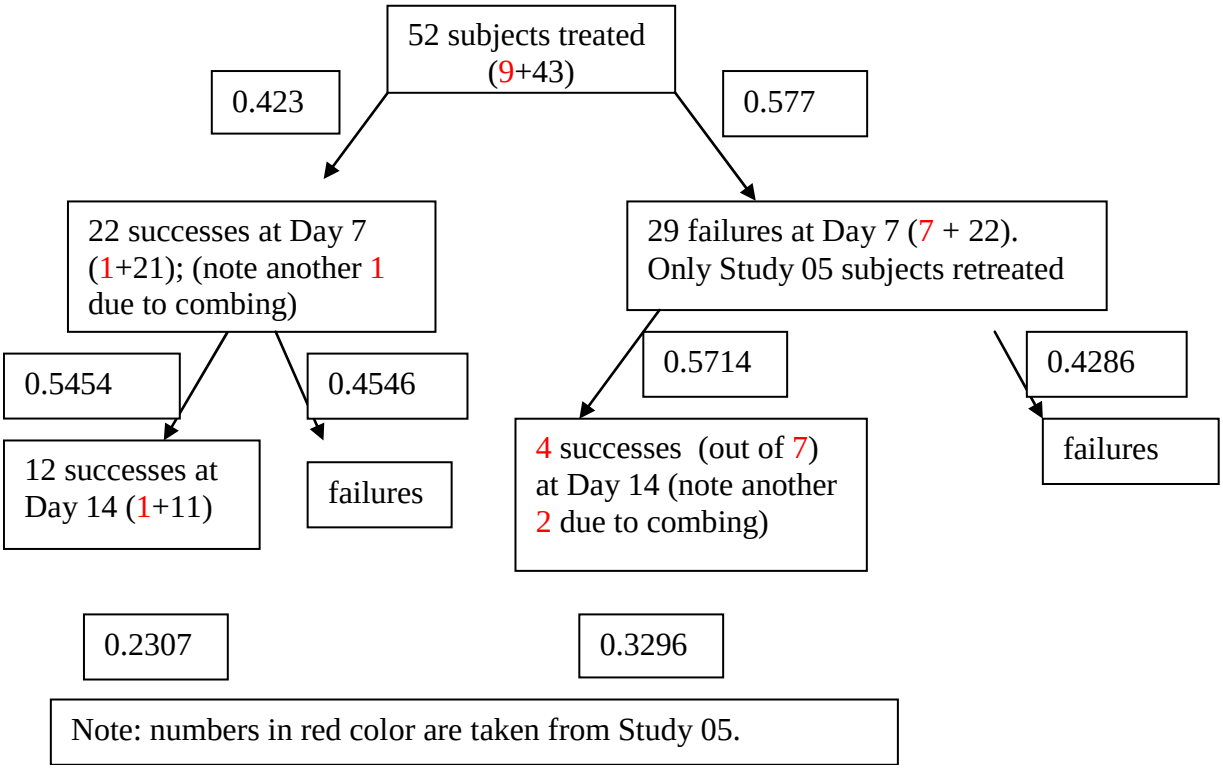
cc
Orig. NDA 22-408
DDDP/Walker
DDDP/Lindstrom
DDDP/Brown
DDDP/Williams
OBIO/Patrician
DBIII/Wilson
DBIII/Alosh
DBIII/Kim

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/

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01/07/2011

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